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Research paper

# Preparation of extruded carbamazepine and PEG 4000 as a potential rapid release dosage form

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**Abstract**

The aim of this research was to use a ram extruder to prepare directly a fast release dosage form with uniform shape and density, containing carbamazepine (C) as a water-insoluble drug and polyethylene glycol 4000 (PEG) as a low melting binder. The potential inclusion of lactose (L) as a hydrophilic filler was also considered. The temperature suitable to ensure a successful extrusion process of several formulations containing PEG in different percentages was found to be below the melting point of the PEG. The influence of composition on the extrusion process of different ram speeds was checked by measuring the pressure at the steady state, the apparent shear rate and the apparent shear stress of a range of mixtures of drug, lactose and PEG. The physical–mechanical properties of extrudates, including tensile strength and Young's modulus, prepared with different ram velocities were also determined. The solid-state physical structure by differential scanning calorimetry (DSC) and X-ray powder diffraction (XRD) was established. The dissolution of the extrudates and their corresponding physical mixtures were compared. The mixtures were found to be shear thinning when extruded; the tensile strength of extrudates was dependent on the composition but not the extrusion rate, while the value of Young's modulus was strongly influenced by the rate of extrusion, but less affected by the composition of the extrudates. The results of DSC and XRD indicated that the solid structure of the extrudates corresponded to that of a physical mixture of the components, hence there had been no change in the physical form of the drug induced by extrusion. In terms of dissolution, the rate of the extrusion process did not influence the performance of the products, whereas the composition did. The extruded mixtures of an equivalent composition exhibited a more rapid release than a simple physical mixture. The addition of lactose reduced the dissolution rate. 

*Keywords*: Carbamazepine; Dissolution enhancement; Extrusion; Polyethylene glycol 4000; Rheology; Young's modulus

## 1. Introduction

The polyethylene glycols (PEGs) have been extensively used as carriers for solid dispersions due to their favourable solution properties, low melting point, rapid solidification rates, low toxicity and low cost [1]. These dispersions are usually manufactured by the melting (fusion), solvent or melting–solvent method [2]. However, very few commercial products are available using this technology, primarily due to their poor handling qualities, physical instabilities on storage, problems of drug/carrier immiscibility, grinding or difficult removal of the solvent [3–5].

For all these reasons, a new processing method to increase the dissolution rate of hydrophobic drugs has been considered involving the use of extrusion technology. This technique, widely used in the plastic industry, has just recently received some attention in the pharmaceutical field. During the process, binder, excipients and active materials are fed into the heated barrel, and extruded through the die attached at the end of the barrel. The molten polymer rapidly solidifies when the extrudate exits the machine through the die. Usually, these extrudates are processed to form powders that are transformed into conventional dosage forms, or cut into small lengths to form pellets. When the shape of the die is controlled, the final product may take the form of a film, pipe, granule or, more simply, a cylinder. Thus, the potential exists for producing a structure directly by extrusion.

Some researchers have successfully used the hot melt extrusion technique. Follonier et al. [6] produced sustained release pellets with a high loading of a freely soluble drug, diltiazem hydrochloride, without significant drug degradation. Aitken-Nichol et al. [7] and Repka et al. [8] applied the melt extrusion technique to manufacture solvent-free films

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for topical delivery of lydocaine hydrochloride, and hydrocortisone or chlorpheniramine maleate, respectively. The hot melt extrusion was also shown to be a viable means for fabricating matrix disks and tablets for sustained release of chlorpheniramine maleate [9,10].

However, the possibility of using the extrusion to produce, in a single stage, a finished product with uniform cylindrical shape and homogeneous density has not yet been fully investigated. The goal of the present study is, therefore, to evaluate the possibility of developing a fast release dosage form by using a ram extrusion process at elevated temperatures. PEG 4000 was chosen as a low melting binder and as an excipient used in melt granulation [11], and carbamazepine, a water-insoluble model drug [12], was incorporated into the extruded cylinders. The effect of adding hydrophilic filler, such as lactose, which could influence the mechanical and dissolution properties of the extrudate, was also considered.

## 2. Materials and methods

### 2.1. Materials

Carbamazepine, reagent grade, was provided from Sigma–Aldrich Chemicals (Steinheim, Germany), polyethylene glycol 4000 (PEG 4000) reagent grade was purchased from Prolabo (Fontenay s/Bois, France) and lactose 200 mesh E.P. grade (Sorbolac® 200) was from Meggle (Wasserburg, Germany). All materials were used as received.

### 2.2. Preparation of mixtures used for the preliminary extrusion experiments

Batches (250 g) of powders were dry blended in a food mixer (Magimix 2800 S Automatic, Grande Cuisine, France) for ten runs including 10 s (mixing) and 1 min (repose). The compositions of the mixtures were (PEG/lactose): 100:0, 95:5, 85:15, 75:25, 55:45, 50:50, 45:55, 40:60, 35:65, 30:70, 25:75, 20:80 (w/w). Evaluation of the content uniformity of the final extrudate established that the mixing process had been successful.

