DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 14(15-17), 2285-2297 (1988)

COATED DRUG CORES IN MULTIPLE UNIT PREPARATIONS INFLUENCE OF PARTICLE SIZE

G Ragnarsson and M O Johansson
Pharmaceutics, AB Hässle, S-431 83 Mölndal, Sweden

ABSTRACT

The influence of the size of barrier-coated drug cores was investigated using a special experimental design. It was shown that the release rate is directly proportional to the surface area of the coated cores. This means, for example, that four times more coating solution should be needed to maintain the release properties if the particle size is reduced to half of its original value. This large effect of particle size variations is important both concerning product quality and production economy.

INTRODUCTION

Coating of drug particles (cores) with polymeric substances is a commonly used method of obtaining extended release from multiple unit preparations, i.e. preparations consisting of a multiplicity of small discrete units.

The cores can be produced in a large number of different ways, such as crystallisation, tumbling agglomeration, compaction and extrusion/spheronisation prior to coating (1, 2) or by phase separation methods (coacervation).

A constant release rate can be obtained during a major part of the total release time (3) provided that the permeability of the barrier film, i.e. the rate-controlling water-insoluble polymeric membrane, remains unchanged.

It is a general experience that large amounts of coating solution may be needed to achieve a low release rate with small cores having a large total surface area. This is in accordance with Fick's law of diffusion. It should be noted, however, that the release process may be a very complex function, not only including diffusion through the film and water-filled pores but also being influenced by osmotic and convective forces (4).

By using larger cores, it should be possible to reduce the amount of coating solution and thus the time and labour involved in the coating process. Small cores may, however, be needed to obtain a multiple unit preparation, good content uniformity when mixed with other particles, and coated cores that can be included in compressed tablets (3).

It is consequently necessary to use a suitable core size and to be aware of the effect of batch-variations in the size of the cores to obtain both good product quality and good manufacturing economy.

It appears that most previous studies on the influence of surface area have been carried out on microcapsules obtained by coacervation processes (5-11). The results have been contradictory. The correlation between the specific surface area and the release rate has often been poor (6) or negative (7-11). Structured water in and around the capsule wall (7), differences in density and porosity between the size fractions (8-10) and aggregation that masks

the true surface area (6, 11) have been suggested as explanations for the unexpected results.

The aim of this work was to investigate how the size of the cores, i.e. the specific surface area, affects the release rate when the cores are coated in a fluid-bed apparatus. A special experimental design was used to obtain distinct fractions of spherical particles coated with a film of the same thickness and quality.

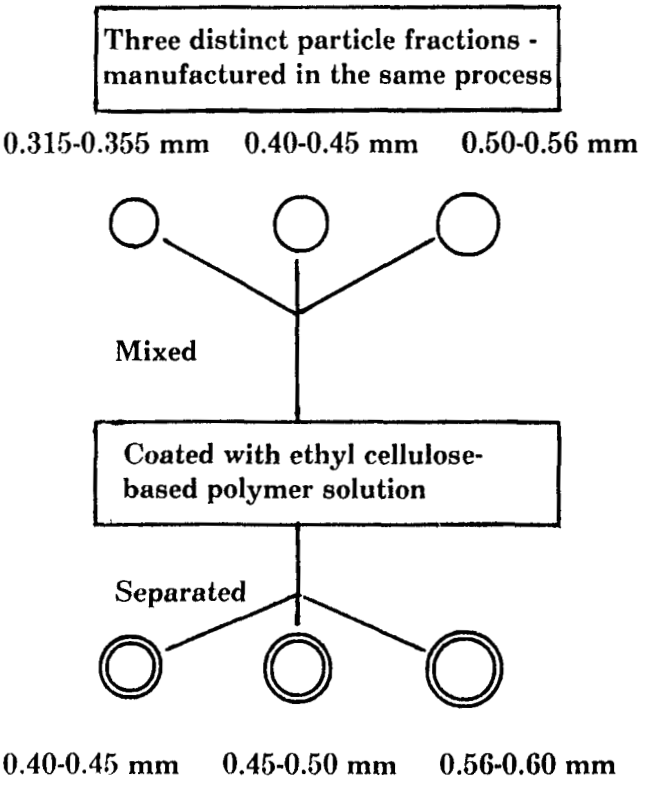
EXPERIMENTAL

Three separate size fractions of technical grade glass beads, 0.150-0.180, 0.224-0.250 and 0.315-0.355 mm, were obtained by sieving in a Retsch laboratory siever. The glass beads were washed with water and ethanol.

The fractions were mixed and an approximately 0.09 mm thick layer of a model substance, metoprolol sorbate, was applied by a crystallisation method. The beads were separated into three fractions, 0.315-0.355, 0.400-0.450 and 0.500-0.560 mm, by sieving.

