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Compaction, compression and drug release characteristics of xanthan gum pellets of different compositions

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Abstract

Compaction and compression of xanthan gum (XG) pellets were evaluated and drug release from tablets made of pellets was characterised. Three formulations were prepared by extrusion–spheronisation and included, among other excipients, diclofenac sodium (Dic Na), at 10% (w/w); xanthan gum, at 16% (w/w); and one of three different fillers (lactose monohydrated (LAC), tribasic calcium phosphate (TCP) and β-cyclodextrin (β-CD)), at 16% (w/w). Five hundred milligrams of pellets (fraction 1000–1400 μm) were compacted in a single punch press at maximum punch pressure of 125 MPa using flat-faced punches (diameter of 1.00 cm). Physical properties of pellets and tablets were analysed. Dissolution was performed according to the USP paddle method. Pellets showed close compressibility degrees (49.27% LAC; 51.32% TCP; and 50.48% β-CD) but densified differently (3.57% LAC; 14.84% TCP; 3.26% β-CD). Permanent deformation and densification were the relevant mechanisms of compression. Fragmentation was regarded as non-existent. The release behaviour of tablets made of pellets comprising LAC or β-CD was anomalous having diffusional exponent (*n*) values of 0.706 and 0.625, respectively. Drug diffusion and erosion were competing mechanisms of drug release from those tablets.

Keywords: Pellets; Extrusion–spheronisation; Xanthan gum; Compaction; Compression; Drug release; Diffusion; Erosion

1. Introduction

Tablets are the most common and popular form of pharmaceutical dosage forms. These solid units usually consist of a mixture of fine powders compacted in a die at an applied pressure to provide a single rigid body of defined mechanical strength (Marshall and Rudnick, 1990). Most recently, there has been an increasing interest in the development of multiparticulate dosage forms in the shape of tablets instead of hard gelatine capsules, as an attempt to overcome the high production costs (Marshall and Rudnick, 1990; Çelik, 1994).

In the field of tablets made of multiparticulates, the goal of many investigations has been the search of reasonable knowledge about the mechanisms involved during compaction of such units (Johansson et al., 1995, 1998; Johansson and Alderborn, 1996, 2001). The common approach is the use of granules as a model system (Wikberg and Alderborn, 1990a,b, 1991, 1992a,b, 1993). It is suggested that four mechanisms are involved in the compression process of irregular granules: fragmentation, deformation, densification and attrition (Çelik, 1994; Johansson et al., 1995). Those mechanisms are related to the structural changes of the model system rather than to the forming primary particles. In spite of the knowledge that has been gathered by using granules in compaction studies, the establishment of better knowledge of the extent of compression involves some complexity due to the occurrence of fragmentation and attrition as a result of the irregular shape and surface roughness of these units. Reasonably, the well-defined shape of pellets enables the improvement of the mechanistic knowledge of the compaction process of porous particles and justifies their use as an alternative model system (Johansson et al., 1995). Furthermore, the design of active drug pellets as well as the choice of suitable ingredients for their production find great contribution on the better comprehension of volume reduction behaviour of such units.

The purpose of this study was to investigate the effect of the physical properties (shape, surface roughness, specific

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surface area, mechanical tensile strength, porosity and pore structure) of matrix pellets on the compression behaviour and tablet forming ability of these units (Johansson et al., 1995, 1998; Johansson and Alderborn, 1996, 2001; Nicklasson et al., 1999a,b). For that purpose, pellets were prepared comprising xanthan gum (XG) as the hydrophilic polymer and one of three different fillers in their formulations. Pellets were also assessed for their degrees of compression and densification and tablets made of pellets were considered for the determination of the mechanical tensile strength, total porosity, appearance of the upper and fracture surfaces in an attempt to add and/or confirm knowledge to the compression mechanism of nearly spherical units formed from other materials than only microcrystalline cellulose (Johansson et al., 1995, 1998; Johansson and Alderborn, 1996, 2001) or binary mixtures of microcrystalline cellulose and filler (Nicklasson et al., 1999a,b). Specifically, this work intends to answer whether pellets prepared in the same way, bearing similar physical characteristics but differing in the type of one of their constituents would differ in their compaction mode. Moreover, dissolution behaviour and drug release from the tablets were investigated in order to derive information for the choice of pellets formulation suitable for tabletting and simultaneously presenting appropriate control release of the active model drug.

Xanthan gum, here employed as the control release agent, is a high molecular weight heteropolyssaccharide gum produced by a pure culture fermentation of a carbohydrate with the microorganism *Xanthamonas campestris*. It has been widely used in oral and topical formulations, cosmetics and food (Wade and Weller, 1994). More recently it has been proven to play a successful role in sustaining release of drugs from hydrophilic matrix formulations (Lu et al., 1991; Talukdar and Plaizier-Vercammen, 1993; Ingani and Moës, 1998). Furthermore, xanthan gum has proved to have higher drug-retarding ability compared to the well-known hydroxypropylmetyl cellulose (Talukdar et al., 1996; Talukdar and Kinget, 1997).

