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The influence of pellet shape and surface properties on the drug release from uncoated and coated pellets

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Abstract

Pellets of different shape, varying from spherical to cylindrical, without and with film coating were tested for their drug release properties. For non-disintegrating uncoated pellets, drug release was found to be inversely related to the pellet porosity. A change of 5% in porosity doubled the value of the mean dissolution time (MDT). As coat thickness increased, the MDT value of coated pellets increased. For those pellets, which are nearly spherical, once a thickness of about 20 μm had been achieved, there was little further reduction in retardation. Pellets produced by extrusion/spheronisation appeared to prolong drug release to a larger extent than those where the extrusion step had been omitted. There was a strong inverse relationship between the surface area by volume of the coated pellets and the value of the MDT. The values of the relative dispersion coefficient (RD), which is an indicator of the drug release mechanism, were related to the amount of fluid used to manufacture the pellets and the pellet shape, in a similar fashion for both uncoated and coated pellets. This suggested that the presence of the film coating changed the rate but not the mechanism of drug release.

Keywords: Drug release; Film coating; Mean dissolution time; Pellet porosity; Pellet shape; Pellet surface area; Relative dispersion coefficient

1. Introduction

In a previous publication (Chopra et al., 2001), it was shown that it was possible to produce pellets of different shapes from the same solid composition by varying the quantity and type of fluid and/or the processing procedures. A total of eight batches of pellets were produced. Four were approximately spherical, and the other four deviated in elongation and general pellet shape. The pellets were thoroughly characterised for the shape, surface roughness, surface area and porosity. It was shown that the application of a film coat (3% solution of ethylcellulose in ethanol containing 17.5% of povidone) could alter the shape (Chopra et al., 2002) of these pellets to a certain extent.

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The ability of pellets to release drug is very important, especially if these pellets are to be used as a controlled-release preparation. In this case the pellets are mostly coated with a polymer film as controlling unit. It is often assumed that the chemical composition of the film and the film thickness are solely controlling drug release. Hence, in development, focus is placed onto these two entities. However, even at constant film properties variability of the drug release can occur.

The aim of this work was to identify pellet properties such as shape or surface texture that could influence drug release performance for a given film composition.

2. Materials and methods

2.1. Materials

Pellets of different shapes were prepared as described by Chopra et al. (2001). Briefly, the four spherical batches were produced using the processes of extrusion/spheronisation employing water (SP) or a water/alcohol mixture (AL) as fluid, or by granulation/spheronisation (GR) and direct spheronisation of the wet mass (DS). The other four pellet batches were all produced by extrusion/spheronisation varying the fluid (water) concentration and/or the spheronisation time. As a result, slightly oval (OV) or dumbbell shaped pellets (DU), long dumbbells (LD) and cylindrical particles (CY) were obtained. A range of film coatings of different thickness up to a maximum of approximately 28 μm was chosen. The amount of coating material required per gram of pellets was estimated taking into account the mean diameter and surface area of the pellets and the calculated volume of the coating layer and its density. A 3% solution of ethylcellulose (Lot MM940104–2, Ethocel®, Dow Chemical Company, Midland, MI, USA) in ethanol (Lot 94120151, Finsprit® 95 v/v–%, Kemetyl, Stockholm, Sweden) containing 17.5% of povidone (Lot 707B–01, PVP; Kollidon® K90, BASF, Ludwigshafen, Germany) was used to provide a film coat with pores sufficient to allow controlled release of a model drug (paracetamol, lot 3D109, H.N. Norton & Co., Harlow, UK). The details of the coating procedure have been described previously (Chopra et al., 2002).

2.2. Determination of pellet properties and film thickness

The assessment of pellet shape, surface area, dimensions, bulk, apparent and effective pellet densities and the porosity derived from the values plus surface roughness has been fully described previously (Chopra et al., 2001), as has been the method to study the film thickness by image analysis (Chopra et al., 2002). Experimental measurements involved appropriate sample size for the measurements made, whereby these samples were taken randomly from the pellets available.