To study the effect of specific surface area under as reproducible conditions as possible, the experimental design shown in Figure 1 was used. The three core fractions were mixed and coated with an ethyl cellulose-based coating solution by top-spray coating in a fluid bed dryer (small scale equipment (0.5 kg), Hässle Workshop). Sufficient coating solution was applied to give an approximately 0.03 mm thick coating layer.

The core particles have a tumbling, boiling motion in a fluid bed chamber and it was therefore assumed that all cores were randomly hit by the small spray droplets irrespective of the core size, giving an even



Particle diameter	Measured
Surface area	Calculated
Density	Measured
Dissolution rate	Measured
Diss. rate per surface area	Calculated

FIGURE 1

Experimental design.

film thickness. An electron microscope (Jeol JSM-T20) was used to confirm this assumption. Both the surface and the cross-section of the films were studied after gold-coating with an ion sputtering technique.

The coated material was separated into three size fractions, 0.40-0.45, 0.45-0.50 and 0.56-0.60 mm. Representative samples for measurements of particle size, density and release rate were obtained by dividing each fraction into smaller portions with a Retsch spinning riffler.

Samples were photographed under a microscope (Wild, type 376788) together with a reference particle of known diameter (0.50±0.01 mm). The photos were further magnified and the diameters of the particles (approx. 150 of each sample) were measured as the projected diameter in a fixed plane with a calliper.

The density was measured with a Beckman air pycnometer (model 930) on 20 g samples (n=5).

The coated cores were almost perfect spheres and the surface area and volume of the particles could thus be calculated from the individual diameter readings. The specific surface area was calculated using the density and total area and volume of each sample.

The USP dissolution apparatus No. 2 (paddle, 100 rpm) was used to measure the in-vitro release rate at 37 °C in a phosphate buffer solution at pH 6.8 (Hitachi UV-spectrophotometer 100-60, 280 nm). Four samples of each fraction were analysed. The release rate at steady state was calculated from the linear part of the release profile (amount released vs time) by regression analysis. The release rate was expressed as amount released per hour from 1 gram of coated cores and amount released from cores having a surface area of 1 cm^2 respectively.

TABLE 1

Size, density and specific surface area of three particle size fractions of coated cores.

Particle size fraction	I	II	III
Sieve interval, mm	0.40-0.45	0.45-0.50	0.56-0.60
Mean particle diameter ± SEM, mm	0.413±0.002	0.483±0.001	0.577±0.002
Density, $g*cm^{-3}$	1.24	1.32	1.40
Specific area, cm^2*g^{-1}	116.4	93.8	73.9

RESULTS AND DISCUSSION

The experiment gave three size fractions of spherical coated cores with a narrow particle size distribution (Table 1). The spherical form (see e.g. Fig. 2) facilitated accurate calculation of particle surface area and volume.

Judged from electron photomicrographs, the thickness of the coat was the same for all three core sizes. The cross section of the film showed that the membrane appears to be rather porous due to the intermittent layering of droplets. Top-spray techniques have been claimed to be more sensitive to process variations and thus less reproducible than bottom-spray techniques (12) but are widely used due to other advantages such as greater process capacity and simpler design. The experimental design shown in Figure 1 was used to eliminate any reproducibility

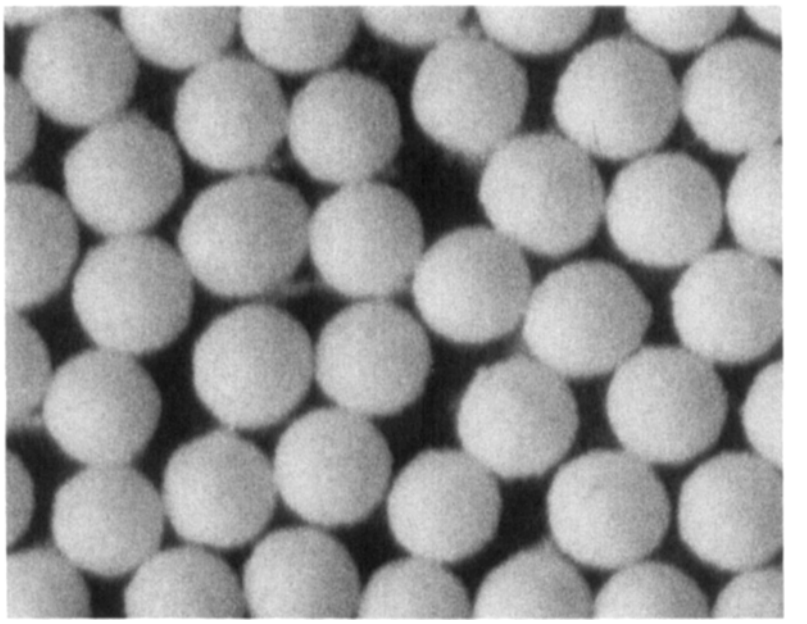


FIGURE 2
Coated spherical cores. Fraction III. Mean particle diameter 0.58 mm.

errors. The film surface of the coarser material appeared, however, to be slightly rougher than the film on the finer fractions. This might indicate that the spraying conditions were less optimal for the coarser cores.

