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Investigation on the co-extrudability and spheronization properties of wet masses

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Abstract

In the present work, preliminary results of co-extrusion and spheronization of wet masses are reported. A ram co-extruder, manufactured in-house, was designed with two concentric single dies mounted on two concentric and independent chambers. This equipment has allowed the production of three types of extrudates (rod or solid extrudates, tubular or hollow extrudates and co-extrudates). Different wet mixtures of microcrystalline cellulose, lactose, a non-soluble in water dye and water were produced and used to feed the chambers of the ram co-extruder. Extrusions of the wet masses were carried out at different speeds of the ram (25–400 mm/min). The extrudates were evaluated according to surface characteristics (by visual inspection), force of extrusion and duration of steady-state (after recording the force applied to the ram and its displacement). Simultaneously, for each process of extrusion it was possible to assess the angles of convergence to the bottom of the chambers for both the external and internal chambers. These angles reflected the high complexity of the extrusion occurring on the external chamber in consequence of its annular geometry, in which the bisecting-line was not parallel to the axis of the extruder, by opposition to the converging angle in the internal chamber, where the bisecting-line was perfectly aligned to the axis of the extruder. Variations in the amount of water in the formulations and the speed of extrusion affected both the production and the quality of the extrudates and their ability to provide pellets. The rod extrudates were the easiest to produce and the relationships between the formulations, the processing conditions and the properties of the extrudates were immediately apparent. On the other hand, co-extrudates were more complex to characterise, although identical relationships between formulations, processing conditions and the properties of the co-extrudates were observed as for the rod extrudates. Different batches of extrudates (rod, tubular and co-extrudates) were spheronized to a maximum spheronization time of 10 min at 1000 rpm. The pellets were characterized with respect to size, size distribution, sphericity and density. Results have shown that for a larger diameter of the co-extrudates, the pellets produced were bigger (≈ 3.38 mm) than the pellets produced from rod extrudates (1.22 mm). For longer times of spheronization, the aspect ratio and the density increased for both pellets produced from rod (0.95 and 1.46 g/cm^3) and co-extrudates (0.90 and 1.47 g/cm^3). The study has shown the potential of this new technology in providing a product with advantages over the traditional spheres produced by extrusion and spheronization.

Keywords: Co-extrusion; Extrusion; Pellets; Spheronization

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1. Introduction

The agglomeration of powder particles is an intermediate process often required in different industries, namely the electronics, ceramics, polymer and food industries (Curran, 1995). To that end, extrusion is a technology widely spread and the extrudates thus obtained can be used as such or processed further, for instance, to produce spheroids. The pharmaceutical industry has adopted the extrusion and spheronization of wet masses for the production of pellets (which can, in turn, be encapsulated or tabletted as produced or after coating to modify the release of the active ingredient) after the pioneering works of Reynolds (1970) and Conine and Hadley (1970). Since then, a large amount of work has been carried out to provide a better understanding of this technology. The influence of the materials on the process and final product (Bataille et al., 1991; Mesiha and Valles, 1993; Junnila et al., 1998, 2000), of the equipment (Vervaet and Remon, 1996; Schmidt and Kleinebudde, 1998) and of the processing conditions (Newton et al., 1995) have been investigated and found to affect the quality of the pellets.

From early reports (Reynolds, 1970) it was realised that pellets produced by extrusion and spheronization presented advantages, such as, higher sphericity, better flowability, more accurate size and narrow size distribution, higher mechanical strength with higher fracture strength and lower friability, over those obtained by other processes. However, since the process encompasses several stages (mixing of the powders, wetting of the mixture, extrusion, spheronization, drying, coating when necessary), thereby increasing the cost of the products, this technology is not as widespread as anticipated. Investigations on easier alternative ways of producing pellets by extrusion and spheronization are, therefore, warranted.