### 2.3. Preliminary extrusion experiments

Fifty-gram samples were taken from the bulk, and each was packed to a constant volume, by applying hand pressure, into the stainless steel barrel (2 cm internal diameter and approximately 20 cm in length) of a ram extruder (ACER2000-Polymer Laboratories, Loughborough, UK), previously thermostatted at the chosen temperature (50, 55, 60°C). After the equilibration time of 25 min, the mass was extruded through a 90° entry die of 2 mm diameter and 5 mm length, using a constant velocity of the piston, and the extrudate was collected in a beaker. To evaluate the rheological properties of the mixtures, the ram speed was varied.

### 2.4. Preparation of mixtures used for the extrusion experiments

The materials were dry blended as described above (Section 2.2). The compositions of the mixtures were (PEG/lactose/carbamazepine): 100:0:0, 90:10:0, 90:5:5, 90:0:10, 80:20:0, 80:10:10, 80:0:20, 60:40:0, 60:20:20, 60:0:40 (w/w).

### 2.5. Extrusion procedure

The extrudates were prepared as described above (Section 2.3), thermostatting the barrel at 50°C and using a constant velocity of the piston (20, 40, 80, 160, 320 mm/min).

### 2.6. Characterization of the extrusion process

The pressure monitored at the steady state of the extrusion process was measured by a pressure transducer fitted at the bottom of the barrel just above the die entry.

For a driven-piston capillary extrusion rheometer, the apparent shear rate at the wall of the die ($\gamma_{app}$), and the apparent shear stress at the wall of the die ($\sigma_{app}$) are given by Eqs. (1) and (2):

$$\gamma_{app} = \frac{\nu R^2}{15 r^3} \tag{1}$$

$$\sigma_{app} = \frac{\Delta P r}{2L} \tag{2}$$

where $\nu$ is the ram velocity (mm/min), $R$ is the radius of the barrel (mm), $r$ is the radius (mm) of the die bore, $L$ is the length (mm) of the capillary and $\Delta P$ the pressure drop across the die (Pa). The apparent viscosity ($\eta_{app}$) is then calculated from Eq. (3):

$$\eta_{app} = \frac{\sigma_{app}}{\gamma_{app}} \tag{3}$$

Rheograms were fitted to the Power–Law equation (Eq. (4)):

$$\gamma = k\sigma^n \tag{4}$$

where $\gamma$ is the shear rate, $\sigma$ is the shear stress, and $k$ and $n$ are the characteristics of the rheological behaviour ($k =$ consistency index, $n =$ flow index). The flow index is equal to unity when the flow is Newtonian. A value either greater or smaller than unity shows a shear thickening or a shear thinning, respectively.

The indices are determined by linear regression according to the logarithmic form of Eq. (5):

$$\ln\gamma = \ln k + n\ln\sigma \tag{5}$$

The flow index is the slope of the line obtained by least-square analysis.

### 2.7. Characterization of the extrudates

The diameters of the ten pieces of extrudate from each lot were determined on a light table by an image analyzer (Seescan Sonata, Seescan Imaging Ltd., Cambridge, UK; zoom-lens 18-108/2.5 Olympus Co., Hamburg, Germany). The same samples were subjected to three point bending with a CT5 testing machine (Engineering Systems, Nottingham, UK), using a distance between the lower supports of 6.4 mm. The breaking load of the extrudates was converted to tensile strength ($\sigma_{max}$) values by the following Eq. (6):

$$\sigma = \frac{F_{max} 8l}{\pi d^3} \quad (6)$$

where $F_{max}$ is the breaking load, $l$ is the distance between the lower supports and $d$ is the diameter of the extrudate. The coefficients of variation of the values of the tensile strength of extrudate samples ranged from 5.3 to 17.1%.

Young's modulus was measured in tension, while bending the extrudate in a three-point loading rig. The general equation of the tensile Young's modulus ($E$) for three-point bending of a rod can be derived from the tensile surface strain at the midpoint of the specimen [13] (Eq. (7)):

$$E = \frac{F_E I}{S_E 48 l} \quad (7)$$

where $F_E$ is the maximum elastic force, $S_E$ is the beam deflection at its midpoint when $F_E$ is reached, $I$ is the inertia of the specimen cross-section and $l$ is the distance between the lower supports. Using the value of $I$ for a circle, the above equation reduces to Eq. (8):

$$E = \frac{F_E 4 l^3}{S_E 3 \pi d^4} \quad (8)$$

In this case, the coefficients of variation ranged from 5.2 to 14.1%.