A small drift (1-3%) in the results was observed during the density measurements, probably due to the porosity of the coating layer. The initial values, excluding the drift, were used as they should best represent the outer surface of the coated cores. The diameters of the three fractions ranged from 0.41 to 0.58 mm giving a specific surface area of 116 to 74 cm^2 / g (Table 1).

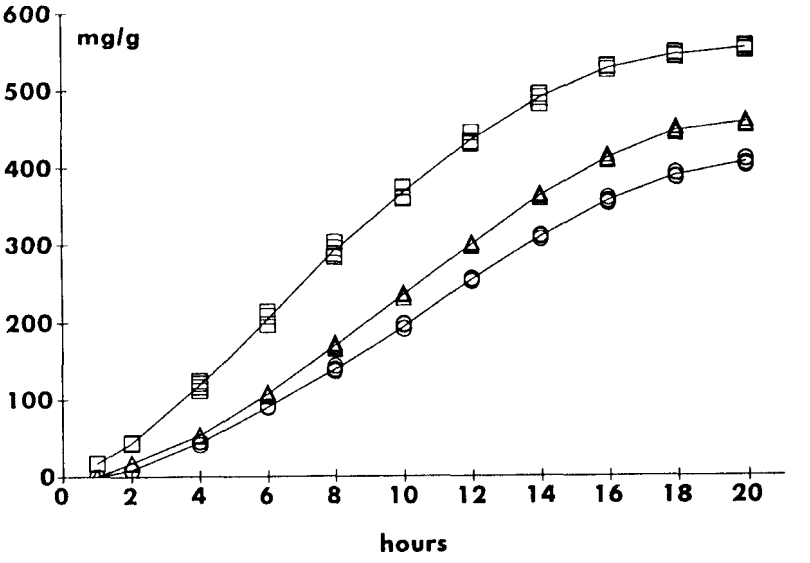


FIGURE 3
In-vitro dissolution of metoprolol sorbate (mg) per g coated cores vs. time from three particle size fractions. □, 0.40 - 0.45 mm; △, 0.45 - 0.50 mm; ○, 0.56 - 0.60 mm. Four analysis per fraction.

The in-vitro release rate was significantly affected by the particle size of the coated particles. The smallest size fraction, with the largest surface area, released metoprolol at the highest rate (Table 2, Fig. 3)

During part of the release time (6-8 hours), the release rate (dm/dt) was constant and was assumed to follow the equation

$$dm/dt = A * K / L$$

where A is the surface area, L the thickness of the coating and K a permeability constant.

TABLE 2

Release rate (± SD) from three particle size fractions, calculated by regression analysis (n=16).

Particle size fraction	I	II	III
Release rate/ gram coated cores, $mg*h^{-1}$	41.6±0.86	32.1±0.30	28.5±0.32
Release rate/ surface area, $mg*h^{-1}*cm^{-2}$	0.357±0.007	0.342±0.003	0.385±0.004

A constant release is possible only as long as the solution within the coated core is saturated. As a consequence of the experimental design, the metoprolol content, and thus the total amount released, will differ between the size fractions. The slope of the linear parts of the release profiles in Figure 3 can, however, be assumed to represent the release rate at steady state according to the equation above.

With the present experimental design, L should be the same for all fractions, as confirmed using the electron microscope. If the permeability constant is not affected by the particle size, which, for example requires that the same film quality is obtained on the different size fractions, the release rate should be proportional to the surface area of the particles. This assumption was supported by the calculated release rates after correction for the particle surface area according to Table 2 and Figure 4.