In the present work, an improvement to the stage of extrusion is suggested through a co-extrusion process with several advantages over the single rod extrusion. By definition, co-extrusion consists of the simultaneous extrusion of two or more materials creating a multi-layered extrudate, the shape of which depends on the shape of the dies used. Probably, the easiest co-extrudate to produce is that consisting of two or more layers forming a lamella. However, this type of co-extrudate would be difficult to spheronize into pellets. As an alternative, the production of concentric cylindrical co-extrudates will easily provide spherical pellets. Co-extruded pellets present several advantages over the conventional ones: (a) simultaneous administration of non-compatible drugs, each presented in a different layer; (b) the external layer may function as a coat to the inner layer, either protecting the active ingredient or tailoring its release; and (c) modulation of the release of the drug either by loading the different layers with different amounts of drug or by incorporating the drug in different matrices (e.g. a prolonged release core and an external layer of rapid drug release).

The aim of this work was to access the co-extrudability and spheronization of wet masses and to provide a preliminary explanation of the variables that affect the processes.

2. Materials and methods

2.1. Materials

Lactose monohydrate EP (Granulac 230, Meggle-Wasseburg, Germany; $>90\%$ of the particles <63 μm, as mentioned by the supplier), microcrystalline cellulose (Avicel PH 101, FMC Corp., Ireland; median particle size 50 μm, by laser diffractometry) and de-mineralised water were used in the different formulations. Sudan III, a red dye (Merck, Germany, median particle size 19 μm, by laser diffractometry) and Carbon black (supplied by Capsifar, Portugal, median particle size 23 μm, by laser diffractometry), both non-soluble in water, were incorporated in the formulations as required.

2.2. Methods

Sizing of the particles of the powders was carried out by laser diffractometry (Coulter LS130, Coulter, USA). The powders considered in the different mixtures (Table 1) were dry-mixed in a planetary mixer (Kenwood Chef, UK) for 15 min.

Table 1
Formulations considered for the production of the extrudates

Mixture	Microcrystalline cellulose	Lactose	Water	Dye[a]
1	31	31	38	
2	35	30	35	
3	39	28	33	
4	30	30	40	
5	31	25	38	6

[a] Sudan III or Carbon black.
Amounts expressed in percentage (w/w).

Wetting of each mixture was carried out by slow addition of de-mineralised water for an extra 10 min. The wet mass was placed in a sealed polyethylene bag and left to rest at room temperature for 12 h prior to extrusion.

The extrusion was carried out with a ram co-extruder fitted to a mechanical press (Lloyd Instruments LR 50K, UK) with a 50 kN load cell that allowed the collection of data for the representation of the extrusion profiles. The co-extruder, built in-house (Fig. 1), was designed with two concentric chambers, one internal (1) and the other external (2). The cross-sections of the internal and external chambers are 122 and 1047 mm^2, respectively. At the bottom of the chambers, two concentric dies are fitted to the chambers. The external die (3) was designed with an external diameter of 5.0 mm and an internal hollow of 4.0 mm (cross-section is 6.7 mm^2), whereas the internal die has a diameter of 1 mm (cross-section is 0.80 mm^2). With such a design, the ratio between the areas of both chambers and dies was kept constant at ≈ 8.5 and therefore, the velocity of the streams was maintained for the materials. The length (L) to diameter (D) ratio was 1 and 20, respectively for the external and the internal dies. The chambers were fed manually and the two coupled rams, one for each chamber, pushed the wet masses towards the bottom of the chambers at the same forcing speed. The internal die (4) was fed directly from the chamber, whereas the external die was fed with the mass passing through a converging chamber (5) that was, itself, filled with the mass of the external chamber, after crossing several holes (6). Consequently, the material moved towards the external die (3), where extrusion occurred simultaneously with the material present in the internal die (4). In the end, both the internal and the external extrudates merged to produce a co-extrudate (7) due to a narrowing of the tip of the external die, to 2 mm. With such equipment, it was possible to produce rod (single) extrudates (the internal chamber and die were used), tubular (hollow) extrudates (external chamber and die) and co-extrudates (both chambers and dies). Throughout the study, combinations of

