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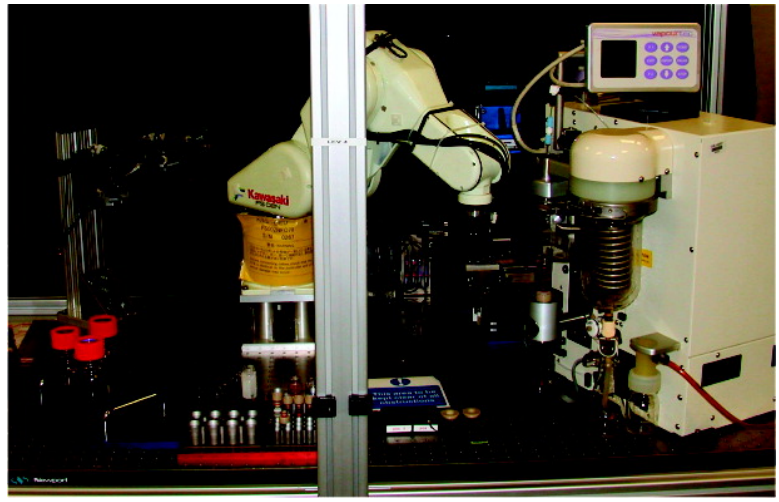

Fully Automated Open Access Platform for Rapid, Combined Serial Evaporation and Sample Reformatting

Otman Benali,* Gary Davies, Martyn Deal, Elizabeth Farrant, Duncan Guthrie,† John Holden,‡ and Rob Wheeler

GlaxoSmithKline Pharmaceuticals, Technology Development, New Frontiers Science Park (North), Third Avenue, Harlow, Essex, CM19 5AW, U.K.

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This paper reports a novel evaporator and its integration with an automated sample handling system to create a high throughput evaporation platform. The Vaportec V-10 evaporator uses a high speed rotation motor (~6000 rpm) to spin the vial containing a sample, creating a thin film of solvent which can be readily evaporated by the application of heat to the vial, while the consequent centrifugal force prevents "bumping". An intelligent algorithm controls pressure and temperature for optimum solvent removal conditions and end of run detection, critical for automation. The system allows the option of evaporation directly from a sample source vial, or alternatively, integrated liquid handling facilities provide the capability of transferring samples portionwise from a (large) source vial or bottle to a (small) daughter container, enabling efficient sample reformatting, with minimum user intervention. The open access system makes significant advances over current vacuum centrifugal evaporators in terms of evaporation rate and ease of automation. The evaporator's main features, the integration of robotics to provide automation, and examples of evaporation rates of a wide range of solvents from a variety of containers are described.

Introduction

The impact of genomics and proteomics and the subsequent generation of large numbers of drug targets has forced the pharmaceutical industry to refine and speed up methodologies for chemical and biological screening.[1,2] This in turn has driven the development of new enabling technologies for chemical synthesis and purification including instrumentation for the high throughput removal of solvents following synthesis, workup, or chromatographic procedures.[3] Evaporation of solvents from vials or tubes in high throughput procedures is typically carried out with a vacuum centrifugal evaporator[4] in which centrifugal force is used to prevent mechanical sample loss due to violent solvent boiling and bumping or using a blow down device, in which a stream of gas is directed downward onto the surface of the warmed sample facilitating evaporation of solvent into the dry gas stream which is subsequently exhausted into a fume hood[5] or collected using an efficient cold trap.[6]

Both approaches are well established in chemistry laboratories,[4,7] but their efficiency is derived from parallelization; as such, they are suitable for large batches but do not provide rapid turn around times on an individual sample basis. In addition, in the case of blow down instruments, sample loss, risk of intersample contamination, and the risk of solvent fumes being vented to the environment are other negative features. In more traditional medicinal chemistry laboratories, most evaporation is carried out using rotary evaporators which, although serial devices, are slow and not amenable to automation.