2.3. Dissolution studies

Pellet dissolution was studied in 900 ml deionised and de-gassed water at 37 ± 0.5 °C in the USP XXI paddle apparatus at 100 rpm (Type PTWII, Pharmatest Apparatebau, Hainburg, Germany) using 200 mg pellets in each dissolution vessel. Samples were analysed using a continuous flow-through system attached to a UV spectrophotometer (Ultrospec II, LKB 4052 TDS, LKB Biochrom Ltd., Cambridge, UK). The wavelength was set to 257 nm, and the results were processed with a commercial dissolution software program (Victor V 286, Datatronic Data AB, Stockholm, Sweden). Readings of absorbance were taken every 15 min for up to a maximum of 24 h or until 100% drug release had been achieved. All results are the mean and standard deviation (S.D.) of six samples.

Statistical analysis of the dissolution data using the concept of area under the dissolution curve (AUC) and mean dissolution time (MDT) was undertaken as suggested by Podczeck (1993). Additionally, the Relative Dispersion Coefficient (RD), which provides an estimate of the release mechanism(s) involved, was obtained as described by Voegele et al. (1988). These calculations were undertaken using customised software.

2.4. Statistical analysis

Statistical analysis was performed using SPSS 10.0 (SPSS Inc, Woking, UK) employing multiple correlation and regression analysis. Models were only accepted if all variables included were statistically significant with a P-value at least equal or smaller than 0.05.

3. Results and discussion

The dissolution of the uncoated pellets was investigated in order to derive the MDT of the drug (paracetamol), to identify a possible release mechanism, and to identify potential relationships with the pellet properties reported earlier (Chopra et al., 2001). These provide basic information, which can be compared with the influence of the film coating in order to establish whether indeed only the chemical composition and coat thickness or additional factors should be monitored to optimise controlled-release pellet formulations. One problem with the mathematical analysis is that two of the pellet batches produced (DU, LD) disintegrated during the dissolution process, whereas all other pellet batches remained intact, yet also released 100% of the drug. However, excluding these two batches the statistical analysis showed that the MDT of the drug from the pellets produced is related to the porosity of the pellets. As can be seen from Fig. 1, there is a decrease in MDT with increasing porosity for the six non-disintegrating batches. The change in MDT with increasing porosity becomes faster the higher the porosity, resulting in a departure from a linear relationship. The two disintegrating batches have generally high porosity values combined with lower values for MDT. The maximum difference in porosity is about 5%, yet the value of the MDT doubles from lowest to the highest porosity. Water penetration into the pellet matrix becomes easier with an increase in porosity, drug dissolution might become faster, and hence drug release is increased. Also, the nearly spherical batches have the lower values of porosity, in particular

