

ANALYTICAL TECHNIQUES FOR THE FORMULATION OF GASTRORETENTIVE TABLETS

In this article, Jamie Clayton, Operations Director, Freeman Technology, Phil Bone, PhD, Technical Service and Applications Specialist, Micromeritics, and Kyu Mok Hwang, PhD, Postdoctoral Researcher, Sungkyunkwan University, discuss the value of analyses such as mercury porosimetry and powder rheology in characterising excipients for gastroretentive tablet formulation, and go on to detail a case study investigating polymer excipients for a novel bilayer floating tablet.

For certain drugs, formulation into a gastroretentive (GR) oral solid dosage (OSD) form can be a successful strategy for improving bioavailability and therapeutic efficacy. Such drugs include those in Biopharmaceutics Classification System (BCS) Class IV, which covers actives with low solubility and low permeability, and as such present some of the toughest formulation challenges. Prime targets for GR OSD forms are drugs for local action in the stomach, with a narrow absorption window (NAW) or with poor solubility or stability under alkaline conditions. Improving the gastroretention of such drugs can boost efficacy, and at the same time enable a streamlined dosing regime via sustained or controlled release. Expandable, swelling, floating, muco-adhesive and high-density systems are all routinely deployed depending on the properties of the drug and the required delivery profile.¹

This article considers the specific challenge of developing floating GR OSD forms and the analytical techniques that can be deployed to support their formulation. Experimental work by researchers at the School of Pharmacy, Sungkyunkwan University² highlights the value and relevance of porosity and powder flowability measurements in the development of novel, bilayer GR tablets.

FORMULATING TABLETS THAT FLOAT IN THE STOMACH

In both the fed and fasting states, the stomach empties on a regular basis, which can be problematic when it comes to the efficacy of OSD forms. Short periods of intense, regular contractions sweep undigested food from the stomach to the small intestine, potentially removing drugs from their preferred location of activity. For drugs that have a NAW in the first part of the gastrointestinal tract (GIT), that are prescribed for local action or

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that only dissolve or absorb effectively under acidic conditions, this action effectively brings drug delivery to a halt, limiting bioavailability.³



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“Sustained release formulations are associated with high patient compliance and provide lower, more consistent drug concentrations, reducing the risk of undesirable systemic effects. Technologies that enhance gastroretention increase the viability of sustained release, with floating tablets being the most practical and widely studied approach.”

A range of different formulation strategies have been deployed to increase gastroretention, notably for sustained release products. Sustained release formulations are associated with high patient compliance and provide lower, more consistent drug concentrations, reducing the risk of undesirable systemic effects. Technologies that enhance gastroretention increase the viability of sustained release, with floating tablets being the most practical and widely studied approach.¹ Formulated to have lower density than the gastric juices (density of approximately 1.0 g/cc), such tablets rise to the top of the stomach to reduce the risk of removal. Examples of commercial floating tablets can be classified on the basis of whether they deploy effervescent or non-effervescent systems, and include products such as Cifran OD[®] (Ranbaxy, India), an antibiotic, and Madopar NBS[®] and Prolopa HBS[®] (both Roche, UK), which are both prescribed for Parkinson’s disease.

The successful formulation of floating GR products relies on controlling the properties of the tablet to achieve the required retention time and drug release profile *in vivo*, under the specified conditions of use. Tablet size, shape and density can all be optimised to meet these goals, with polymers frequently incorporated to impart buoyancy via swelling or the incorporation of air. However, formulation is complicated by the need to:

- Achieve immediate buoyancy – delayed buoyancy, such as that imparted by slowly swelling polymers, risks premature product loss
- Ensure that the tablet is sufficiently mechanically robust to withstand gastric action for the duration of drug delivery
- Simultaneously control both the drug release profile and tablet residence time – often parameters that are manipulated to improve strength or buoyancy simultaneously impact drug release.

Measurement of the physicochemical properties of excipients and the finished product provides a foundation for the development of a successful product.