2. Materials

Diclofenac sodium (Dic Na) (BP grade) was purchased from Capsifar, Oeiras, Portugal and used as the model drug. Xanthan gum (dynamic viscosity 1470 mPa s, according to the supplier), purchased from Capsifar, Oeiras, Portugal, was employed as the main binder. Microcrystalline cellulose powder (MCC) (Microcel® 101) obtained from Sagran, Milan, Italy, was the support excipient. Lactose monohydrate (LAC) (mean particle diameter 32.04 μm. Granulac® 200, Meggle, Wasserburg, Germany), tribasic calcium phosphate (TCP) (mean particle diameter 15.72 μm, Lusifar, Lisbon, Portugal) and β-cyclodextrin (β-CD) (mean particle diameter 59.60 μm, Kleptose®, Roquette, Lestrem, France) were used as filler. Povidone (Kolidon® K30, BASF) was purchased from Lusifar, Lisbon, Portugal, and employed as a secondary binder. All the materials were used as received without further treatment. The granulation liquid was a solution (50% v/v) consisting of distilled water and ethanol 95% (commercial grade).

3. Methods

3.1. Powder particle size determination

The particle size determination of the fillers (lactose, tribasic calcium phosphate, and β-cyclodextrin) was carried out in a Malvern Master Sizer (Series 2600C, Malvern Instruments Ltd., Malvern, UK). The mean values for the particle diameter by volume are presented ($n = 3$).

3.2. Preparation of pellets

Three pellets formulations were prepared. All formulations were based in microcrystalline cellulose, 50% (w/w); diclofenac sodium as the model drug, 10% (w/w); xanthan gum as the control release agent, 16% (w/w); povidone as a secondary binder, 8% (w/w); and filler excipient, 16% (w/w). Formulation 1 (PF#1) comprised lactose monohydrate as the filler, while formulations 2 (PF#2) and 3 (PF#3) comprised tribasic calcium phosphate and β-cyclodextrin, respectively. Pellets were prepared by extrusion–spheronisation. Ethanol/water mixture 50% (v/v) was used as the binding liquid according to previous work (Santos et al., 2002). Dry powder mixtures, except for the povidone, were blended in a planetary mixer for 20 min. Povidone was included in the formulations as a solution in the binding liquid. The appropriate total quantity of the liquid, which gave the suitable wet mass for extrusion thus the best pellets in terms of roundness (visual inspection), was determined by trial and error. The wet masses were extruded in a screen extruder (Caleva model 10, Dorset, England) equipped with a standard screen 1 mm diameter apertures and rollers rotating at 60 rpm. The extrudates were transferred to the spheroniser (Caleva model 250, Dorset, England) equipped with a crosshatch plate (250 mm diameter) and processed at 1000 rpm rotating speed. The resultant pellets were dried in a fluid bed processor (Uni-Glatt, Glatt GmbH, Binzen, Germany) with the inlet air flow at 50 °C during 20 min.

3.3. Characterisation of pellets

The characterisation of the pellets was performed on the 1000–1400 μm sieve fraction obtained using a set of standard sieves (DIN/ISO 3310-1, Retsch, F. Kurt Retsch GmbH & Co. Haan, Germany) following a $\sqrt{2}$ progression from 500 to 2000 μm of sieve openings. Sieve shaker (AS 200 Control "g", Retsch GmbH & Co., Haan, Germany) operated during 15 min with the oscillation height of 1.5 mm.

3.3.1. Apparent particle density

The apparent particle density of the pellets was determined using a gas pycnometer (Multipycnometer, Quantachrome Co., UK) with helium as the test gas. All pellet formulations were analysed in triplicate.

3.3.2. Effective particle density and pore structure

Porosity parameters (intrusion–extrusion isotherms, pore size distribution, pore surface area and average pore diameters) and effective particle density were assessed using mercury porosimetry (PoreSizer 9320, Micromeritics, Norcross, GA, USA). The relationship between the intruded volume of mercury and the intrusion pressure was analysed. The intrusion pressures were between 0.01 and 208 MPa. The pore sizes corresponding to the intrusion pressures were calculated assuming cylindrical pores and a surface tension for mercury of 485 mN/m. The mercury/material advancing and receding contact angles were 130°. Each pellet formulation was analysed in triplicate.

3.3.3. Intragranular porosity

The intragranular porosity of pellets (ε) was calculated according to Eq. (1). The apparent density of the pellets was measured by picnometry (Section 3.3.1) and effective density of the pellets was measured by mercury picnometry (Section 3.3.2). Pellet formulations were analysed in triplicate.

$$\varepsilon = 1 - \frac{\text{effective density of the pellets}}{\text{apparent density of the pellets}} \quad (1)$$

3.3.4. Tensile strength

The tensile strength of pellets ($\sigma_{f(s)}$) of the different formulations was assessed using a universal testing instrument with a 5 kg load cell (CT-5, Engineering Systems, Nottingham, UK). The pellets were strained until failure occurred. The load was recorded and the tensile strength was calculated applying the values for the failure load (F) and the radius of the pellet (R) according to Eq. (2) (Shipway and Hutchings, 1993; Salako et al., 1998). Fifty pellets of each formulation were analysed.

$$\sigma_{f(s)} = \frac{0.4F}{\pi R^2} \quad (2)$$

3.3.5. Image analysis

Size and shape of the pellets were concomitantly derived using an image analysis system (Seescan solitaire 512, Seescan, Cambridge, UK) connected to a black and white camera (CCD-4 miniature video camera module, Rengo Co. Ltd., Toyohashi, Japan), zoom lens (18-108/2.5, Olympus Co., Hamburg, Germany), and top position cold light source (Olympus Co., Hamburg, Germany). Aspect ratio of pellet, Feret diameter and shape factor e_R were derived from image analysis and used for statistical analysis. Shape factor e_R is based on a two-dimensional outline analysis and considers both the geometrical shape and the surface texture of the agglomerate (Podczeck and Newton, 1994). For the shape factor e_R, a value of unity considers a perfect spheroid although a value close to 0.6 describes a particle of good sphericity. One hundred pellets of each formulation were analysed.

