



# christison Particle Technologies

SPECIAL CREDIT CRUNCH EDITION 2008

## Particulate Contamination of Parenterals

Parenteral is the term used to describe the administration of a drug in a manner other than through the digestive tract. Typically this means by intravenous or intramuscular injection.

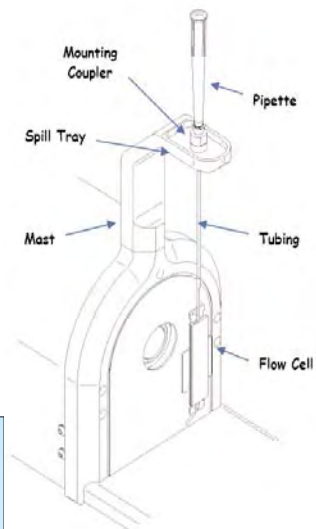
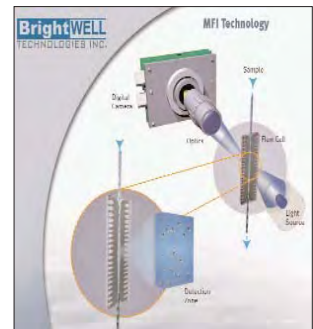
The European and US Pharmacopoeia require that undissolved particles unintentionally present in the solutions be monitored and fall within prescribed limits. The stated methods include light blockage/obscuration and microscopic particle count tests. The contaminating injected particulate matter has been shown to include glass and rubber and these are known to damage organs such as the liver, and brain. The obscuration methods described have limited resolution when the particulates are opaque or clear when compared with the medium they are floating in. This is because the light source, typically laser light, is transmitted through the particle and results in a distorted sensor response, effectively resulting in the particle being ignored or sized much smaller than it is. The use of digital imaging, such as Micro-Flow imaging (MFI) or for dry powders the Camsizer shown overleaf are not influenced by opacity as the software distinguishes particle boundaries and not overall particle shadows. The ability to store images of each particle provides important data confirmation unavailable to light obscuration techniques. Christison can perform testing using light obscuration and digital imaging in compliance with GMP. We're currently extending our capabilities to include Cytotoxic compounds.

## SILICONE MICRO-DROPLETS IN PROTEIN FORMULATIONS DETECTION AND ENUMERATION

Silicone oil micro-droplets are believed to induce aggregation and particle formation of some proteins and antibodies in parenteral formulations. Because silicone oil is commonly employed as a lubricant on container components throughout the pharmaceutical industry, this is a significant practical concern. In order to characterize and limit the effect, it is desirable that populations of droplets and protein particulates which are simultaneously present in a sample formulation be independently detected and quantified. Performing this analysis is a challenging assignment and very difficult with existing particle analysis techniques. Micro-Flow Imaging (MFI) is an emerging technology that utilizes digital imaging and morphology analysis to detect and enumerate different particle types contained within fluid samples. In this

study, the feasibility of using MFI to resolve a mixed population of silicone oil droplets and protein particulates was explored. Individual samples of silicone oil micro-droplets were generated by sonication and samples of aggregated protein particulates were generated by a freeze-thaw method. The morphological signatures of the individual sample types were analyzed using MFI. Visual analysis of the images captured for the two individual samples indicated that the software filter could achieve an accuracy of ~96%. A software filter based on these particle morphology measurements was then applied to a mixture of the original samples.

Deepak K. Sharma, Peter Oma, Sampath Krishnan - email sales@christison.com for the complete article submitted to Pharmaceutical Technology (in press)



For pharmaceutical and life science applications, Micro Flow Imaging (MFI™) is a cost effective, simple, versatile and powerful technology which delivers superior sensitivity, accuracy, statistical validity, repeatability, images, and data management. The integration of digital microscopy, micro-fluidics and image processing technologies provides a single solution for a wide variety of particle analysis applications.

Micro-Flow imaging (MFI™) is a flow microscopy technology which operates by capturing images of suspended particles in a flowing stream. During operation, images are displayed on the system monitor in real time. The images are used to produce a particle database including count, size, transparency and shape parameters. The database can be interrogated to produce particle size distributions and isolate sub-populations using any measured parameter.