WHICH ANALYTICAL TECHNIQUES CAN HELP?

While the formulation of floating GR OSD products has much in common with that of conventional tablets, the need to understand and control buoyancy is distinct. Furthermore, excipients, such as sublimating agents, that can be used to impart porosity (and by extension buoyancy) can increase the cohesiveness of tableting blends, making them harder to process.² Against this backdrop, the following analytical techniques are noteworthy in terms of their ability to provide valuable insight.

Mercury Porosimetry – Detailed, Comprehensive Pore Size Characterisation

Mercury porosimetry quantifies median pore size, pore size distribution and other porosity parameters, from measurements of the amount of mercury that penetrates a sample as a function of pressure (Figure 1). Washburn’s equation describes the direct correlation between pore size and the pressure required for pore filling. Relative to other techniques for porosity characterisation, mercury porosimetry is fast and accurate, offers a very wide dynamic range – from a pore size of 3 nm to 0.36 mm – and generates more detailed results. For example, it can be used to determine tortuosity within a tablet and information about pore shape.

Using mercury porosimetry on tablets generates data that can inform on mechanical strength and fluid transfer within the tablet. Pore structure governs fluid transfer and quantifies the resistance to fluid penetration of the tablet, elucidating its wetting characteristics.⁴ If a tablet exhibits any elastic behaviour due to the incorporation of polymeric additives, then this would also be observable in a comparison of mercury intrusion and extrusion profiles. Such data can elucidate disintegration behaviour and provide fundamental insights into dissolution performance. For GR OSDs, detailed porosity measurements can make it easier to understand how to simultaneously engineer tablet robustness and buoyancy.

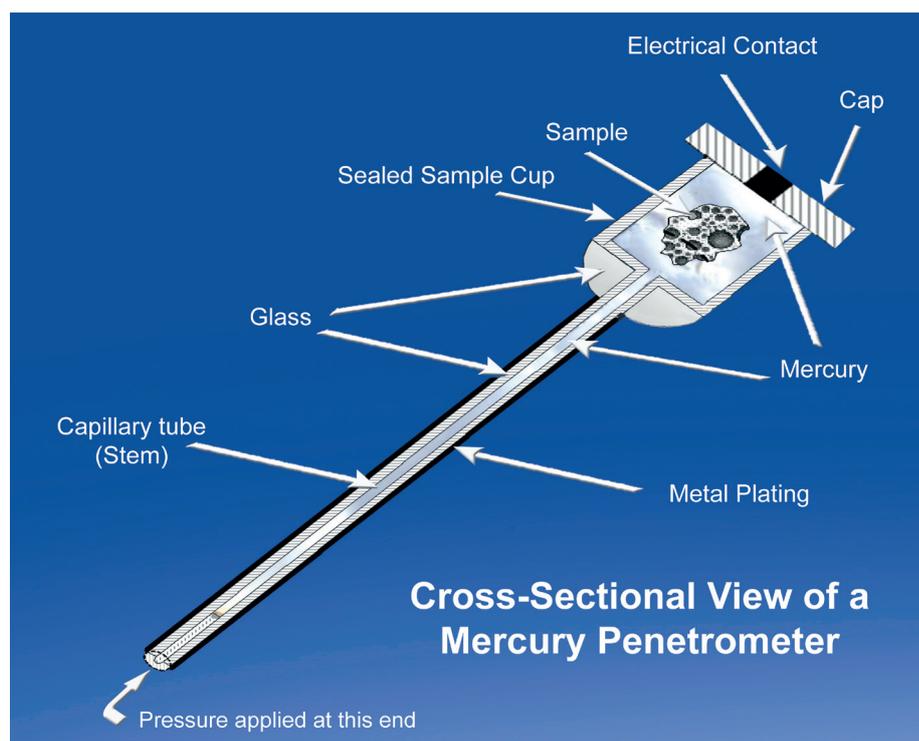


Figure 1: Mercury porosimetry involves measurement of the amount of mercury forced into the pores of a sample as a function of pressure.