3.3.6. Surface roughness

Surface of pellets were analysed by applying a non-contacting laser profilometer (UBM Microfocus Measurement System, UBM Messtechnik GmbH, Ettlingen, Germany). The roughness parameters were determined using the UBSOFT software, which also provides a three-dimensional profile of the surface of the analysed particle. The laser spot size was 1 μm, the aperture angle was 53°, and the scanning speed was 100 points/s. The measured area was a square of 0.25 mm × 0.25 mm dimension with a resolution of 500 points/mm in both the *X*- and *Y*-directions. The R_{tm} (mean peak to valley ratio) parameter derived from the surface roughness measurements was used for the statistical analysis. It describes the arithmetic average of the largest height difference, each equivalent to the sum of the largest peak and the deepest valley derived from the line scan of a surface profile, in each of 25 rectangles obtained by splitting the surface into a 5 × 5 grid. This parameter provides information about the surface that a two-dimensional line scan would not detect. Six pellets of each formulation were analysed.

3.3.7. Specific surface area

Pellets samples were analysed by applying the BET technique for specific surface area using the gas adsorption technique with nitrogen as the adsorbate gas (ASAP 2000, Micromeritics, Norcross, USA). Specific surface area was determined by applying the BET model to the equilibrium isotherm within pressures of 0.05–0.30 psia. Six experimental points (BET multipoint) and only one experimental point (BET single point) were used for calculation. Samples were outgassed by applying vacuum at room temperature during 24 h prior to the determination of the specific surface area. Three samples of each pellet formulation were analysed.

3.3.8. Deaggregation of pellets from unlubricated tablets

Tablets of unlubricated pellets were prepared (Section 3.4) and gently shacked in a Petri dish. The deaggregated pellets obtained were then passed through a standard sieve of 1000 μm diameter apertures (DIN/ISO 3310-1, Retsch, F. Kurt Retsch GmbH & Co. Haan, Germany). The pellets retained in the sieve were hereafter referred to as retrieved pellets.

3.3.9. Degree of compression

Unlubricated pellets were compressed (Section 3.4). The degree of compression of the pellets was calculated by applying Eq. (3) (Johansson and Alderborn, 1996) ($n = 10$).

$$C_{\%} = \frac{H_o - H_p}{H_o} \times 100 \quad (3)$$

where H_o is the estimated height of pellet bed in-die before compression derived from the poured bulk density and fill weight of the pellets, and the die diameter. H_p is the height of the compact. The poured bulk density of the pellets was determined in a 250 ml glass cylinder (inner diameter of 3.5 cm).

3.4. Statistical analysis

Analysis of variance (ANOVA) was performed using SPSS version 10.0 for windows (SPSS Inc., Chicago, USA) employing an error probability of $P = 0.05$.

3.5. Preparation of tablets

Unlubricated pellets were compressed using a single punch press (Speca Press–Automatic Press, Speca Ltd., Kent, England) at maximum punch pressure of 125 MPa. Press was equipped with flat-faced punches of 1.00 cm diameter. Punches and die were lubricated before every compaction with magnesium stearate suspension (1% w/w in ethanol). 500 mg (±0.5) sample of pellets of size fraction 1000–1400 μm were accurately weighed and manually filled into the die. The prepared tablets were stored in a dieccator at room temperature for at least 48 h before being subjected to any characterisation to remove any residual humidity.

3.6. Characterisation of tablets

3.6.1. Mechanical tensile strength

Tablets were compressed diametrically in a material testing machine (Erweka TBH28, Erweka Apparatebau GmbH, Bizen, Federal Republic of Germany) at a compression rate of 5 mm/min. The mechanical tensile strength of the tablets (σ) was calculated according to Fell and Newton (1970) (Eq. (4)) applying the force needed to fracture the tablet (P) and the diameter (D) and thickness (T) of the tablet. Ten tablets of each pellet formulation were analysed.

$$\sigma = \frac{2P}{\pi DT} \tag{4}$$

3.6.2. Total porosity

The total porosity (ε_{Total}) was calculated by applying the bulk density of the compact and the apparent particle density of the powder mixture. The bulk density of the tablets was derived from the dimensions and weight of the compacts as well as the apparent particle density of the pellets ($n = 10$).

3.7. Microscopy

Photomicrographs of the pellets and the upper and fracture surfaces of the tablets were taken with a scanning electron microscope (SEM) (Philips XL20, Philips, Eindhoven, The Netherlands) for visual inspection of the shape and the surface texture of pellets before and after compaction, as well as the mode of compaction of the pellets.

3.8. Dissolution testing

In vitro dissolution tests were performed according to the USP paddle method using a dissolution apparatus (VK 7000 Dissolution Testing Station, Vankel, Essex, England). The test employed 1000 ml of pH 7.4 phosphate buffer at 37 °C as the dissolution medium and paddles rotating at 100 rpm. Samples were continuously collected and analysed by UV-Vis spectrophotometer (UV-1603 Shimadzu, Shimadzu Co., Kyoto, Japan) at 277.5 nm every 15 min over 24 h. Pellets and tablets were analysed in triplicate.

