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# Design of a fluid energy single vessel powder processor for pharmaceutical use

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**Abstract**

This study introduces a motionless novel single vessel powder processor designed to carry out all of the unit operations in the preparation of powders for tableting. The processor used controllable fluid dynamics to provide the energy for each unit operation. The vessel design was evaluated using a computational fluid dynamics model which indicated the flow necessary for the intended processing operations to take place. The processor performance was evaluated experimentally for two unit processes: particle size reduction and dry powder mixing. The processor was found capable of reducing the size of lactose granules from a median particle diameter of 459 μm to a median particle diameter of 182 μm within 5 min under optimal process conditions. It was found that a formulation containing lactose granules (373 μm median particle diameter) and a model drug, sodium chloride (30 μm), could be mixed to an improved degree of homogeneity in comparison with equivalent powders blended using a conventional turbulent tumbling technique. It was concluded that a processor having controllable fluid dynamics offered the potential to perform multi-task processing of powders. 

*Keywords:* Particle size reduction; Powder mixing; Single vessel processing; Granulation; Equipment design

## 1. Introduction

The most commonly used techniques in preparing powders for tableting are wet granulation and direct compression (Armstrong, 1988). Direct compression is the simpler technique, requiring

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only the blending of the drug with specialised excipients prior to tablet compaction. In many cases, however, the properties of pharmaceutical powders do not allow successful tableting, and these powder systems require modification, most commonly by employing a wet granulation process. Conventional wet granulation techniques can involve up to eight separate unit operations (see Fig. 1), each requiring transfer of material from one processing vessel to another (Armstrong, 1988). Modern processing equipment, such as fluid bed granulators and high-speed mixer/granulators, are able to combine some of the unit operations, thereby reducing the number of material transfers. The benefits of this approach include increased economy, improved quality assurance and, in some cases, enhanced product functionality (Cliff, 1991; Kay, 1997). A number of attempts have been made to minimise the number of processing vessels required (Poska, 1991; Robin et al., 1994), however, the technology to perform all of the sub-operations required for wet granulation processing between ingredient dispensing and compaction of the final granules into tablets is not yet available.

This study introduces a number of prototype designs which were developed with the requirement of carrying out the following sub-operations within a single vessel: drug and excipient milling, dry mixing, wet massing/granulation, drying, granule milling and secondary blending. A further design constraint was that all powder movement within the vessel should be carried out without the presence of moving parts within the vessel chamber. In this preliminary work, the characterisation of a novel single vessel processor (SVP) for the unit processes of particle size reduction and dry powder mixing is considered.

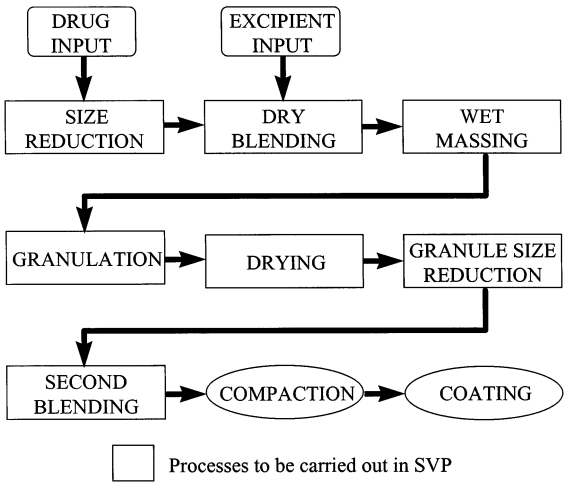
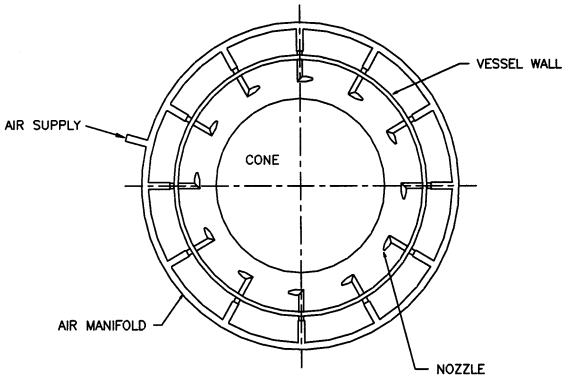



Fig. 1. A summary of the sub-operations performed during tablet manufacture using wet granulation.