A new evaporator recently developed by Vaportec Ltd. overcomes many of these disadvantages, offering the possibility of performing evaporation from a wide range of vials in a fast serial manner. It also offers the ability to provide a seamless sample reformatting and evaporation process from a wide variety of vessels into a destination vial compatible with standard compound collection storage formats. However, the requirement to manually load and unload vials does much to offset the benefits of faster evaporation times. One way to overcome this issue is to integrate the evaporator into an automated platform for around-the-clock unattended operation. The components of the evaporator and examples of its performance, together with its integration with a six-axis Kawasaki[8] robot for automated open access, rapid, sequential evaporation, and sample reformatting processes, are described.

Experimental Details

Instrumentation. The V-10[9] was developed by Vaportec[10] as part of a collaboration with GSK and is shown in Figure 1. The system is composed of a touch screen which inputs and displays different parameters for manual control, a vial rotation motor mounted on a Z axis drive motor which loads the vial to the rotating vacuum connection sealed by pressing the open vial aperture against the latter to maintain the reduced pressure, an integrated vacuum pump controlled by a pressure sensor, a heater nozzle arranged to direct the hot air flow over the surface of the vial, a noncontact infrared

* Corresponding author. Mailing address: 29 Station Road, Shepreth, Cambridgeshire, SG8 6GB, U.K. Phone : +44(0) 7952394118. E-mail: otman.benali@uniqsis.com.
† Vaportec Ltd., Place Farm, Ingham, Suffolk, IP31 1NQ, U.K.
‡ Aitken Scientific, Oxford Road, Thame, Oxfordshire, OX9 2AH, U.K.

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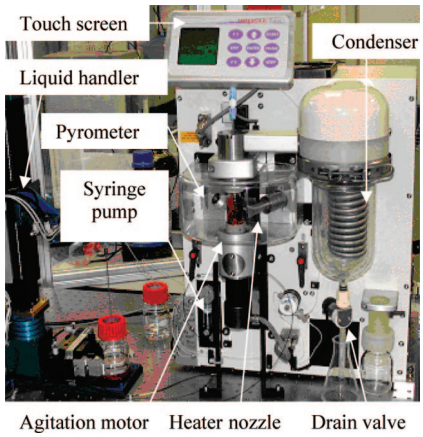

Figure 1. Main Components of the V-10.

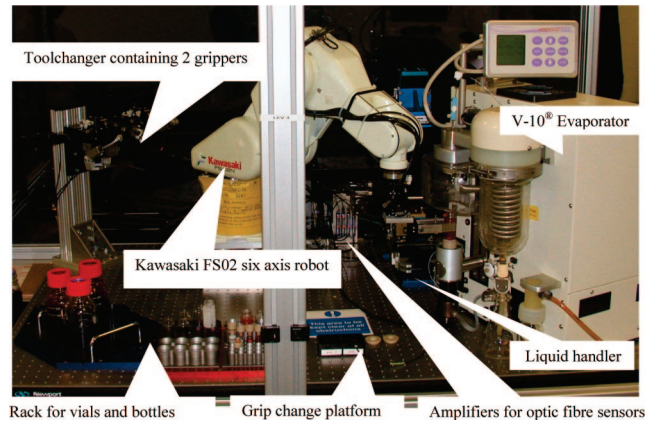

Figure 2. V-10 Integrated into a Six-Axis Kawasaki Robot.

(IR) temperature sensor arranged to sense the temperature of the walls of the container to control the evaporation process, and a refrigerated stainless steel condenser with defrost facility connected to a solenoid actuated drain valve.[11]

The system can operate in two modes: direct evaporation or reformatting evaporation. In the first mode, the sample is evaporated in the source vial. The reformatting evaporation mode allows samples containing large volumes of solvent to be concentrated into smaller vials compatible with the compound collection storage format. In this mode, an integrated syringe pump coupled to an injection station is used to transfer liquid from a large vessel or overfull vial into the evaporation vial.