3.9. Drug release study

Analysis of drug release data derived from the dissolution tests were fitted to the exponential Eq. (5) (Korsmeyer et al., 1983).

$$\frac{M_t}{M_\alpha} = kt^n \tag{5}$$

where M_t is the amount of drug released at time t, M_α the nominal total amount of drug, M_t/M_α the fraction of drug released within the range 0.1–0.6 at time t, k is the kinetic constant (t^{-n}) that incorporates the properties of the polymeric system and the drug, and n is the diffusional exponent of the drug release that is used to characterise the transport mechanism. In the case of tablets, $n = 0.45$ for Case I (Fickian diffusion), $n = 0.89$ for Case II transport, $0.45 < n < 0.89$ for anomalous behaviour (non-Fickian transport).

For the characterisation of drug release rate, the mean dissolution time (MDT) was calculated according to Eq. (6) using the n and k values derived from Eq. (5) (Möckel and Lippold, 1993).

$$\text{MDT} = \frac{n}{n+1}k^{-1/n} \tag{6}$$

Furthermore, to calculate the approximate contribution of the diffusional and relaxational mechanisms on the release of the model drug, data was fitted to the heuristic model (Eq. (7)) (Alfrey et al., 1966; Ritger and Peppas, 1987; Peppas and Sahlin, 1989).

$$\frac{M_t}{M_\alpha} = k_1 t^m + k_2 t^{2m} \tag{7}$$

The first term in the right-hand side of Eq. (7) refers to the Fickian contribution while the second term being the Case II erosional contribution. The coefficient m is the purely Fickian diffusion exponent for a device of any geometrical shape that exhibits controlled release. The value of m (0.43) for the tablets under investigation was determined from the plot of aspect ratio of the tablets (diameter/thickness) against diffusional exponent according to Peppas and Sahlin, 1989. Drug release data was fitted to Eq. (7) by non-linear regression

analysis using PRISM version 3.03 software for windows (GraphPad Software Inc., San Diego, CA, USA). The percentage of the drug released due to the Fickian mechanism (F_{mech}) was calculated according to Eq. (8) whereas the ratio of relaxational (R_{mech}) over Fickian (F_{mech}) mechanisms contribution was calculated according to Eq. (9) (Peppas and Sahlin, 1989).

$$F_{mech} = \frac{1}{1 + (k_2/k_1)t^m} \quad (8)$$

$$\frac{R_{mech}}{F_{mech}} = \frac{k_2}{k_1} t^m \quad (9)$$

4. Results and discussion

4.1. Characterisation of pellets

The physical characteristics of the matrix pellets prepared are presented in Table 1. ANOVA revealed that the three matrix pellets formulations could be regarded as of similar sphericity once no statistical difference was noticed for the shape factor ($P = 0.148$). It could be noticed a close relation of the surface roughness of the pellets to the particle size of the fillers (Section 2). Filler of the smallest particle size resulted in pellets of smother surface. However, no significant statistical difference was noticed between the surface roughness of pellets of the different formulations ($P = 0.246$).

Although xanthan gum matrix pellets of the different formulations could be regarded as of similar shape and surface roughness, their dissimilarity in terms of porosity and resistance against fracture were statistically relevant. Pellets including TCP were the most porous and more susceptible to fracture followed by those comprising β-CD and LAC, respectively. The pore size distributions (expressed as the log differential intrusion volumes versus pore diameter − log scale) of the pellets are shown (Fig. 1) and were used for reason of comparison. The pore size distributions of the pellets were similar but the average pore diameter by volume (defined as the pore diameter at which 50% of the total volume of intruded mercury is intruded), which is greatly affected by the number of large pores, was smaller for pellets comprising tribasic calcium phosphate. All the formulations showed a peak in pore size distribution in the range of macropores (>0.005 μm in diameter) (Allen, 1997).

Pore size distribution of pellets comprising β-CD or LAC were quite similar as well as their average pore diameter by volume reflecting on close average pore diameters and porosities derived from the mercury intrusion measurements. On the other hand, the inclusion of TCP in matrix pellets formulation resulted in pellets of pore size distribution spread towards smaller diameters with smaller average pore diameter by volume. Therefore, those pellets revealed to be more porous comprising pores of smaller average diameter compared to the β-CD and LAC pellets.

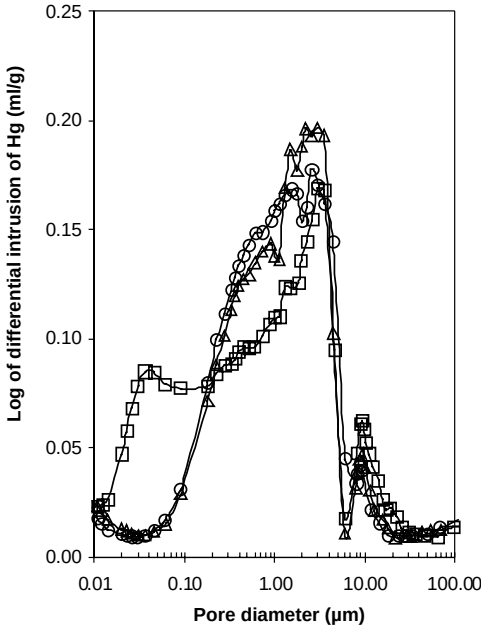

Fig. 1. Distribution of pore diameter of pellets PF#1 (○), PF#2 (□) and PF#3 (△) as a function of the differential mercury intrusion.

