DEVELOPMENT AND CHARACTERIZATION OF NEW FUNCTIONALIZED POLYURETHANES FOR SUSTAINED AND SITE-SPECIFIC DRUG RELEASE IN THE GASTROINTESTINAL TRACT

María Dolores Campiñez[a], Elena Benito[b], Lucía Romero-Azogil[b], Ángela Aguilar-de-Leyva[a], María de Gracia García-Martín[b], Juan Antonio Galbis[b], Isidoro Caraballo[a].

[a]Department of Pharmacy and Pharmaceutical Technology, University of Seville, Profesor García González 2, 41012 Seville, Spain.

[b]Department of Organic and Pharmaceutical Chemistry, University of Seville, Profesor García González 2, 41012 Seville, Spain.

mcampinez@us.es, ebenito@us.es, lrazogil@us.es, aguilardeleyva@us.es, graciagm@us.es, jgalbis@us.es, caraballo@us.es

Corresponding author: María Dolores Campiñez; mcampinez@us.es

Telephone number: +34 954556136

Fax number: +34 954556083

Department of Pharmacy and Pharmaceutical Technology; University of Seville.

C/Profesor García González 2. 41012, Seville, Spain.

ABSTRACT

The main objective of the present paper has been the development and study of two new biodegradable polyurethanes, PU(dithiodiethanol-DTDI) and PU[(^{i}Pr)Man-DTDI], to be used as sustained matrix forming excipients. Furthermore, their capacity to act as excipient for colon drug delivery systems has been evaluated. Thus, SeDeM diagrams have been obtained to investigate their suitability to be processed through a direct compression process. Matrices containing 10–30% w/w of the polymers and theophylline anhydrous as model drug have been manufactured. Release studies have been carried out using a modified dissolution assay simulating pH and redox conditions for the gastro intestinal tract, including colon. Drug dissolution data have been analyzed according to the main kinetic models and their Excipient Efficiencies for prolonged release have been calculated. The principal parameters of the SeDeM Expert system, such as the parametric profile (mean radius) and the good compression index obtained for the polymers are above the values considered as adequate for direct compression even without addition of flow agents. The obtained values for Excipient Efficiency show good ability of the polymer to control the drug release. Finally, in the case of PU(dithiodiethanol-DTDI), a clear increase in the release rate has been observed when the formulation is subjected to colon simulating conditions.

Keywords

Excipient efficiency; matrix systems; polyurethanes; SeDeM; Sustained release; Site-especific drug delivery.

1. INTRODUCTION

The rational design of polymers for the development of novel biomedical applications is being a hot topic in the synthesis of new materials. In the last years, a wide range of natural and synthetic polymers with particular biomedical applications, capable of undergoing degradation by hydrolytic or enzymatic mechanism, have been synthesized (Nair and Laurencin, 2007).

Among the synthetic materials used in biomedicine, polyurethanes (PUs) are being widely investigated due to their low toxicity, potential biodegradability, biocompatibility, and versatile structures (Ferris et al., 2010; Galbis et al., 2016; Weisenberg and Mooradian, 2002). Numerous articles and reviews have reported exhaustive studies on degradability of polyurethanes, mainly processes involving hydrolytic, enzymatic, and oxidative pathways (Blackwell and Gardner, 1979; Blackwell and Lee, 1984; Loredo-Treviño et al., 2012; Lundberg et al., 2010; Lyman, 1960; Santerre et al., 2005; Storey et al., 1994a; Tang et al., 2009). Furthermore, the introduction of hydrolysable linkages besides the urethane bonds leaded to an improvement in the degradation rates of the materials (Agag, 2006; Vardareli et al., 2006). For instance, the introduction of disulfide bonds into polyurethane skeletons makes these linkages prone to a rapid cleavage in a reductive environment by the action of the natural tripeptide glutathione (γ-glutamylcysteinylglycine, GSH) (Paz et al., 2010; Rechichi et al., 2008; Storey et al., 1994b).

In the latest years, thanks to the collaborative work between our research teams, new polyurethanes have been synthesized and studied to be employed as matrix forming excipients for oral sustained drug delivery (Campiñez et al., 2015, 2013; Ferris et al., 2014). The results showed a noticeable reduction of the drug release rate just employing 20% w/w (or even 10% w/w) (Campiñez et al., 2015, 2013). This fact is very important in order to design a controlled release system because these dosage forms usually contain a high drug load. Besides, reduction of the total amount of excipient administered to the body reduces the potential risk of negative effects.

Therefore, in order to combine the good properties of PUs with the introduction of disulfide bonds into their skeletons to increase the biodegradability rate in a reductive environment, in this work we have developed new functionalized materials as sustained release excipients. Thus, the incorporation of D-mannitol as sugar monomer into the polymer backbone will enhance properties as biodegradability as well as biocompatibility (Galbis et al. 2016). These polymers have been tested considering both, conventional oral route and colon drug delivery.

Oral sustained release drug delivery systems are pharmaceutical formulations that provide a slow release rate of the drug, being this factor the limiting step in controlling the arrival of the drug to the systemic circulation (Costa et al., 2004; Nokhodchi et al., 2012). Therefore, these systems lead to a lower fluctuation of the drug concentration in plasma. As a consequence, the peak plasma levels of the drug will be reduced and the valley plasma levels will be increased, with respect to a conventional dosage form. Moreover, the therapeutic concentration of drug is maintained over a longer period of time and the time between doses is increased. This fact improves patient compliance, which is one of the main factors affecting the success of a treatment.

Among the different oral sustained release dosage forms, matrix tablets are the most widely employed because of their low cost and ease of manufacture. Our research group has a wide experience in the design of these systems (Campiñez et al., 2016; Casas et al., 2015; Mason et al., 2015). Novel formulation tools as percolation thresholds, Excipient Efficiency or *in silico* methods have been employed to study the internal structure of these systems. We have studied critical points of drugs and polymers, including both hydrophilic and inert matrices (Gonçalves-Araújo et al., 2008; Miranda et al., 2006) in order to obtain information for a science-based development of the pharmaceutical formulations that allows to “design the quality” instead of testing it, hence reducing time and cost in drug development.

On the other hand, colon-specific drug delivery is an emerging field in pharmaceutical technology. Targeted drug delivery into the colon is highly desirable for local treatment

of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amebiosis, colonic cancer, local treatment of colonic pathologies. Another potential benefit could be the increase in bioavailability of certain drugs (Philip and Philip, 2010). Therefore, the development of a delivery system with the ability of releasing the drug in the colon at a sustained rate would be highly beneficial.

The main objective of the present paper has been the synthesis and characterization of new biodegradable polymers and the study of their ability to be used as sustained release excipients. Furthermore, the capacity of these excipients to be used as vehicles in colon-specific delivery systems has been evaluated carrying out a modified dissolution assay simulating gastro intestinal and colonic drug release.

2. MATERIALS AND METHODS

2.1. Materials

Theophylline anhydrous and the new polymers PU(dithiodiethanol-DTDI) (**PU4**) and PU[(^{i}Pr)Man-DTDI] (synthesized with two different molecular weights 40000 Da (**PU5**) and 90000 Da (**PU5'**)) were used in the manufacture of the matrix tablets. The API was purchased from Acofarma (Barcelona,Spain) and the polymers were synthesized as described in method section.

Commercial reagents were purchased from Sigma-Aldrich Chemical Co. (Madrid, Spain) and used as received. Solvents of high purity grade were dried by appropriate standard procedures when necessary.

2.2. Methods

2.2.1. Preparation of PU(dithiodiethanol-DTDI) (PU4) and PU[(^{i}Pr)Man-DTDI] (PU5)

A round-bottom flask was loaded with 3 mmol of the monomer 2,2'-dithiodiethanol (**1**) or 3,4-*O*-isopropylidene-D-mannitol (**2**) (Wiggins, 1946) and the system was treated with three cycles of vacuum-argon before the addition of dried THF (3 mL). The mixture was stirred to get a solution, then 2,2'-ditiodiethyldiisocyanate (**3**) (3 mmol) (Teramura et al., 2007) was added under an argon atmosphere, followed by one drop of the

catalyst [dibutyltin (II) dilaurate]. Stirring was continued at room temperature for 24 hours. Finally, the reaction mixture was treated with *tert*-butyl alcohol (0.6 mL) for 30 minutes, and added dropwise into cold diethyl ether (200 mL). The precipitated polymer was filtered, washed with diethyl ether and dried under vacuum at 40°C for 24 h. The polyurethanes PU(dithiodiethanol-DTDI) and PU[(^{i}Pr)Man-DTDI] were isolated as white solids in 86 and 90% yields, respectively.