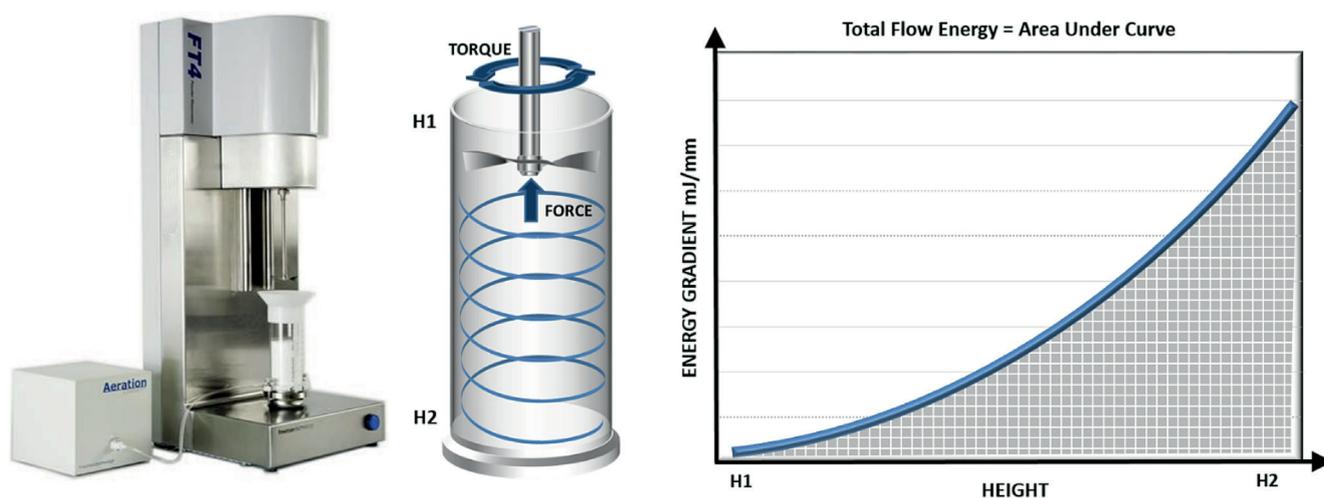


Figure 2: Dynamic testing can quantify the flow behaviour of powders in a consolidated, moderate stress, aerated or fluidised state.

Dynamic Powder Testing – Sensitive, Relevant Powder Flowability Measurement

Powder flowability can be assessed using a range of techniques, including those specified in United States Pharmacopeia (USP) 1174 – shear cell testing, flow through an orifice, angle of repose and tapped density methods. However, experience underlines the superior sensitivity and relevance of dynamic powder testing for many pharmaceutical applications, including tableting.⁵ Dynamic testing involves the generation of flow energy values from measurements of the axial and rotational forces acting on a precision-engineered blade as it rotates through a powder sample. Powders can be tested in a consolidated, moderate stress, aerated or fluidised state to simulate the process of interest, a capability which sets dynamic testing apart from other methods (Figure 2).

Dynamic properties are measured using well-defined, largely automated protocols, including basic flowability energy (BFE) and specific energy (SE), which respectively quantify the confined (forced flow) and unconfined (gravity flow) flow properties of a powder in a low stress state. Dynamic measurements are highly repeatable and reproducible, and the technique is associated with exemplary sensitivity, with the ability to differentiate powders that other test methods classify as identical.

Flowability is a critical characteristic for tableting blends that impacts the efficiency of die filling and, more generally, the ease and consistency of powder movement through a tableting press. Indeed, flow additives are routinely incorporated into tableting blends to enhance flowability and facilitate the production of high-quality tablets of uniform weight at an economically attractive rate. With dynamic testing it is possible to quantify flow behaviour under

different conditions to directly simulate specific steps of the tableting process. Furthermore, since instrumentation for dynamic testing also enables shear and bulk property measurement, it is also possible to generate highly relevant data for hopper discharge (shear cell and permeability) and tablet compression (bulk density, permeability and compressibility).