### 2.8. Particle size and shape analysis

A small amount of powder (carbamazepine or lactose) was suspended in a refractive index liquid (McCrone Scientific Ltd, London, UK), chosen according to powder solubility and difference in refractive index. A few drops of the homogeneous suspension were placed on a glass slide and covered with a slide cover slip. The shape factors and particle size characteristics were measured using an image analyzer (Seescan Solitaire 512, Seescan, Cambridge, UK) connected to a microscope (BH 2, Olympus, Tokyo, Japan) via a black/white camera (CCD-4 miniature video module, Rengo, Toyohashi, Japan). The calibration was carried out with transmission graticules (Graticules, Tombridge, UK). At least 500 particles were examined for each powder batch. The size was determined as the mean number average Feret's diameter, while the shape was expressed as an aspect ratio and the shape factor described by Podczeck [14]. The Feret's diameter gives a measure of the potential size, the aspect ratio gives a measure of elongation, while the shape measures provide a qualification of particle morphology.

### 2.9. Morphological analysis

The surface characteristics of the extrudates were observed by scanning electron microscopy (SEM). Pieces of extrudate were sputter-coated with Au/Pd using a vacuum evaporator and then examined using a scanning electron microscope (XL20 Philips, Eindhoven, Netherlands) at 10 kV voltage using the secondary electron technique.

### 2.10. Thermal analysis

Differential scanning calorimetry (DSC) measurements were performed using a Perkin–Elmer DSC 7 equipped with a refrigerating system (Perkin–Elmer, Beaconsfield, UK). The samples, containing slices of extrudate weighing approximately 5 mg, were placed into the DSC under a nitrogen atmosphere and heated from −15 to 220°C at a scanning rate of 20°C/min. The same procedure was followed for samples of pure carbamazepine, lactose and PEG.

Thermal analyses of the physical mixtures, prepared by simply mixing the components in the same weight ratios as the extrudates, were carried out using a differential scanning calorimeter (Mod. TA 4000, equipped with a measuring cell DSC 20 Mettler, Greifensee, CH). Samples, containing about 2 mg of carbamazepine or lactose, were placed in pierced aluminium pans and heated at a scanning rate of 20°C/min from 25 to 210°C.

### 2.11. X-ray powder diffraction

Samples of extrudates, physical mixtures and raw materials were studied by means of the X-ray powder diffraction technique (XRD) using a diffractometer (STOE D500, Siemens, Munich, Germany) with $CuK_\alpha$ radiation ($\lambda = 1.5418$ Å), monochromatized by a secondary flat graphite crystal. The scanning angle ranged from 5 to 35° of 2θ, the steps were 0.1 of 2θ and the counting time was 2 s/step.

### 2.12. Dissolution studies

The dissolution test was performed according to the USP 23 method I. A dissolution apparatus (TPWS 2C Pharma Test, Hamburg, Germany) was employed with a stirring rate of 100 revs./min and maintained at 37 ± 0.1°C. The dissolution media was 900 ml of freshly demineralized water.

An accurately weighed piece of extrudate, containing a suitable amount (18 mg) of carbamazepine for sink conditions ($C \ll C_s$) was introduced to the basket and dissolved into 900 ml of dissolution medium. The aqueous solution was filtered and continuously pumped to a flow cell in a spectrophotometer (CecilCE 2020, Cecil Instruments, Cambridge, UK) and absorbance values were recorded at the maximum wavelength of the drug (285 nm). The poly-

mer did not interfere with the UV analysis. The results were the average of triplicate experiments, and standard deviations did not exceed 5% of the mean values.

The same procedure was followed for physical mixtures and samples containing the same amount of pure drug as a powder.

To characterize the dissolution profiles, analysis of the dissolution results was also carried out by determination of two statistical moments: the mean dissolution time (MDT) of carbamazepine and variance of dissolution time (VR), and an associated parameter, the relative dispersion of the concentration–time profile (RD), as previously described by Pinto et al. [15].

## 3. Results and discussion

In order to check the range of processability of various PEG/lactose formulations depending on the temperature, preliminary experiments have been carried out using three different temperatures (50, 55 and 60°C). As can be seen from Fig. 1, at the temperature of 50°C, it was possible to extrude mixtures containing an amount of melting binder ranging from 30 to 100%. This range narrowed when the temperature was increased. As the temperature increased, the minimum level of PEG which allowed extrusion decreased slightly, but there was a dramatic drop in the limiting upper range where the system becomes fluid in nature and exits the die without the need for the application of pressure.

Further experiments were carried out at 50°C to study the influence of five different ram speeds (20, 40, 80, 160 and 320 mm/min) on the properties of the extrudates. Comparison with the thermal analysis shows that extrusion takes place at least 11°C below the melting point of the systems. Hence, the material is 'softened' but not molten. Different experiments were carried out using a constant rate for each process. Attempts to change the extrusion speed during the process were not satisfactory, as it was extremely difficult to recognize steady state periods within the extrusion profiles that allow the measurements of the extrusion pressure. In this phase, the range of tested formulations also included carbamazepine, following the composition reported in Section 2.4.

