ELSEVIER

International Journal of Pharmaceutics 120 (1995) 95–99

international journal of pharmaceutics

The assessment of the scale-up performance of the extrusion/spheronisation process

J.M. Newton [a,*], S.R. Chapman [a], R.C. Rowe [b]

[a] Department of Pharmaceutics, The School of Pharmacy, University of London, 29–39 Brunswick Square, London WC1N 1AX, UK
[b] Zeneca Pharmaceuticals, Macclesfield SK10 2NA, UK

Received 11 November 1994; accepted 13 December 1994

Abstract

The ability to predict the spheronisation performance of a standard extrudate over a 125-fold range has been assessed in terms of spheroid quality produced. It has been found possible to predict the performance of a 25 kg batch on a 65.6 cm diameter production spheroniser from experiments (with a 22.9 cm diameter laboratory spheroniser). To achieve such prediction it is necessary to use a good quality extrudate and operate the spheroniser at rotational speeds which give the same linear peripheral velocity of the plate.

Keywords: Extrusion/spheronisation; Roundness; Scale-up

1. Introduction

The scaling up of any pharmaceutical formulation can present numerous problems, and considerable reliance is placed on past experience in overcoming such problems. Most pharmaceutical processes have a considerable body of knowledge which can aid scale-up, but the process of extrusion/spheronisation, first reported by Reynolds (1970) and Conine and Hedley (1970) is of recent usage and has considerably less literature than other solid dosage form processes, such as granulation, tabletting, encapsulation and coating. While the literature contains information on formulation factors, there is little reported work on the factors involved in the scaling-up process. To simplify the number of factors involved in an investigation, the variables due to scaling up the extrusion process were eliminated by processing a standard extrudate and evaluating only the scaling of the spheronisation stage.

2. Materials and methods

2.1. Materials

Equal parts of microcrystalline cellulose, Avicel PH 101 (FMC Corp., Philadelphia, USA), and lactose (extra fine Unigate, UK), formed the basis of the formulation, and were mixed with 12 parts distilled water as the binding fluid.

* Corresponding author.

0378-5173/95/$09.50
SSDI 0378-5173(94)00425-0

2.2. Methods

2.2.1. Preparation of extrudate

Avicel and lactose were mixed in a 30 kg capacity planetary mixer (Hobart, London, UK) for 10 min, the water was added and mixing continued for a further 20 min. The resulting wet powder mass was extruded through a pilot scale cylinder type commercial extruder (Model G100/160/S Alexanderwerk, Germany). All extrudate collected was sealed in a large plastic drum to reduce moisture loss during the course of the experiment.

2.2.2. Spheronisation

A 22.9 cm plate and equivalent drum were used on a Caleva spheroniser (G.B. Caleva Ltd, Sturminster Newton, Dorset, UK), at a plate speed of 900 rpm, giving a linear peripheral speed of 424.1 cm s^{-1}. Separate batches for each load of 200 g, 500 g and 1 kg were spheronised for each of the 1, 2, 5, 10 and 20 min residence times. The granules were then tray dried at 60°C to constant moisture level. Samples were taken and their size and shape determined.

The 22.9 plate and drum were removed from the spheroniser base and replaced with a 38.2 cm plate and drum. Loads of 500 g, 1 kg, 3 kg and 5 kg were spheronised for residence times of 1, 2, 5, 10 and 20 min at a plate speed of 540 rpm, thus maintaining the linear peripheral speed of 424.1 cm s^{-1} used for the smaller diameter plate. A separate batch was run for each residence time for loads up to and including 3 kg, and the granules tray dried at 60°C to constant moisture level, then sampled, shaped and sized. One batch only was run for the 5 kg load, and a representative sample of granules removed from the moving mass at 1, 2, 5, 10 and 20 min, as the small amount of granules lost through sampling would have a negligible effect on the momentum of the whole mass, and hence would not influence the spheronising process. The sampled granules were then tray dried at 60°C.