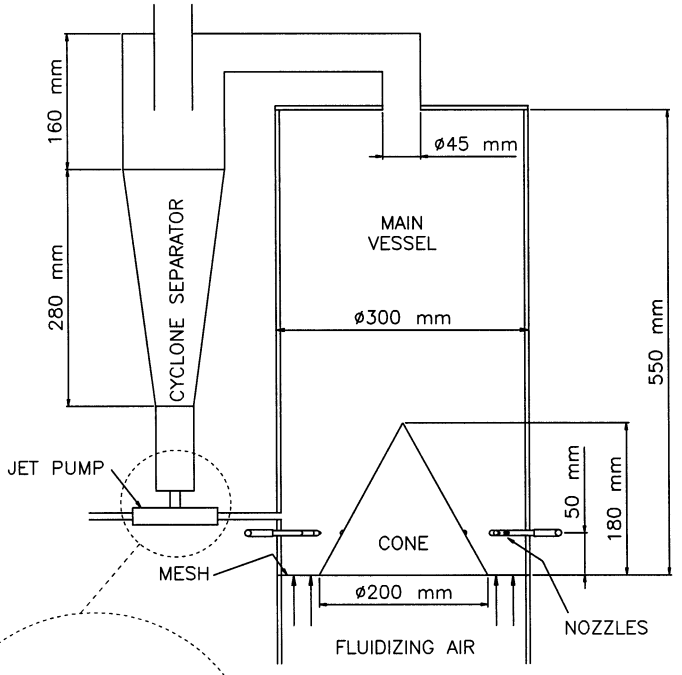
A number of different techniques may be used in milling pharmaceutical powders, the most common being ball milling, hammer milling, cone milling and fluid energy milling (Lantz, 1990). Fluid energy or jet mills operate by the acceleration of particles using high pressure jets of a gaseous fluid (usually air), so that they collide with each other or a part of the grinding chamber, causing comminution by particle impact and attrition. In some processing applications, such as ordered mixing (Staniforth, 1980) and dry powder inhalation products (Johnson, 1997), powder particles must be milled to sizes below 5 μm, which is usually achieved by fluid energy milling (Hallworth, 1987). This method of milling also has the advantage that no moving parts come into contact with the product.

The most widely used mixers in pharmaceutical dry mixing operations are tumbling and bladed agitator mixers (Lantz and Schwartz, 1990). A further group of powder mixers is that which employs fluid flows providing either agitation (Akiyama et al., 1986) or fluidization (Krambrok, 1976). This group of mixers is able to mix powders very quickly (Miles and Schofield, 1970) and also without contact of moving parts with the pharmaceutical materials. The use of fluid flows in fluid bed granulation and drying is a well established technique (Kristensen and Schaefer, 1987).

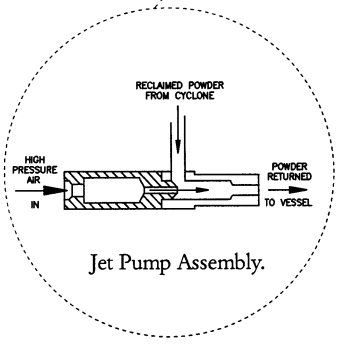
It was therefore intended to investigate whether fluid flows could be used to achieve a combination of the milling, mixing and granulation processes by developing a processor based on controllable fluid dynamics.




Plan View.




Side View.




Jet Pump Assembly.

Fig. 2. The SVP Mark IV.

## 2. Prototype design

### 2.1. Pre-prototype development

An initial prototype was constructed using a Perspex cylinder, approximately 300 mm in diameter and 250 mm high. Six L-shaped nozzles positioned in a circular arrangement around the base of this vessel provided a vortex air motion which was intended to be similar to the flow pattern found in a bladed system such as a conventional high-speed mixer/granulator (Holm, 1997). It was found that a conical structure, placed in the centre of the base, was able to eliminate a region of low particulate movement in this part of the vessel and some particle size reduction and limited powder mixing was found to occur.

In order to increase the movement of particles around the base of the vessel, it was found that the addition of fluidizing air, directed through the base, was able to reduce frictional contact between the particles and the base sufficient to allow improved size reduction and mixing characteristics (Bates and Ball, 1993). In this case the central cone was replaced by a 'honeycomb' distributor plenum.

### 2.2. The SVP Mark IV

Following these initial investigations, a prototype processor, the 'SVP Mark IV', (Kay, 1997) was constructed as shown in Fig. 2.

A hollow cylinder of clear Perspex of wall thickness 6 mm was used for the main vessel wall so that powder movements could be observed during operation of the processor. This was fitted with a mesh base of 100 μm aperture diameter. This provided support for powder within the vessel, whilst allowing uniform fluidization of the powder bed when air was introduced through the base. A lid provided with a rubber o-ring seal was attached to the top of the vessel using four case clasps. A polyethylene cone was fixed to the centre of the vessel base to prevent the formation of a dead area in this part of the vessel.

Fluidizing air was ducted into the bottom of the vessel from a centrifugal fan (Type D28, 0.75 kW, Robert Stahlschmidt Elektromotorenwerk, Germany) of fan diameter 180 mm, blade width 12 mm and blade angle 20°. This could be operated at a maximum rotational speed of 2800 rpm, which produced a calculated maximum air flow rate of 0.0456 $m^3/s$.