4.2. Compression of pellets

Visual examination of the upper and fracture surfaces microphotographs of the tablets of the different types of matrix pellets revealed that pellets remained as coherent individual units after compression even though some cracks could be observed (Fig. 2). No evidence of different mechanisms of compression could be noticed.

The three types of pellets formulation showed compression-induced changes in shape as noticed by the visual inspection. Pellets were flatted after the process of compression. It was evidenced a lost of the original curvature of the pellets that compared satisfactorily with previous reports (Johansson and Alderborn, 1996, 2001). A clear example of the induced change of shape during compression is presented in Fig. 3a and b. SEM revealed marked change in the shape of the pellets showing zones on the surface of the unit that became flat. This is an indication that marked pellet deformation occurred in the same direction of the applied stress during compression (Johansson et al., 1995). This also implies that volume reduction of these units could have been an important change induced during compression. If the compression process inferred slight change of size but allowed a distinct change of the spherical shape towards flat surface, it is supposed that densification of the structure of the units took place then an increase of the apparent density of the particles after compression and consequent reduction of the porosity would be expected. In fact, such increase of the density was noticed (Table 1). Matrix pellets comprising TCP had higher increase, raising its density after compression in approximately 15% of their original apparent density, while those comprising LAC or β-CD slightly increased

Table 1
Physical characteristics of matrix pellets[a]

Pellet formulation	Apparent particle density[b] (g/cm^3)	Apparent particle density[c] (g/cm^3)	Effective particle density[b,d] (g/cm^3)	Intragranular porosity[b] (%)	Specific surface area[b] (m^2/g)
PF#1	1.517 (0.0008)	1.571 (0.0046)	1.091	28.10 (0.037)	1.159 (0.016)
PF#2	1.625 (0.0001)	1.866 (0.0160)	1.116	31.31 (0.004)	4.851 (0.057)
PF#3	1.503 (0.0006)	1.552 (0.0003)	1.096	27.07 (0.030)	1.118 (0.012)

Mechanical tensile strength (MPa)	Shape factor, e_R	Roughness (μm)	Degree of compressibility (%)	Degree of densification (%)
1.76 (0.439)	0.56 (0.119)	10.847 (2.918)	49.27 (0.317)	3.57 (0.325)
1.32 (0.280)	0.55 (0.123)	8.663 (1.069)	51.32 (0.618)	14.84 (0.980)
1.55 (0.278)	0.53 (0.109)	11.585 (4.160)	50.48 (0.341)	3.26 (0.024)

[a] Mean value (S.D.).
[b] For the original pellets.
[c] For the retrieved pellets.
[d] Determined by mercury intrusion measurements.

their density in around 3%. If pellet fragmentation is considered minimal or non-existent and densification was limited for the LAC and β-CD matrix pellets, then the high volume reduction of the bed of these pellets (Table 1) was a result of the repositioning of the units followed by deformation.

The porosity of the original pellets can influence the degree of deformation and densification of the individual pellet (Talukdar et al., 1996). TCP matrix pellets were more porous, more susceptible to fracture and resulted in a more compressible structure thus more sensitive to deformation and densification. An explanation for that observation rises from the hypothesis that, during compression, the primary particles within the pellet flow in its structure to find new relative positions thus being affected by the porosity of the units. The size of the primary particle is one of the key factors affecting the above-mentioned repositioning. TCP, here the filler of smallest particle size, resulted in matrix pellets of more propensity to repositioning hence of higher degree of compression and furthermore of higher densification.

Table 2
Physical characteristics of tablets formed from matrix pellets compacted at 125 MPa[a]

Tablets	Height (mm)	Total porosity (%)	Tensile strength (MPa)
TF#1	0.470	11.12 (0.545)	1.876 (0.120)
TF#2	0.449	22.52 (0.962)	2.971 (0.453)
TF#3	0.469	6.51 (0.621)	2.383 (0.140)

[a] Mean value (S.D.).

4.3. Compaction of pellets

Pellets of higher intragranular porosity resulted in tablets of higher tensile strength (Table 2). Results confirmed that the porosity of the pellets, ruled by the characteristics of the type of filler in their composition, is a key factor influencing the tensile strength of the tablet. In addition, it was observed that tablets of higher total porosity were of higher tensile strength. This observation is not in accordance with previous reports (Johansson and Alderborn, 1996; Johansson et al., 1995; Nicklasson et al., 1999a,b), which observed almost independence of the original porosity of the particles