2.2.2. Characterization of the new polyurethanes

The characterization of the two polyurethanes was carried out in the Microanalysis Laboratories of the CITIUS Service, at University of Seville, Spain. Elemental analyses were performed using an Analyzer LECO CHNS 932 (Saint Joseph, MI, USA) and a Sartorius Micro Balance M2P (Madrid, Spain). IR spectra were recorded on a JASCO FT/IR-4200 spectrometer (Easton, MD, USA). ^{1}H and ^{13}C NMR spectra were recorded using a Bruker Advance AV-500 spectrometer (Francfort, Germany) at 300°K. Chemical shifts (δ) were reported as parts per million downfield from Me_4Si. Two-dimensional spectra (2D) as ^{1}H-^{1}H homonuclear (COSY) and ^{13}C-^{1}H heteronuclear shift correlation (HETCOR) were also recorded. Molecular weights were determined by gel permeation chromatography (GPC) using a Waters equipment (Milford, MA, USA) provided with a refractive-index detector 2414. *N,N*-dimethylformamide (DMF) containing LiBr (5.8 mM solution) was the mobile phase. 100 µL of 0.1% (w/v) sample solution were injected and chromatographed with a flow of 1 mL min^{-1}. HR3 and HR4 Waters Styragel columns (7.8 x 300 mm) linked in series and protected with a guard column, thermostated at 60 °C were used. Molar mass averages and their distributions were calculated against polystyrene standards.

The thermal behavior of the polyurethanes was examined by differential scanning calorimetry (DSC) using a TA DSC Q200 Instrument (Milford, MA, USA) calibrated with indium. DSC data were obtained from samples of 4-6 mg at heating/cooling rates of 10 °C min^{-1} under a nitrogen flow of 20 mL min^{-1}. The melting temperature (T_m) was taken as the maximum of the endothermic peak appearing on heating traces recorded at 10

°C min^{-1}, and the glass transition temperature (T_g) was taken as the temperature for the inflection point seen on heating traces recorded at 20 °C min^{-1} from samples quenched from the melt.

Themogravimetric analyses (TGA) were performed on a TA SDT Q600 thermobalance (Milford, MA, USA). Polymer samples with a weight around 3-4 mg were heated at a rate of 10 °C min^{-1} within the temperature range of 30-600 °C under an inert atmosphere.

The polymerization reaction assays were performed in the absence of humidity, under an inert atmosphere. All glassware was heated overnight at 80 °C before used. The pure monomers were dried under vacuum and stored under an inert atmosphere until required.

2.2.3. Characterization of PU(dithiodiethanol-DTDI) (PU4)

GPC data: M_w 17458; M_n 15382; M_w/M_n 1.13. IR: v (cm^{-1}) 3341 (N-H, O-H), 1682 (C=O), 1529 (N-H and N-CO).

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 2.76-2.84 (m, 4H, SCH_2CH_2O and terminal SCH_2CH_2OH), 2.93-2.99 (m, 4H, SCH_2CH_2NH), 3.28 (c, 4H, J= 6.3 Hz, CH_2NH), 3.64 (c, J= 6.2 Hz, terminal CH_2OH), 4.20 (t, 4H, J= 6.0 Hz, CH_2O), 4.86 (t, J= 5.4 Hz, terminal CH_2OH), 7.35 (bs, 2H, NH).

^{13}C NMR (DMSO-d_6, 125 MHz): δ (ppm) 37.0 (SCH_2CH_2NH), 37.4 (SCH_2CH_2O), 39.7 (CH_2NH), 41.1 (terminal SCH_2CH_2OH), 59.4 (terminal CH_2OH), 61.8 (CH_2O), 155.9 (CO).

Anal. calcd. for ($C_{10}H_{18}N_2O_4S_4 \cdot 0.5H_2O$): C, 32.68; H, 5.21; N, 7.62; S, 34.89. Found: C, 32.82; H, 4.93; N, 7.34; S, 33.77.

TGA data: T_d: 239 °C (Decomposition temperature associated to 10% weight loss) and T_{ds}: 249 °C (Maximum decomposition temperature associated to 87% weight loss).

DSC data: T_m: 109 °C; ΔH_m: 41 J g^{-1} (Melting enthalpy); T_g: -0.8 °C.

2.2.4. Characterization of PU[(^{i}Pr)Man-DTDI] (PU5 and PU5')

GPC data: M_w 52845; M_n 45075; M_w/M_n 1.17 (**PU5**); M_w 97103; M_n 62256; M_w/M_n 1.56 (**PU5'**).

IR: v (cm^{-1}) 3320 (N-H, O-H), 1693 (C=O), 1525 (N-H and N-CO), 1250 [$C(CH_3)_2$].

^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm) 1.29 (s, 6H, CH_3), 2.72-2.81 (m, 4H, CH_2S), 3.20-3.31 (m, 4H, CH_2NH), 3.43-3.63 (m, 2H, H-3, H-4), 3.64-3.74 (m, 2H, H-1_a, H-6_a), 3.81-3.96 (m, 2H, H-2, H-5), 4.09-4.18 (m, 2H, H-1_b, H-6_b), 4.40-5.30 (several m, OH, *cross* H-2, *cross* H-5), 7.26 (bs, 2H, NH).

^{13}C NMR (DMSO-d_6, 125 MHz): δ (ppm) 27.2 (CH_3), 27.3 (*cross* CH_3), 31.3 (CH_2S), 37.4 (CH_2NH), 64.9 (*cross* C-1, *cross* C-6), 65.8 (C-1, C-6), 70.0 (C-2, C-5), 72.8 (*cross* C-2, *cross* C-5), 78.9 (*cross* C-3, *cross* C-4), 79.2 (C-3, C-4), 108.6 {*cross* [$\underline{C}(CH_3)_2$]}, 108.9 [$\underline{C}(CH_3)_2$], 155.8 (*cross* CO), 156.3 (CO).

Anal. calcd. for ($C_{15}H_{26}N_2O_8S_2 \cdot H_2O$): C, 40.53; H, 6.35; N, 6.30; S, 14.42. Found: C, 40.28; H, 6.20; N, 6.31; S, 14.51.

TGA data: T_d: 243 °C (Decomposition temperature associated to 10% weight loss) and T_{ds}: 258 °C (Maximum decomposition temperature associated to 90% weight loss).

DSC data: T_g: 61 °C.

2.2.5. Preformulation studies of PU4 and PU5 using the SeDeM method

An expert system called SeDeM method, which was developed by Suñé Negré et al. at the University of Barcelona, Spain, (Suñé Negré et al., 2013) was used to carry out the preformulation studies of the polymers employed. This method is based on the experimental measurement of a number of rheological parameters of the powder followed by normalization of their values and division in different groups depending on the property that they are measuring (as dimension, compressibility, flowability/powder flow, lubricity/stability and lubricity/dosage).

Rheological studies were carried out for the polymers applying the techniques indicated in the SeDeM Method (Suñé Negré et al., 2013).

Bulk density (ρ_{bulk}) and tapped density (ρ_{tapped}) were measured in accordance with the method described in European Pharmacopoeia (European pharmacopoeia, 7th

edition). Both parameters were determined in triplicate using 9.9 g of the polymer **PU4** and 6.2 g of **PU5**.

The bulk density was obtained according to the Equation 1.

$$\rho_{bulk} = {}^{m}/_{V_{bulk}} \qquad (1)$$

Where ρ_{bulk} is the bulk density (g/mL), *m* is the mass (g) and V_{bulk} is the apparent volume (mL).

The tapped density was determined from the tapped volume (V_{tapped}) occupied by the powder after repeated taps until the difference between successive measures was less than 2 ml. The volume taken is the value obtained after 1250 taps.

The tapped density was obtained according to Equation 2.

$$\rho_{tapped} = {}^{m}/_{V_{tapped}} \qquad (2)$$

Where ρ_{tapped} is the tapped density (g/mL), *m* is mass (g) and V_{tapped} is the volume after tapping (mL).

Carr index *(IC%)* (Equation 3) and Hausner's index *(IH)* (Equation 4) were calculated from the results of ρ_{bulk} and ρ_{tapped} and can be used to predict the compressibility and flowability of the powders. Sponginess index (*IS*) has been calculated according to Equation 5.

$$IC\% = ((\rho_{tapped} - \rho_{bulk})/\rho_{tapped}) * 100 \qquad (3)$$

$$IH = \rho_{tapped}/\rho_{bulk} \qquad (4)$$

$$IS = (\rho_{tapped} - \rho_{bulk})/(\rho_{tapped} * \rho_{bulk}) \qquad (5)$$

The flowability was measured using a funnel type described in European Pharmacopoeia (European pharmacopoeia, 7th edition). This funnel had a height of 9.5 cm, an external diameter of 7.2 cm, an internal diameter of 1.8 cm and an angle of 45º with respect to the vertical.