The results for the different particle sizes (Table 2) are not identical, but it appears reasonable

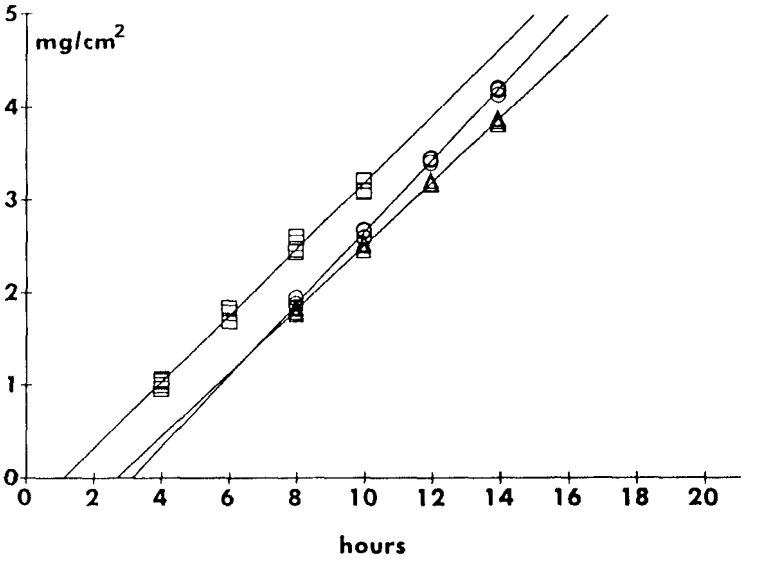


FIGURE 4
In-vitro dissolution of metoprolol sorbate (mg) per unit time and surface area of three particle size fractions of coated cores. □, 0.40 - 0.45 mm; △, 0.45 - 0.50 mm; ○, 0.56 - 0.60 mm.

to conclude that the deviation (less than ± 7% of the mean value) is within the experimental error.

As shown in Figure 1., the surface area calculation is based on the coated cores and not on the uncoated cores. By using a reliable sampling technique, we could thus make sure that the material used in the specific surface area measurements was practically identical with the material in the in-vitro dissolution test. The results will not be affected by any losses during the coating and sieving processes.

The results can be used to predict the effect of a changed diameter of the uncoated cores, since the coating layer is rather thin, 5-8 % of the total diameter of the coated cores.

The area A has previously been defined (e.g. in 8 and 9) as $N*4*\Pi*R_1*R_2$, where N is the number of particles, R_1 is the radius of the cores and R_2 is the radius of the coated cores. With a film thickness of 0.03 mm, R_1 will be R_2 - 0.03 mm. Recalculation of the release rate per surface area in Table 2, using A-values obtained by this method, naturally altered the magnitude of the calculated values. The differences between the size fractions were still very small and in fact slightly reduced. The calculation method will thus not affect the general conclusion that the release rate of the coated cores seems to be directly proportional to the surface area.

CONCLUSIONS

The coating layer seems to be built up in a similar way on "small" and "large" particles within the tested particle size range (0.4-0.6 mm). The proposed method of studying the influence of particle size on the release properties thus seems to be suitable.

The results indicate that the release rate from barrier-coated cores is directly proportional to the surface area of the material.

Some practical consequences are that

- when reducing the particle diameter **d** to half of its original value, the amount of coating solution has to be doubled to obtain the same film thickness (at the same density and content and a thin coating layer compared with **d**) and

- when reducing **d** to half of its original value, four times more coating solution is needed to maintain the release rate per gram of coated cores

(the release rate is in general proportional to the film thickness (13))

These findings have consequences for both product quality and production economy.

ACKNOWLEDGEMENTS

We are grateful to Dr Michael Wirth and Ylva Weimar for carrying out the chemical analysis and to Prof John Sjögren for valuable discussions.

REFERENCES

1. C. Eskilson, Manuf. Chem., 56 (3), 33 (1985) ibid 56 (4), 49 (1985).

2. M.J. Gamlen, ibid, 56 (6), 55 (1985).

3. G. Ragnarsson, A. Sandberg, U.E. Jonsson and J. Sjögren, Drug Dev. Ind. Pharm., 13, 1495 (1987).

4. I. Ghebre-Sellassie, R.H. Gordon, R.U. Nesbitt and M.B. Fawzi, Int. J. Pharm., 37, 211 (1987).

5. P.B. Deasy, M.R. Brophy, B. Ecanow and M.M. Joy, J. Pharm. Pharmacol.,32, 15 (1980).

6. A.M. El-Helw and J.R. Nixon, J. Microencapsulation, 4, 111 (1987).

7. I. Jalšenjak and T. Kondo, J. Pharm. Sci., 70, 456 (1981).

8. R. Senjkovič and I. Jalšenjak, J. Pharm. Pharmacol., 33, 279 (1981).

9. R. Senjkovič and I. Jalšenjak, Pharm. Acta Helv., 57, 16 (1982).

10. V. Vidmar, I. Jalšenjak and T. Kondo, J. Pharm. Pharmacol., 34, 411 (1982).

11. A. El-Raheem El-Helw, Acta Pharm. Technol., 33, 145 (1987).

12. D.M. Jones , Pharm. Technol., 9 (4), 50 (1985).

13. P. Magron, M Rollet, J.L. Taverdet and J.M. Vergnaud, Int. J. Pharm., 38, 91 (1987).