ELSEVIER

International Journal of Pharmaceutics 136 (1996) 1–11

international journal of pharmaceutics

Research papers

Numerical simulation of milling processes as an aid to process design

A. Annapragada*, A. Adjei

Abbott Laboratories, Pharmaceutical Products Division, 1400 Sheridan Road North Chicago, IL 60064-4000 USA

Received 27 September 1995; revised 11 January 1996; accepted 22 January 1996

Abstract

The design of milling processes for pharmaceutical materials can be done in a rigorous fashion using a simplified version of the Generalized Aggregation-Fragmentation Equation which contains only fragmentation terms. This entails formulation of a detailed mathematical model for the fragmentation process in the mill, the evaluation of a parameter of the model (the collision efficiency) from simple experiments and, finally, the utilization of the model to design a new process. In this work, a bead milling process for the manufacture of aerosol particles is modelled in pass-by-pass mode and the model is shown to accurately predict the performance of the mill in both pass-by-pass and flow-recycle modes. The model is then used to investigate the effects of design parameter variations in the flow-recycle mode.

Keywords: Milling; Generalized Aggregation-Fragmentation Equation; Aerosol particles

1. Introduction

It has been demonstrated in previous work that the optimum delivery of aerosol particles into the deep lung takes place when the particles are between 1 and 10 μ in diameter (Adjei and Garren, 1990; Johnson et al., 1989; Newman et al., 1985). This has profound implications on the development of pulmonary delivery dosage forms. It becomes necessary to carefully micronize the drug particles into the 1–10 micron range and then package them into a commercially viable primary package. Traditionally, the size reduction of particles has been done by dry milling followed by dispersion of the milled particles into an appropriate liquid medium. Several complications plague this process, including (1) the explosive nature and reactivity of fine powders due to increased

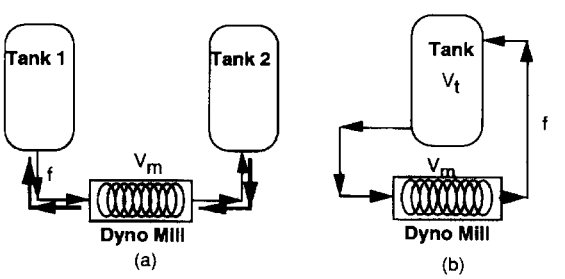

Fig. 1. (a) Pass-by-pass milling. (b) Continuous-flow milling.

* Corresponding author.

PII S0378-5173(96)04465-1

surface area, and (2) the agglomeration of milled particles which prevents good dispersion. In order to overcome these difficulties, cryogenic milling processes which maintain the particles in a nonflammable propellant vehicle at low temperatures during the milling have been developed by Abbott Laboratories. The milling itself takes place in a high speed bead mill. A complete description of the mill is available elsewhere (Glen Mills Model KDL).

A typical process used for development purposes and the manufacture of clinical supplies utilizes a system as illustrated in Fig. 1a. The liquid medium, Freon R11, containing the drug particles is passed from a charge vessel through the mill to a collection vessel. One complete transfer of this kind is referred to as a 'pass'. Upon completion of the first pass, the collection vessel and the charge vessel are interchanged, and the process is repeated.

Due to environmental concerns, alternatives to the CFC medium and propellant are desirable for future formulation efforts. Among the alternative milling media, the frontrunner is tetrafluoroethane, HFC-134a, which has significantly lower ozone depletion potential. However, it also has significantly higher vapor pressure and lower critical point. Therefore, any system using HFC-134 in the liquid state will have to operate at lower temperatures and higher pressures than the corresponding R-11 system. It has therefore been suggested that the 2-tank pass-by-pass milling system would be impractical on a production scale due to the switching of tanks that will have to be done at every pass. A practical alternative would be a continous milling system where the output of the mill would be mixed back into the main reservoir as shown in Fig. 1b. However, the performance of such a milling system would differ from the conventional pass-by pass system of Fig. 1a. The objective of this work is therefore to achieve predictive capabilities which will allow us to quantitatively predict the changes in mill performance as a function of changing input and process parameters. This would allow us to greatly simplify the design and scale-up of a production system.

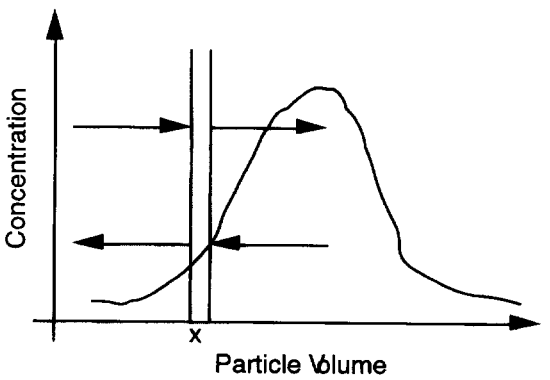

Fig. 2. Representation of particle intensive property distribution.