The rest angle is an indirect method that indicates the cohesivity of a powder and is used to estimate its flow properties (European pharmacopoeia, 7th edition). This is the angle of the cone formed when the product is dropped through a funnel placed at 2 cm of height with respect to the horizontal. This parameter is calculated according to the Equation 6.

$$tg\ (\propto) = h/r \qquad (6)$$

Where *h* is the height of the cone and *r* is the radius of the cone, the assay was carried out in six replicates.

The loss on drying (%HR*)* was measured according to the method proposed by the European Pharmacopoeia (European pharmacopoeia, 7th edition). The samples were dried in a heater at 105 ± 2 ºC until a constant weight is obtained. This assay has been carried out in three replicates.

The hygroscopicity was determined in three replicates as the increase in sample weight after being kept in a humidifier at ambient relative humidity of 76% (±2%) and room temperature for 24 h.

The percentage of particles measuring <45 µm was determined as the percentage of particles that pass through a 45 µm sieve subjected to vibration for 10 min at speed 60 (Retsch, model AS 200, Germany).

For the determination of the homogeneity index, a sieving test employing the following sieve sizes: 0.710 mm, 0.500 mm, 0.355 mm, 0.180 mm, 0.090 mm, 0.045 mm was carried out. Sieves were subjected to vibration during 10 min at speed 60 (Retsch, model AS 200, Germany). The percentage of product that was retained in each sieve was calculated. Equation 7 was applied to the data obtained.

$$I\theta = \frac{F_m}{100+(d_m-d_{m-1})F_{m-1}+(d_{m+1}-d_m)F_{m+1}+(d_m-d_{m-2})F_{m-2}+(d_{m+2}-d_m)F_{m+2}+\cdots+(d_m-d_{m-n})F_{m-n}+(d_{m+n}-d_m)F_{m+n}} \qquad (7)$$

Where *Iθ* is the relative *homogeneity index*, informing about the homogeneity of the particle-size distribution in the range of the fractions under study. F_m is the percentage

of particles in the majority range; F_{m-1} is the percentage of particles in the range immediately below the majority range; F_{m+1} is the percentage of particles in the range immediately above the majority range; n is the order number of the fraction studied under a series with respect to the majority fraction; d_m is the mean diameter of the particles in the majority fraction; d_{m-1} is the mean diameter of the particles in the fraction of the range immediately below the majority range; d_{m+1} is the mean diameter of the particles in the fraction of the range immediately above the majority range.

Once the parameters described were determined, they were normalised, in order to situate their values in a scale from 0 to 10, in such a way that the maximum (10) and/or minimum (0) value of every normalised parameter corresponds to the natural limit of the parameter before normalisation. Table 1 and Table 2 show the limits before normalisation and the factor applied to each parameter.

The normalised values, also called radius values (*r*), were then plotted in the SeDeM Diagram. The radius values are connected with lineal segments. In this case, the SeDeM Diagram was made with eleven parameters as previous studies for another novel polyurethane (Campiñez et al., 2015).

To determine whether the product is suitable for direct compression using this numerical method, the following indexes were calculated based on the SeDeM Diagram.

Parametric index (*IP*) was calculated according to Equation 8.

$$IP = {}^{No.\rho \geq 5}/_{No.Pt} \qquad (8)$$

Where *No. p ≥ 5* indicates the number of parameters whose values are equal to or higher than 5 and *No.Pt* indicates the total number of parameters studied.

The acceptability limit would correspond to:

$IP \geq 0.5$

Parametric profile index (*IPP*) corresponds to the mean *r* value of all parameters.

The acceptability limit corresponds to:

$IPP = mean\ r \geq 5$

Good compression index (*IGC*) was calculated following equation 9.

$IGC = IPP * f$ (9)

Where *f* is a reliability factor and was calculated with the equation 10.

$f = {}^{polygon\ area}/_{circle\ area}$ (10)

The acceptability limit was calculated by equation 11.

$IGC = IPP * f \geq 5$ (11)

2.2.6. Preparation of the matrix tablets

Table 3 shows the compositions of the different formulations and Figure 1 shows an image of the tablets formulations as an example. Theophylline anhydrous and the polymer were blended for 5 minutes in a Turbula mixer (Willy A. Bachofen, Basel, Switzerland) employing different percentages. Batches were prepared by direct compression in an eccentric tabletting machine (Bonals A-300, Barcelona, Spain) using manual feeding and applying the maximum compression force accepted by the formulation. The tablets were prepared using 9-mm diameter punches and the target weight was 250 mg.

2.2.7. Drug dissolution tests

Gastro-intestinal dissolution tests were carried out employing a variation of the pharmacopoeial paddle method in a Sotax AT7 Smart USP dissolution apparatus (Allschwil, Switzerland). During the test, the formulation was exposed to four phases simulating in subsequent order the stomach, jejunum, distal ileum, and proximal colon. The method chosen was proposed by Ferris et al. 2014 and is a variation of the formerly proposed by Schellekens et al., 2007. This method describes a gastro-intestinal simulation system mimicking pH and transit times (see Table 4) through the gastro-intestinal tract up to the proximal colon. At the end of each phase, a switch solution was added to obtain the required composition of the next phase. The rotation speed of the paddle was 50 rpm and the temperature of the dissolution medium was

kept at 37 ± 0.5 °C. In order to have a better simulation of the physicochemical conditions in the colon, we modified the method reported by Schellekens et al., (Schellekens et al., 2007) creating a reductive environment during last phase, corresponding to the colon. For this purpose, the experiments were carried out under an argon atmosphere, and glutathione was added to the media up to a final concentration of 5 mM. Several samples (5 mL each) were withdrawn at each period of time during 12 hours and measured in an Agilent 8453 UV/VIS spectrophotometer (California, USA). The theophylline content was calculated using a previously determined calibration curve at 272 nm.

2.2.8. Dissolution data analysis

Drug release data were analyzed according to Zero Order, Higuchi (Higuchi 1963), Korsmeyer (Korsmeyer, et al. 1983), and Peppas&Sahlin (Peppas and Sahlin 1989) dividing the release profiles in two phases. The first phase corresponds to the stomach and jejunum and the second one to distal ileum and proximal colon, in order to study the release mechanism in the different gastro-intestinal phases.

$$M_t/M_\infty = k_0 * t \qquad (12)$$

$$M_t/M_\infty = k_h t^{1/2} \qquad (13)$$

$$M_t/M_\infty = k_k t^n \qquad (14)$$

$$M_t/M_\infty = k_d t^m + k_r t^{2m} \qquad (15)$$

Where M_t / M_∞ is the fraction of drug released at time t (M_∞ corresponds to the amount of drug released at time infinite), k_0 is the zero-order release constant eq (12), k_h is the Higuchi's release rate constant on eq (13), k_k is the Korsmeyer's kinetic constant on eq (14), t is the release time and n is the Korsmeyer's time exponent that depends on the release mechanism and the shape of the matrix tested (Ritger and Peppas 1987). k_d is the diffusional rate constant, k_r is the erosion/relaxation rate constant on equation (15)

and *m* is the purely Fickian diffusion exponent (which depends on the geometrical shape of the delivery device through its aspect ratio).

2.2.9. Efficiency of the excipient

The *Excipient Efficiency* (*EE*) for controlling the drug release has been calculated with the novel equation proposed by Casas et al. (Casas et al., 2015) for inert matrices using the total porosity of the system and the slope of the Higuchi's equation corrected by the drug solubility (see equation 16).

$$EE = (\varepsilon/k_H) * (1/(1.963 - 0.246 lnCs)) \qquad (16)$$

Where *EE* is the efficiency of the excipient, ε is the total porosity, k_H is the Higuchi rate constant and C_s is the drug solubility.

3. RESULTS AND DISCUSSION

3.1. Preparation and characterization of the polyurethanes

The synthesis of the new polyurethanes **PU4** and **PU5** (Scheme 1) was carried out by a procedure consisting of the treatment of the commercially available diol 2,2'-dithiodiethanol (**1**) or 3,4-*O*-isopropylidene-D-mannitol (**2**) (Wiggins, 1946) in THF with 2,2'-ditiodiethyldiisocyanate (**3**) (Teramura et al., 2007) in the presence of dibutyltin (II) dilaurate as catalyst for 24 h at room temperature. Compound **3** has been widely employed as a crosslinking agent, and we now describe its use as a monomer to prepare polyurethanes containing a high rate of disulfide bonds along the polymer chains. The polyurethanes were isolated by precipitation in diethyl ether, followed by filtration and washed with the same solvent. Finally, the products were dried under vacuum to give white solid materials in high yields (86-90%). Other solvents such as DMSO were also assayed but colored materials and lower yields were obtained.