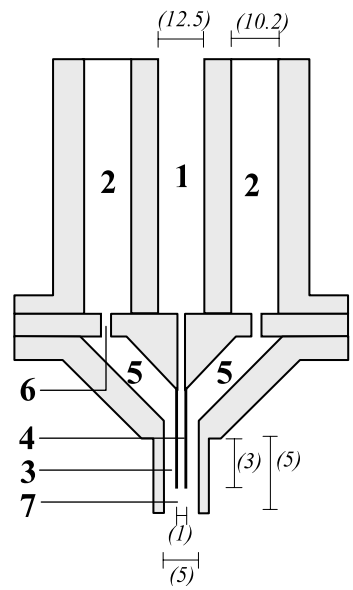

Fig. 1. Schematic representation of a ram co-extruder (side view). (1) Internal chamber with internal ram; (2) external chamber with external ram; (3) external die; (4) internal die; (5) external die feeding area; (6) connecting orifices to the external feeding die area; and (7) co-extrudate exit. Dimensions (mm) are shown in brackets.

white and coloured (with Sudan III or Carbon black) wet masses (mixtures 1 and 5, Table 1) placed in either the internal or the external chambers were co-extruded at different speeds of the ram (varying from 25 to 400 mm/min).

Convergent flow patterns of simple and tubular extrudates were assessed after filling either the internal or the external chambers with alternate layers of mixture 1 (17 g) and mixture 5 (5 g with Carbon black) (adapted from Harrison et al., 1984). The ram was displaced at both 25 and 100 mm/min and for each speed, plugs were collected at different times of extrusion. For tubular extrudates (25 mm/min) five extrusions were run, each one stopping at different displacements of the ram. For the single and tubular extrudates (100 mm/min) only two runs were considered. The plugs were cut and the convergence angles measured. In a different set of experiments, both internal and external chambers were used to produce co-extrudates.

The extrudates (single, tubular and co-extrudates) were spheronized in a radial plate spheronizer (GB Caleva, model 230, UK) at 1000 rpm, for different periods of time. Drying of either extrudates or spheroids was carried out in an oven (Memmert, Germany) overnight, at 105 °C. The extrudates were characterised by analysis of the force versus displacement curves, visual inspection and scanning electron microscopy (Philips Analytical, UK). Pellets, on the other hand, were characterised for size and size distribution (sieving for 5 min, Retsch, Germany), sphericity (aspect ratio, with two perpendicular dimensions measured in pellets chosen at random with a calliper or a microscope Olympus, as adequate), density (helium pycnometry, Accupyc 1330, Micromeritics, USA) and surface defects (scanning electron microscopy and visual inspection).

3. Results and discussion

The design of the apparatus allowed not only the production of single extrudates (Fig. 2a), but it was also possible to produce tubular (hollow) extrudates (Fig. 2b) or co-extrudates (Fig. 2c), depending on which of the chambers was filled.

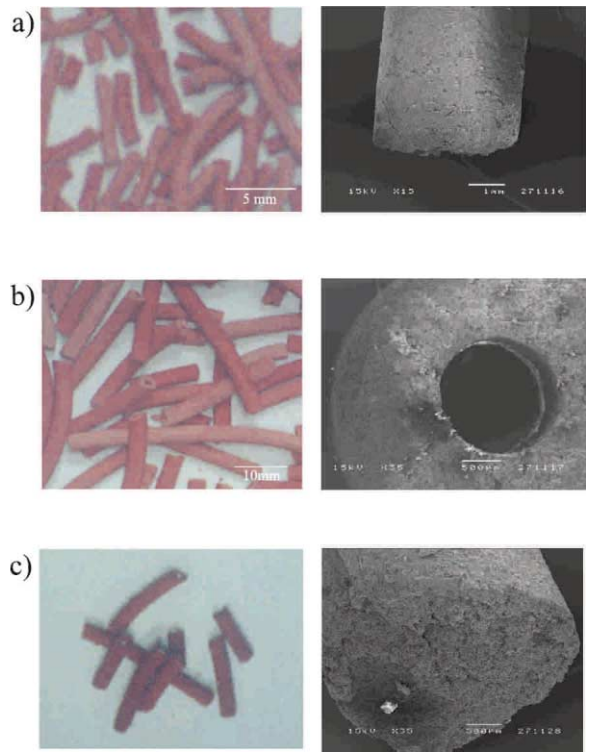

Fig. 2. Photographs of extrudates (left: photographs; right: scanning electron micrographs) (a) rod extrudate; (b) tubular extrudate; and (c) co-extrudate.