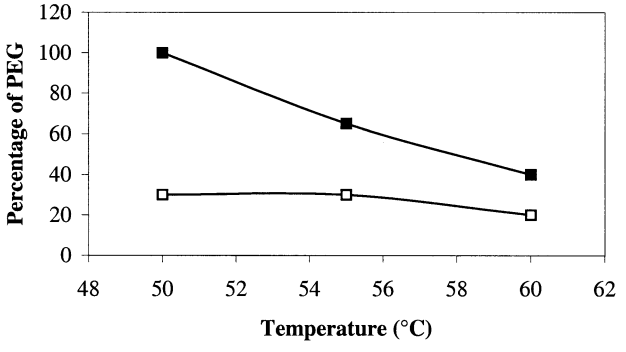


Fig. 1. Effect of the temperature on the processability of PEG/lactose formulations: (■), maximum permitted amount of PEG; (□), minimum required amount of PEG.

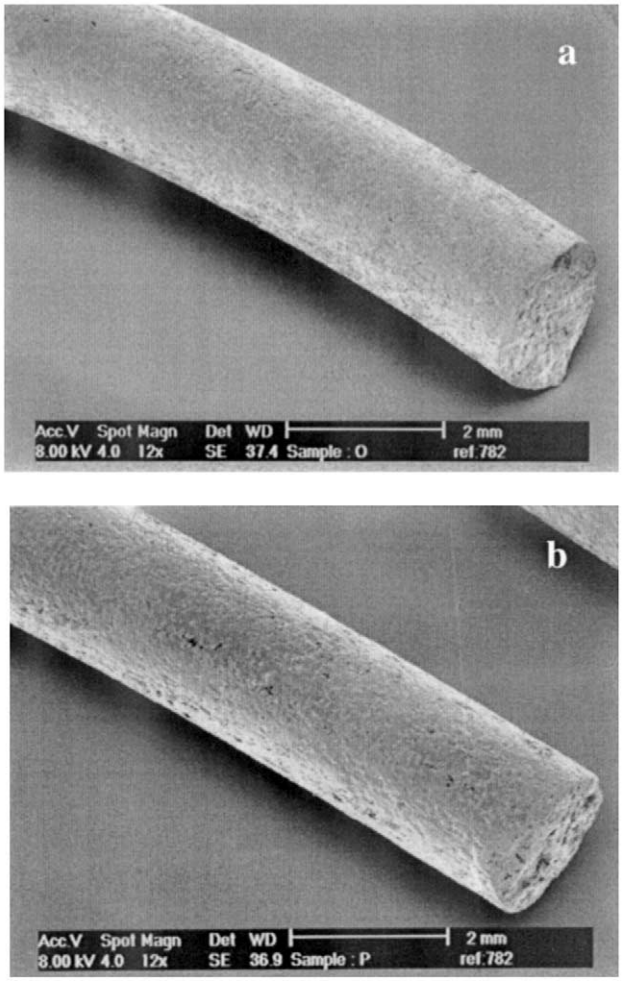


Fig. 2. SEM of 80P/20C extrudates prepared with different ram velocities: (a), 20; and (b), 320 mm/min.

A satisfactory regularity in shape and a smooth surface was obtained in most extrudates, as shown in the examples of Fig. 2. The mean diameter (ten replicate measurements for each value) was found to be independent of the composition of the extrudates and the ram speed used for their preparation. A comparison between the diameter of the extrudates (ranging from 1974 to 2026 μm) and the die (2.000 μm) attested to the absence of significant phenomena of expansion or contraction after the exit of the mass from the die.

In all the systems, a significant increase of the extrusion pressure was found when increasing the ram speed. Furthermore, there was a significant ($P = 0.01$) negative correlation between the polymer content and the extrusion pressure, i.e. the higher the polymer content, the lower the extrusion pressure. Analyzing the extrusion profiles of extrudates containing the same amount of PEG, ternary mixtures showed lower values for extrusion pressure than