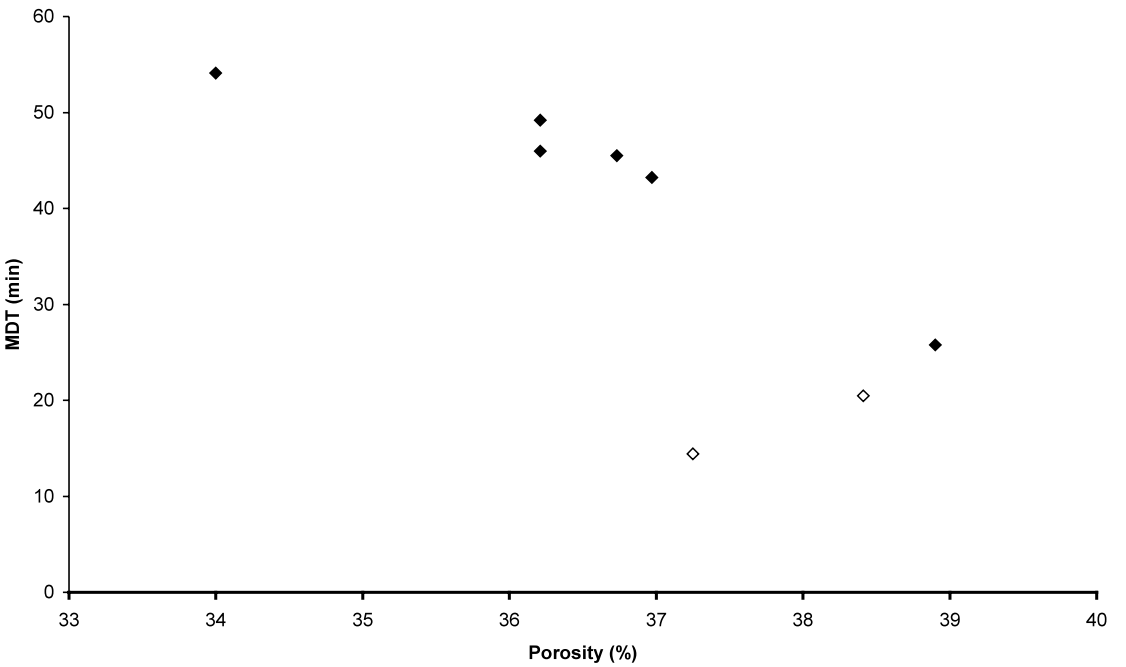

Fig. 1. The influence of pellet porosity on the MDT of drug from uncoated pellets (open symbols: pellets disintegrated during dissolution tests).

batch SP, which was made by extrusion/spheronisation using water as the binder fluid. The more the pellets deviated from sphericity, the higher was their porosity, suggesting that the pellet shape is also important for the drug release.

The influence of film coating thickness on the drug release from nearly spherical pellet batches is shown in Fig. 2a. The MDT increases with an increase in film coating thickness up to about 20 μm, above which the MDT appears to have reached an approximately constant value. Two groups of pellets can be identified by the similarity of the MDT as a function of the film coating thickness, namely (1) batches SP and AL; and (2) batches GR and DS. The former had been produced by extrusion/spheronisation, whereas the latter were manufactured without the extrusion step. The pellets produced by extrusion/spheronisation appear to prolong the drug release to a slightly larger extent that those where the extrusion step had been omitted. Thus, not only the film coating but also the internal structure of the pellet influences the drug release. However, the relationship to pellet porosity, as found for the uncoated pellets, no longer exists.

In Fig. 2b, the relationship between MDT and film coating thickness is illustrated for the non-spherical batches. The drug dissolution from the cylindrical batch (CY) changes very little with an increase in film coating thickness. This might be due to the film being unevenly distributed around the body and the edges of the cylinders. The release was considerably extended for the long dumbbells (LD), when compared with the cylinders, matching that of the nearly spherical pellets. However, the greatest prolongation was achieved for batches OV and DU. In all four cases, however, it appears as though the increase in film coating thickness did not result in a levelling off of the MDT at the highest thickness values, as observed for the spherical pellets, suggesting that a further retardation of the drug release might be achieved by applying thicker coatings. The larger prolongation of the drug release for those pellets, which clearly deviate from sphericity could be explained by the boundary layer model described by Niebergall et al. (1963), which suggests that the dissolution rate is controlled by a hydrodynamic boundary layer surrounding the drug releasing unit. As postulated by Mosharraf and Nyström (1995), elongated, more irregular particles could be surrounded by an on average thicker hydrodynamic boundary layer, through which the dissolved drug has to diffuse, extending the time of drug release. Alternatively, one could assume that the hydrodynamic boundary layer surrounding a spherical pellet is of the same thickness at all points from the pellet surface. This allows the dissolved drug to diffuse equally in all directions from the pellet surface through this layer into the dissolution medium. Considering an elongated particle, however, one could assume that the boundary layer is significantly thinner along the sides and much thicker at the ends of the pellets. Hence, dissolved drug will encounter a different diffusion layer thickness in different directions, and the total area for more rapid diffusion is restricted to the sides of the pellets. Hence, the overall effect is a more pronounced prolongation of drug release.