The MFI Series B Sampling Module is designed to meet the low sampling volume requirements of bio-pharmaceutical formulation development and processing with sample volume down to 200 microlitres

**"My first rule – the golden rule – ensures that over the economic cycle the Government will borrow only to invest, and that current spending will be met from taxation"**

Hansard, 6 ser, vol 297 col 304 (2 July 1997) from the first Budget speech

# Determination of the Particle Size and Shape of Pharmaceutical Granules using the Camsizer Digital Image Processing System

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Pharmaceutical granules often have irregular shapes and variable sizes, and are commonly prepared from mixtures of dry active substances, fillers and excipients using mills and sieving.

More recently a "retard drug" form consisting of dry granules, which release the active drug over time, is benefitting patients compared to conventional drug forms.

Figure 1 shows a combination of the anti-asthmatic agent theophylline with ammonium methyl methacrylate copolymer and ethyl cellulose. The greater the surface area to the particle volume and the smaller the particle, the more rapid the release of active substance.

The most relevant calculation of surface/volume ratio was found to be based on an ellipsoid (see figure 2). In order to predict the release behaviour, surface area, volume and size distribution of the granules are required.

These can be measured using the Camsizer® dynamic image analysis system in which the granules free fall

past two CCD cameras measuring different size ranges, size and shape being evaluated in real time over typically five minutes analysis time.

21CFR compliant software is also available for the Camsizer particle size and shape analyser.

Many mathematical parameters available in the Camsizer® software enable detailed characterisation of these irregularly shaped and sized granules. Theophylline release rates from five known sized sieve fractions of granules were studied (see figure 3) along with particle size and shape in order to provide a model for unknown granule fractions.

In conclusion, the Camsizer® is a more efficient alternative to traditional image analysis for characterising size and shape of inhomogeneous granular materials.

Determination of the surface/volume ratio describes exactly individual granule fractions such that the future release profile prediction of unknown granule fractions will become a reality.



Fig.1. Diffusion front in a drug after 10 hours release. Left: 2 areas can be recognized: a) inner (lighter) area, structure with active substance and b) outer (darker) area, structure without active substance. Right: Magnification of the transition zone. Upper half: Active substance not yet dissolved; lower half: active substance has been dissolved and the structure is empty

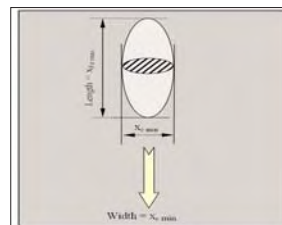


Fig. 2 Ellipsoid calculation model

$$V_{\text{Ellipsoid}} = \frac{X_{Fe\max} \cdot (X_{c\min})^2 \cdot \pi}{6}$$

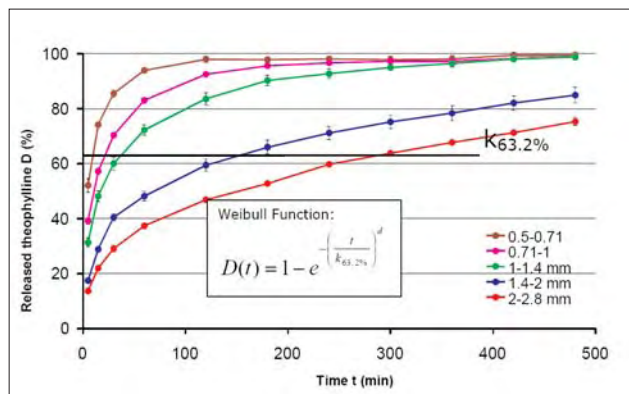


Fig. 3: Release rate as a function of granule size for the 5 fractions studied. The smaller the granule, the greater the amount of theophylline released.  $t$  is the time in minutes and  $d$  a formulation-dependent constant with the value 0.5