2. Theory

2.1. Development of governing equations

The milling of particles falls under the general category of 'size reduction' processes (Perry, 1973). The governing equation which describes the evolution of a multiparticle system has been variously called a 'population balance' (Ramkrishna, 1985) or 'Smoluchowski's Equation' (for the researcher who first demonstrated its utility in studying the coagulation of colloidal particles (von Smoluchowski, 1916)). The following treatment follows that set forward by Ramkrishna (1985) and Ziff and Vigil (1989).

In a formal sense, assume a Volume Distribution c(x,t) of particles which describes the probability of finding, at a time t in a population of particles, a particle with a given volume x. Such a distribution function could be represented as in Fig. 2.

Any particles in this population are considered as interacting with each other and the environment in a fashion which causes changes in the distribution. For a given differential slice of this distribution therefore, we can write a 'balance' as below:

$$\frac{\partial c_{(x,t)}}{\partial t} = J_{<x} - J_x + I_{>x} - I_x \quad (1)$$

where J's refer to processes which cause an increase in the particle volume, and I's refer to

processes which cause a decrease in the particle volume. The subscripts refer to the volumes of the particles which contribute to the corresponding flux.

The mechanisms of increase and decrease in the particle volume are obviously of importance in constructing the exact nature of I's and J's. Assuming that particle growth occurs through binary collisions, and that particle size decreases occur through fragmentation to smaller particles, we can write:

$$\frac{\partial c(x,t)}{\partial t} = \frac{1}{2}\int_0^x k(y,x-y)c(y,t)c(x-y,t)dy - c(x,t)\int_0^\infty k(x,y)c(y,t)dy - a(x)c(x,t) + \int_x^\infty a(y)b(x|y)c(y,t)dy \quad (2)$$

where k(p,q) is the aggregation rate expression or kernel for the aggregation of particles of volume p and q, a(p) is the breakup rate constant for the breakup of a particle of volume p, and b(p|q) is the conditional probability of formation of a particle of volume p from the breakup of a particle of volume q. The product a(p)b(p|q) is referred to as the breakup kernel, analogous to the aggregation kernel k(p,q). The variable y is the dummy variable of integration. This equation is called the Generalized Aggregation Fragmentation equation (GAF). The terms on the right-hand-side of this equation are as follows:

Term 1: Aggregation of particles smaller than x to form particles of volume x
Term 2: Aggregation of x particles to form larger particles
Term 3: Fragmentation of x particles to form smaller particles
Term 4: Fragmentation of particles larger than x to form particles of volume x

For a purely fragmentive process such as milling, it is reasonable to assume that the first two terms on the right hand side of the GAF are negligible. We can therefore write the generalized fragmentation equation:

$$\frac{\partial c(x,t)}{\partial t} = a(x)c(x,t) + \int_x^\infty a(y)b(x|y)c(y,t)dy \quad (3)$$

Similarly, the generalized aggregation equation can also be written with the first two terms of the GAF.

The natures of a and b are obviously of paramount importance in solving the fragmentation equation. Expressions can be derived by observing the physics of the particular process. The term a is often referred to as the fragmentation rate kernel since it embodies the functionality of the fragmentation rate independent of the particle concentration.

In the mill used in this work, the milling is carried out by attrition of the particles in a liquid medium between glass beads. The mill contains a high speed rotor which causes the contents to move in a circular fashion. Axial motion exists due to the flow through the mill. However, the glass beads are filtered out of the flow before the mill exit. The magnitude of the flow velocity is quite small compared to the tip-speed of the rotor, therefore it is reasonable to assume that axial motion does not contribute significantly to milling while the circular motion dominates it.

It is reasonable to assume that the rate of breakup of particles is proportional to the rate of collision of the particles with the glass beads. The collision rate of particles in dilute systems is used often in the kinetic theory of gases. According to this theory, neglecting the fact that the beads/particles are actually far from dilute, the collision rate R_x of particles of radius r_x with beads of radius r_b can be approximated by:

$$R_x = C_x C_b \pi \sqrt{2}\,\frac{v_x + V_b}{2}(R_x + r_b)^2 \quad (4)$$

where v_X is the linear velocity of a particle with volume x, v_b is the linear velocity of a bead, C_x is the concentration (# /vol) of the particles with volume x and C_b is the concentration (# /vol) of the beads. In this work, we assume that (1) the speed of beads and particles are identical, and equal to the tip speed of the rotor, and (2) the dilute expression derived from kinetic theory is also applicable in the non-dilute system in the mill. Given these assumptions, we can then write

the fragmentation rate kernel of particles which collide with the beads as:

$$a(x) = \eta\pi\sqrt{2}\,\frac{V_x + V_b}{2}(r_x + r_b)^2 \quad (5)$$

where η is the 'collision efficiency' or the fraction of collisions which result in a fragmentation. Note that this expression only depends on the properties of the beads and the particle under consideration, i.e. particle-particle collisions are not considered as having the potential to cause fragmentation.