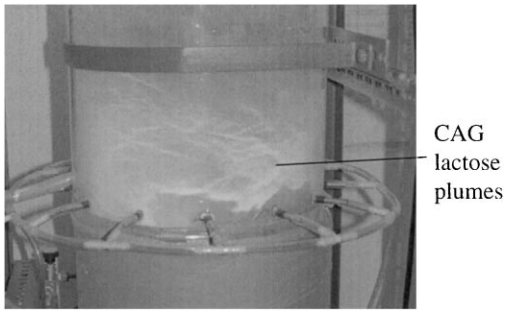



Fig. 3. Photograph of flow patterns of lactose powder generated during the operation of the SVP Mark IV.

Twelve L-shaped high pressure jet nozzles of 1 mm output diameter were located around the base of the vessel and connected to a compressed air manifold. A compressed air feed of approximately 550 kPa was able to supply each nozzle at a validated (Kay, 1997) pressure of up to 30 psi (207 kPa). The design of the nozzles was such that they could be adjusted for angle and depth within the vessel as required. A needle valve allowed control of the nozzle output pressure.

The attachment of a cyclone separator to the vessel lid enabled the removal of entrained particles from air leaving the vessel during operation of the air inputs. The gas outlet of the cyclone was allowed to vent to atmosphere and the dust outlet was attached to a jet pump. High pressure air was directed through the jet pump nozzle, causing air to be drawn through the top hole. This produced a suction effect which returned powder from the cyclone dust outlet back into the main vessel.

The Mark IV SVP was found to provide more uniform and widespread powder movement than previous designs and powder losses from the vessel were also greatly reduced. The powder flow patterns achieved within the vessel can be seen in Fig. 3. A further advantage of the Mark IV design over the previous designs was that it was not

necessary to maintain a fluidizing air input at all times, thus making it easier to control the process and to remove powder at the end of processing.

## 3. Particle size reduction

### 3.1. Materials

Two grades of granular lactose (α-lactose monohydrate) were selected as model test materials. These were of similar particle size ranges, but were prepared by different methods and consequently could be expected to exhibit different physical strength properties.

The first test material was a pharmaceutical quality commercially-available granular lactose (CAGL), CrystaLac 40 (Meggle, Wasserberg, Germany). The second material was granulated lactose manufactured using SorboLac 400 lactose powder (Meggle, Wasserberg, Germany). This particular grade of material has a higher specific surface area and finer particle size than CAGL. The granulation was performed in a high-speed mixer/granulator, using water (20% w/w compared to dry powder) as a binding liquid. The granules were fluid-bed dried to a moisture content of less than 5% w/w and granules outside the sieve fraction 250–500 μm were discarded. This material was termed high-speed mixer/granulated lactose (HSMGL).

### 3.2. Methods

Either CAGL or HSMGL material in 500g lots were placed in the SVP vessel and size reduction carried out over 30 min. Three lots of each material were processed in the SVP at nozzle pressures of 10, 20 or 30 psi. (69, 138 and 207 kPa, respectively) and the nozzle output air pressures were validated using a pressure transducer (type P722-022 pressure sensor, Schaevitz, UK.).

Representative samples of approximately 1.5 g were obtained from four positions in the powder bed using a sampling thief at each of the following times after the initialisation of size reduction: 0, 1, 2, 3, 4, 5, 7.5, 10, 15, 20, 25 and 30 min. Particle size analysis was performed in triplicate with low angle laser light scattering (LALLS) equipment (Malvern Mastersizer X, Malvern Instruments, Malvern, UK) using a dry powder feeder technique.

Scanning electron microscopy (SEM) was used to produce images of particles at different stages of milling. The specimens were prepared by mounting a representative powder sample onto a conducting carbon-coated adhesive pad fixed to an aluminium stub. The sample was then coated with a layer of gold using a sputter coater (EHV model S150B, Edwards High Vacuum, Sussex, UK). Specimens prepared in this manner were examined using a scanning electron microscope (JEOL T330 SEM, Japanese Electron Optics, Tokyo, Japan) operating with an incident beam of 10 keV at a working distance of 25 mm.

Table 1
Summary of change in median particle diameter during milling of CAGL in the SVP Mark IV at different nozzle pressures

| Nozzle pressure (psi) | Median particle diameter (μm) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Milling time (min) | | | | | | | | | | | |
| | 0 | 1 | 2 | 3 | 4 | 5 | 7.5 | 10 | 15 | 20 | 25 | 30 |
| 10 | 459 | 401 | 415 | 390 | 330 | 314 | 283 | 272 | 230 | 236 | 221 | 199 |
| 20 | 459 | 345 | 358 | 287 | 261 | 281 | 211 | 233 | 196 | 194 | 174 | 167 |
| 30 | 459 | 297 | 227 | 197 | 199 | 182 | 180 | 172 | 163 | 157 | 160 | 157 |