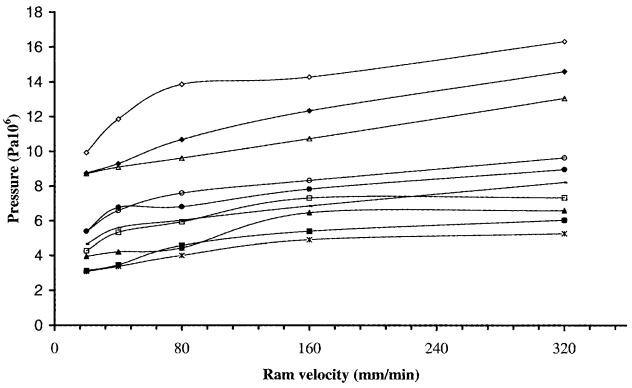


Fig. 3. Extrusion pressure at the steady state as a function of ram speed of the following systems: (◇), 60P/40L; (◆), 60P/40C; (△), 60P/20L/20C; (○), 80P/20L; (●), 80P/20C; (_), 80P/10L/10C; (□), 90P/10L; (▲), 90P/10C; (■), 90P/5L/5C; (*), 100P.

binary mixtures of equal particulate contents. Between these, the samples containing lactose and PEG showed the highest pressure (Fig. 3). An understanding of the behaviour exhibited by these systems can be obtained when considering the particle size and shape (Table 1) of carbamazepine and lactose particles. These results indicated that carbamazepine particles are elongated parallelograms which can be defined as needle-shaped particles, as is evident from its mean aspect ratio (1.741) and shape factor (7.29), even allowing for the heterogeneity of the particle distribution (probably due to the size reduction phenomena of needle-shaped particles). Lactose particles are quite homogeneous in size and shape characteristics, and can be represented by a tomahawk-like shape. The needle-shaped carbamazepine particles will tend to align in the direction of an applied shear, arranging themselves regularly in the softened surrounding material parallel to the die wall. Hence, they provide a lower resistance to flow and have low apparent viscosity.

On the other hand, a decrease of the viscosity was noticed when increasing the amount of PEG into the formulations and the velocity of the piston. The latter indicates the shear thinning behaviour of these systems. A further confirmation of the non-Newtonian behaviour can be seen from the rheograms of the systems (Fig. 4), where the values for the flow index, $n$, are smaller than unity (Table 2). These values are also very similar for all the systems, ranging from 0.14 to 0.26. These results indicated that the consistency of all the systems are non-Newtonian in their behaviour at this

Table 1
Size and shape analysis results of carbamazepine and lactose[a]

| | Feret's diameter (μm) | Aspect ratio | Shape factor |
|---|---|---|---|
| Carbamazepine | 56.56 ± 63.0 | 1.74 ± 0.72 | 7.29 ± 0.51 |
| Lactose | 16.00 ± 11.30 | 1.39 ± 0.29 | 7.41 ± 0.55 |

[a] Means ± SD.

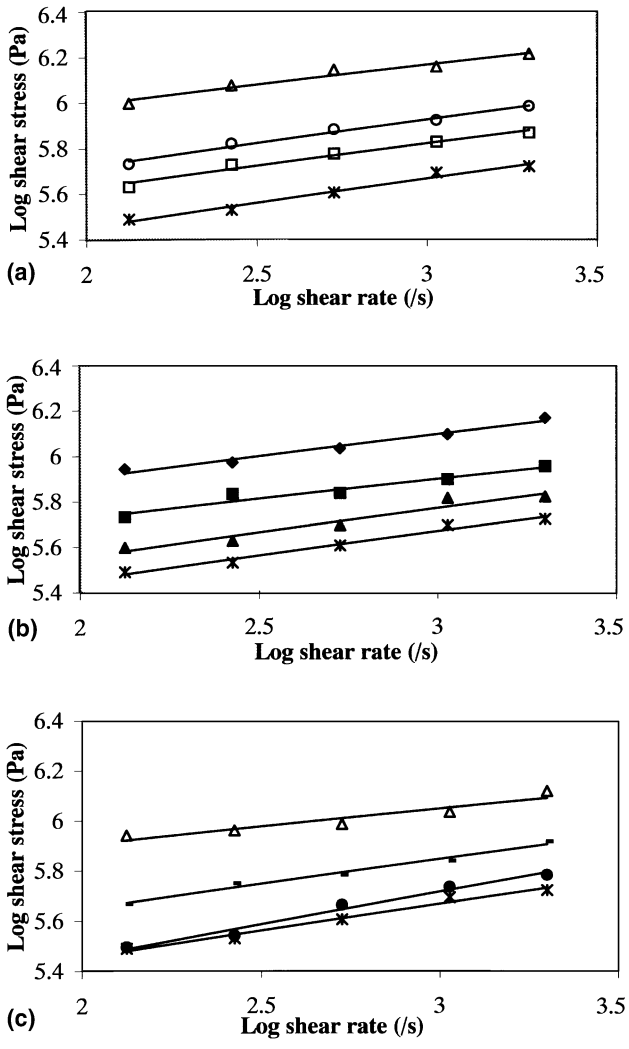


Fig. 4. Rheograms of the systems: (a), PEG/lactose: (△), 60P/40L; (○), 80P/20L; (□), 90P/10L; (*), 100P; (b), PEG/carbamazepine: (◆), 60P/10C; (■), 80P/20C; (▲), 90P/10C; (*), 100P; (c), PEG/lactose/carbamazepine: (△), 60P/20L/20C; (_), 80P/10L/10C; (●), 90P/5L/5C; (*), 100P.