The conditional breakup probability b(x|y) denotes the probability of formation of a particle of volume x from the breakup of a particle of volume y, and can be approximated in many ways. For this work, we consider binary fragmentation with a 'uniform' breakup probability. When a particle breaks, two fragments are formed, with mass (and hence volume) being conserved. The volume of the fragments therefore adds up to the volume of the parent particle. In addition, the uniform probability distribution allows fragments of all sizes to be formed with equal probability. It can be shown (Ziff and Vigil, 1989) that under these conditions, the breakup probability can be written as:

$$b(x|y) = \frac{1}{y} \quad (6)$$

The physical interpretation of this expression is that the larger the particle is, the larger the number of potential fragment sizes it can break into, and therefore the smaller the probability of occurrence of each fragment size. While this is not obvious for continuous distributions, it is trivial to derive for discrete distributions.

Substituting these expressions for a and b into the generalized fragmentation equation then gives us a rate expression for the breakup of a population of particles.

2.2. Pass-by-pass system

The pass-by-pass system is easy to visualize as a Continous Stirred Tank Reactor with ideal mixing. The space time can be conveniently approximated as:

$$\tau = \frac{V_m}{f} \quad (7)$$

where V_m is the void volume of the mill and f is the volumetric flowrate through the mill. Therefore, each pass through the mill can be evaluated as a batch system at reaction time 1τ, 2τ, 3τ, etc. The void volume V_m would include the free volume in the mill after the beads are filled plus the void volume between the beads. The solution to the pass-by-pass problem therefore consists of a solution to equations (3–7) with appropriate initial conditions.

2.3. Continuous system

The continous system is approximated as a combination of two CSTR's as shown in Fig. 1b. The first CSTR is the mill itself, while the second one is the reservoir tank. The assumptions in this analysis are:

(1) The size reduction takes place entirely in the mill, and not in the reservoir.

(2) The volume of tubing connecting the two units is negligible compared to the volume of the reservoir (V_t) and mill (V_m).

If $c_1(x,t)$ is the size distribution of particles leaving the reservoir, and $c_2(x,t)$ the size distribution of particles leaving the mill, we can write:

$$\frac{\partial c_1(x,t)}{\partial t} = \frac{f}{V_t}(c_2(x,t) - c_1(x,t)) \quad (8)$$

and

$$\frac{\partial c_2(x,t)}{\partial t} = a(x)c_2(x,t) + \int_x^{\infty} a(y)b(x|y)c_2(y,t)dy + \frac{f}{V_m}(c_1(x,t) - c_2(x,t)) \quad (9)$$

The solution to the continuous milling problem therefore consists of the solution to equations (4–9) with appropriate initial conditions.

2.4. Solution technique

2.4.1. Choice of domain

As mentioned earlier, there are no known analytical solutions to this complex system of integro-differential equations. We therefore seek numerical solutions. For systems with both aggregation and fragmentation present, it is not possible to define a finite domain for the solution since there is always the possibility of growing an ag-

gregate larger than the upper limit of the computational domain. For purely fragmentive systems however, it is possible to define a lower limit below which size it is extremely unlikely that the milling system will generate a particle. The upper limit in size space can conveniently be chosen to be at the largest size of the initial condition, since in the absence of aggregation, no larger size particles can ever be generated.

2.4.2. Discretization

The size distribution was approximated in volume space as below:

$$c(x,t) = \sum_{1}^{n} K_i \delta_i \quad (10)$$

where k_i's are relative weights of the size distribution at the positions of the Kronecker δ functions $\delta_{i...n}$ in volume space. This resulted in each of the equations (3), (8) and (9) being reduced to a series of n ordinary differential equations which could be conveniently solved by the DEPISODE initial value problem solver (Schiesser, 1991).

One pitfall in the numerical solution of the generalized fragmentation equation is the lack of closure of mass balance. Consider equations (3) and (10) for the case of i = 1. This corresponds to the case of fragmentation of particles which lie in the smallest size interval included in this analysis. Based on equations (5) and (6), there is a finite rate of fragmentation out of this smallest size interval, which is not accounted for in any other size interval. The total mass in this simulation will therefore decrease with time. It was found that this reduction in mass was small (2–4% per time step). Therefore, the mass balance was artificially closed by distributing this loss in mass uniformly over the entire distribution.

3. Experimental

Continuous milling experiments were conducted using the KDL Dynomill (0.6 liter volume), using Dextrose as the milled particles suspended in a Freon R11 medium containing Span-85 surfactant to prevent aggregation of the particles.