Statistical analysis of the values of the MDT as a function of the uncoated and coated pellet properties identified a strong relationship between the surface area by volume of the coated pellets and the MDT (see Fig. 3). The value of the MDT decreases as the value of the pellet surface area increases. However, this is not a simple relationship, as the ratio of MDT to surface area did not result in a constant value for all pellets. The approximately spherical coated pellet batches GR and DS have nearly the same surface area and also a similar value for MDT. On the other hand, the coated pellet batches LD and OV have also a similar value for the surface area, but in this case the values for MDT are significantly different. This implies some influence of pellet shape on the drug release, and similar arguments to the influence of the hydrodynamic boundary layer provide a potential explanation. The coated batch CY has the lowest value of surface area and the lowest value of MDT, again indicating gross variability in film coating thickness along the cylinder length and the ends.

The calculation of the RD coefficients as proposed by Voegele et al. (1988) to identify a common release mechanism resulted in values between

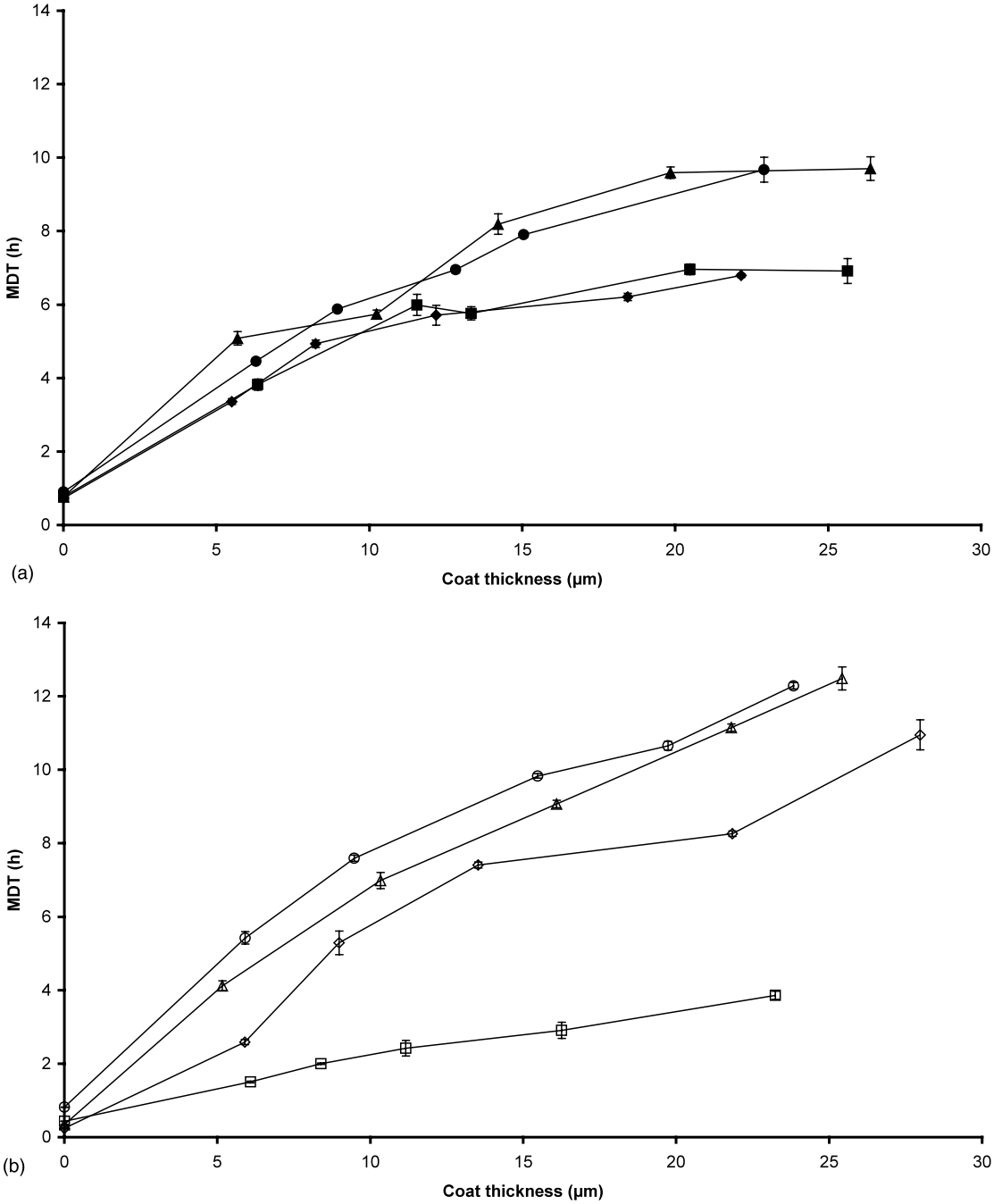

Fig. 2. MDT as a function of film coating thickness for (a) nearly round pellets, and (b) elongated pellets. ● = SP; ▲ = AL; ◆ = GR; ■ = DS; ○ = OV; △ = DU; ◇ = LD; □ = CY.