temperature. The shear thinning behaviour of the systems indicates that the mixtures are probably more easily

Table 2
Flow ($n$) and consistency ($k$) indices of the extruded systems

| Formulation[a] | $n$ | $k$ (kPa/s) | $R^{2b}$ |
|---|---|---|---|
| 100 P | 0.21 | 5.03 | 0.98 |
| 90P/10L | 0.19 | 5.24 | 0.97 |
| 90P/10C | 0.21 | 5.13 | 0.93 |
| 90P/5L/5C | 0.26 | 4.94 | 0.98 |
| 80P/20L | 0.21 | 5.31 | 0.98 |
| 80P/20C | 0.17 | 5.38 | 0.94 |
| 80P/10L/10C | 0.20 | 5.25 | 0.98 |
| 60P/40L | 0.17 | 5.65 | 0.96 |
| 60P/40C | 0.19 | 5.52 | 0.97 |
| 60P/20L/20C | 0.14 | 5.62 | 0.90 |

[a] P, PEG; L, lactose; C, carbamazepine.
[b] Linear determinant.

processed at higher shear rates, which may also have implications in melt granulation systems. Previous data [16] regarding PEG's flow properties demonstrated an essentially Newtonian behaviour and only a negligible shear thinning, when lactose was included in the systems. However, Rowley et al. [16] determined the flow characteristics at temperatures above the melting point of the polymer, whilst in this case, the temperature of 50°C allows the softening of the polymer but not the melting. In terms of consistency index values ($k$), the results of the systems ranged from 4.94 to 5.65, indicating a softened material, with a good capability to be extruded [17]. The consistency value increased when decreasing the amount of melting binder in the systems, thus following the same trend as the pressure required for the extrusion process.

With the aim of testing the effect of the different ram speeds and composition on the mechanical properties of the extrudates, the tensile strength of ten pieces of extrudate prepared with the lowest (20 mm/min) and the highest (320 mm/min) extrusion rate, whose diameter had been previously measured, was determined. The tensile strength was calculated using the equation reported above (Eq. (6); Fig. 5). Two-way analysis of variance with five different extrusion speeds and 13 different compositions established that there was no statistical difference in the tensile strength values as a result of different extrusion rates, but there was a significant difference ($P = 0.05$) between the compositions. Similar analysis of the values of Young's modulus, calculated from Eq. (8) and illustrated in Fig. 6, established a significant difference ($P = 0.05$) between the extrudates at 20 and 320 mm/min ram speed, but no significant difference between the different levels of powder content. Thus, the composition influences the fracture properties, presumably by altering the ability to allow crack propagation through the specimen, but does not alter the degree of recoverable deformation (elasticity). The reverse is true for the recoverable deformation, where this does not change with composition but the structural changes induced by shearing during extrusion strongly influence the deformability. Thus, the polymer dominates the recoverable deformability, but the solids dominate the fracture properties.

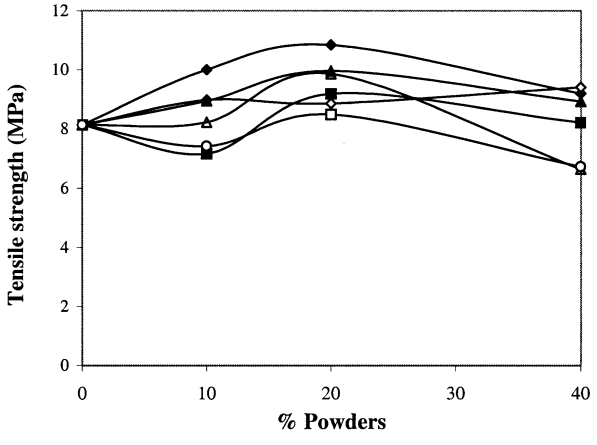


Fig. 5. Tensile strength/composition plots: (◆), PEG/lactose extrudates (320 mm/min); (◇), PEG/lactose extrudates (20 mm/min.); (▲), PEG/carbamazepine extrudates (320 mm/min); (△), PEG/carbamazepine extrudates (20 mm/min); (■), PEG/lactose/carbamazepine extrudates (320 mm/min); (□), PEG/lactose/carbamazepine extrudates (20 mm/min).