In experiments on the production scale spheroniser (65.6 cm diameter plate) loads of 3, 5, 10, 20 and 25 kg were spheronised for 20 min at a plate speed of 340 rpm, maintaining the linear peripheral speed constant at 424.1 cm s^{-1}.

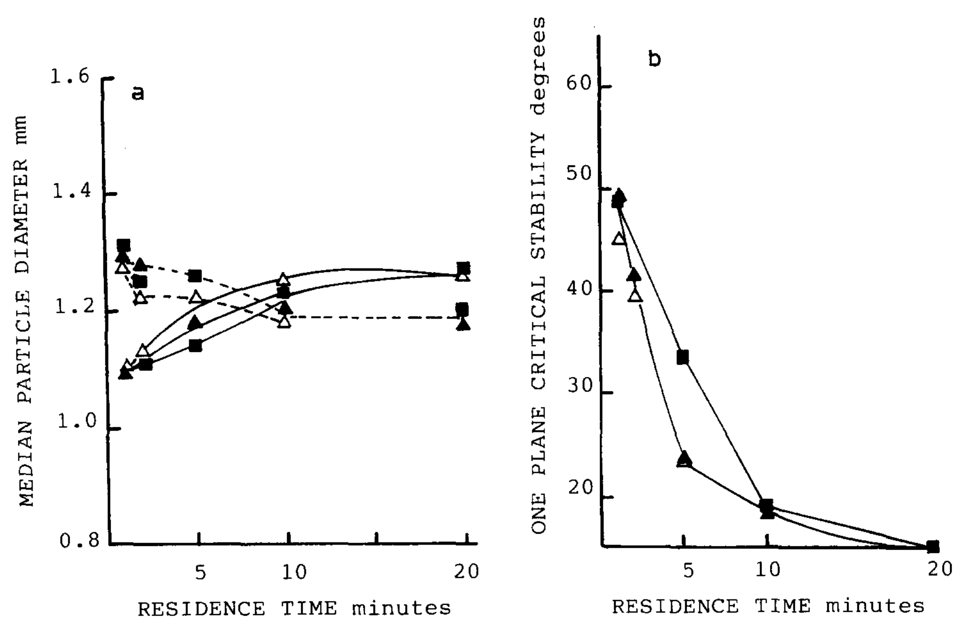

Fig. 1. Effect of load and residence time on (a) the number (broken line) and weight (continuous line) median diameter of granules, and (b) one plane critical stability of granules within largest size fraction for spheronisation at 900 rpm on a 22.9 cm plate, (△) 0.2 kg, (▲) 0.5 kg and (■) 1 kg.

2.2.3. Characterisation of spherical granules

The distribution of particle size by weight was determined by sieving 200 g of granules on a $\sqrt{2}$ progression of sieves using a sieve shaker (Endecott London, UK) and a sample of approx. 1000 granules was separated using a spinning riffler (Microscal Ltd, London, UK). The particle size distribution by number was determined with a Hiac Particle Counter (Criterion Model PC 320, Hiac House, London, UK), linked to a dry sample feeder. The PC 320 works on a light blocking principle and provides a projected area diameter in six channels, here set to give a $\sqrt{2}$ progression from 500 to 1400 μm to enable comparison to be made with the sieve analysis.

2.2.4. Shape analysis

The shape of the granules in the most frequently occurring sieve fraction was determined by the method described by Chapman et al. (1988) giving a roundness as an OPCS value. The results are the mean of 46 particles.

3. Results and discussion

The elimination of the extrusion process as a variable by the use of a constant extrudate allows concentration on the influence of the spheronisation process. The range of quantity of extrudate processed extends from 0.2 kg on the 22.9 cm plate to 25 kg on the 65.6 cm plate, representing a 125-fold increase in scale. It is possible when within one plate size to use a range of loads and with the range of plate sizes chosen it was always possible to produce some given loads on each of two diameters of plate.