Table 2
Summary of change in median particle diameter during milling of HSMGL in the SVP Mark IV at different nozzle pressures

| Nozzle pressure (psi) | Median particle diameter (μm) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Milling time (min) | | | | | | | | | | | |
| | 0 | 1 | 2 | 3 | 4 | 5 | 7.5 | 10 | 15 | 20 | 25 | 30 |
| 10 | 373 | 355 | 304 | 317 | 339 | 274 | 297 | 241 | 195 | 151 | 154 | 127 |
| 20 | 373 | 316 | 251 | 249 | 198 | 188 | 163 | 141 | 121 | 118 | 115 | 109 |
| 30 | 373 | 245 | 238 | 202 | 164 | 155 | 134 | 131 | 107 | 115 | 117 | 107 |

### 3.3. Results and discussion

Data describing the changes in median particle diameter during milling are summarised in Tables 1 and 2 for CAGL and HSMGL, respectively.

Fig. 4 shows the change in size distribution of CAGL when milled over 30 min at a nozzle pressure of 30 psi. It can be seen from this graph that after 1 min of milling, firstly that the modal size of the CAGL was reduced and secondly it exhibited a unimodal distribution. This latter observation is noteworthy since milling operations usually result in bimodal distributions and may therefore be indicative of a non-standard size reduction mechanism.

The effect of milling time at a nozzle pressure of 30 psi on the particle size distribution of HSMGL can be seen in Fig. 5. In this case, the size distribution takes on a bimodal character after 1 min milling time. This is a classical response profile for the early stages of a milling process.

On this evidence, it is suggested that in the case of CAGL, most of the agglomerates were reduced to their constituent crystallites within the first minute of milling at 30 psi; the stage of milling at which all, or nearly all, individual crystallites have been liberated from the agglomerates is termed the 'point of complete deagglomeration' (POCD) and is considered to be a key SVP process parameter.

In contrast to CAGL, the HSMGL agglomerates appear to be broken down less easily into their constituent crystallites and hence, after a milling time of 1 min, exhibit a bimodal distribution in which many of the agglomerates are still largely intact, but a proportion of them have been broken into individual crystallites. This implies that the bond strength between crystallites in HG-MGL are stronger than those in CAGL. This theory is further supported by the SEM photomicrographs (Figs. 6 and 7), which show a larger proportion of agglomerates in the HSMGL after 1 min of milling than are present in CAGL.

Further examination of Fig. 4 presents a downward trend for the modal size of CAGL. However, after about 1 min milling time, the modal and median sizes are less affected by increasing milling time. This suggests that most of the agglomerates have been broken down into their constituent crystals after 1 min and any further reduction in particle size is probably due to fragmentation of the individual crystallites by edge abrasion as shown in Fig. 8.

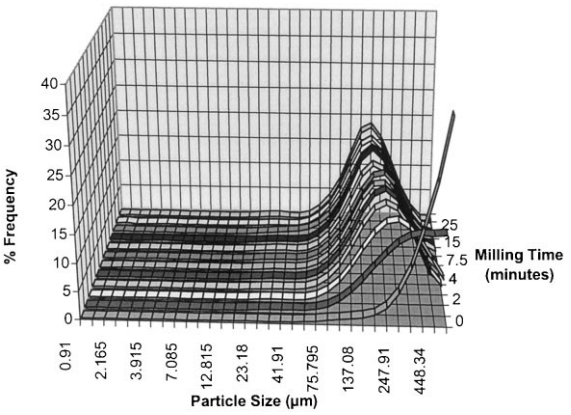



Fig. 4. Relationship between particle size distribution of CAGL and milling time in the SVP Mark IV at a nozzle pressure of 30 psi.

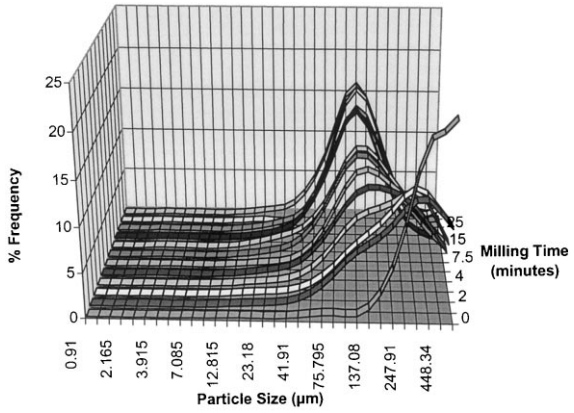



Fig. 5. Relationship between particle size distribution of HSMGL and milling time in the SVP Mark IV at a nozzle pressure of 30 psi.

This mechanism may suggest that fragmentation of the component crystals would lead to the formation of a fine particle fraction in the later stages of milling and hence a bimodal size distribution. However, there is no evidence in the particle size data to suggest this is the case. This may be explained by a preferential removal of fines by the SVP since observation of the SVP during milling indicated that a certain amount of fine particulate material was entrained in the air leaving the cyclone separator.