CASE STUDY: DEVELOPING A BILAYER GR TABLET WITH HYDROPHOBIC POLYMERS

A recent study by researchers at Sungkyunkwan University illustrates the challenges of GR formulation and the insights provided by the aforementioned analytical techniques.² The goal of the study was to develop a strong bilayer floating GR tablet for the sustained release of rebamipide (RBM). A BCS IV drug used to treat gastric ulcers and gastritis, RBM has low oral bioavailability, due to poor, regionally variable permeation. A GR sustained release formulation has the potential to significantly enhance the therapeutic potential of RBM, which currently relies on high-frequency dosing. In contrast to conventional practice, the researchers chose to investigate the use of a hydrophobic, rather than hydrophilic, polymer to create a strong, inert matrix capable of withstanding gastric action, post-hydration.

Tablets were prepared using two discrete powder blends, one to form the GR layer, the other to form the drug release layer. The GR layer was a blend of polymer – either Kollidon® SR (BASF, Ludwigshafen, Germany) or polyethylene oxide (PEO) 7M (Polyox® WSR 303 – DuPont, Wilmington, DE, US) – and varying levels of camphor (Junsei Chemical, Tokyo, Japan), a sublimating agent. The drug layer was a

wet granulated blend of RBM (Estech Pharma, Seoul, South Korea) and dicalcium phosphate (DCP) (Calipharm A®, Innophos, NJ, US) mixed with colorant and polymers to control erosion and the rate of drug release. MgSt (Daejung Chemical, Siheung, Korea) and Aerosil® R972 (Evonik, Essen, Germany) were added to both blends ahead of compaction to improve flowability and tableting performance.

Complete tablets were produced using a two-step process. The first step involved manual filling of the die with the GR layer, followed by pre-compression. The drug layer was then added, and the entire tablet was subject to a compression force in the range 0.5–1.5 tons. Tablets were then dried at 60°C for 12 hours in a vacuum oven to ensure complete sublimation of the camphor prior to stabilisation and subsequent analysis. Single GR layer tablets were also produced for further analysis.

A range of analytical tests was applied to rationalise and optimise the performance of the tablets, including:

- Gas pycnometry (AccuPyc 1340 – Micromeritics) to determine the volume fraction of the polymeric drug release agent in the drug layer
- Scanning electron microscopy (SEM) (JSM-6010 plus LA model scanning microscope – Jeol, Tokyo, Japan) to investigate particle morphology
- Tests to assess tablet performance – hardness, hydrated drug layer strength, buoyancy and dissolution performance.

Porosity Measurements

Mercury porosimetry measurements (AutoPore IV 9500 V1.09 – Micromeritics) were carried out in accordance with the standard protocols for the instrument to investigate the structure of the GR layer.

	Kollidon® SR	PEO 7M
Median Pore Diameter (V) (nm)	1981.5	6888.8
Median Pore Diameter (Area) (nm)	4.1	12.7
Average Pore Diameter (4V/A) (nm)	40.7	295.9
Bulk Density (g/mL)	0.7852	0.7653
Apparent (Skeletal) Density (g/mL)	1.1388	1.1215
Porosity (%)	31.0491	31.7625

Table 1: Porosity metrics and pore size distribution data for GR single layer tablets produced using 20% camphor and a 1 ton compression force.