The new polymers were characterized by GPC (Figure 2), FTIR-ATR (Figure 3) and NMR spectroscopies, and thermal and elemental analyses. The latest were in full agreement with those calculated for the expected compositions. The weight-average molecular weights were in the range of 17500–97000 g mol^{-1}, and the low

polydispersities values of 1.1 and 1.5 showed a good control of the polymerization processes.

The chemical structures of polyurethanes were ascertained by FTIR-ATR and ^{1}H NMR and ^{13}C NMR; all these data and assignments are detailed in the experimental section. Characteristic IR absorption bands of the urethane group, and the sugar moieties in the case of **PU5**, were observed at the predicted positions and with the expected intensities.

In all cases, NMR spectra were in full concordance with the expected chemical structures of the polyurethanes. The ^{1}H NMR spectra of **PU4** showed signals corresponding to terminal OH groups, and their corresponding carbons were also observed by ^{13}C NMR (Figure 4). NMR spectra of **PU5** revealed certain degree of crosslinking due to the reaction of the secondary hydroxyl groups of the D-mannitol moiety with the diisocyanate **3**. This crosslinking effect could be easily identified by NMR, thus the ^{13}C NMR spectra showed two different signals for the carbonyl group and additional signals for the expected carbons of the sugar chain (Figure 5). From the ^{1}H NMR spectra, a 10% of crosslinking extension was estimated. Assignments of the signals corresponding to crosslinking reactions are depicted in the experimental section with the abbreviation "*cross*".

The thermal properties of the synthesized polymers were studied by TGA and DS. TGA studies (Figure 6) revealed that **PU4** and **PU5** were stable to thermal degradation under inert atmosphere up to 220 °C with a decomposition onset temperature associated to 10% weight loss around 240 °C. The degradation of **PU4** and **PU5** proceeded in one stage at 249 and 258 °C respectively, with a total associated weight loss about 90%.

The DSC studies (Figure 7) showed that **PU4** was semicrystalline with T_m 109 °C and a melting enthalpy of 41 J g^{-1} at the first heating. The second heating showed T_g at -0.8 °C. In contrast **PU5** showed an amorphous behavior without a thermal transition associated to the fusion, indicating that the polymer has a certain grade of crosslinking

as previously it had been observed. The second heating after a rapid cooling showed a T_g of 61 °C.

3.2. Preformulation studies of PU4 and PU5 using the SeDeM method

SeDeM method provides information about the rheology of a powder, indicating its ability for direct compression (Suñé Negré et al., 2013). Furthermore, this expert system shows the strong and weak aspects of the powder, providing a rational basis for the design of a direct compression formulation, contributing to build up a database that improves the formulations (Campiñez et al., 2016b) and helping to correct the weak points of a substance with other components of the formulation.

For this purpose a number of rheological parameters were measured, grouped and normalized. After that, the results were graphically expressed in form of a SeDeM diagram, providing unified results, which constitute a useful database for preformulation and formulation. These values were normalized and represented as radii in a diagram, making possible the comparison of the results of the different assays in order to detect the properties that need to be improved. This way, the information provided allows obtaining the final formulation of tablets by direct compression in an easy way. Furthermore, the SeDeM expert system evaluates the attributes having an impact on the quality of the final product, making possible the improvement of the formulation from a science based perspective, in agreement with the principles of Quality by Design (QbD), described in the guidelines of the International Conference on Harmonisation (ICH Q8) (EMEA, 2004. Guideline on ICH Topic Q8, Note for Guidance on Pharmaceutical Development)

Table 5 shows the results obtained for the characterization of the PU(dithiodiethanol-DTDI)

(**PU4**) and PU[(^{i}Pr)Man-DTDI] (**PU5**) using the SeDeM method.

The obtained values were normalized and represented as radius values in the diagram shown in Figure 8 for **PU4** and Figure 9 for **PU5**. This provides intuitive and valuable

information about the type of substances that would be adequate for obtaining a direct compression powder blend containing these excipients.

The results of the Parametric Profile (mean radius) (5.31 for **PU4** and 5.78 for **PU5**) and the Good Compression Index (5.00 for **PU4** and 5.45 for **PU5**), are higher than 5, therefore they are considered as adequate for direct compression without adding a flow agent. Being these values better than those reported for another new polyurethane studied previously (Campiñez et al., 2015) and even higher than the value reported for hydroxypropylmethyl cellulose (HPMC) (Saurí et al., 2014), one of the most used excipient for controlled release.

In summary, the results of the SeDeM studies indicate that both polyurethanes can be considered as direct compression excipients, which indicates that their rheological properties are clearly above the average values for pharmaceutical excipients.

Using the SeDeM diagram, the goodness of these polymers to be used for direct compression can be easily appreciated. Additionally, it is possible to see the strong points and the weaknesses of the powders. For example, for **PU4**, one of its strong aspects is the compressibility, having a mean incidence of this value higher than 7 over 10. However, one of the weak points in the rheological properties of this polymer is the flowability, which can notably benefit from the use of a Flow Aid excipients or Direct Compression fillers.

3.3. Drug dissolution tests

The dissolution profiles of the different batches are shown in Figure 10. The ability of both polymers to control the drug release is reflected in the substantial decrease in the drug release rate caused by the increase in the polymer concentration, much more noticeable in the polymer **PU4**. For example batch 1, with 10% of **PU4** releases around 95% w/w of theophylline at 6 hours in comparison with batch 3, with 30% of polymer, which releases about 55% of theophylline after 6 hours of assay. By the contrast, batches prepared with **PU5** show a decrease of the release rate less pronounced than in the case of **PU4**.

On the other hand, the influence of the molecular weight on the release rate has been studied. For this purpose, the polymer **PU5** was synthesized with two different molecular weights (*ca*. 40000 Da and 90000 Da respectively). Batches with a concentration of 10%, 20% and 30% of this polymer (**PU5'**) were prepared (batches 7, 8 and 9, respectively) and were subjected to the dissolution tests, keeping the same conditions than the previous assays. The obtained profiles are shown in Figure 10, in comparison with the formulations prepared with **PU5** (batches 4 to 6). Despite a higher degree of polymerization of the excipient is typically related to a slower drug release, the results exhibited in Figure 10, did not show a significant influence of the molecular weight on the release profiles. This could be due to the fact that other formulation factors, like for example rheological properties, compactibility, compressibility or particle distribution inside the matrix, are masking this influence.

Concerning the capacity of these excipients to be used as vehicles for site-specific in the gastro intestinal tract, both, **PU4** and **PU5** show a faster release when they are subjected to the colon simulating phase, that can be attributed to an increase of the biodegradability of the disulfide bonds of the polymers in the reductive environment. This effect is more evident in the case of **PU4**. Nevertheless, it is interesting to note that in formulations containing **PU5**, the effect is more evident for the polymer with a lower molecular weight (batches 4 to 6) in comparison with batches 7 to 9. This higher susceptibility to degradation in reductive environment is interpreted as an easier accessibility of dissolution medium to the disulfide bonds of the polymer chain, in case of a lower degree of polymerization.

Based on the release profiles, and on the degree of variability shown by the studied formulations, it can be concluded that the percolation threshold of both excipients is located between 20 and 30% w/w of polymer. In this sense, it is interesting to note that the formulations below the critical point of the polymers (10% and 20%) show a higher susceptibility to the reductive conditions, which is attributed to the lower accessibility of

the release medium to the drug, when the polymer forms a coherent insoluble network throughout the system, i.e., for formulations containing 30% w/w of polymer.

The faster release rate in the colon-simulating environment showed by the obtained polymers, especially **PU4**, has a high importance in the field of site-specific release in the GI tract suggesting that the obtained polymers could be potential candidates for excipients of colon targeted drug delivery systems.

3.4. Release kinetics analysis

Drug release data have been analyzed according to Zero order, Higuchi (Higuchi 1963), Korsmeyer (Korsmeyer, et al. 1983), and Peppas&Sahlin (Peppas and Sahlin 1989) kinetic models. Table 5 shows the fit of the data to these models.

In general, the release constant decreases as the concentration of excipient increases. Furthermore, the release constants for the second phase are higher than the constants for the first phase. This fact supports the biodegradability of the disulfide bonds of the polymers in the reductive environment.