The effect of reducing the milling nozzle pressure was investigated. As expected, the rate of milling was reduced with decreasing nozzle pressures for both materials. The times taken to reach the POCD for CAGL and HSMGL at different nozzle pressures and the median particle diameter of the materials at these times are summarised in Table 3.

The milling data suggests that for CAGL, the maximum milling capability of the SVP was to mill the material to a median particle diameter of approximately 160 μm. This appears to have been achieved at nozzle pressures of 30 and 20, but not at 10 psi. The maximum milling capability of the SVP for HSMGL appears to be to a median particle diameter of approximately 110 μm. It is speculated that different milling conditions, such as higher nozzle pressures or changing the geometry of the vessel, may result in an increase in the

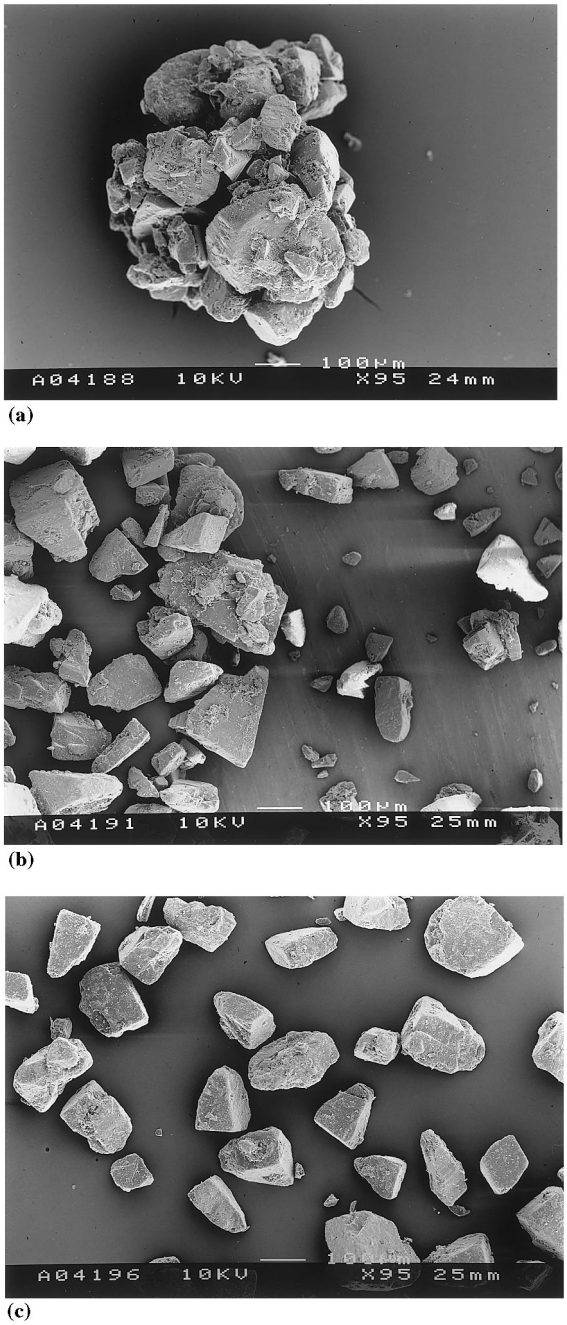
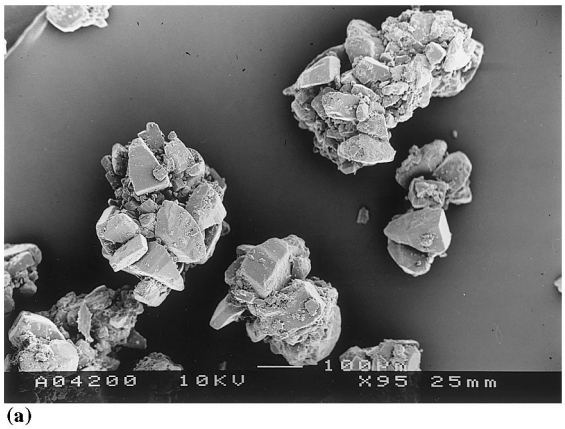
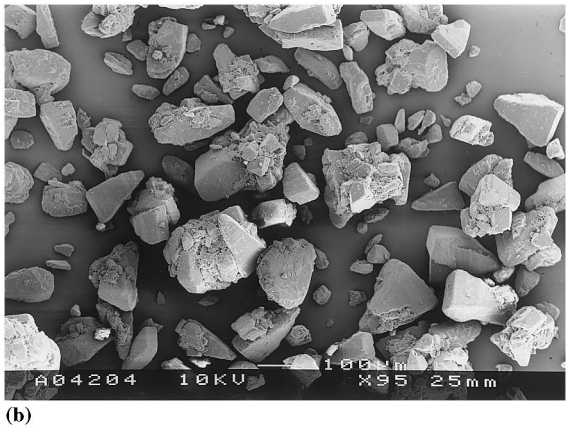