3.1. Simple extrusion

Extrusion of mixture 1 through the internal die was possible, providing extrudates with smooth surfaces for speeds of extrusion ranging from 25 up to 400 mm/min. Speeds of the ram higher than 400 mm/min and lower than 25 mm/min were not considered. Fig. 2(a) shows the photographs (left) and the scanning electron micrographs (right) of homogeneous extrudates with smooth surfaces produced at 75 mm/min from mixtures 1 and 5 (including Sudan III). The extrusion forces at steady state to produce these extrudates were 1.3 and 1.5 kN, respectively. The force versus displacement curve (not shown) was characterised by a long steady state followed by a sudden increase on the extrusion force at the end of the extrusion. These extrudates were subsequently spheronized and some properties of the pellets produced are

Table 2
Properties of granules produced from extrudates and co-extrudates

Time of spheronization (s)	Percentage of pellets in each size (mm) range								Aspect ratio ($n = 20$)	Density (g/cm^3) ($n = 3$)
	0.50–0.71	0.71–1.00	1.00–1.40	1.40–2.00	2.00–2.80	2.80–4.00	Median	IQR		
Pellets from simple extrudates										
30	0	12	80	8	0	0	1.231	0.261	0.85 ± 0.06	1.45 ± 0.002
300	0	8	89	3	0	0	1.185	0.230	0.87 ± 0.05	1.44 ± 0.001
600	0	4	95	1	0	0	1.215	0.215	0.95 ± 0.02	1.46 ± 0.001
Pellets from co-extrudates										
30	0	0	0	3	17	80	3.338	0.400	0.72 ± 0.08	1.40 ± 0.001
300	0	0	0	7	11	82	3.385	0.501	0.89 ± 0.09	1.48 ± 0.001
600	0	0	0	4	9	87	3.400	0.461	0.90 ± 0.04	1.47 ± 0.002

IQR, interquartile range.

shown in Table 2 (upper part). As seen, the majority of the pellets collected throughout the spheronization process were in the range of 1.00–1.40 mm diameter. The results have shown a decrease in the size distribution with time of spheronization and a simultaneous increase in sphericity, as ascertained by higher values for the aspect ratio. Attempts to prepare pellets, with identical quality to those mentioned above, from extrudates produced with the other formulations described in Table 1 failed. This may be due to the fact that the extrudates produced were of poorer quality themselves. The extrusion of these has shown a small steady-state stage followed by a long forced flow stage, where the force of extrusion increased constantly. The surface of the extrudates was not as smooth as those produced from mixture 1. A possible explanation for these observations may be the fact that the proportion between the microcrystalline cellulose and water is critical to plasticise the wet mass. When the water content in the mixture decreased (mixtures 2 and 3, Table 1) the extrusion of the masses became more difficult. On the other hand, when the amount of water increased (mixture 4, Table 1), the extrudates produced were overwet and large agglomerates were produced in the spheronizer.

3.2. Tubular extrusion

The use of the external die and chamber of the extruder has allowed the production of tubular (hollow) extrudates, as described by Al-Ghazawi (1994). Due to the novel design of the extruder and its potential application in the pharmaceutical field, it was deemed useful to attempt a characterisation of the flow within the converging chamber to the external die. In order to achieve that, the different formulations in Table 1 were considered, particularly mixtures 1 and 5 (Sudan III or Carbon black). It was, therefore, possible to define the angle of convergence to the holes between the chamber and the converging zone to the die (mixture 5 with Carbon black) and the influence of different speeds of extrusion over the quality of the extrudates (mixture 1). The other formulations were tested at a fixed extrusion speed (200 mm/min).