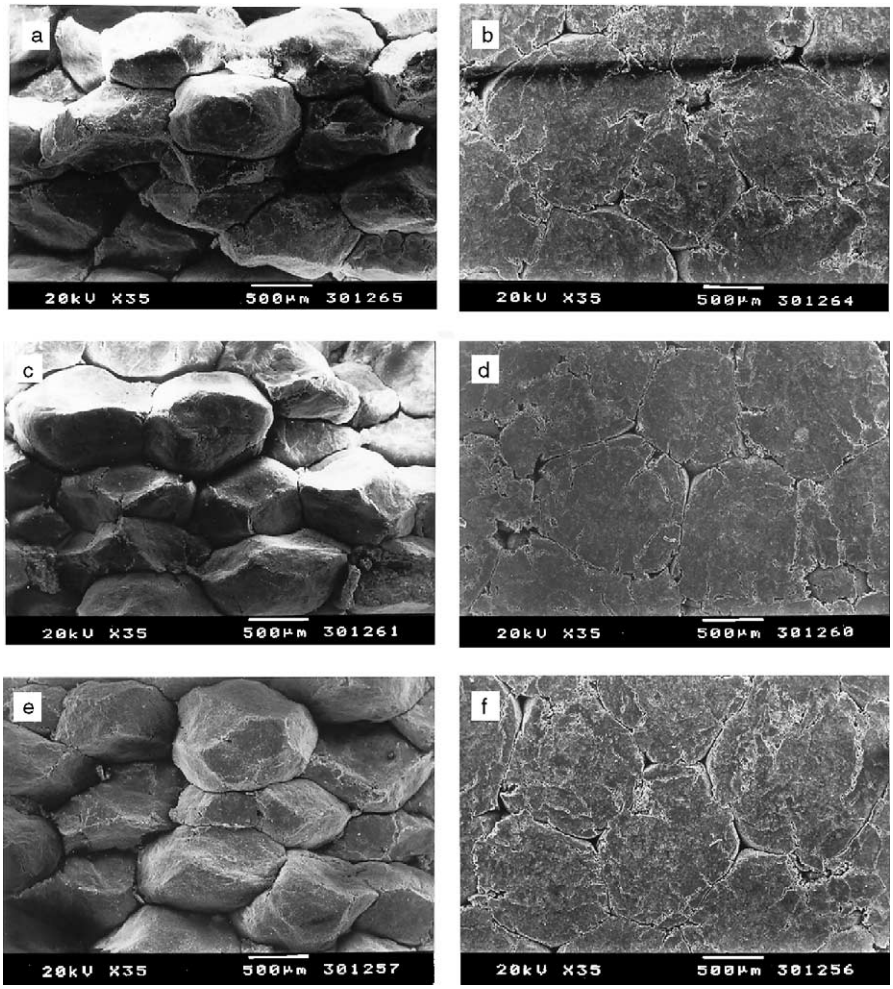

Fig. 2. SEM microphotographs of the fracture surface and the upper surface of tablets of xanthan gum matrix pellets: (a and b) TF#1; (c and d) TF#2; (e and f) TF#3. The white bar denotes 500 μm.

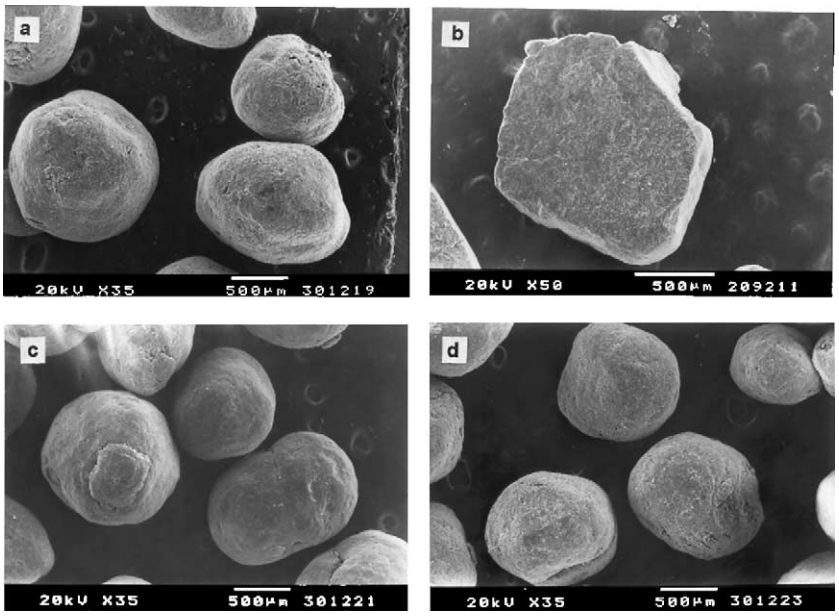

Fig. 3. SEM microphotographs of xanthan gum matrix pellets: (a) original pellets PF#1; (b) retrieved pellet PF#1; (c) original pellets PF#2; (d) original pellets PF#3. The white bar denotes 500 μm.

and the total tablet porosity for agglomerates of the same composition but of different porosities. Here, the total tablet porosity was found related with the intragranular porosity and the mechanical tensile strength of the pellets. However, results for xanthan gum pellets including LAC or β-CD were not as expected. Nevertheless the similarities of the porous structure of these two types of pellets seem to be a reasonable explanation.

All three matrix pellets formulations resulted in very close degrees of compression. Nevertheless, pellets including TCP were the most compressible although resulted in tablets of higher total porosity and simultaneously densified. According to observations of the SEM microphotographs of the surface of facture of the tablets, it could not be inferred any great difference in the deformation modes of the different kinds of pellets. Hypothetically, TCP matrix pellets should be more elastic thus more deformable than matrix units comprising LAC or β-CD, according to the results for the mechanical tensile strength.

Analysis of the results revealed that the matrix pellets of higher degree of compression resulted in tablets of higher tensile strength. These pellets revealed to be more susceptible to compression since they were of smaller mechanical tensile strength thus more elastic and less brittle than the others. Such behaviour is probably consequence of the filler solubility in the liquid used for wet granulation during the preparation of the pellets, i.e., for the water-soluble fillers lactose and β-cyclodextrin, the crystallisation of the dissolved particles during the drying process of the wetted pellets resulted in a greater degree of close interparticulate contact hence less elastic and more brittle agglomerates (Dyer et al., 1994; Santos et al., 2002).