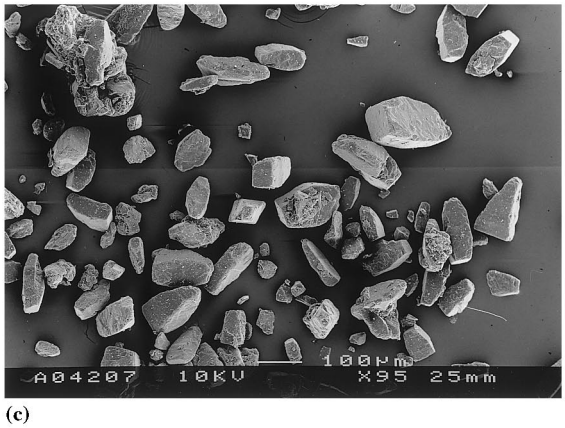

Fig. 6. Scanning electron micrographs of CAGL before and after milling at a nozzle pressure of 30 psi: (a) unprocessed particle, (b) after 1 min processing, and (c) after 30 min processing.




(a)




(b)




(c)

Fig. 7. Scanning electron micrographs of HSMGL before and after milling at a nozzle pressure of 30 psi: (a) unprocessed particle, (b) after 1 min processing, and (c) after 30 min processing.

milling capacity as well as an increase in the rate of milling.

## 4. Mixing

### 4.1. Materials

Lactose powder (CrystaLac 40, Meggle, Wasserberg, Germany) was used as the major component (90%) and sodium chloride crystals (Lot No. 40414 40408011, Aldrich Chemical, Gillingham, Dorset, UK) the minor model drug component (10%) of a 500 g binary powder mix. Sodium chloride was selected as a model drug to allow conductivimetric analysis over a wide concentration range without requiring sample dilutions. The median particle diameter of the lactose was 373 μm and that of the sodium chloride was 30 μm as measured by LALLS.

This difference in the particle diameters of the two components was deliberately selected so as to encourage the formation of interactive mixes in which finer particles become adhered to the surfaces of coarser, 'carrier' particles.

### 4.2. Methods

The efficiency of the SVP for mixing two dry powders was compared with other mixing techniques with known efficiencies: geometric mixing and turbulent tumbling mixing.

#### 4.2.1. Geometric mixing

Geometric mixing, or trituration, was performed by placing 50 g sodium chloride crystals and 50 g lactose granules into a large mortar and mixing thoroughly by hand for 5 min using a pestle. A further 100 g lactose was added and similarly mixed, followed by a 200 g quantity of lactose, which was also mixed for 5 min. The final 100 g of lactose was added and the whole mixture thoroughly mixed for a further 15 min.

#### 4.2.2. Turbulent tumbling mixing

Milled sodium chloride crystals (50 g) and lactose granules (450 g) were placed into a 2 l glass jar and its lid was sealed. This was then posi-

tioned in a Turbula mixer (type T2C, Glen Creston, Stanmore, Middlesex, UK), which was operated at speed II for 30 min.

*4.2.3. Operation of the SVP*

Lactose granules (450 g) were placed into the bottom of the SVP, on top of which 50 g of sodium chloride was gently loaded. The fluidizing fan was turned on at its maximum speed providing an air volume throughput of approximately 2 $m^3$/h and the jet nozzles supplied with air at a pressure of 30 psi.

These conditions were maintained for a period of 30 min after which the air supply was terminated and the powder removed from the vessel for sampling and analysis.

*4.2.4. Powder sampling*

The material obtained from each mixing experiment was emptied onto a clean, flat surface with a minimum of agitation, so that samples could be taken from the resulting powder heap. Thirty samples of approximately 500 mg were taken at random from the mixture using a sample thief.

*4.2.5. Model drug assay*

The samples (500 mg) were placed in a 50 ml volumetric flask, then dissolved and diluted to 50 ml using freshly distilled, deionised water at 25°C. A conductivity meter (type CDM80, Radiometer, Denmark) and cell (type CDC104, Radiometer, Denmark) was calibrated, then each sample solution was assayed for sodium chloride content based on the conductivity of the solution. Controls showed that, as expected, lactose did not add to the conductivity.

*4.3. Results and discussion*

As expected, the most efficient mixing of the materials tested was obtained by manual geometric mixing, which provided a coefficient of variation of 0.93%. The value of using this technique was to provide evidence that a homogeneous mixture could be obtained using the materials under investigation. The results using manual geometric mixing may be considered as a benchmark for other mixing techniques. Since the method of homogeneity testing can be considered to give values that are a composite for mixing and segregation, any segregation phenomena that occur during the mixing process are taken into account.