The mill speed was set to 2000 RPM with a slurry flowrate of 200 ml/min. The dextrose/Freon R11 slurry was recirculated through the mill with the use of a diaphragm pump. Propylene glycol cooled to 0°C was used as the coolant for the jacket of the milling chamber. Dry ice was added to the bath at 1-h intervals during the experiments to maintain the temperature of the coolant in the jacket at around −10°C to 0°C. Two days before the start of the run, 1 l of glass beads 0.7–1.0 mm diameter were washed and dried using standard procedures to remove any contaminants in the glass beads. At the same time, 500 g of dextrose was placed in a glass beaker and dried at 50°C in a vacuum oven. For the batch milling process, the Freon R11, Dextrose and Span-85 were charged to the feed tank (A). The mixture was then blended by recirculating material through the pump back into the feed tank. The milling was then started by feeding the material through the mill into the collection tank (B). Once all the material was passed into the collection tank (B), the positions of tanks (A) and (B) were interchanged and the process was repeated by feeding the material from tank B to A through the mill. At the end of each pass, samples were drawn from the current collection tank and analyzed in a Malvern 2600 Fraunhoffer Diffraction particle size analyzer. The initial size distribution of particles and the size distributions of particles in subsequent passes of a pass-by-pass milling run are shown in Figs. 3 and 4 respectively. By integrating the appropriate portions of the differential distributions, it is possible to calculate the fraction below a particular cut diameter. For this work, the mass fractions below 20 μ, 10 μ and 4 μ were calculated. For the single tank flow-milling experiments, the procedure was very similar. The bead cleaning and mill cooling procedures were identical. The procedure for pre-blending the charge was slightly different due to the changed configuration of the mill and tank. After charging the tank, the material was recirculated through the mill with the mill turned off till the liquid appeared uniform. The mill was then started and the time of start was counted as the Zero time for the experiment. Samples were drawn from the mill outlet at regular intervals during the experiment

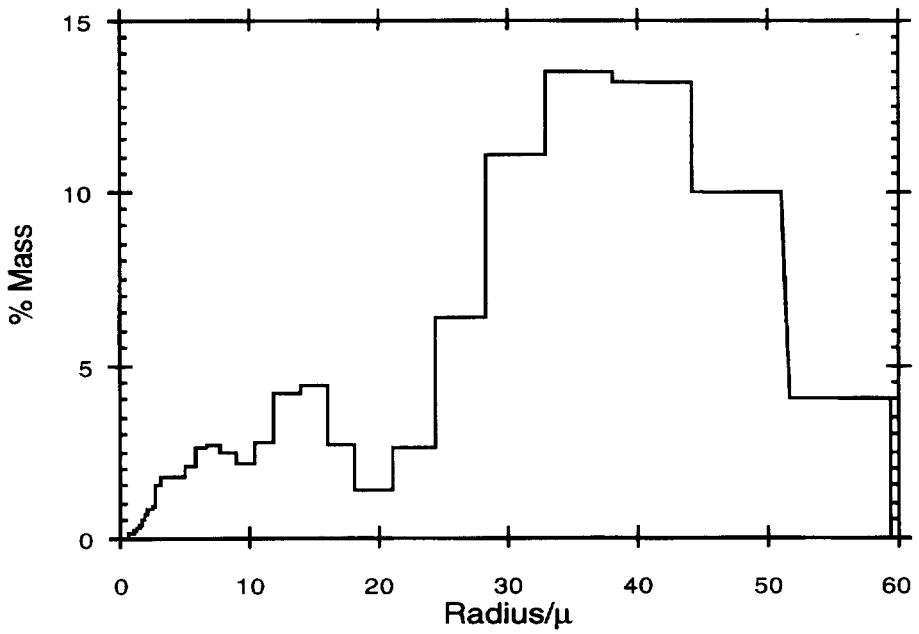

Fig. 3. Initial size distribution of dextrose to be milled.