Table 3 shows the results of the visual inspection carried out on tubular extrudates produced from different mixtures and extrusion rates. The standard mixture 1, extruded at different speeds in different experimental runs, provided extrudates, the quality of which decreased as the extrusion rate increased. This observation may suggest that the forces generated within the extrudate during extrusion cannot be accommodated after a fast extrusion and, consequently, the quality of the extrudate is poor. Simultaneously, the extrusion forces increased continuously from 2.1 up to 5.2 kN when the extrusion rate increased from 25 to 400 mm/min (mixture 1, Table 3). One way to overcome such limitation is by increasing the amount of water in the formulation (mixture 4 versus mixture 1, Table 3) or increasing the amount of hydrophobic materials in the formulation proportionally to the water content (mixture 5 versus mixture 1, Table 3). In fact, at the same extrusion rates, formulations with higher water content performed better than the others. The improvement on the quality of the extrudates is probably due to the plasticising effect that water exerts on the formulation and its lubricant effect in the process of extrusion. The extrusion of mixtures 1 and 5 (with Sudan III) produced extrudates of high quality, as shown in the photograph and micrograph of Fig. 2(b).

Table 3
Quality of tubular extrudates produced as a function of the speed of extrusion and formulation

Mixture[a]	Speed of extrusion (mm/min)					
	25	50	75	100	200	400
1	3	3	3	2	2	1
2	–	–	–	–	2	–
3	–	–	–	–	2	–
4	–	–	–	–	3	–
5[b]	–	–	–	–	3	–

[a] Mixture 1 was extruded in separate runs at increasing speeds and, at a constant rate of extrusion (200 mm/min), all formulations were evaluated.

[b] Formulation including Sudan III.

1, poor (shark skin); 2, fair (roughness); 3, good; –, not determined.

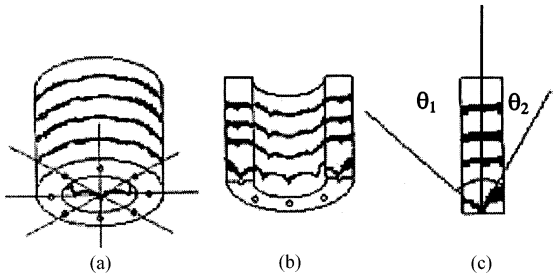

Fig. 3. Schematic representation showing the procedure followed for the calculation of the angle of convergence to the connecting die orifice to the external feeding die area (a) tubular extrudate; (b) cross-section of the tubular extrudate; and (c) determination of the total angle of convergence (θ_t) and partial angles (θ_1 and θ_2).

The converging angles (θ_t) of the wet mass to the hole at the bottom of the external chamber (6, Fig. 1) were assessed when partial extrusions of alternating layers of mixture 1 and mixture 5 (with Carbon black; Table 1) were carried out. As a control, the converging angle to the die (θ_t) was also calculated for the extrusion at the internal die and chamber (single extrudate). The plugs, collected from the chambers at different displacements of the ram, were cut and the converging angle (θ_t), as the sum of θ_1 and θ_2, was measured, as shown in Fig. 3(a–c). The results of the measurements are summarised in Table 4 and the approximate displacements considered were superimposed on extrusion profiles observed for the complete extrusions (Fig. 4a,b). As a consequence of the design of the extruder, it was impossible to measure the angle of convergence near the die. However, assuming that the angle of convergence is a property of the material (Harrison et al., 1984), there must be a relationship between the angle of convergence measured at the bottom of the chamber and the one measured at the entrance of the die. Bearing in mind these limitations, the