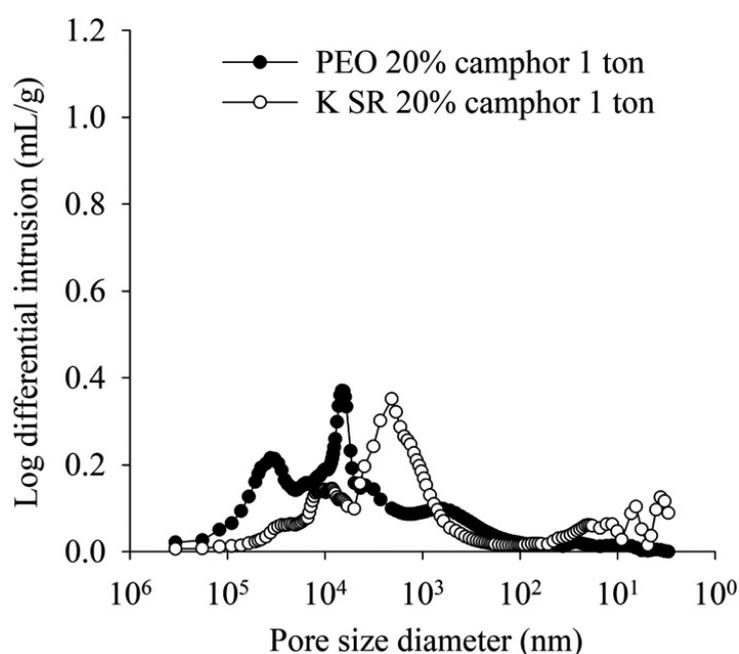


Figure 3: Fluid intrusion for two tablets with differing pore diameters.

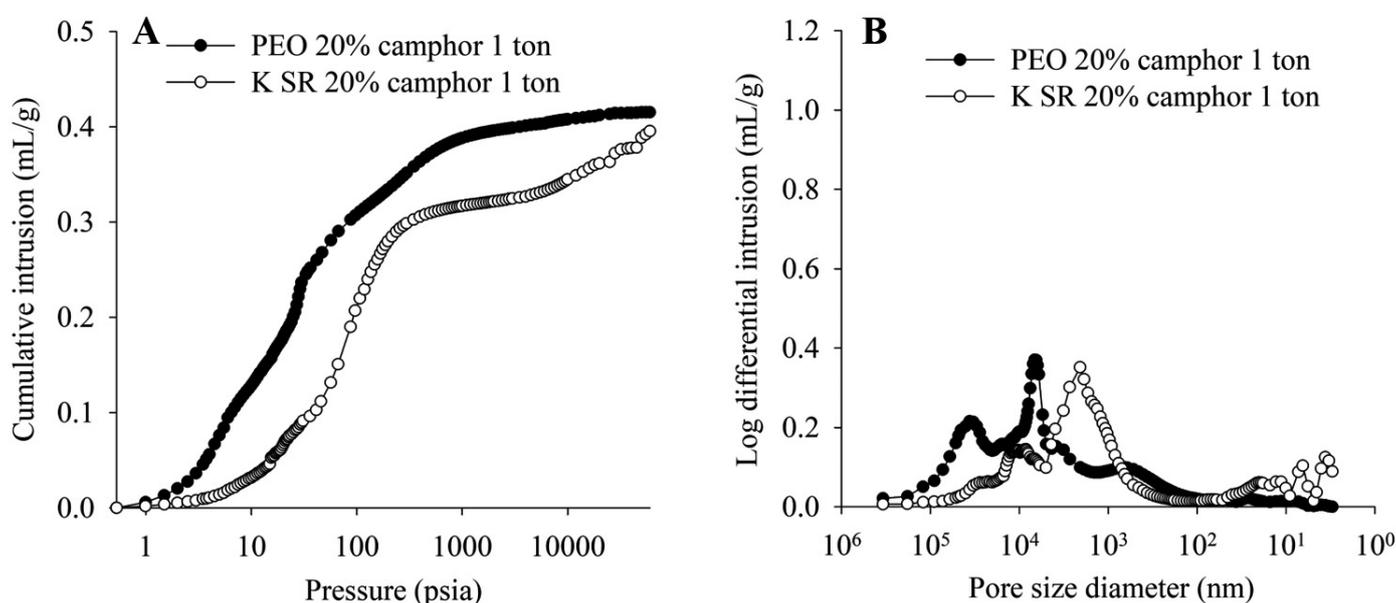


Figure 4: Porosimetry data showing the impact of camphor concentration and compression force.