The time exponent, indicative of the release mechanism “n” was examined in the Korsmeyer’s equation. Values near 0.5 are indicative of a diffusion mechanism whereas values higher to 1 indicate an erosion mechanism. According to Table 6, the time exponents are closer to 0.5 for the Korsmeyer’s equation for both polymers in the stomach/jejunum phase, whereas in the ileum/colon phase are higher than 1. This indicates that the drug release follows predominantly the mechanism of diffusion in the first phase, whereas the erosion is predominant in the second phase.

3.5. Excipient Efficiency for controlled release

The Excipient Efficiency is a parameter that provides an estimation of the capacity of an excipient to reduce the drug release rate (Casas et al., 2015). This parameter has been calculated for the new excipients developed in this work.

The values calculated for the Excipient Efficiency of the different batches prepared with the polymers are shown in Table 6.

This parameter should be calculated employing formulations in which both, the drug and the excipient are percolating the system (i.e., they are above their critical points). Therefore, in this case, the batches containing 30% of excipient have been selected. The obtained values are clearly higher than the obtained for commercial excipients as Eudragit RS PM (5.59 $min^{1/2}$ mg^{-1} ml), which is one of the most employed inert matrix forming excipients.

4. CONCLUSIONS

The newly synthesized polymers PU(dithiodiethanol-DTDI) (**PU4**) and PU[(^{i}Pr)Man-DTDI] (**PU5**) show a high ability to form matrix systems, and are able to act as controlled release excipients.

According to the SeDeM method, these new biodegradable polymers show adequate rheological properties to be used as matrix forming excipient by direct compression, even without adding of flow agents.

Furthermore, the polymer **PU4** shows the capacity to be used as vehicle in colon-specific delivery systems.

These facts together with their biodegradability and biocompatibility make these polymers excellent controlled release matrix forming excipients. Additionally, the polyurethane **PU4** is a potential candidate to be used in the development of new colon targeting drug delivery systems.

Acknowledgements

The authors would like to express their gratitude to the Spanish Ministry of Economy and Competitiveness and FEDER Funds (European Union) for the support of the project MAT2012-38044-C03-01 and MAT2012-38044-C03-02 and the Regional Government of Andalusia for the support of the project P12-FQM-1553.

REFERENCES

Agag, T., 2006. Preparation and properties of some thermosets derived from allyl-functional naphthoxazines. J. Appl. Polym. Sci. 100, 3769–3777. doi:10.1002/app.23502

Blackwell, J., Gardner, K.H., 1979. Structure of the hard segments in polyurethane elastomers. Polymer (Guildf). 20, 13–17.

Blackwell, J., Lee, C.D., 1984. Hard-segment polymorphism in MDI/diol-based polyurethane elastomers. J. Polym. Sci. Part A-2, Polym. Phys. 22, 759–772.

Campiñez, M.D., Aguilar-de-Leyva, Á., Ferris, C., de Paz, M.V., Galbis, J.A., Caraballo, I., 2013. Study of the properties of the new biodegradable polyurethane PU (TEG-HMDI) as matrix forming excipient for controlled drug delivery. Drug Dev. Ind. Pharm. 39, 1758–1764. doi:10.3109/03639045.2012.736516

Campiñez, M.D., Caraballo, I., Puchkov, M., Kuentz, M., 2016. Novel Polyurethane Matrix Systems Reveal a Particular Sustained Release Behavior Studied by Imaging and Computational Modeling. AAPS PharmSciTech 0–9. doi:10.1208/s12249-016-0613-0

Campiñez, M.D., Casas, M., Caraballo, I., 2016b. International Journal of Clinical Pharmacology & Pharmacotherapy Characterisation of the Ability of Carbamazepine for Processing It through Direct Compression Applying the New Expert System SeDeM 1, 1–5.

Campiñez, M.D., Ferris, C., de Paz, M.V., Aguilar-de-Leyva, A., Galbis, J., Caraballo, I., 2015. A new biodegradable polythiourethane as controlled release matrix polymer. Int. J. Pharm. 480, 63–72. doi:10.1016/j.ijpharm.2015.01.011

Casas, M., Aguilar-de-Leyva, Á., Caraballo, I., 2015. Towards a rational basis for selection of excipients: Excipient Efficiency for controlled release. Int. J. Pharm. 494, 288–295. doi:10.1016/j.ijpharm.2015.08.002

Costa, E., Arancibia, A., Aïache, J.M., Costa Arancibia, A., Aïache, J.M., E., 2004. Sistemas matriciales, Acta Farm Bonaerense.

EMEA, 2004. Guideline on ICH Topic Q8, Note for Guidance on Pharmaceutical Development., n.d.

European Pharmacopoeia Commission, Council of Europe, European Directorate for the Quality of Medicines, 2010. European pharmacopoeia, 7th edition, n.d.

Ferris, C., de Paz, M.V., Aguilar-de-Leyva, A., Caraballo, I., Galbis, J.A., 2014. Reduction-sensitive functionalized copolyurethanes for biomedical applications. Polym. Chem. 5, 2370–2381. doi:10.1039/c3py01572f

Ferris, C., Violante de Paz, M., Zamora, F., Galbis, J.A., 2010. Dithiothreitol-based polyurethanes. Synthesis and degradation studies. Polym. Degrad. Stab. 95, 1480–1487. doi:10.1016/j.polymdegradstab.2010.06.021

Galbis, J.A., García-Martín, M. de G., de Paz, M.V., Galbis, E., 2016. Synthetic Polymers from Sugar-Based Monomers. Chem. Rev. 116, 1600–36. doi:10.1021/acs.chemrev.5b00242

Gonçalves-Araújo, T., Rajabi-Siahboomi, A.R., Caraballo, I., 2008. Application of percolation theory in the study of an extended release Verapamil hydrochloride formulation. Int J Pharm. 361, 112–117.

Loredo-Treviño, A., Gutiérrez-Sánchez, G., Rodríguez-Herrera, R., Aguilar, C.N., 2012. Microbial Enzymes Involved in Polyurethane Biodegradation: A Review. J. Polym. Environ. 20, 258–265. doi:10.1007/s10924-011-0390-5

Lundberg, P., Bruin, A., Klijnstra, J.W., Nyström, A.M., Johansson, M., Malkoch, M., Hult, A., 2010. Poly(ethylene glycol)-based thiol-ene hydrogel coatings?curing chemistry, aqueous stability, and potential marine antifouling applications. ACS Appl. Mater. Interfaces 2, 903–912. doi:10.1021/am900875g

Lyman, D.J., 1960. Polyurethanes. I. The solution polymerization of diisocyanates with ethylene glycol. J. Polym. Sci. 45, 49–59. doi:10.1002/pol.1960.1204514505

Mason, L.M., Campiñez, M.D., Pygall, S.R., Burley, J., Gupta, P., Storey, D., Caraballo, I., Melia, C.D., 2015. The influence of polymer content on early gel-layer formation in HPMC matrices: The use of CLSM visualisation to identify the percolation

threshold. Eur. J. Pharm. Biopharm. doi:10.1016/j.ejpb.2015.06.019

Miranda, A., Millán, M., Caraballo, I., 2006. Study of the critical points in lobenzarit disodium hydrophilic matrices for controlled drug delivery. Chem Pharm Bull. 54, 598–602.

Nair, L.S., Laurencin, C.T., 2007. Biodegradable polymers as biomaterials. Prog. Polym. Sci. 32, 762–798. doi:10.1016/j.progpolymsci.2007.05.017

Nokhodchi, A., Raja, S., Patel, P., Asare-Addo, K., 2012. The role of oral controlled release matrix tablets in drug delivery systems. BioImpacts 2, 175–187. doi:10.5681/bi.2012.027

Paz, M.V. de, Zamora, F., Begines, B., Ferris, C., Galbis, J.A., 2010. Glutathione-Mediated Biodegradable Polyurethanes Derived from l-Arabinitol. Biomacromolecules 11, 269–276.