It is notable that the results indicate a mean content which is slightly less than the theoretical value of 10.0% sodium chloride. This may have occurred through agitation of the material causing a loss of fine particles to the external environment since the mixing vessel was not enclosed during the mixing process. Since this lost fine material would have been predominantly composed of sodium chloride particles this may account for the low content.

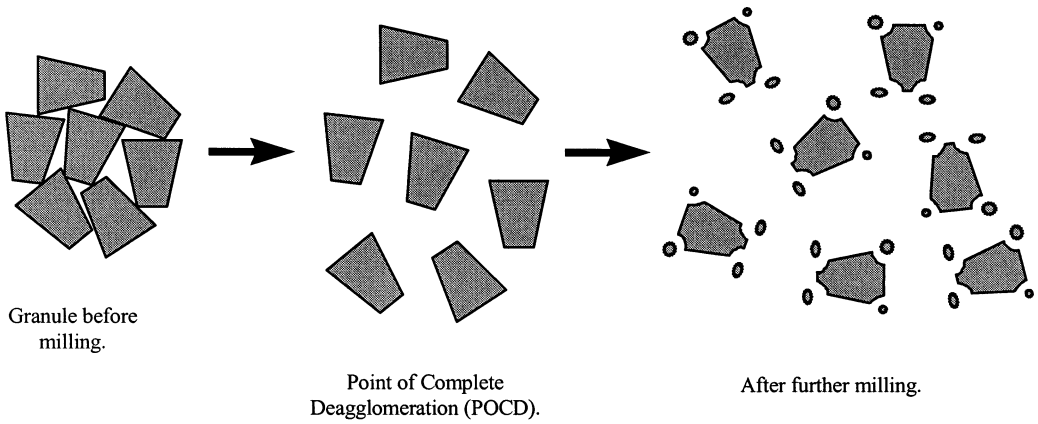



Fig. 8. Proposed milling mechanism of CAGL and HSMGL in the SVP Mark IV.

Table 3
Summary of time taken to reach POCD and median particle diameter at POCD for CAGL and HSMGL at different nozzle pressures

| Material | Nozzle pressure (psi) | Time taken to reach POCD (min) | Median particle diameter at POCD (μm) |
|---|---|---|---|
| CAGL | 30 | 1 | 297 |
| HSMGL | 30 | 5 | 155 |
| CAGL | 20 | 3 | 287 |
| HSMGL | 20 | 10 | 141 |
| CAGL | 10 | 5 | 314 |
| HSMGL | 10 | 20 | 151 |

The quality of mix obtained by using the turbulent tumbling technique was poor, being characterised by a coefficient of variation of 15.20%. This was probably due to a lack of internal shear forces, particularly between initial fine particle agglomerates of sodium chloride, provided by tumbling mixing. These forces are necessary for the formation of interactive powder mixtures.

The effect of the shearing force which is imparted onto a powder mixture containing two components, one of which is much finer than the other is shown diagrammatically in Fig. 9. This figure shows an agglomerate of the fine component, which is mixed with larger carrier particles. A low shear force takes the easiest route through the powder, which in this case is around the exterior of the carrier particles and the fines agglomerate. A high shear force is able to pass between individual particles in the agglomerate and hence break it up so that it may be distributed over the carrier surfaces and form an interactive mix. The geometric manual mixing technique imparts a large shear force on the powder by the grinding action of the mortar and pestle. This causes the adhesive component (sodium chloride) to be redistributed onto the carrier particle surface.

Aggregates, which may be of a similar particle size to the carrier lactose particles, remain intact in the turbulent tumbling technique due to this lack of shear, so reducing the homogeneity of the mix.

It was considered that the high shear conditions created by the high pressure air nozzles within the SVP would be able to break up the agglomerates during the mixing evaluation in a similar fashion to that which would be expected in a bladed mixer.

A value for the coefficient of variation of less than 5% is generally considered necessary in most pharmaceutical powder mixing processes (Kay, 1997). The SVP provided a mixing capability characterised by an average coefficient of variation of 2.49%. As shown in Table 4, this is represents an improved mixing efficiency over turbulent tumbling mixing. The motion of powder within the SVP during its operation was observed to display large regions of recirculating flow, which enable mixing to occur (see Fig. 3).

The SVP design was tested using a computational fluid dynamics (CFD) model (STAR_CD, Version 3, Computational Dynamics, London, UK). The model allowed different flow regimes to

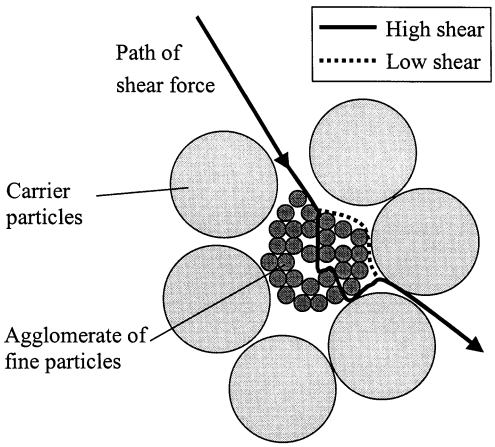



Fig. 9. Schematic representation of the path of the shear force following application of high and low shear forces in interactive mixing.