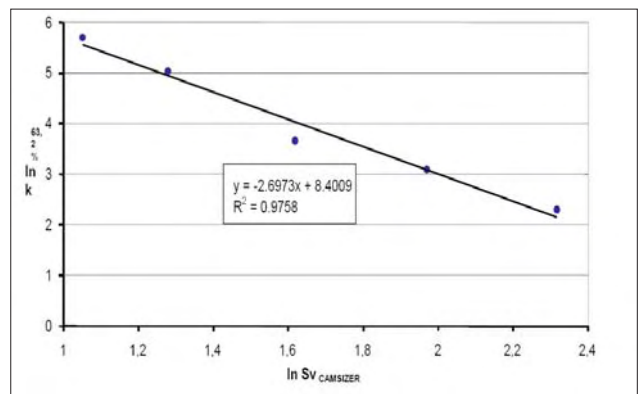


Fig. 4: shows the relationship between the surface/volume ratio  $Sv$  (determined with the Camsizer) and the Weibull parameter  $k_{63.2\%}$ , determined via the release profile

"Gordon Brown said that this would be a Budget based on prudence for a purpose and that guides us also in our approach to public spending"  
Hansard, 6 ser, vol 308 col 111 (17 March 1998) From the 1998 Budget speech.

## Bostwick Consistometer now available in two lengths

The Bostwick Consistometer is a simple, dependable instrument which accurately determines sample consistency by measuring the distance that a material flows under its own weight. The unit is made of stainless steel and has two levelling screws and a spirit level. The spring-operated gate is held by a positive release mechanism, permitting instantaneous flow of sample to be measured. The trough is graduated in 0.5cm divisions to permit accurate measurement of flow. Supplied complete with instructions for use. It is used extensively by preservers, producers of jams, jellies and other highly viscous products such as tomato paste, tomato ketchup, mayonnaise, gravies, sauces, fillings, frostings, soup etc. The Bostwick is invaluable to many industries to predetermine formulas and standardise production lots.

Monthly mortgage lending before credit crunch	£30 billion
UK Government monthly tax income before credit crunch	£30 billion



*Stainless Steel construction  
Engraved graduations  
Portable and easily cleaned  
Spring loaded gate  
Complies to R-81294D & ASTM F1080-93  
Longer length Bostwick has 60 x 0.5cm graduations and is ideal for thinner soups and gravies*

Approx number of investment bankers working in the City of London prior to the credit crunch	100,000
Approx number of investment bankers non-domiciled in UK for tax purposes	40,000

## Waring Laboratory Blenders



*1-litre Waring Blenders*



*21/24CB9E 4-litre Blender*

Visit our web site or email us at [sales@christison.com](mailto:sales@christison.com) for more information on the many containers and accessories we keep in stock. We also stock thousands of spare parts. If you need help with your blending application our Technical Sales department will be pleased to advise you. Tel: 0191 478 8120



All Waring blenders are ruggedly constructed and designed for frequent use when processing free-flowing material with a high liquid content. The wide range of blending accessories meet the most demanding needs.

The motor bases on all 1-Litre blenders have epoxy coated motor housings and are complete with either a stainless steel or heat resistant glass container each fitted with a standard blending assembly. All containers supplied with new blenders have a handle and a two-piece vinyl/styrene lid.

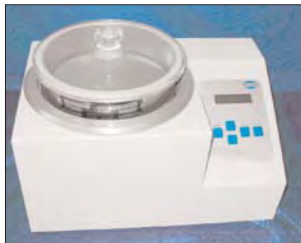
The two-speed 2-Litre blender has a powerful 1-HP motor and will grind, shred, disintegrate or mix a wide

spectrum of free-flowing materials with a high liquid content. All 1-Litre and Mini containers can be used on the 2-Litre motor base unit providing the 21/AD2 adaptor is purchased. The top of the range 4-Litre blender is ruggedly constructed, easy to move and clean.