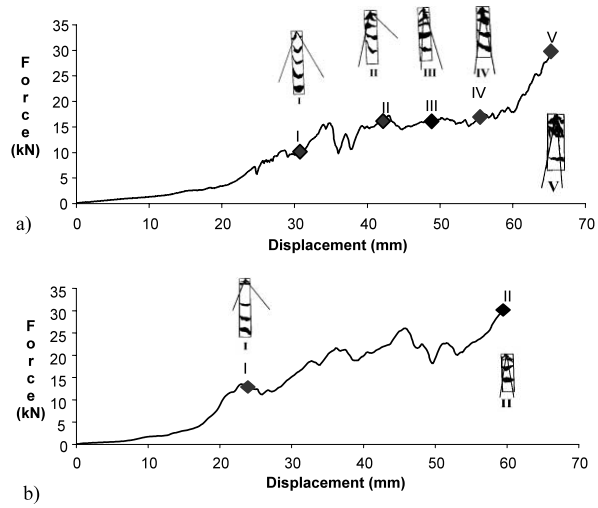

Fig. 4. Evolution of the angle of convergence throughout tubular extrusion. Tubular extrusion from layers of mixtures 1 and 5 at (a) 25 mm/min and (b) 100 mm/min.

Table 4
Total and partial angles of convergence for different extrudates, measured when alternate layers of mixtures 1 and 5 were extruded

Type of extrudate	Stage of displacement[a]	Extrusion rate (mm/min)	Total angle of convergence $\theta_t = \theta_1 + \theta_2$ (°)	Partial angle θ_1 (°)	Partial angle θ_2 (°)
Simple	[b]	100	61	30.5	30.5
Tubular	I	25	53	32	21
	II	25	58	44	14
	III	25	20	16	4
	IV	25	18	9	9
	V	25	16	4	12
Tubular	I	100	52	32	20
	II	100	15	6	9

[a] Stage of displacement (for more details see Fig. 4a,b).
[b] Measurement taken at steady-state.
θ_1, partial angle of convergence measured from the bisecting-line to the inside of the chamber. θ_2, partial angle of convergence measured from the bisecting-line to the outside of the chamber. (4) Measurement taken at steady-state.

results in Table 4 are, nevertheless, worth discussing. As expected, the angle of convergence measured for the simple extrusion was large (mixture 1 produced a long steady-state in the extrusion profile) and the bisecting-line divided the angle in two identical halves ($\theta_1 = \theta_2 \approx 30.5°$). On the contrary, the measurements carried out on the plugs of the tubular extrudates have shown a different pattern. As the extrusion proceeded, the angle of convergence decreased from values around 53° (stage I, Fig. 4a) down to 16° (stage V, Fig. 4a). For initial stages of extrusion, the angle of convergence (θ_t) was high (more than 50°) decreasing with the process of extrusion to values below 20°. Once the extrusion rate was increased from 25 to 100 mm/min (Fig. 4b) the extrusion profile was modified, since the extrusion force increased abruptly at earlier stages, reflecting changes in the flow pattern or forced flow. The narrowing of the angle of convergence may be related to changes within the mass, namely to partial drying that may have occurred at the final stages of the extrusion process. For the same wet mass, the total angle of convergence (θ_t) at the beginning of the extrusion (stage I, Table 4) was identical for both extrusions, carried out at 25 and 100 mm/min. The most important feature, however, is the fact that the bisecting-line, parallel to the axis of the extruder, split the angle of convergence (θ_t) into two angles of different magnitude (θ_1 and θ_2, Table 4). Throughout steady-state, the larger angle was directed to the inner side of the extruder, suggesting that the movement of the mass was occurring preferentially at the inner side. On the other hand, at later stages of the extrusion process, the pattern was reversed and the smaller angle was the one facing the inner wall of the chamber, indicating that the flow pattern had changed from the steady-state to the forced flow stage, as anticipated. It is also worth mentioning that changes in the extrusion rate did not affect the angle of convergence (Table 4; Fig. 4), results consistent with the work of Harrison et al. (1984).