The data shown in Table 1 and Figure 3 show the impact of polymer choice on developed porosity. Although average porosity and density are similar in each case, the Kollidon® SR formulation has much smaller pores. This difference may be attributable to the differing morphology of the two polymers; the Kollidon® SR particles are finer – a volume-weighted average particle diameter of around 60 μm compared with 157 μm for the PEO 7M – with a more regular, spherical shape and smoother particle surface (SEM data – not shown). The hollow structure of the Kollidon® SR and small cavities in the particles might also be a contributing factor. In contrast, the PEO 7M particles are larger, denser and more irregular in shape.

Figure 4 shows data illustrating the impact of camphor concentration and compression pressure on the porosity of Kollidon® SR samples. These results show that total porosity can be increased either by reducing compression force or increasing camphor concentration. The only two formulations that produced floating bilayer tablets were those with the highest total porosity, those produced with 20% camphor at 0.75 tons and 0% camphor at 0.5 tons. The data also suggest that the inclusion of camphor results in an appreciable population of relatively large pores, relative to those produced by the compaction process. These results are again consistent with the SEM data, which show that, after sublimation, the Kollidon® SR matrix, though quite coherent, includes many pores that are substantially bigger than neighbouring particles.

	Parameters	Kollidon® SR	PEO 7M
Conventional Methods	Angle of Repose (°)	29 ±1	33 ±2
	Carr's Index (%)	8 ±1	12 ±3
FT4 Powder Rheometer	Basic Flowability Energy (mJ)	55.30 ±0.89	295.37 ±12.21
	Specific Energy (mJ)	2.33 ±0.14	8.40 ±0.18
	Flow Rate Index	1.53 ±0.04	2.75 ±0.47
	Conditioned Bulk Density (g/mL)	0.487 ±0.006	0.406 ±0.002

Table 2: Flow property data for GR blends incorporating 20% camphor.

These results illustrate the importance of measuring pore size distribution rather than averaged porosity metrics, which failed to detect differences between the two polymers. They also show how camphor and compression force can be manipulated to achieve highly porous tablets that also have the strength and hardness required; tablets produced with excessive levels of camphor or at low compression were shown to lack viable hardness. Such insights are critical when developing tablets that combine the required mechanical characteristics with *in vivo* buoyancy.

Flowability

The flow behaviour of GR blends incorporating optimised levels of camphor was characterised using traditional techniques (angle of repose and Carr's index) and by dynamic testing (FT4 Powder Rheometer® – Freeman Technology) using standard testing protocols for the instrument (Table 2).⁶ The dynamic parameters measured include BFE, SE and flow rate index (FRI), which is determined by measuring BFE as a function of blade-tip

speed (FRI is defined as BFE at 10 mm/s divided by BFE at 100 mm/s).

Both traditional powder testing methods classify the Kollidon® SR as having 'excellent' flow properties compared with the 'good' classification of the PEO 7M. However, the variability of these data is such that the two powders are barely differentiated, particularly by Carr's Index. Furthermore, the results are contrary to expectations on the basis of particle size, since finer particles typically exhibit relatively poor flowability. In contrast, the dynamic and bulk property values exhibit greater repeatability and more robust differentiation. In addition, since dynamic testing enables the simulation of process conditions, these properties can be used to investigate which formulations are likely to perform well in the various steps of a tableting process.

BFE data reflect flow behaviour under forced conditions, such as in the feed frame of a tablet press. BFE values for PEO 7M are substantially higher than for Kollidon® SR, indicating that it presents greater resistance to flow under these conditions and is more likely to perform poorly in this type of unit

operation. This result may be attributed to the smooth, regular morphology of the Kollidon® SR particles, which is typically more conducive to good flow characteristics.