4.4. Dissolution test and drug release studies

Plots of the fraction of drug released versus time for the three matrix pellets formulations and their respective tablets are shown in Fig. 4. The release of the model drug from all the three different pellets formulations was immediate. During the test the pellets absorbed water showing extensive swelling and released their entire drug content due to the disruption of the structure. Pellets comprising the specified

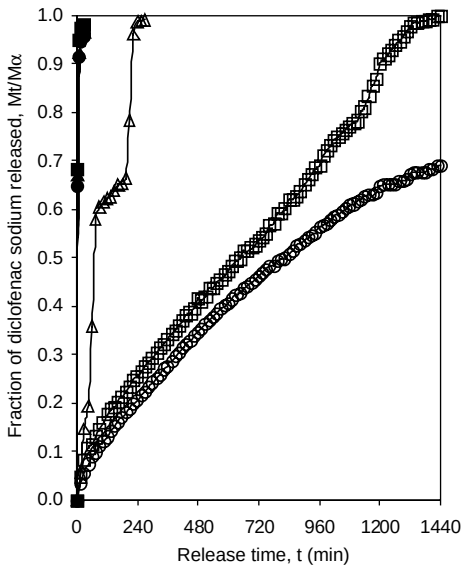

Fig. 4. Fraction of diclofenac sodium released (M_t/M_α) from pellets PF#1 (●), PF#2 (▲) and PF#3 (■); and tablets made of pellets TF#1 (○), TF#2 (△) and TF#3 (□), as a function of release time, *t*.

amount of that gum (16% w/w) could not maintain the integrity of the structure and sustain drug release over the experimental time. On the other hand, tablets made of matrix pellets tested under the same conditions showed similar behaviour: penetration of the medium into the core followed by swelling of the structure, but the integrity of the structure was kept except for tablets formed from matrix pellets comprising TCP. The structure behaved as a swollen sponge-like arrangement slowing drug release over the experimental time.

Drug release from the tablets was a result of hydration of the xanthan gum, which swelled at a great extension forming a barrier through which drug diffused. Erosion of the tablets was probably an important mechanism of drug release since gradual lost of size of the swollen tablets was noticed by visual inspection during dissolution. Visual examination of the remaining tablets comprising lactose matrix pellets after completion of the dissolution tests revealed that the inner core of the cylindrical tablets remained intact without further penetration of the medium. This explains the incomplete release of the model drug after the period of 24 h of dissolution test.

It is noteworthy that the tablets made of matrix pellets did not function as multiparticulate systems and remained as monolithic systems, which granted the release control of the model drug. Visual inspection of the tablets during dissolution also revealed that the swollen tablets were constituted of swollen pellets at the surface of the tablets that gradually eroded and then replaced by inner swollen units as the medium liquid penetrated the tablet. Initially it was observed a burst effect for the tablets of pellets comprising TCP, 60% of the model drug was released in the first hours, which the majority corresponded to the content of deaggregated pellets from the surface of the tablet. Following, small amounts of the drug were released until the complete disruption of the swollen tablet took place then releasing its residual drug content.

To elucidate the possible release mechanism, the release rates ($M_t/M_\alpha\,\mathrm{min}^{-1}$) were analysed based on the method proposed by Korsmeyer et al. (1983) (Section 3.9). The release behaviour of the tablets was found to be anomalous (non-Fickian) having release exponent values (n) 0.7059 and 0.6251 for the tablets formed from LAC and β-CD matrix