Attempts to produce spheroids from hollow extrudates yielded pellets of poor quality. Once the tubular extrudates were broken into small segments, as spheronization progressed, the tips of the extrudates became rounded and the central orifice was almost closed, as ascertained by visual inspection. Spheroids were then cut at the equatorial plane and it was apparent that the internal walls of the extrudate had collapsed, almost closing the space left between the walls. The dimensions of the hollow centre of the spheroids were, therefore, more inferior to those of the hollow space of the tubular extrudate, the centre was not spherical and the tips (equivalent to the tips of the extrudates) remained open after spheronization. The surface of such spheroids was smooth and the sphericity of the forming spheroids also increased with time (data not shown).

3.3. Co-extrusion

Co-extrudates were produced by filling both chambers either with mixture 1 or mixture 5 (Sudan III) and vice-versa. Consequently, co-extrudates with a white or coloured external layer were produced and, in either case, some common features were observed. Fig. 5 reflects a standard profile of extrusion for the different mixtures submitted to extrusion at 200 mm/min. After a short compression stage, a first steady-state phase related to the extrusion of the material in the internal chamber was observed (stage 'A' to 'B', Fig. 5). The second steady-state corresponds to the simultaneous extrusion of the materials from both chambers (stage 'C' to 'D', Fig. 5) and the extrusion force is the addition of both forces, at steady-state, for the internal and external extrusion of masses. The force observed at the first steady-state was 2.5 kN, whereas for the second steady-

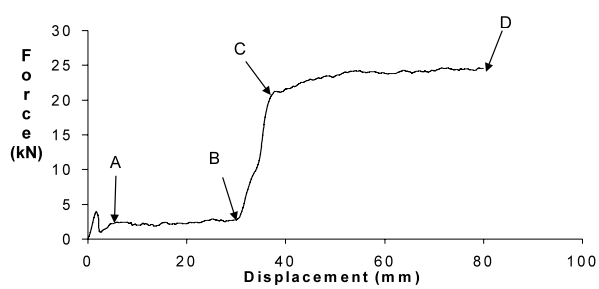

Fig. 5. Force versus displacement curve for a co-extrudate. (A–B) Single extrusion; (C–D) co-extrusion.

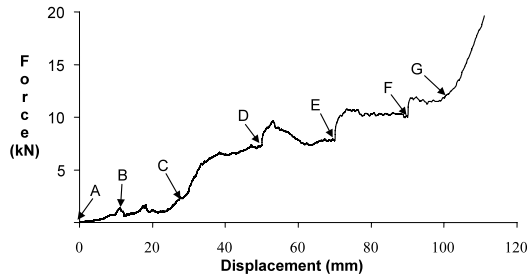

Fig. 6. Multi-stage extrusion profile of a co-extrudate. (A–B) Compression phase; (B–C) 5 mm/min; (C–D) 10 mm/min; (D–E) 20 mm/min; (E–F) 50 mm/min; (F–G) 100 mm/min; (G) end of extrusion.

state the force was 25 kN, a 10-fold increase. A possible explanation for such high force required for the extrusion in the external die lies in the fact that the internal extrudate shear between the material and the extruder wall occurred only in the external surface, whereas the external extrudate shear occurred at both internal and external wall surfaces of the extruder. Another plausible explanation is the fact that the filling of the external die, due to the design of the co-extruder, is a difficult process since the path that wet mass has to use until it reaches the vicinity of the die is more tortuous, as described previously. As expected, an increase in the speed of extrusion was reflected by an increase on the force of extrusion. Fig. 6 shows the profile of a multistage extrusion where, by increasing the speed of extrusion from 0 to 100 mm/min, the applied force also increased (from 0 to 11.6 kN), before it reached a forced flow. Simultaneously, the quality of the extrudate decreased, i.e. as speed increased, rough surface and shark skin appeared on the surface of the co-extrudates (Table 5). From Table 5, it is apparent that, at the same rate of extrusion, a decrease in the water content in the formulations had contributed to produce extrudates of worse quality.

Both the internal and the external layer of the co-extrudate seemed to adhere easily (Fig. 2a), suggesting that independently of the formulations used, the interface between the two layers had vanished making it impossible to differentiate between them even by electron microscopy (Fig. 2a). The observation suggests that the molecules of a drug, if present, would find a continuous release path.