Starting with the 22.9 cm plate, loads of 0.2, 0.5 and 1 kg can be prepared. Following the process in terms of changes in median diameter by weight, by sieve analysis, will provide an indication of the changes in the width of the granules, while measuring by number provides an indication of the changes in length. Fig. 1a illustrates that for all loads tested, the width and the length move towards an approximately constant value, the length decreasing and the width increasing. This is accompanied by a reduction in

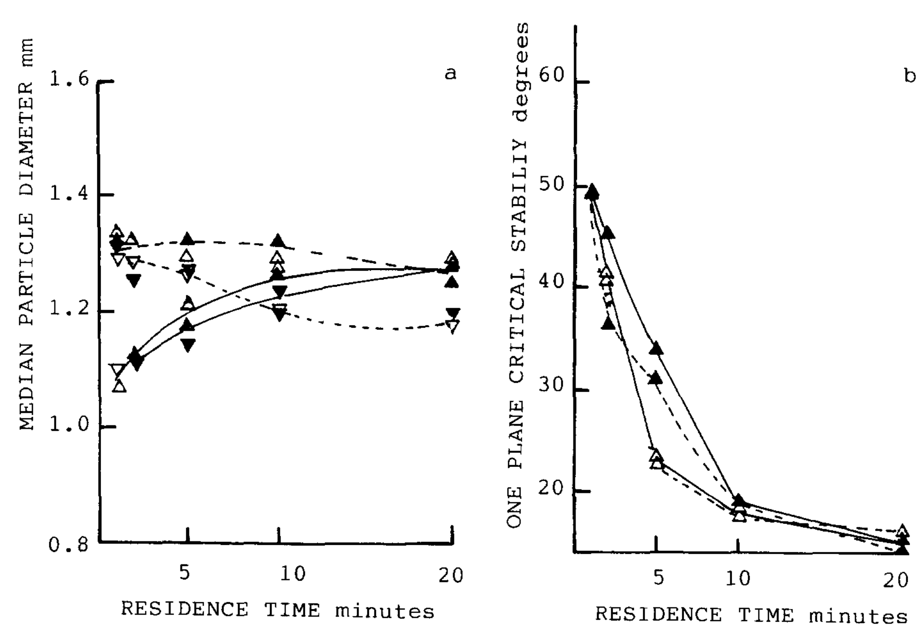

Fig. 2. Effect of load and residence time on (a) the number (broken line) and weight (continuous line) median diameter of granules, 0.5 kg (▿) and 1.0 kg (▾) spheronised at 900 rpm on a 22.9 cm plate with 0.5 kg (▵) and 1.0 kg (▴) spheronised at 540 rpm on 38.6 cm plate, and (b) one plane critical stability of granules in largest sieve fraction for spheronisation at 900 rpm on 22.9 cm plate (continuous line) and at 540 rpm on 38.1 cm plate (broken line), (▵) 0.5 kg and (▴) 1 kg.