0.12 and 0.22 in all cases. These values cannot be related to one of the common release mechanisms (0.3 for zero-order, 0.6 for cube root, 0.8 for pseudo-first order, 1.0 for first order release). It is consistent with findings by Flaig (1974), who considered that in most cases several mechanisms will overlap, for example, drug dissolution, water penetration and diffusion of the dissolved drug towards the dissolution medium. Also, the above models are usually fitted to the dissolution curves using the release-time profiles between 20–25 and 60–80% of drug release only, which is not a true evaluation of the total release process. In contrast, the determination of the RD values is based on the whole drug release-time profiles. Also, the drug release was here determined from an assembly of several hundred pellets to give 200 mg in each experiment. The individual pellets probably will not release their drug in an identical fashion hence the release profiles will provide average release behaviour with an average release mechanism. The systematic change in RD values with level of fluid used to produce the pellets and the pellet shape is illustrated in Fig. 4a and b for the uncoated and coated pellets, respectively. The relationships shown in these graphs are based on the following multiple regression equations for uncoated (1.1) and coated pellets (1.2):

$$\mathrm{RD} = 0.073 \pm 0.022 + 0.084 \pm 0.022 \cdot F + 0.045 \pm 0.014 \cdot e_{\mathrm{R3}} \quad (1.1)$$

$$\mathrm{RD} = 0.072 \pm 0.018 + 0.080 \pm 0.019 \cdot F + 0.067 \pm 0.017 \cdot e_{\mathrm{R3}} \quad (1.2)$$

where F, fluid concentration; and e_{R3}, three-dimensional shape factor as defined by Podczeck