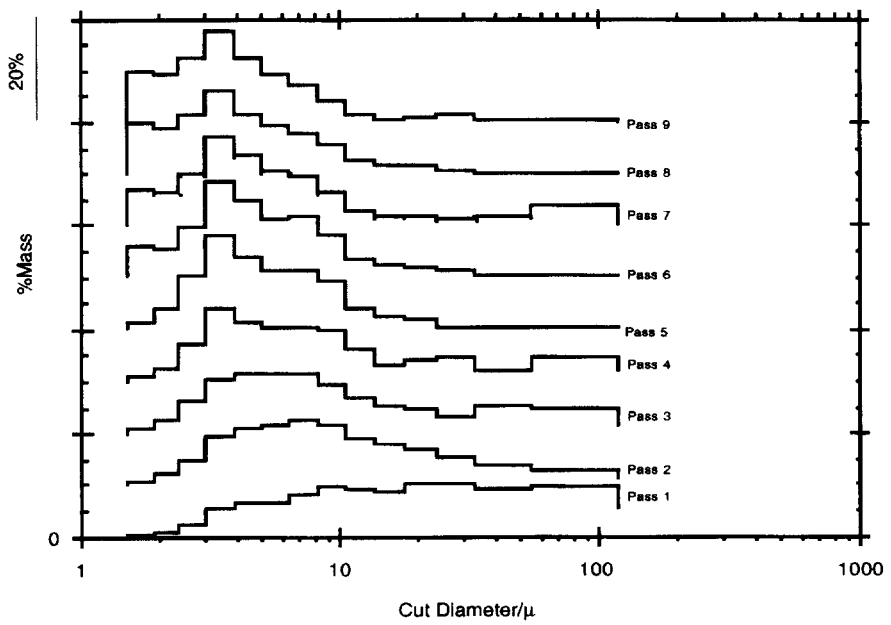

Fig. 4. Size evolution of Dextrose particles as a function of passes through mill.

and the particle size distribution determined in the Malvern 2600 Fraunhoffer Diffraction particle size analyzer.

4. Results and discussion

The entire system of equations for the pass-by

pass system (equations 3–7) was programmed using FORTRAN-77 on a HP720 PA-RISC workstation. The size space was discretized into 200 size classes from 0 to 60 microns diameter, with uniform widths of 0.3 microns. This resulted in a system of 200 Ordinary Differential Equations (ODE's) to be solved simultaneously. The DEPISODE code from Lawrence Livermore for the solution of ODE's was used to solve this system. The initial condition (starting size distribution) was that of unmilled material shown in Fig. 3. Typical run-time for the code was 5 min. Size distributions for pass-by-pass simulations with collision efficiencies from 1×10^{-4} to 1×10^{-3} were calculated. Integrating these curves below diameters (20 μ, 10 μ and 4 μ) yielded the mass fractions below those diameters for each of these cases. The graph in Fig. 5 shows a comparison between experimental and simulated results for a collision efficiency of 9×10^{-4}. The agreement for particles below 20 μ and 10 μ is excellent, while that for particles below 4 μ is not nearly as good. There are two possible reasons for this discrepancy: (1) The Fraunhofer Diffraction method for determining particle size distributions has limitations at the lower end of its size range. It is likely to severely underpredict the mass fraction of small particles (Annapragada and Adjei, in press). It is possible that the < 4 μ fraction was underpredicted in these measurements. (2) It is possible that the energy required to fragment smaller particles is greater than that for larger particles due to the increased surface energy requirements of smaller particles. A correction may have to be introduced to the fragmentation kernel to account for this deviation. Other reasons may also exist for this discrepancy; at this time we do not have a more rigorous explanation for this deviation.

The system of equations for the flow-milling system was also solved with the same collision efficiency parameter value of 9×10^{4}. The integrated values below 10 μ diameter are shown in Fig. 6 along with the experimental data for two single tank runs. As can be seen, the model predicts the performance of the continuous system quite well. It should be noted that there is only one adjustable parameter in this model, the collision efficiency parameter which is estimated from the pass-by-pass data. It is reasonable to expect that this parameter will remain constant for a given combination of beads and milled material.

The continuous model can now be used to probe the effects of other process changes. While some of these simulations may not be completely accurate due to deviations from the assumptions of the model, they allow us to estimate to a first approximation, the effects of various process changes. The simulations can therefore be used to identify a range of operating parameters which can then be explored in detail in experiments. This can cut down dramatically on the time and effort needed to design and optimize a process. An example of this approach is the choice of continuous milling parameters for the experiment shown in Fig. 6 which were chosen from the results of the simulation.

The continuous milling model can now be used to predict the effects of various parameter changes. This is illustrated in Figs. 7–10. Fig. 7 shows the effect of different mill speeds as calculated from the model. A reduction in mill speed reduces the rate of size reduction. Fig. 8 shows the effect of changing flowrates through the mill. At higher flowrates, the rate of size reduction is apparently increased. This is attributed to the lowered residence time in the mixing tank at higher flowrates and therefore an effective larger number of passes through the mill for the particles. Fig. 9 shows the effect of varying bead size on the simulation results. At smaller bead sizes, the rate of size reduction is increased. This can be attributed to increased collision frequency of small beads with the particles due to the increase in total number of beads. In Fig. 10, it can be seen that bead volume in the mill does not affect the rate of size reduction as significantly as the other variables.