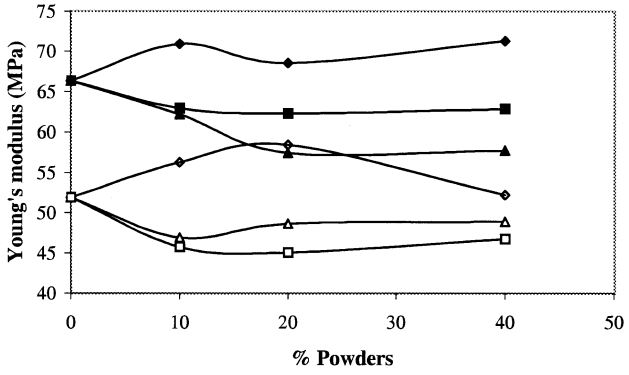


Fig. 6. Young's modulus/composition plots: (◆), PEG/lactose extrudates (320 mm/min); (◇), PEG/lactose extrudates (20 mm/min); (▲), PEG/carbamazepine extrudates (320 mm/min); (△), PEG/carbamazepine extrudates (20 mm/min); (■), PEG/lactose/carbamazepine extrudates (320 mm/min); (□), PEG/lactose/carbamazepine extrudates (20 mm/min).

To test the influence of the different ram velocities and composition on the dissolution properties of the extrudates, the samples of extrudates containing carbamazepine prepared with the lowest and the highest extrusion rate were subjected to dissolution, allowing comparison of the dissolution from the extrudates with that from the corresponding physical mixtures and the drug alone. For brevity, only the profile of PEG/carbamazepine 90:10 w/w physical mixture (Fig. 7) is reported. Analysis of the results by determination of the statistical moments of MDT and VR, and the associated parameter RD, between 0 and 60 min, provides

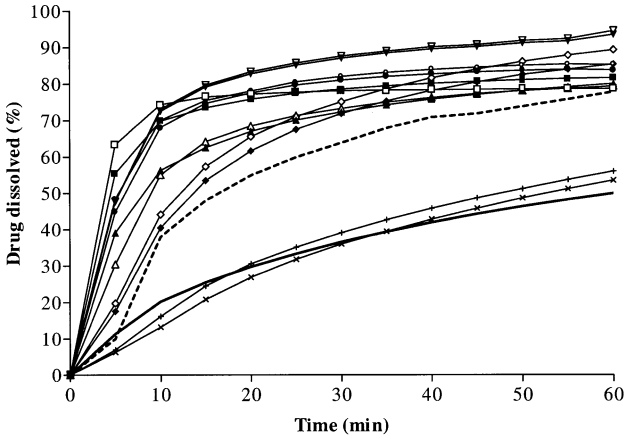


Fig. 7. In vitro dissolution test of the systems containing carbamazepine: (▼), 90P/10C (320 mm/min); (▽), 90P/10C (20 mm/min); (■), 90P/5L/5C (320 mm/min); (□), 90P/5L/5C (20 mm/min); (●), 80P/10L/10C (320 mm/min); (○), 80P/10L/10C (20 mm/min); (▲), 80P/20C (320 mm/min); (△), 80P/20C (20 mm/min); (- - -), 90P/10C physical mixture; (◆), 60P/20L/20C (320 mm/min); (◇), 60P/20L/20C (20 mm/min); (×), 60P/40C (320 mm/min); (+), 60P/40C (20 mm/min); (−), carbamazepine.

Table 3
Assessment of statistical moment analysis models of dissolution[a], as a function of extrudates prepared with different ram speed and drug loading, compared with the drug alone and a physical mixture[b]

| Sample | AUC (% min) | MDT (min) | VR ($min^2$) | RD |
|---|---|---|---|---|
| Carbamazepine | 996 | 19.85 | 277.14 | 0.70 |
| 90P/5L/5C (320) | 539 | 6.58 | 80.39 | 1.86 |
| 90P/5L/5C (20) | 336 | 4.25 | 27.25 | 1.51 |
| 90P/10C (320) | 854 | 9.11 | 135.06 | 1.63 |
| 90P/10C (20) | 886 | 9.35 | 145.19 | 1.66 |
| 90P/10C (p.m.) | 1285 | 16.44 | 200.59 | 0.74 |
| 80P/10C/10L (320) | 617 | 7.34 | 65.09 | 1.21 |
| 80P/10C/10L (20) | 640 | 7.36 | 80.12 | 1.44 |
| 80P/20C (320) | 852 | 10.61 | 159.23 | 1.41 |
| 80P/20C (20) | 830 | 10.43 | 125.58 | 1.16 |
| 60P/20L/20C (320) | 1350 | 15.77 | 188.85 | 0.76 |
| 60P/20L/20C (20) | 1388 | 15.49 | 193.99 | 0.81 |
| 60P/40C (320) | 1273 | 23.68 | 267.12 | 0.48 |
| 60P/40C (20) | 1257 | 22.35 | 264.98 | 0.53 |

[a] From 0 to 60 min.
[b] Extrusion rate: 20 or 320 mm/min.

the results in Table 3. There are no significant differences ($P = 0.05$) between the values of the MDT of the extrudates prepared with different ram velocities. From all the formulations tested, an enhancement in the drug dissolution rate compared with the drug alone was observed, with the only exception being the formulation containing 40% of carbamazepine, which showed dissolution profiles similar to the drug alone. In general, the greater the amount of polymer (PEG), the greater the improvement. The systems containing drug and PEG alone exhibited the highest dissolution rate and extent of dissolution of the drug than the systems also containing lactose, as can be seen by comparing ternary and binary systems containing the same percentage of drug.