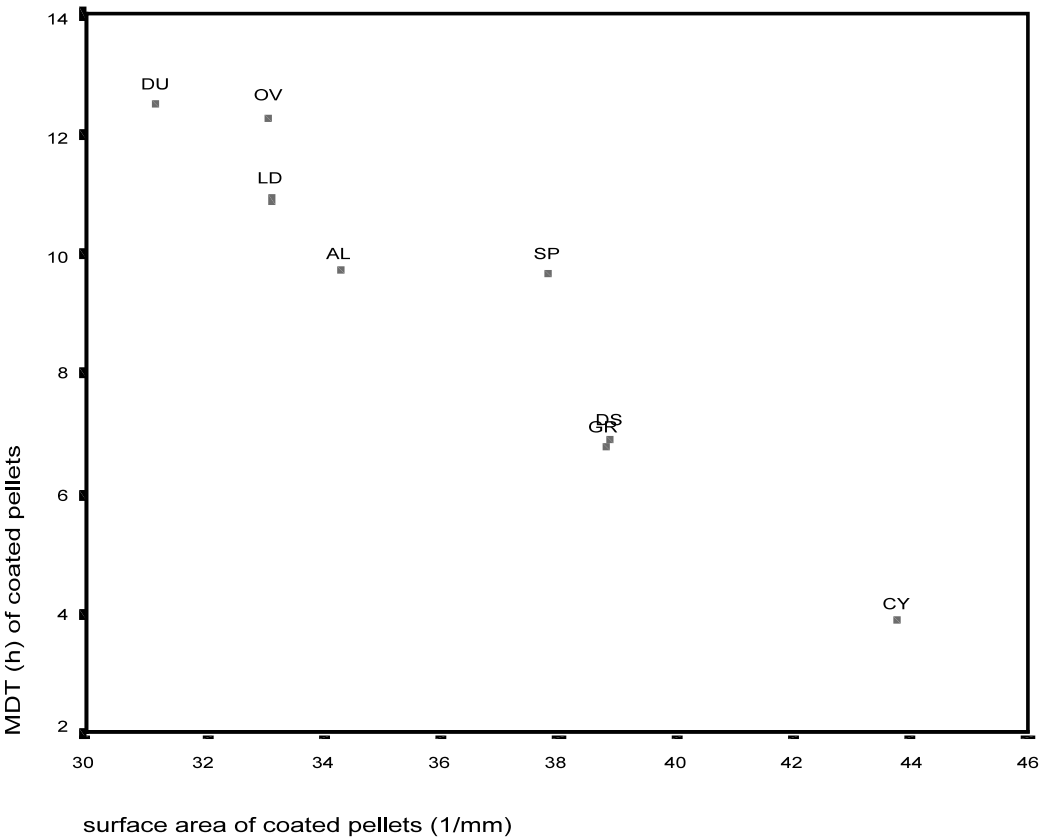

Fig. 3. MDT as a function of surface area by volume of coated pellets.