Spheronization of co-extrudates was possible: the co-extrudates were cut in the spheronizer's plate and the process of spheronization followed an identical mechanism as for the rod extrudates. Some properties of the pellets produced are shown in Table 2 (lower part). Generally, the pellets obtained were larger than 3 mm diameter (2.80–4.00 mm, Table 2). The density of the pellets produced by co-extrusion was identical to the density of pellets produced by single extrusion (1.47 and 1.46 g/cm^3, respectively). Moreover, their sphericity was comparable to that obtained for pellets from simple extrudates and, after 600 s of spheronization, a large portion of pellets developed high sphericity (as suggested by the high value for the aspect ratio, 0.90, Table 2). The increase in sphericity with spheronization time is also demonstrated in Fig. 7 (photographs a–c of samples of pellets collected at 30, 300 and 600 s of spheronization). Also shown in Fig. 7(d) is a scanning electron micrograph from pellets spheronized for 600 s showing the smooth surface of a highly spherical pellet (inset). Equatorial cuts of the pellets have shown, by visual inspection, that the core was round and centred in the spheroid and that the external layer coated almost completely the core of the extrudate.

In conclusion, this work has shown the flexibility of the apparatus described in producing good quality extrudates—rods, hollow cylinders or co-extrudates. Although the dimensions of the extrudates were different, some properties and features were common allowing the comparison of the

Table 5
Quality of co-extrudates produced as a function of the speed of extrusion and formulation

Mixture[a]	Speed of extrusion (mm/min)			
	75	100	200	400
1	3	3	2	1
2	–	2	–	–

[a] Each mixture was used to fill both chambers at each run. 1, poor (shark skin); 2, fair (roughness); 3, good; –, not determined.

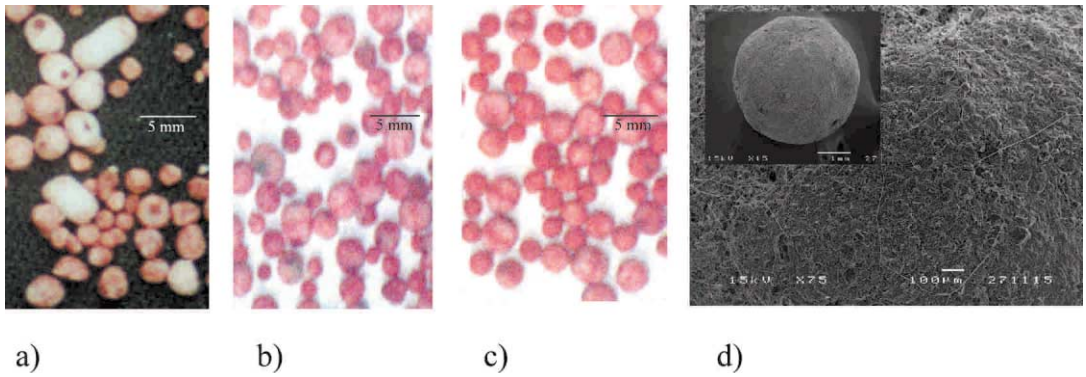

Fig. 7. Pellets produced by co-extrusion. Photographs of pellets taken after (a) 30; (b) 300; and (c) 600 s of spheronization and (d) scanning electron micrograph of pellets after 600 s of spheronization.

results with caution. As anticipated, in the technology described the fundamentals of extrusion hold true, namely the effect of the formulation (particularly the water content) and the processing conditions. The extrusion of the material in the external chamber is more complex than in the internal chamber, as reflected by the angle of convergence. The complex pathway from the chamber to the die has to be elucidated further. It was possible to produce good quality pellets from co-extrudates, anticipating their potential as drug carriers, either in terms of protection or extended release of the drug. Furthermore, it is legitimate that co-extrusion has the potential to reduce the number of processing steps to which, at present, pellets by extrusion and spheronization, are submitted.

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