Table 4
Coefficient of variation obtained from each mixing technique

| Mixing method | Coefficient of variation (%) | Mean content (%) |
|---|---|---|
| Manual geometric mixing | 0.93 | 9.41 |
| Turbulent tumbling mixing | 15.20 | 9.49 |
| Mixing in the SPV Mark IV | 2.49 | 8.17 |

be studied, an example of which is shown in Fig. 10, and indicated relatively few dead regions where particles could settle (MacGregor et al., 1998). Experimental testing showed that the CFD predictions appeared to be exhibited by the SVP. The lack of dead spots predicted in the CFD model was also considered to exist experimentally and was assumed to be a major reason for enhanced mixing efficiency. The combination of fluidizing air, which was supplied to all of the flat regions of the vessel base, with the swirling flow fields generated by the high pressure air nozzles ensured that the flow patterns within the SVP attained sufficiently turbulent conditions and fluctuating velocities within the powder bed to perform the mixing process. The high shear created by the action of the high pressure air nozzles facilitated the mixing of a binary powder system consisting of powders of widely differing particle sizes, thus enabling the formation of interactive powder mixes.

## 5. Conclusion

A prototype SVP was designed with the aid of a computational fluid dynamics model and was found to be capable of performing the sub-operations of granule size reduction and dry powder mixing. There was also some evidence that the SVP was capable of providing primary size reduction of materials. The flow patterns induced in powder within the processor could be readily observed and displayed a strong swirling flow field which was well fluidised.

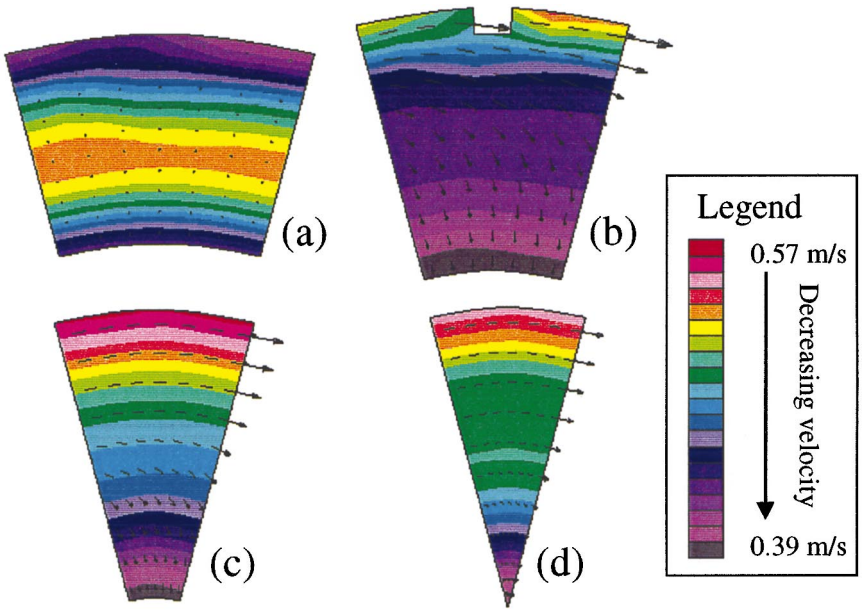



Fig. 10. Example of the CFD model of the SVP Mark IV for single phase flows. The model shows 1/12 cross-sections of the vessel in the plan view at (a) the base of the vessel, (b) 50 mm from the base (nozzle outlet height), (c) 100 mm from the base, and (d) 180 mm from the base (apex of the cone). The arrows indicate the direction of the airflow. Relative flow velocity magnitudes are indicated by reference to the colours in the legend.

Particle size reduction was found to be rapid for the batch size investigated; the speed and extent of granule size reduction was considered to be at least equivalent to that which could be attained using conventional techniques of secondary size reduction in granulation. It is envisaged that greater size reduction could be obtained by increasing the nozzle pressures.

The mixing achieved within the SVP was found to be rapid and more homogeneous than that achievable with a similar powder system using a conventional low shear mixing technique.

The principle of using controllable fluid dynamics to perform multi-task processing of powders has been demonstrated. The SVP offers the potential for the batchwise preparation of powders for tableting and capsule filling within a single vessel.

One problem that was encountered with the current SVP design was in separating very fine particles from the gas stream using a cyclone separator. In order to improve this aspect of processing, it is anticipated that future designs will require the addition of a fibrous filter system.

The SVP concept is considered to form the basis for a continuous bladeless processor, capable of integration into a closed, automated and controllable manufacturing system in which raw materials can be processed into final dosage forms without manual intervention.

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