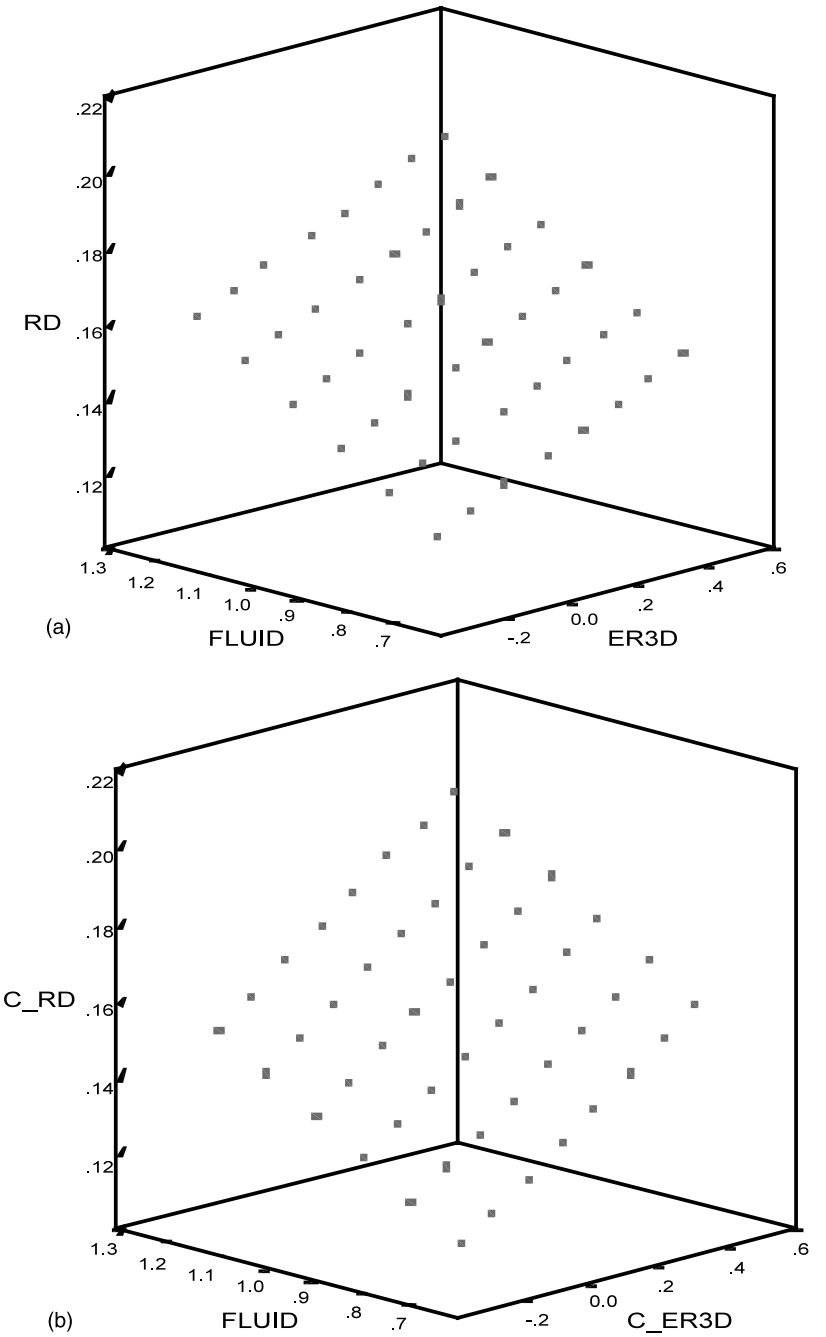

Fig. 4. Relationship between RD coefficient and the quantity of fluid used in the preparation of the pellets and the three-dimensional shape factor e_{R3} for uncoated (a) and coated (b) pellet batches. C_ER3D/ER3D = three-dimensional shape factor for coated/uncoated pellets; C_RD/RD = relative dispersion coefficient for coated/uncoated pellets; FLUID = amount of fluid used to prepare the pellets (provided as fluid to solid ratio).

and Newton (1995). Both equations show a high level of relationship ($R^2 > 0.9$) between the variables included in the equation, and a satisfactory fit of the experimental data Root Mean Square deviation (RSMD < 0.2%). The graphs (Fig. 4a and b) and the equations are almost identical indicating that, although only one set of the pellets is coated, the release mechanisms are similar and respond in the same manner to the variables involved. This suggests that the presence of the film coating is not the sole controlling factor of drug release, but the pellet cores are of equal importance for the release mechanism of the drug. Hence, while the release mechanism is probably a function of the pellet core, the release rate is mainly a function of the film coating applied.

4. Conclusions

For non-disintegrating uncoated pellets, drug release appears to be inversely related to the pellet porosity. Here, a change of 5% in porosity doubled the value of the MDT. As coat thickness increases, the MDT value of coated pellets increases. For those pellets, which are nearly spherical, once a thickness of about 20 μm has been achieved, there appears to be little further reduction in retardation. Pellets produced by extrusion/spheronisation prolong drug release to a larger extent than those where the extrusion step has been omitted. There is a strong inverse relationship between the surface area by volume of the coated pellets and the value of the MDT. The values of the RD, which is an indicator of the drug release mechanism, can be related to the amount of fluid used to manufacture the pellets and the pellet shape, in a similar fashion for both uncoated and coated pellets. This suggested that the presence of the film coating changed the rate but not the mechanism of drug release. The results demonstrate that it is important to consider the properties of the pellets and their manufacturing process equally to the film coating parameters, if reproducible product release characteristics are to be achieved.

Acknowledgements

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