5. Conclusions

The numerical simulation technique is capable of approximating the effects of various process changes on the milling of Dextrose. The power of

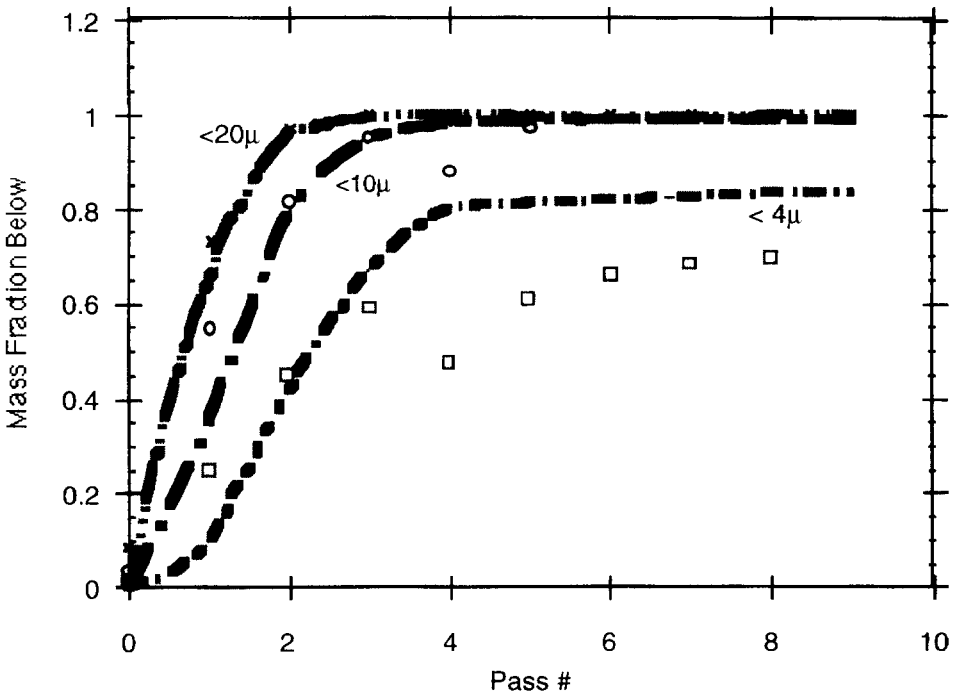

Fig. 5. Evolution of mass fractions below 20 μ, 10 μ and 4 μ for a collision efficiency of 9e-4. The points are the experimental data, the lines are simulation results.

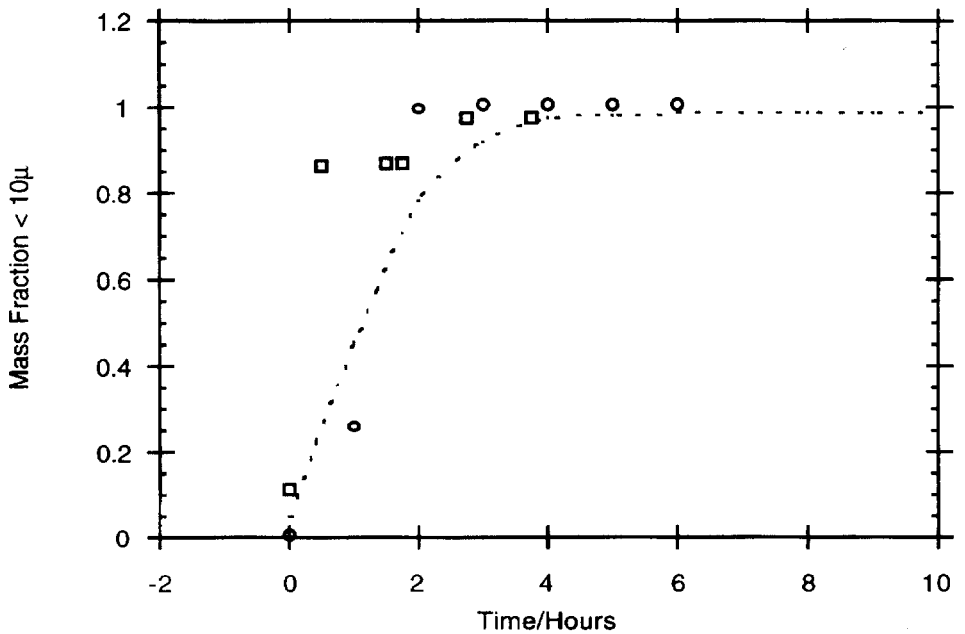

Fig. 6. Comparison of simulation and experiment for continuous milling. The points are the experimental data, the line is the simulation result.