The epoxy coated motor base unit has push-button control panel and full traction rubber feet for greater stability. The stainless steel container has two handles and a see-through clamp-on polycarbonate lid. Any 1-litre or mini container can be used on the 4-Litre motor base providing the 21/AD1 adapter is purchased

**"The British economy is today growing faster than all the other G7 economies - growth stronger this year than the euro area, stronger than Japan and stronger even than America."**  
Gordon Brown 2007 Budget

## Precision air jet sieve



The microprocessor controlled precision air jet sieve **LPS200K** is used for the determination of size distribution of fine particles down to 20 microns. Perfect for pharmaceutical powders and ideal if you're testing to BS EN 933-10:2001 (part 10: geometrical properties of aggregates 'Assessment of Fines - Grading of Fillers' by air jet sieving). Air is conducted through the sieve by a rotating slot, variable in speed from 0 - 45 rpm while the air jet deagglomerates the sample and keeps the sieve mesh from 'blinding'. The sieving time and rotor speed are indicated together with the negative pressure and the comparable gas stream volume, all operations being controlled by a five button menu guided control pad. Perfect for rugged and precise sampling during production or where laboratories are close to the production area.

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## Christison stainless steel test sieves



200mm and 300mm diameter, full or half-height  
Woven wire mesh or Square/Round Hole perforated plate  
Precision frames give strength and positive nesting  
Manufactured in accordance with ISO3310/1&2:2000  
Apertures accurately measured by computerised optical equipment  
All sieves are Individually numbered to provide full traceability  
email: sales@christison.com for availability and price lists



Endecott EFL heavy duty sieve shakers are suitable for use with 100mm, 200mm and 300mm diameter sieves



Fritsch Analysette 3 sieve shaker for wet or dry sieving using standard 100mm and 200mm diameter laboratory test sieves

Hourly Pay For CEO of Lehman Brothers in 2007 **\$17,000**  
UK Government Debt Per Household in 2008 **£24,000**

## New Fritsch Premium Line Planetary Ball Mill *a quantum leap into the nano class*



Planetary ball mills have long been a popular tool for the finest size reduction of powders down to the micrometre range. In many industry segments, however, this is no longer sufficient and demand now exists for the creation of nano size particles.

The pharmaceutical industry, for example is very interested in producing new medications with active ingredients at the

nanometre scale. They are more rapidly absorbed into the body and improving the bio-availability significantly reduces the therapeutic dosages. Also, using lower levels of active ingredients reduces undesired side effects whilst maintaining the same therapeutic effects. Milling down to nanometer ranges requires the application of very high energy and therefore significantly higher rotational speeds than those allowed by typical planetary ball mills. The new premium line mills attain speeds of up to 1100 rpm, generating over 150% more energy application which significantly reduces the grinding time. The new integrated milling bowls are much easier and safer to handle

The unique action of the Rotap sieve shaker produces accurate, consistent particle analysis testing results. Designed to be used in a stationary testing environment and requiring very little maintenance. Mechanical action is applied to the test sieves in two dimensions, firstly a horizontal circular motion (278 oscillations) and second, a vertical tapping motion (150 taps per minute). Combined, these actions allow material particles to stratify and seek critical openings in the screening media. These uniform mechanical movements allow for dependable and reproducible test results.



## Traces of heavy metals in toys



The plastic toy is broken down into component parts



The parts are pre-ground in the Pulverisette 19 cutting mill then milled to analytical fineness in the Pulverisette 14 Variable Speed Rotor Mill and are now ready for analysis



Toys must be safe and when testing for heavy metals it is important that the sample for analysis is correctly prepared. For initial pre-grinding the Fritsch Pulverisette 19 universal cutting mill offers a fast throughput without cross-contamination and the mill is easy to clean. Further grinding to analytical fineness can then be carried out in the Pulverisette 14 variable speed rotor mill which has speeds of up to 20,000rpm and a choice of sieve inserts and rotors. It is very useful for temperature sensitive materials like styrene, polyester, pvc, synthetic resins etc which can be embrittled by the addition of liquid nitrogen.



Pulverisette 14 Variable Speed Rotor Mill

Pulverisette 19 universal cutting mill

*"Just as our monetary discipline is the foundation of our economic strength, our fiscal discipline is the foundation of the strength of Britain's finances"*  
Gordon Brown 2007 Budget