Philip, A.K., Philip, B., 2010. Colon targeted drug delivery systems: a review on primary and novel approaches. Oman Med J 25, 79–87. doi:10.5001/omj.2010.24\nOMJ-D-10-00028 [pii]

Rechichi, A., Ciardelli, G., D'Acunto, M., Vozzi, G., Giusti, P., 2008. Degradable block polyurethanes from nontoxic building blocks as scaffold materials to support cell growth and proliferation. J. Biomed. Mater. Res. - Part A 84, 847–855. doi:10.1002/jbm.a.31349

Santerre, J.P., Woodhouse, K., Labow, R.S., 2005. Understanding the biodegradation of polyurethanes: From classical implants to tissue engineering materials. Biomaterials 26, 7457–7470. doi:10.1016/j.biomaterials.2005.05.079

Saurí, J., Millán, D., Suñé-Negre, J.M., Pérez-Lozano, P., Sarrate, R., Fàbregas, a., Carrillo, C., Miñarro, M., Ticó, J.R., García-Montoya, E., 2014. The use of the SeDeM diagram expert system for the formulation of Captopril SR matrix tablets by direct compression. Int. J. Pharm. 461, 38–45. doi:10.1016/j.ijpharm.2013.11.029

Schellekens, R.C.A., Stuurman, F.E., van der Weert, F.H.J., Kosterink, J.G.W., Frijlink,

H.W., 2007. A novel dissolution method relevant to intestinal release behaviour and its application in the evaluation of modified release mesalazine products. Eur. J. Pharm. Sci. 30, 15–20. doi:10.1016/j.ejps.2006.09.004

Storey, R.F., Wiggins, J.S., Puckett, A.D., 1994a. Hydrolyzable poly(ester-urethane) networks from L-lysine diisocyanate and D,L-lactide/ε-caprolactone homo- and copolyester triols. J. Polym. Sci. Part A Polym. Chem. 32, 2345–2363. doi:10.1002/pola.1994.080321216

Storey, R.F., Wiggins, J.S., Puckett, A.D., 1994b. Hydrolyzable poly(ester-urethane) networks from L-lysine diisocyanate and D,L-lactide/ε-caprolactone homo- and copolyester triols. J. Polym. Sci. Part A Polym. Chem. 32, 2345–2363. doi:10.1002/pola.1994.080321216

Suñé Negré, J.M., Roiġ Carreras, M., García, R.F., Montoya, E.G., Lozano, P.P., Aġuilar, J.E., Carmona, M.M., Ticó Grau, J.R., 2013. SeDeM Diagram: an expert system for preformation, characterization and optimization of tablets obtained by direct compression, in: Formulation Tools for Pharmaceutical Development. pp. 109–135. doi:10.1533/9781908818508.109

Tang, H., Li, W., Fan, X., Chen, X., Shen, Z., Zhou, Q., 2009. Synthesis, preparation and properties of novel high-performance allyl–maleimide resins. Polymer (Guildf). 50, 1414–1422. doi:10.1016/j.polymer.2009.01.037

Teramura, Y., Kaneda, Y., Iwata, H., 2007. Islet-encapsulation in ultra-thin layer-by-layer membranes of poly(vinyl alcohol) anchored to poly(ethylene glycol)–lipids in the cell membrane. Biomaterials 28, 4818–4825. doi:10.1016/j.biomaterials.2007.07.050

Vardareli, T.K., Keskin, S., Usanmaz, A., 2006. Thermal Degradation of Poly(Allyl Methacrylate) by Mass Spectroscopy and TGA. J. Macromol. Sci. Part A 43, 1569–1581. doi:10.1080/10601320600896900

Weisenberg, B.A., Mooradian, D.L., 2002. Hemocompatibility of materials used in microelectromechanical systems: platelet adhesion and morphology in vitro. J.

Biomed. Mater. Res. 60, 283–91. doi:10.1002/jbm.10076

Wiggins, L.., 1946. The acetone derivatives of hexahydric alcohols; triacetone mannitol and its conversion into d-arabinose. J. Chem. Soc. 13–14.

Fig. 1. Tablets corresponding to batch 6.

Fig. 2. GPC of **PU4** and **PU5.**

Fig. 3. ATR-FTIR of **PU4** and **PU5.**

Fig. 4. HSQC NMR of **PU4**.

Fig. 5. ^{13}C NMR of PU5 (signals marked due to crosslinking)

Fig. 6. TGA of **PU4** and **PU5**.

Fig. 7. DSC of **PU4** and **PU5.**

Fig. 8. SeDeM Diagram for **PU4.**

Fig. 9. SeDeM Diagram for **PU5.**

Fig. 10. Dissolution profiles prepared with 10% (○), 20% (Δ), and 30% (□) w/w of PU4. Dissolution profiles prepared with 10% (X), 20% (*), and 30% (▲) w/w of PU5 with a molecular weight of ca. 40000 Da, and with 10% (▼), 20% (+), and 30% (■) w/w of PU5' with a molecular weight of ca. 90000 Da. Details about phases I-IV are described in Table 4.

Scheme 1. Synthesis of polyurethanes **PU4** and **PU5**.