The enhanced dissolution of carbamazepine from the physical mixture demonstrated a solubilizing effect of the PEG, as already reported [18] when a solid dispersion is used. Extrudates displayed significantly higher and faster dissolutions than corresponding physical mixtures. As the extrudates rapidly disintegrated in the test, the improved dissolution could be associated with enhanced surface contact between the drug and dissolution medium. The more intimate incorporation of the drug into the surrounding hydrophilic materials into the extrudates provided a more efficient wetting of the drug in comparison with the simple physical mixture.

The release rate mechanisms of the drug, identified from the values of RD, show that dissolution from the 60P/20L/20C extrudates and the reported physical mixture can be associated with a pseudo first order (class 2), whilst the 60P/40C extrudates correspond to a cube root release (class 3). It was not possible to represent the release rate mechanisms obtained from the other extrudates, probably because different mechanisms functioned at the same time in the process of dissolution, rapid release initially followed by a slower process as the extrudates become depleted of drug. It appears that, if enhancement of dissolution is required, then it is not possible to incorporate 40% of drug.

The in vitro dissolution behaviour of the extrudates was considered in the light of the physical characterization performed with DSC and XRD analyses. From DSC analysis, it could be noticed that the peak ranged from 61.2 to 65.7°C for all extrudates and physical mixtures compared with 64.9°C for pure PEG. There were no differences in thermal and X-ray (Fig. 8) parameters between the samples prepared with different extrusion rates. These results indicated that the solid structure of extrudates was quite similar to that of physical mixtures of the components, as one would expect if it is the PEG that deforms and not the drug crystals. The evaluation indicated that there was no gross change in crystal structure, suggesting that any enhanced dissolution was associated with ensuring contact of the surface of the drug crystals with the dissolution fluid.

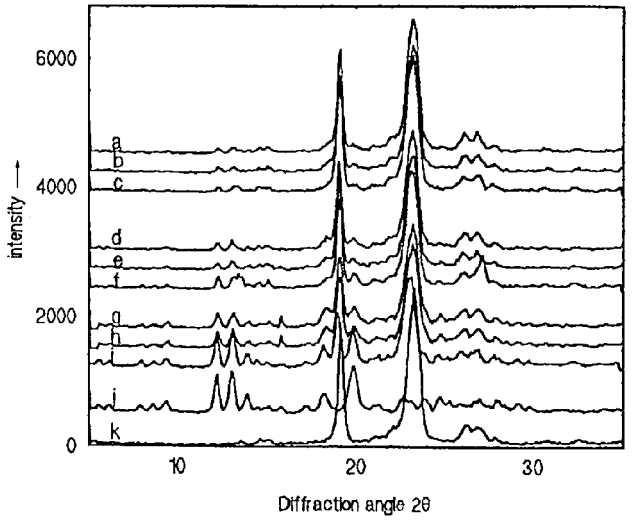


Fig. 8. X-ray diffraction patterns of PEG/carbamazepine systems: (a), 90P/10C (320 mm/min); (b), 90P/10C (20 mm/min); (c), 90P/10C physical mixture; (d), 80P/20C (320 mm/min); (e), 80P/20C (20 mm/min); (f), 80P/20C physical mixture; (g), 60P/40C (320 mm/min); (h), 60P/40C (20 mm/min); (i), 60P/40C physical mixture; (j), carbamazepine; (k), PEG.

## 4. Conclusions

It can be concluded that the extrusion process is a viable method to produce, in a single step, fast release dosage forms for carbamazepine, by using lactose as a hydrophilic filler and PEG 4000 as a binder at a temperature below its melting point. These extrudates, homogeneous in shape and size and with smooth surfaces, were easily produced thanks to their flow and consistency properties. When extruded, the mixtures were shear thinning. They had appropriate mechanical properties to act as a dosage form themselves. The tensile strength of extrudates was dependent on the composition but not on the extrusion rate, while the value

of Young's modulus was strongly influenced by the rate of extrusion but not by the composition. Since the results of DSC and XRD indicated that the solid structure of the extrudates substantially corresponded to that of a physical mixture of the components, and the extrudates rapidly disintegrated in the test, the improved dissolution of the carbamazepine could be associated with enhanced surface contact between drug and dissolution medium.

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