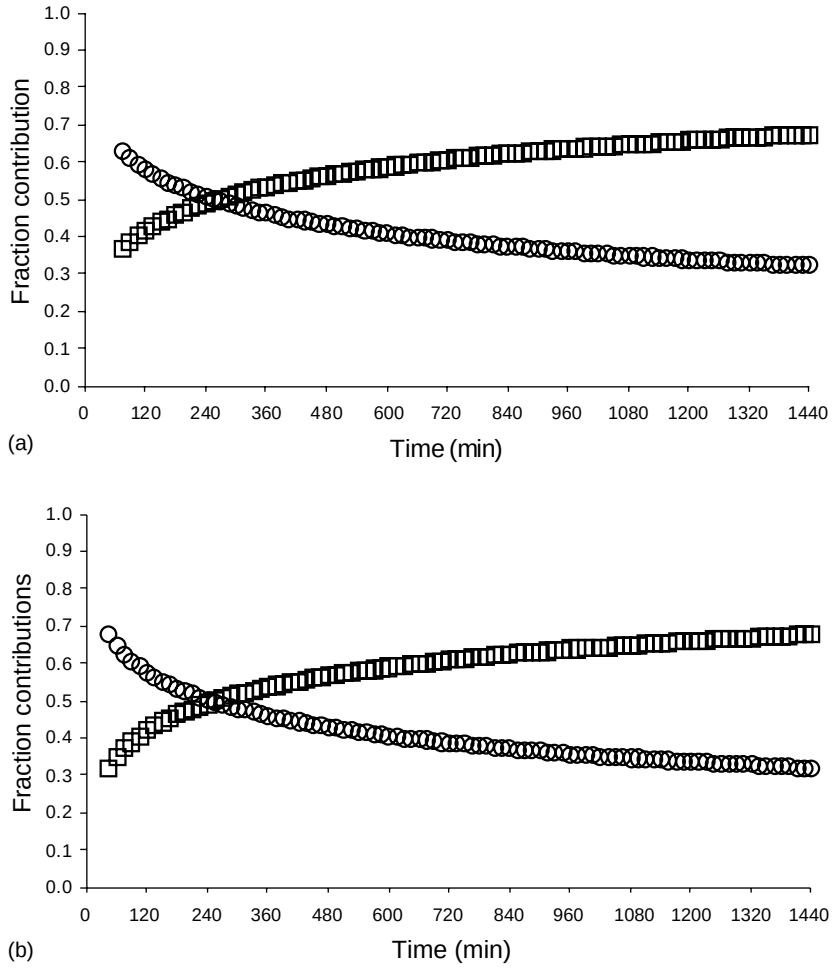

Fig. 5. Fraction contribution of the Fickian diffusion (○) and the erosion (□) mechanisms from tablets made of pellets formulation as a function of release time (a) TF#1 ($k_1 = 0.0104\,\mathrm{min}^{-0.43}$ and $k_2 = 9.57 \times 10^{-4}\,\mathrm{min}^{-0.86}$); (b) TF#3 ($k_1 = 0.0123\,\mathrm{min}^{-0.43}$ and $k_2 = 11.44 \times 10^{-4}\,\mathrm{min}^{-0.86}$).

Table 3
Values of release kinetic constants (k_1: Fickian mechanism; k_2: relaxational mechanism), release exponent (n), coefficient of determination (R^2) and mean dissolution time (MDT) for tablets made of matrix pellets

Tablet formulation	Model	k_1	k_2	n	R^2	MDT (min)
TF#1	1[a]	$0.0044\,\text{min}^{-0.7059}$	–	0.7059	0.9993	901.88
	2[b]	$0.0104\,\text{min}^{-0.43}$	$9.57 \times 10^{-4}\,\text{min}^{-0.86}$	–	0.9853	–
TF#3	1[a]	$0.0086\,\text{min}^{-0.6251}$	–	0.6251	0.9984	775.07
	2[b]	$0.0123\,\text{min}^{-0.43}$	$11.44 \times 10^{-4}\,\text{min}^{-0.86}$	–	0.9889	–

[a] $M_t/M_\alpha = k_1 t^n$.
[b] $M_t/M_\alpha = k_1 t^m + k_2 t^{2m}$, where $m = 0.43$ for the tablets under investigation and according to Peppas and Sahlin, 1989.

pellets, respectively (Table 3). Previous works reported that Fickian diffusion through the hydrated xanthan gum matrix is not the only mechanism accounting for drug release (Sujja-areevath et al., 1996; Sujja-areevath et al., 1998). Swelling and erosion occur concurrently resulting in moving frontier conditions, which continuously modifies the diffusivity of the drug. The effectiveness of xanthan gum as a hydrophilic polymer capable of slowing drug release is due to its high swelling and solvent penetration rate coupled with its moderate erosion rate (Sujja-areevath et al., 1998).

The fraction of the model drug released from tablet of β-CD matrix pellets is higher than that from tablet of LAC matrix pellets since the beginning of dissolution. The overall release rate of the model drug from tablets TF#3 is higher than that from tablets TF#1. Such observation is in accordance with the derived values for the kinetic constant k_1 and is confirmed by the smaller MDT value (∼13 h) for tablets of β-CD pellets and higher MDT value (∼15 h) for tablets of LAC pellets (Table 3). This is indicative that the properties of the tablets and, probably, the properties of the original pellets constituting the tablets are influencing the release of the model drug.

To investigate the Fickian diffusion and relaxational (erosion) mechanisms over the first 60% of drug release for tablet formulations TF#1 and TF#3, the values of the Fickian constant k_1 and the relaxational constant k_2 were calculated (Table 3). The estimated contributions of the two mechanisms are shown graphically in Fig. 5. Both Fickian constants k_1 and relaxational constants k_2 for the two tablet formulations were very close. Fickian diffusion was predominant during the first 4 h of the dissolution time while polymer erosion gradually increased then became the predominant mechanism for the rest of dissolution time. Such behaviour is well explained by the increase of thickness of the viscous gel layer around the matrix that creates a longer path length for diffusion which is followed by polymer chain relaxation, disentanglement and erosion (Sujja-areevath et al., 1998).

5. Conclusion

Permanent deformation of the pellets was found to be the most relevant mechanism involved in the compression of these units. Evidence of fragmentation of the pellets during the compression process was noticed, however such occurrence was limited to very little extension and regarded as not relevant. In addition to permanent deformation, densification was considered as a significant mechanism of compression since not only the visual examinations detected such occurrence but also the physical analysis results supported its importance.

Pellet's matrix integrity was destroyed in the first hour of dissolution test due to the disruption of the agglomerate's structure probably because of the excessive swelling of the gum. For the tablets made of pellets, destruction of the matrix integrity was only noticed for those made of pellets comprising tribasic calcium phosphate as the filler. Possibly this was a result of increased total porosity of the tablet due to drug release.

Tablets made of xanthan gum pellets comprising lactose or β-cyclodextrin did not function as multiparticulate systems. Nevertheless drug release over the dissolution period was controlled for both of the monolithic systems. For those systems, drug release behaviour was characterised by anomalous (non-Fickian) diffusion transport mechanism. Furthermore, it is inferred that drug diffusion and erosion are competing mechanisms of drug release from those systems. Fickian diffusion was predominant during the first 4 h of dissolution then relaxational mechanism dominated until the end of the test.

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