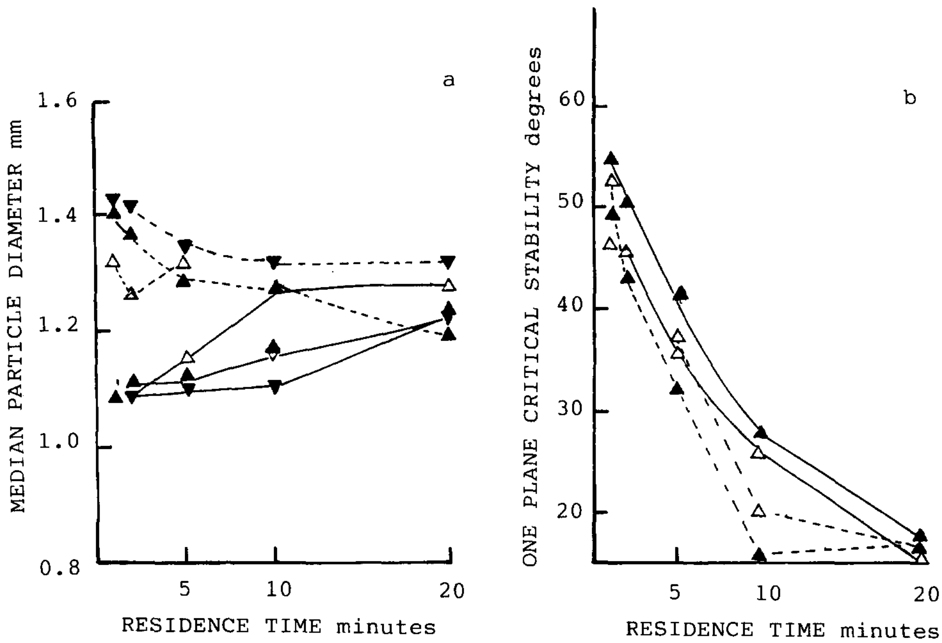

Fig. 3. Effect of load and residence time on (a) the number (broken line) and weight (continuous line) median diameter of granules, (△) 3 kg on 38.1 cm, (▽) 3 kg on 65.6 cm plate, (▲) 5 kg on 38.1 cm, (▼) 5 kg on 65.6 cm plate, and (b) one plane critical stability of granules within largest sieve fraction for 3 kg (△) and 5 kg (▲) spheronisation at 540 rpm on 38.1 cm plate (broken line) and at 300 rpm on 65.6 cm (continuous line) plates.

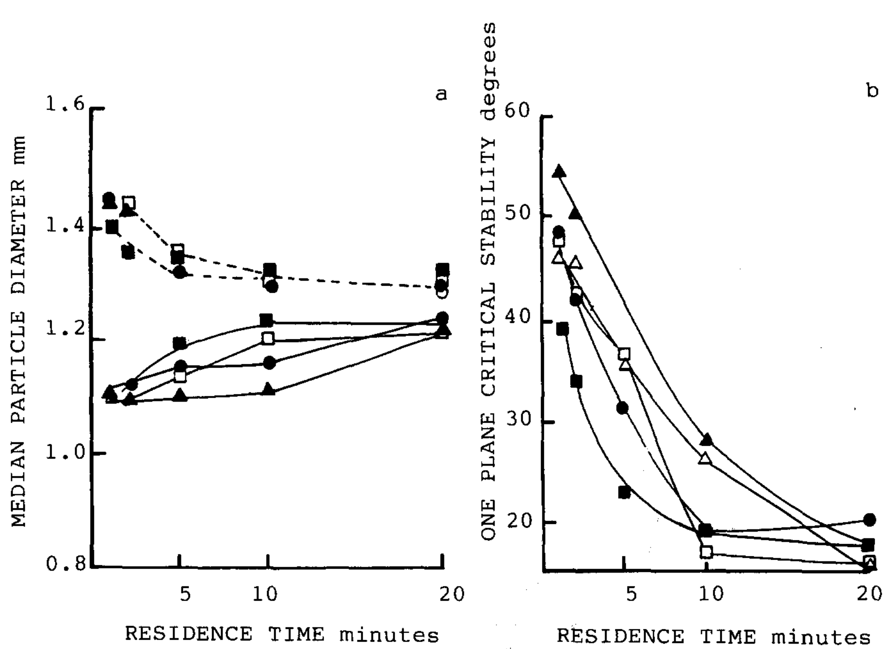

Fig. 4. Effect of load and residence time on (a) the number (broken line) and weight (continuous line) median particle diameters of granules, and (b) one plane critical stability for granules spheronised at 300 rpm on a 68.6 cm plate, (△) 3 kg, (▲) 5 kg, (■) 10 kg, (□) 20 kg and (●) 25 kg.

the value of the OPCS, indicating a production of a round granule (Fig. 1b). The changes occur more rapidly with the lower loads.