SE data are more relevant to gravitational powder flow, but similarly highlight the greater flowability of the Kollidon® SR. SE values are strongly influenced by inter-particle friction and mechanical interlocking. These results again suggest that the PEO 7M is the more cohesive powder and further underline the impact of the morphology of the Kollidon® SR, which is likely to reduce mechanical and frictional forces within the powder.

FRI data similarly indicate the greater cohesiveness of the PEO 7M, since more cohesive powders are generally more sensitive to changes in flow rate because of their greater tendency to entrain and trap air. Bulk density data for the two polymers supports the hypothesis that the Kollidon® SR is more efficiently packed and contains less air. From a practical perspective, these data suggest that the PEO 7M is likely to be more sensitive to changes in processing rate.

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In summary, the flow data provide consistent evidence that the Kollidon® SR blend is likely to perform better at every stage of the tableting process, compared with an equivalent PEO 7M blend, with dynamic testing providing more sensitive and relevant insight than can be accessed via traditional methods.

CONCLUSION

The development of GR tablets, and more specifically floating tablets, is a promising strategy for active ingredients that are not easily delivered via more conventional OSD forms. However, formulating such tablets is a demanding task, complicated by the need to engineer both buoyancy and the mechanical strength required to withstand gastric action for an appreciable residence time.

The study presented here shows how mercury porosimetry and powder rheology can be applied to generate data to support excipient choice and successful product development. Both techniques played a role in helping researchers to develop

a successful bilayer tablet with a highly porous, hydrophobic GR layer with superior mechanical strength and tableting properties, compared with conventional hydrophilic alternatives.

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ABOUT THE COMPANIES

Freeman Technology, a Micromeritics company, specialises in systems for measuring the flow properties of powders and has more than 15 years' experience in powder characterisation. It invests significantly in R&D and applications development, and provides full support alongside its range of products.

Micromeritics is a supplier of high-performance systems to characterise particles, powders and porous materials with a focus on physical properties, chemical activity and flow properties. The company's technology portfolio includes: pycnometry, adsorption, dynamic

chemisorption, intrusion porosimetry, powder rheology, activity testing of catalysts, and particle size. Micromeritics has R&D and manufacturing sites in the US, UK and Spain, and direct sales and service operations throughout the Americas, Europe and Asia. Micromeritics systems are the instruments of choice in more than 10,000 laboratories of the world's most prestigious government and academic institutions and most innovative companies. The company's world-class scientists and responsive support teams enable customer success by applying Micromeritics technology to the most demanding applications.

Sungkyunkwan University is a national university with 622 years of history and tradition. The university has led the development of higher education in Korea by challenging and innovating with a mind for sharing and coexistence. Sungkyunkwan University intends to make a leap forward to become a globally leading university and contribute to the prosperity and development of humanity along with other prestigious universities in the world.

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Jamie Clayton is Operations Director at Freeman Technology. He graduated from the University of Sheffield (UK) with a degree in Control Engineering and is responsible for overall management of company activities, including the R&D, production, sales and customer support teams. During his time with the company, Mr Clayton has worked as a mentor with several academic groups and is an active member of ASTM F42. He is also a regular contributor to conferences and workshops on the topic of powder rheology and works closely with clients on the application of the company's technology.

Phil Bone is a Technical Service and Applications Specialist at Micromeritics, and studied Medicinal Chemistry at the University of Leeds. This and an industrial placement during his degree have created a lifelong interest in pharmaceuticals. A PhD on the computational design and synthesis of analogues of a glycopeptide antibiotic further strengthened that interest. Following his PhD, Dr Bone worked at a CRO that specialised in sono-crystallisation and particle engineering, before becoming a service engineer covering laser diffraction and image analysis systems. He joined Micromeritics as a service engineer in 2015, and last year moved into a hybrid role to offer greater support to the company's pharma customers. He now covers service and application support for the UK.

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