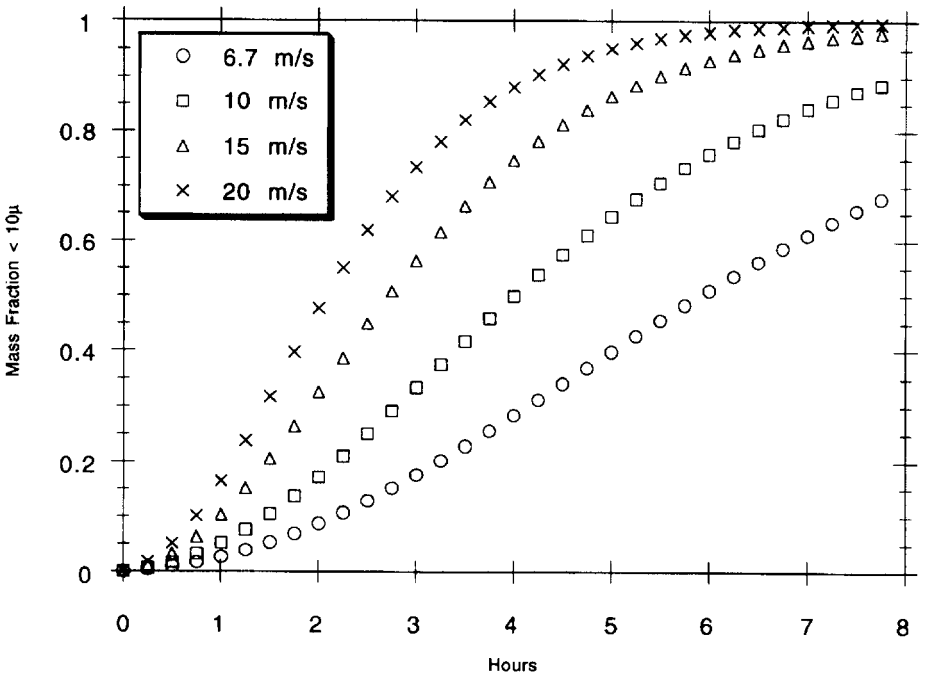

Fig. 7. Effect of mill speed on continuous milling: Simulation.

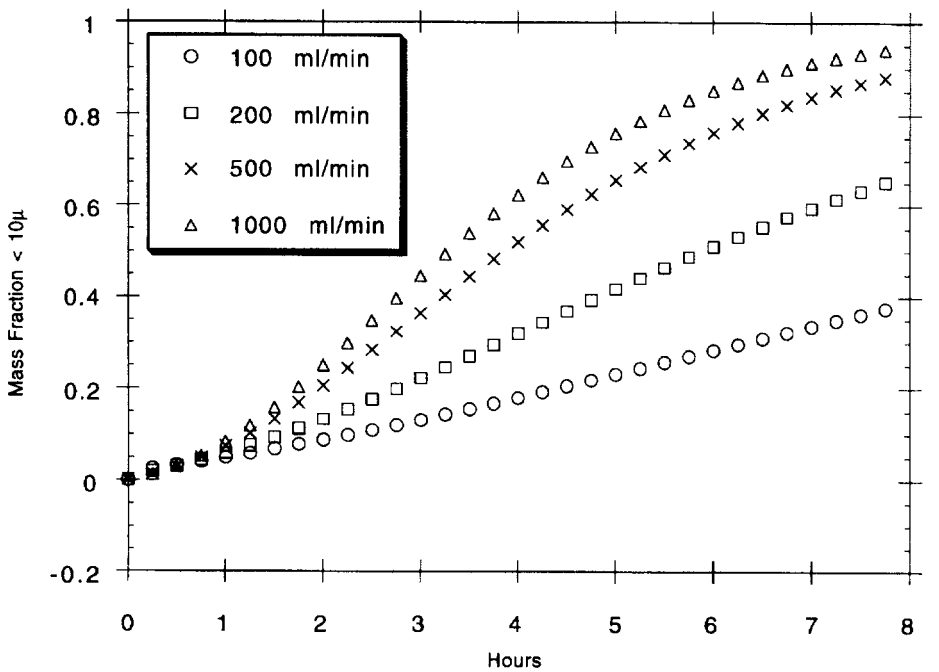

Fig. 8. Effect of flowrate on continuous milling performance: Simulation.