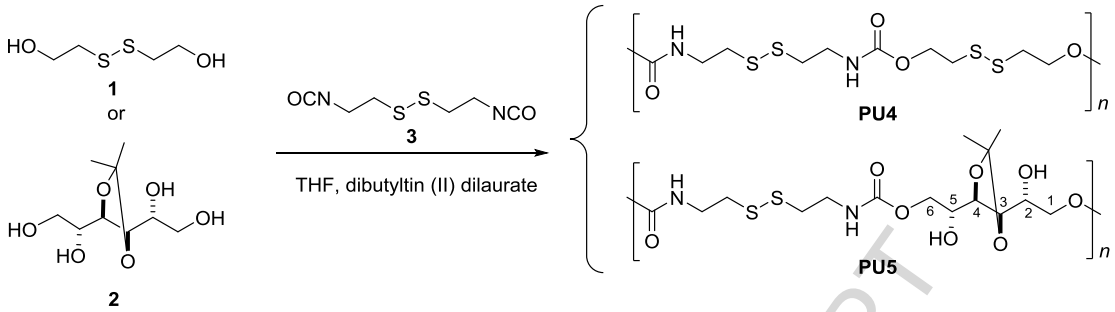

Figure 1

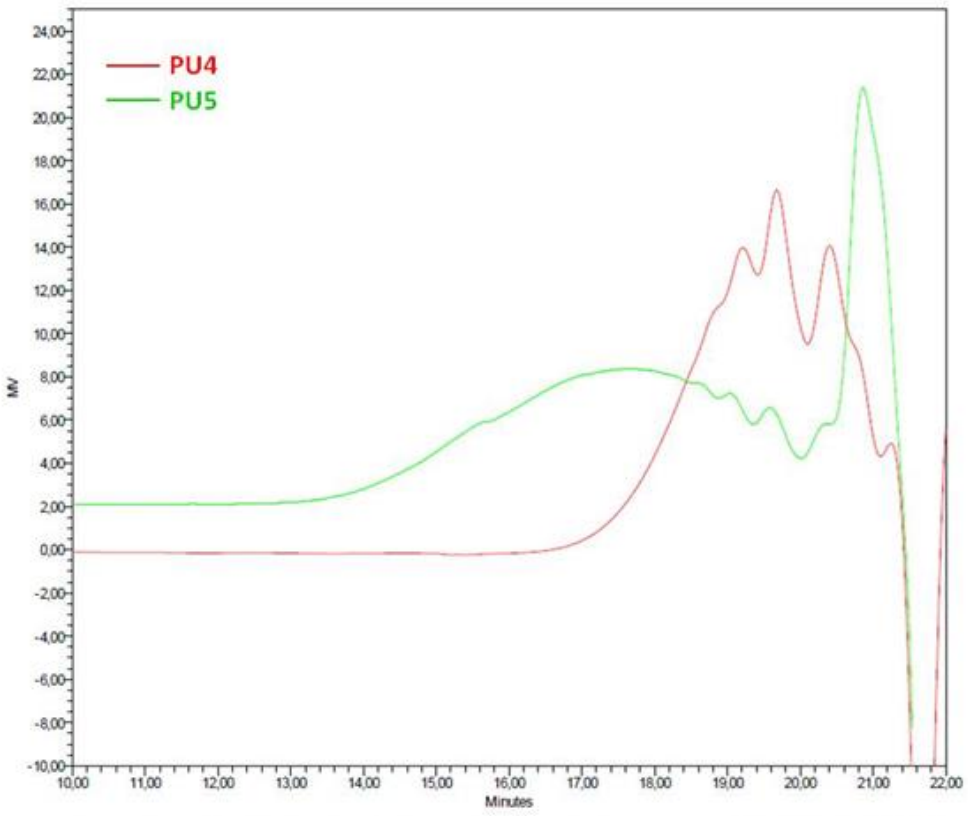

Figure 2

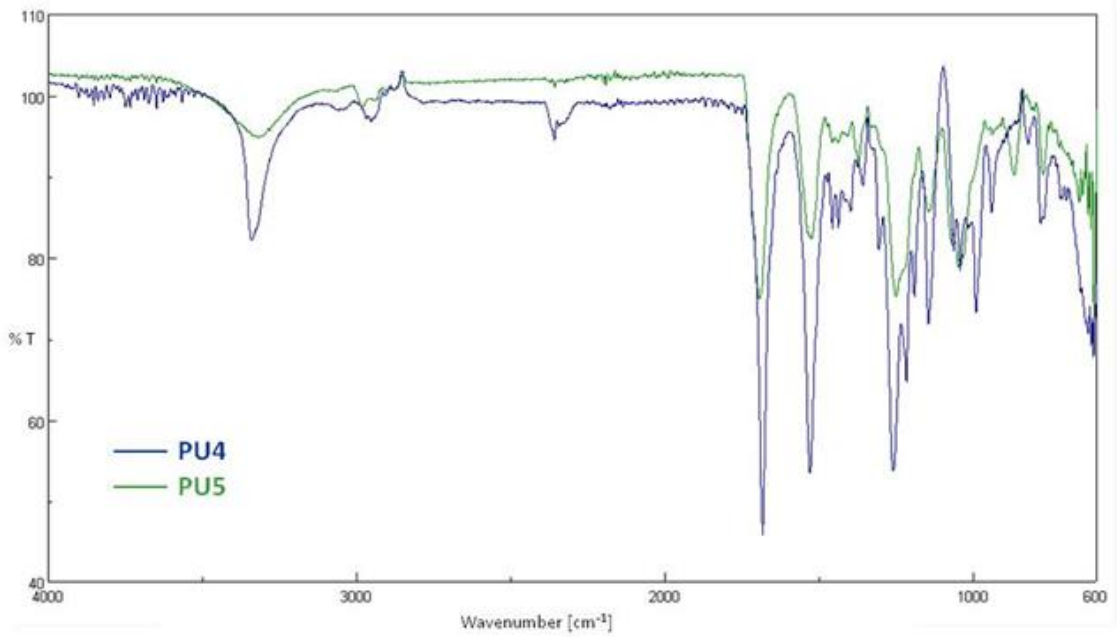

Figure 3

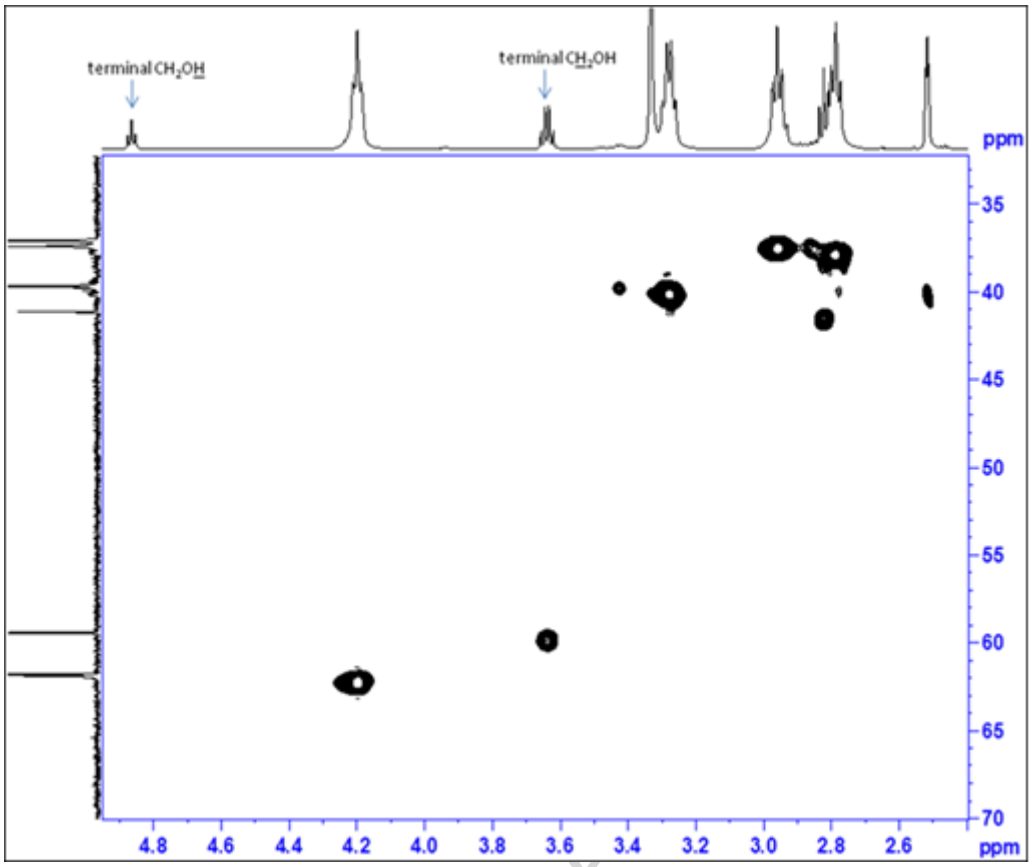

Figure 4

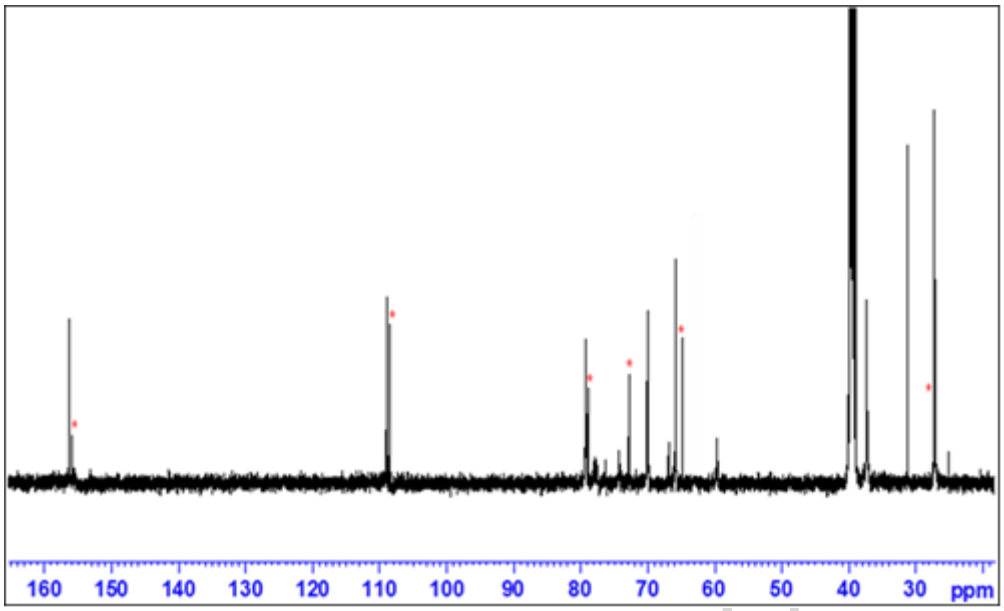