In order to allow unattended operation of samples from multiple vial types, automation is required to move vessels around the system between the sample racks, injection station, and evaporator.[12] A Kawasaki FS02 six-axis industrial robot was selected due to the ease of integration, robustness, accuracy, and ability to access the evaporator. Three interchangeable grippers were selected with a tool changer which allowed gripping tools to be changed as required. The three tools include an internal gripper used to pick and place vials from the sample racks and the grip change platform, a finger gripper designed to access the V-10 stage to place and retrieve vials, and a bottle gripper to move sample bottles to and from the injection station. Three inductive sensors,[13] one per position, were used to confirm the availability of tools on the tool changer. Optical sensors[14] and associated amplifiers were installed to sense availability of the V-10 stage for loading/unloading, the presence of the vial on the V-10 stage, and the presence of the vial at grip change platform. All sensors are wired into the FS02 control box from where their outputs are accessible to the controlling software. Additionally, each gripper was fitted with a sensor allowing the gripper position to be determined to confirm that the expected vessel type has been selected.[15]

The system is controlled via an intuitive software application developed in collaboration with Aitken Scientific, "Evaporate Express" (Figure 3).[16] Defining a new evaporation run is performed via a simple two step wizard. Step 1: Select the source and destination rack types. Step 2: For each sample, select the volume to be evaporated, the method (e.g., aqueous, high boiling point) and mode (direct or multisample as defined below). Once the wizard is complete, the samples can be evaporated. At any point, it is possible to rerun the wizard to edit parameters of any unstarted samples or to add new samples to the worklist.

Materials. 30 and 20 mL vials are commercially available from VWR International. Haystack bar coded vials were supplied by Automation Partnership. Duran bottles (50–500 mL) were used for sample transfer. Compounds and organic solvents were purchased from commercial sources.

Evaporation and Recovery Measurements. An approximately 0.1 mM stock solution of each compound in each test solvent was prepared. The vials were tared, an amount of the test solution was added (8 mL to the 20 mL vial, 10 mL to the 30 mL vial), and the corresponding mass of each compound was calculated. After evaporation to dryness on the V-10, vials were reweighed to determine the amount of solvent evaporated. Each vial was then dried overnight, under vacuum, in a desiccator and reweighed to determine the amount of material lost during evaporation (recovery). To test the "Haystack" vials, 2 mL of an approximately 0.25 mM solution of each test compound in DMF was added to each tared vial before evaporation.

^{1}H NMR spectra were recorded on a Bruker Avance-400 spectrometer at 400 MHz. The samples were weighed on a Sartorius CP224S precision balance.

Direct Evaporation Mode. The sample is evaporated in the source vial. The 20 and 30 mL vials used fit directly into the evaporator. These vials have a diameter of 28 mm and a constriction in the neck which prevents sample from contaminating the vacuum connection as it is spun. A 20 mL vial can contain a maximum of 8 mL. At GlaxoSmithKline (GSK), smaller straight-sided 4 mL "Haystack" vials are used as standard for submissions into the compound collection. This vial type requires an adaptor fitted to the base plate. In addition, a vial neck adapter was developed which prevents sample from exiting the bottle and the contamination of the V-10 during spinning. The sequence of events is as follows: the robot picks the vial from the sample rack using the internal gripper, places it on the grip change platform, changes the internal gripper for the finger gripper at the tool change station, returns to the grip change platform, and loads the vial to the evaporation station. The Z axis drive motor moves the container vertically to the rotating vacuum connection sealed by pressing the open aperture against the seal of the vacuum connection to