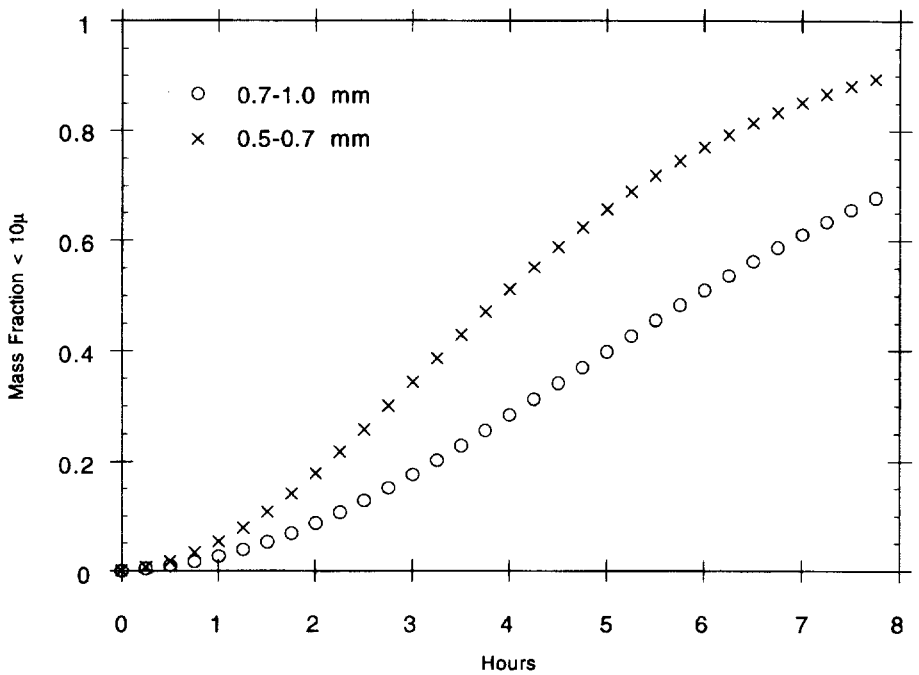

Fig. 9. Effect of bead size on continuous milling performance: Simulation.

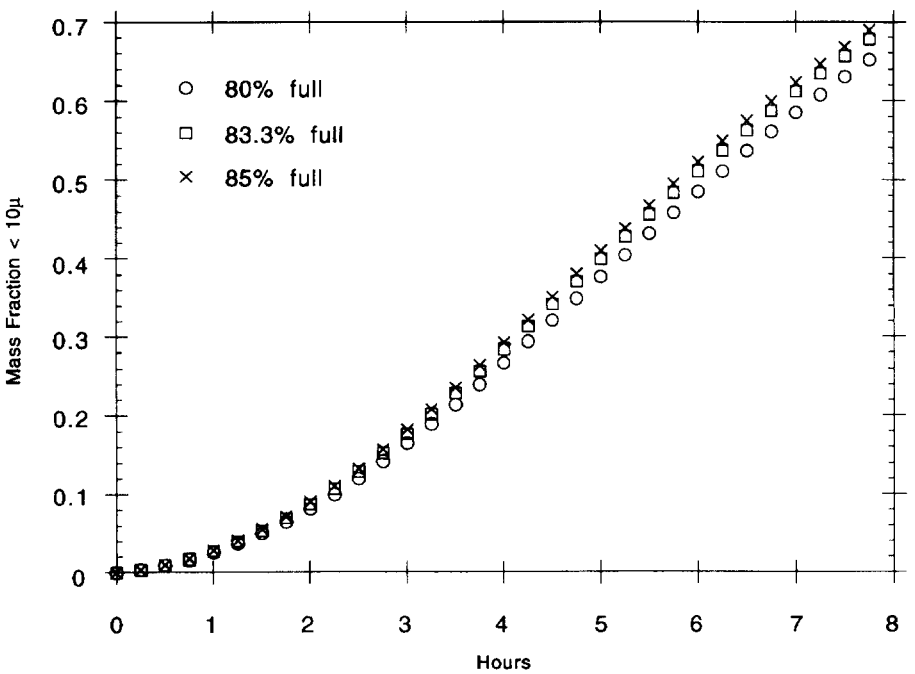

Fig. 10. Effect of bead volume on continuous milling performance: Simulation.

this technique has been demonstrated by its ability to predict the flow parameters needed to run a continuous single tank milling system with comparable performance to a pass-by-pass system. The effects of various other parameter changes can be explored using the simulation. Acceptable parameter ranges for new process design can be bracketed from this simulation. This has been demonstrated for the design of a continuous flow milling process based on data from a batch process.

Acknowledgements

Many thanks to Aileen Chou and Dennis Lee for assistance in the milling experiments and conducting the particle size analyses.

References

Adjei, A. and Garren, J. *Pharmaceut. Res.*, 7(6) (1990) 565–569.

Annapragada, A. and Adjei, A., *Int. J. Pharm.*, (in press).

Glen Mills Model KDL, Product Literature. Available from Glen Mills, NJ.

Johnson, M.A., Newman, S.P., Bloom, R., Talee N. and Clark, S.W., *Chest*, 96(1) (1989) 6–10.

Newman, S.P., Pellow, P.G.D., Clay, M.M. and Clarke, S.W., *Thorax*, 40(9) (1985) 671.

Perry, R.H., (Ed.), "Chemical Engineers Handbook" 5th Edition, Section 8, McGraw Hill, 1973.

Ramkrishna, D., *Rev. Chem. Eng.*, 3(1) (1985) 50–95

Schiesser, W.E., The Numerical Method of Lines, Academic Press Inc., 1991.

von Smoluchowski, Physik. Z. 17 (1916) 557–585.

Ziff, R. and Vigil, R.D., *J. Coll. Int. Sci.*, 133(1) (1989) 257–264 and references therein.