Processing 0.5 and 1 kg on the 38.1 cm plate produces slightly different median length of granules, but the widths and values of OPCS essentially are very similar to those produced on the 22.9 cm plate with equivalent peripheral speeds (see Fig. 2a and b). Thus, the same response can be provided with the same load on different plate diameters. The overlap in plate performance can also be demonstrated by comparing equivalent levels (3 and 5 kg) on the 38.1 and 65.6 cm diameter plates (see Fig. 3). Again, particularly in terms of median weight diameter and roundness, the same product can be produced with the two different plate diameters. For these loads, the smaller diameter plate appears to be more effective. It would appear that the lower loads are less effective on the larger plate. This is confirmed by experiments with the loads ranging from 3 to 25 kg on the 65.6 cm diameter plate (see Fig. 4a and b). Again, the higher loads appear to require a longer time to achieve effective roundness.

The ability, therefore, to predict the performance of an extrudate on the three different sizes of spheroniser can be emphasised if the change in roundness is considered in terms of the number of revolutions a granule will undergo when being processed, whether this is on a relatively small (22.9 cm) or a full-scale manufacturing size (65.6 cm) machine. The results for particle roundness derived for each plate size are represented in Fig. 5, which clearly shows that irrespective of load or plate diameter as the number of revolutions increases, the roundness improves, generally in a linear manner with the log of the number of revolutions. What these results, however, do not emphasise is that for a good formulation, once a suitable shape has been reached it does not change significantly. This can be observed in the way the results for the different loads converge to provide a consistent product.

Thus, when a good quality extrudate is produced, it is possible to predict the performance of a 25 kg production batch prepared on 65.6 cm diameter from the performance of a 0.2 kg batch prepared on a 22.9 cm plate. In fact, recent experiments have indicated that similar extrapolation can be made by spheronising 20 g of extrudate on a 10.16 cm diameter plate (Milojevic, 1993). This extrudate was produced by a ram extruder with a 1.24 diameter barrel with a 1 mm diameter die of 4 mm length, with the loss of only 0.5 g of material. Thus, it is possible to undertake preliminary formulations with small quantities of materials which could be scaled up to production levels.

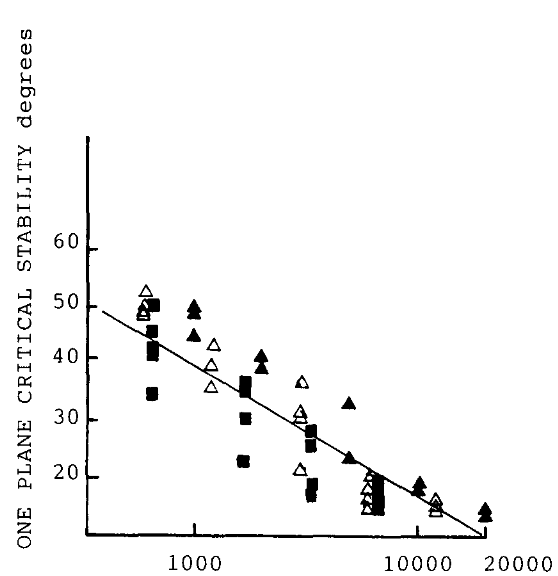

Fig. 5. Change in the value of one plane critical stability with the number of revolutions of the spheroniser plate for granules from within the largest sieve fraction for batches spheronised on (△) 22.9, (▲) 38.1 and (■) 65.6 cm diameter plate.

References

Chapman, S.R., Rowe, R.C. and Newton, J.M., Characterisation of the sphericity of particles by the one plane critical stability. *J. Pharm. Pharmacol.*, 40 (1988) 503–505.

Conine, J.P. and Hedley, H.R., Preparation of small solid pharmaceutical spheres. *Drug Cosmet.Ind.*, 106 (1970) 38–41.

Milojevic, S., Amylose coated pellets for colon-specific drug delivery. Ph.D thesis, University of London (1993).

Reynolds, A. D., A new technique for the production of spherical particles. *Mfg Chem. Aerosol News*, 41 (1970) 40–43.