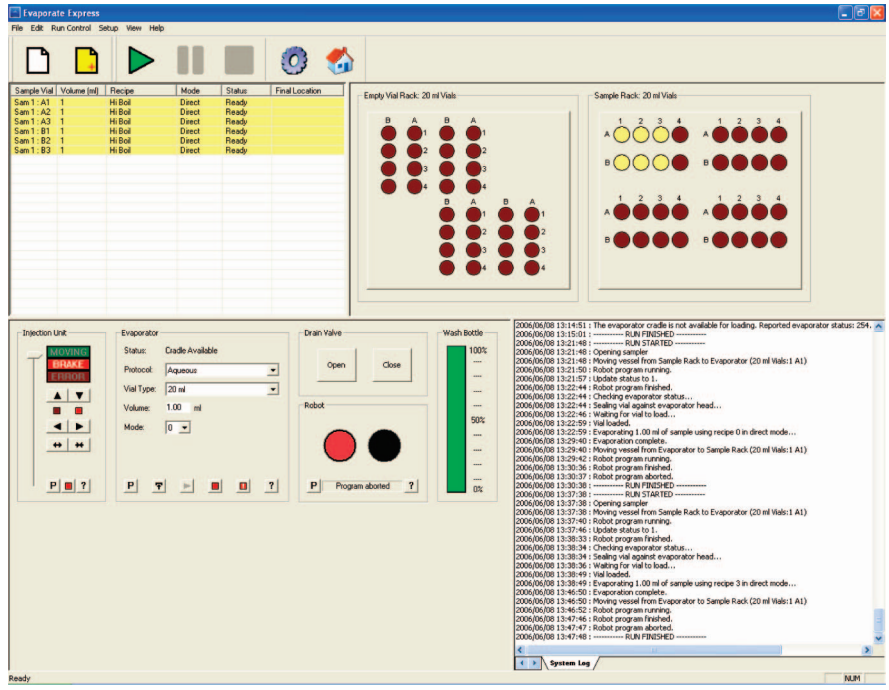

Figure 3. Software To Control the Automated System.

Table 1. Evaporation Times in V-10 for Various Solvent Types in a Variety of Vials

entry	vial type	solvent	evaporation time (min:s)	solvent evaporated (%)	recovery
		Phthalic Anhydride (Solid)			
1	30 mL vial	DCM	5:00	100	101
2	30 mL vial	CH_3CN	6:50	99.9	99
3	30 mL vial	DMF	7:30	99.8	101
4	30 mL vial	H_2O/ CH_3CN	13:10	98.5	98
5	20 mL vial	DMF	7:00	99.7	100
6	Haystack (4 mL)	DMF	10:10	99.5	98
		4-Dimethylaminobenzylamine (Liquid)			
7	30 mL vial	DCM	5:00	100	99
8	30 mL vial	CH_3CN	6:50	99.9	100
9	30 mL vial	DMF	7:30	99.7	99
10	30 mL vial	H_2O/CH_3CN	13:05	98.2	99
11	20 mL vial	DMF	7:00	99.8	101
12	Haystack (4 mL)	DMF	10:30	99.5	100

maintain the reduced pressure. The rotation motor spins the vial at up to 6000 rpm The high speed rotation and the vertical orientation allow the surface area of the solution in the vessel to be maximized and provides sufficient centrifugal force to prevent "bumping". The vacuum is then applied causing the temperature to decrease as evaporation commences. This is detected by the IR sensor, and the desired evaporation temperature is maintained by the application of heated air over the surface of the vial. The end of evaporation is detected automatically when the power required to maintain the set temperature is equivalent to that of a vessel containing the dry sample. The vacuum is then released, and on reaching atmospheric pressure, the rotation motor stops and the vial is lowered and picked by the robot to return it to the rack.

Reformatting Evaporation Mode. The total volume of the liquid to be transferred is specified in the software. An empty vial is placed by the robot in the V-10, and an aliquot is aspirated and dispensed to it. This is dried as above. Once dry, the next aliquot is aspirated and dispensed and so on until the entire sample is dried. To allow sample transfer in this way, the vial must be returned to atmospheric pressure following each evaporation cycle. The vial from the evaporator is then moved to the collection rack, and the source vial is returned to the sample rack.

Results and Discussion

To test the system in direct evaporation mode, evaporation of a wide variety of solvents in different size containers for solid or liquid compounds was carried out. For low boiling point solvents (e.g., DCM) in the 30 mL vial, the sample was evaporated quickly to dryness (~5 min, entries 1 and 7, Table 1) regardless of the physical form of the dissolved compound. For higher boiling solvents (e.g., acetonitrile), the evaporation time was about 7 min (entries 2 and 8, Table 1). For the highest boiling point solvent tested (DMF), all of the solvent was evaporated in ~8 min (entries 3 and 9, Table 1). Aqueous mixtures were readily evaporated, 99.5% of the solvent was removed in ~13 min. The best centrifugal evaporator would typically take up to 16 h for 30 mL 50/50 by volume of water/CH_3CN[9b]. Furthermore, the dried samples proved easier to dissolve using the "redissolve"

functionality[17] than typically observed in vacuum centrifugal evaporators, where dried solid typically takes the form of a poorly soluble glass. Evaporation efficiencies were similar for both the 20 and the 30 mL vial (entries 3 and 5 and 9 and 11, Table 1), but the Haystack vial evaporation times were slightly longer (∼11 min), either due to the poor heat transfer because of the label surrounding the vial or the increased wall thickness (entries 6 and 12, Table 1).

Similar tests were carried out, for all compounds, in the rotary evaporator with no mass loss observed.

To demonstrate the reformatting evaporation mode of a solution from a large source bottle, 500 mg of NaCl in 500 mL of 30% acetonitrile/water was fed sequentially as 12 mL aliquots using a syringe pump into a 30 mL vial. The throughput of evaporation was ∼50 mL/h, and the recovery was ∼100%. Therefore, larger volumes are best concentrated in a rotary evaporator then transferred to a small vial for storage. Ice accumulated in the condenser during the evaporation process but did not cause any damage to the condenser pot or significantly reduce the rate of evaporation. It is anticipated that, for larger volumes, the introduction of an automated defrost would be necessary.

Other vial types have been used successfully (data not shown) including the 2 mL or the 1.5 mL high recovery vials (available from Agilent Technologies). The recovery of material was satisfactory, indicating no sample loss during evaporation. ^{1}H NMR analysis of two dried samples, evaporated one after another, confirmed no cross-contamination was occurring during evaporation. Samples of higher initial concentration were successfully evaporated, although the amount of solvent evaporated was less (only 95% of the high boiling solvent was evaporated for a 1.5 mM solution of phthalic anhydride in DMF).

Conclusion

We have described the technical specifications of the V-10, a novel evaporator for use in rapid sequential evaporation. A high rate of evaporation of a variety of solvents from different vials has been demonstrated, along with the ability to reformat samples from large vessels to small vials. We have demonstrated the integration of a V-10 evaporator with automation, facilitating unattended and open access evaporation of arrays of samples and seamless integration of sample reformatting and evaporation processes. This allows the V-10 to be used effectively in a modern chemistry laboratory in a flexible way, allowing multiuser access with the ability to add additional samples to the work list at any time.

In its current configuration, it is not possible to evaporate DMSO and corrosive mixtures on this system. The rating of the vacuum pump supplied prohibits the removal of DMSO, and the acid sensitive nature of some of the wetted parts, particularly in the condenser, precludes the evaporation of corrosive mixtures.

Further development of the system would increase its capabilities, including the possibility of evaporating DMSO and handling corrosive mixtures. The ability to interface with a wider range of sample vessels, including such routine tools as the round-bottomed flask, would further enhance the potential.

A future development of the automated system will replace the three tools and tool changer with a single, multifunctional tool capable of handling all vessel types in use in the system. This will simplify the automation, increasing reliability and reducing cost.

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(9) (a) Baxendale, I. R.; Deeley, J., Griffith-Jones, C. M.; Ley, S. V.; Saaby, S.; Trammer, G. K. *Chem. Commun.* **2006**, 2566–2568. (b) Guthrie, D. (Vapourtec Ltd) *Solvent evaporator*. WO 065799 A1, 2005.
(10) The V-10 is commercially available from Biotage. The first prototype was validated and automated by the Technology Development department at GSK.
(11) 2-Port, 2-position, normally closed valve which is commercially available from BioChem Valve INC.
(12) The injection station, the grippers to hold different size and shape containers, and racks were custom-made for an unreported automated platform for continuous flow synthesis.
(13) SCHUNK Type INW 80/S-M8.
(14) Keyence Fibre optic head, FU-35FZ, amplifier FS-V21RP or FS-V31P.
(15) SCHUNK FPS-F5.
(16) Aitken scientific Ltd., Oxford Road, Thame, Oxfordshire, 0X9 2AH, U.K.
(17) The V-10 offers the possibility to redissolve dried samples, for example, for the purpose of solvent exchange, by using the integrated liquid handling facility to add a second solvent following evaporation and then spinning the vial at high speed for the required time.

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