Figure 5

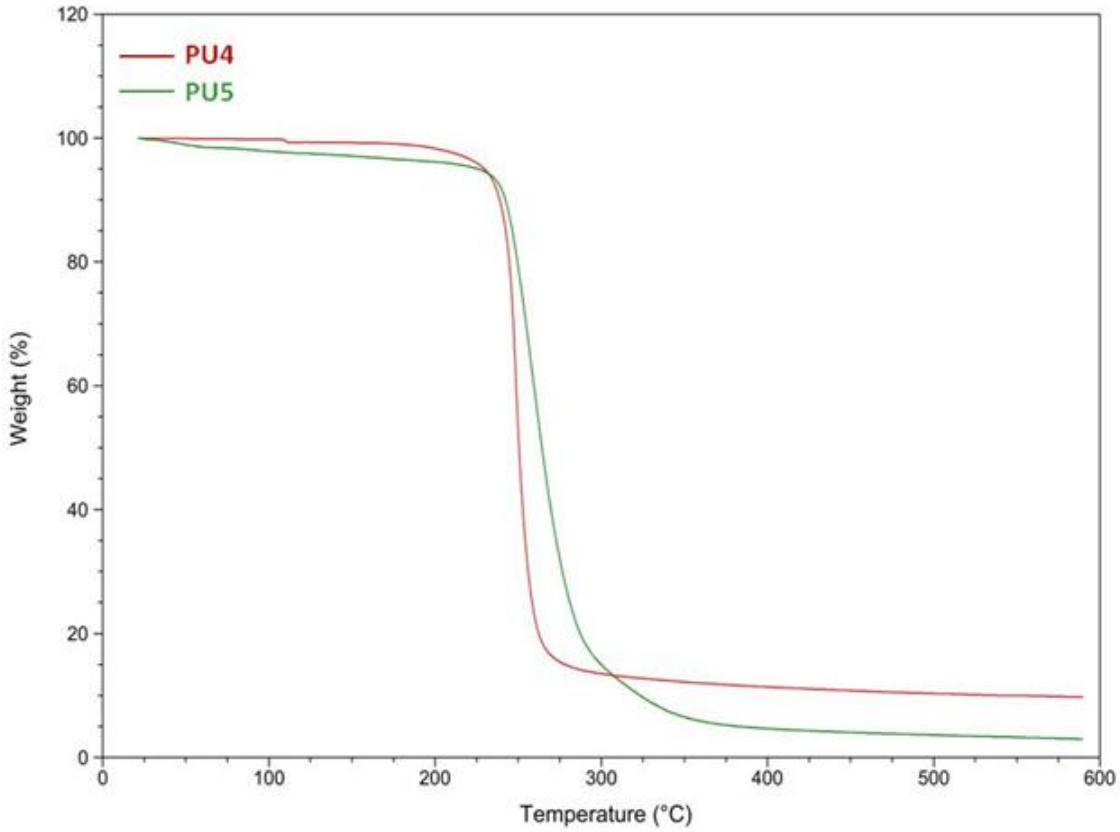

Figure 6

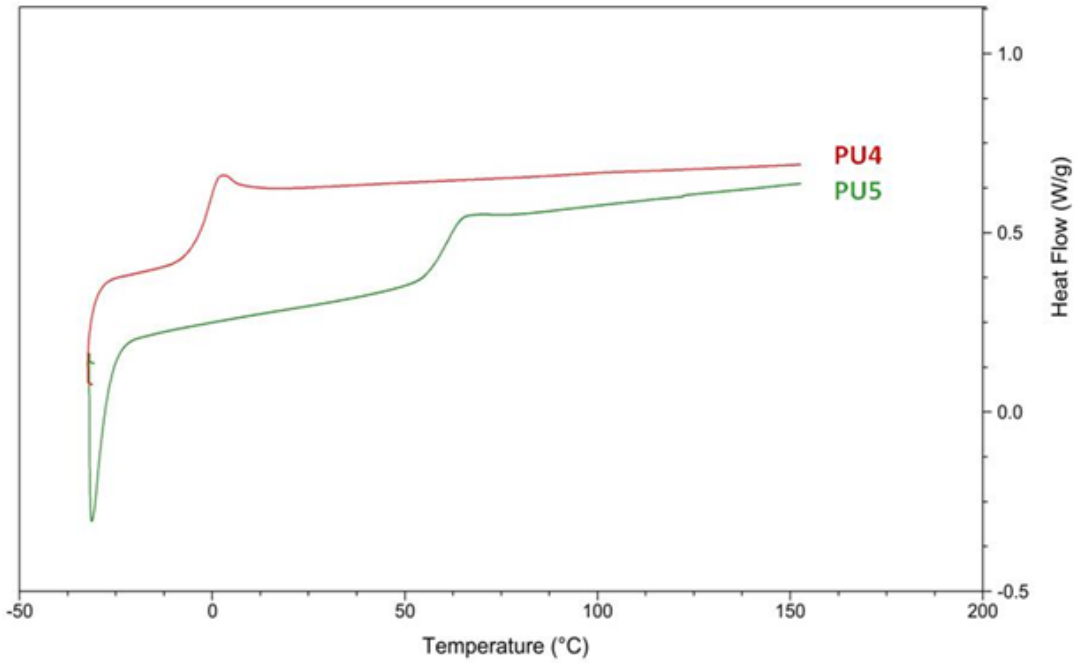

Figure 7

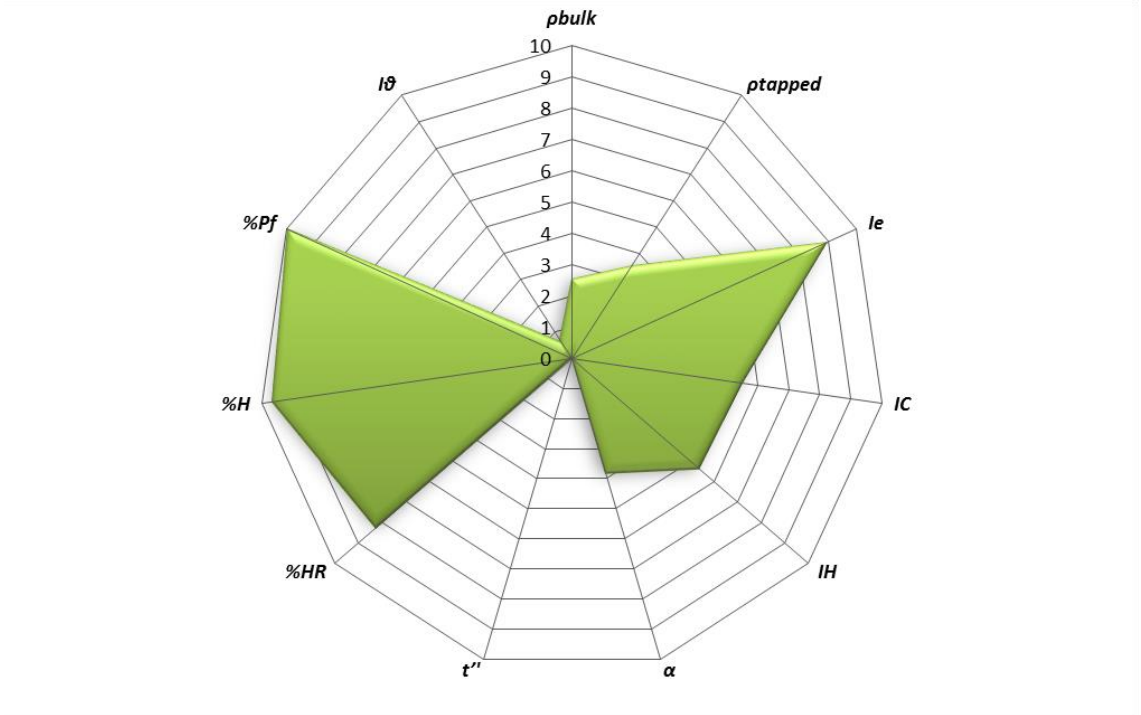

Figure 8

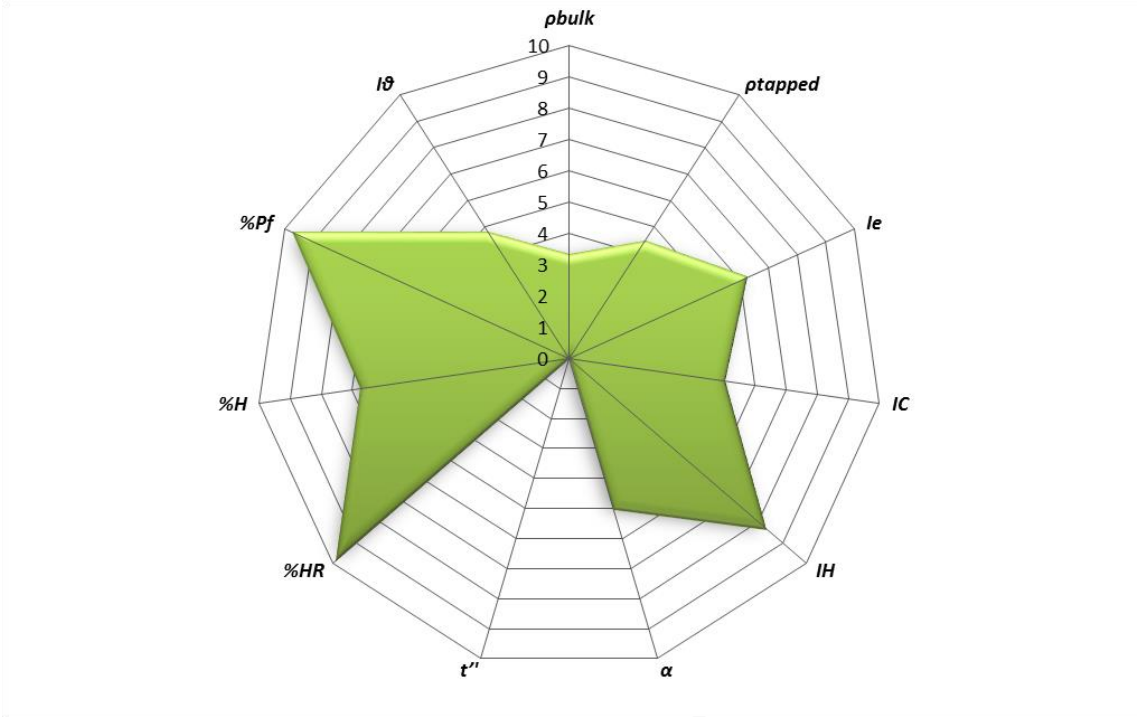

Figure 9

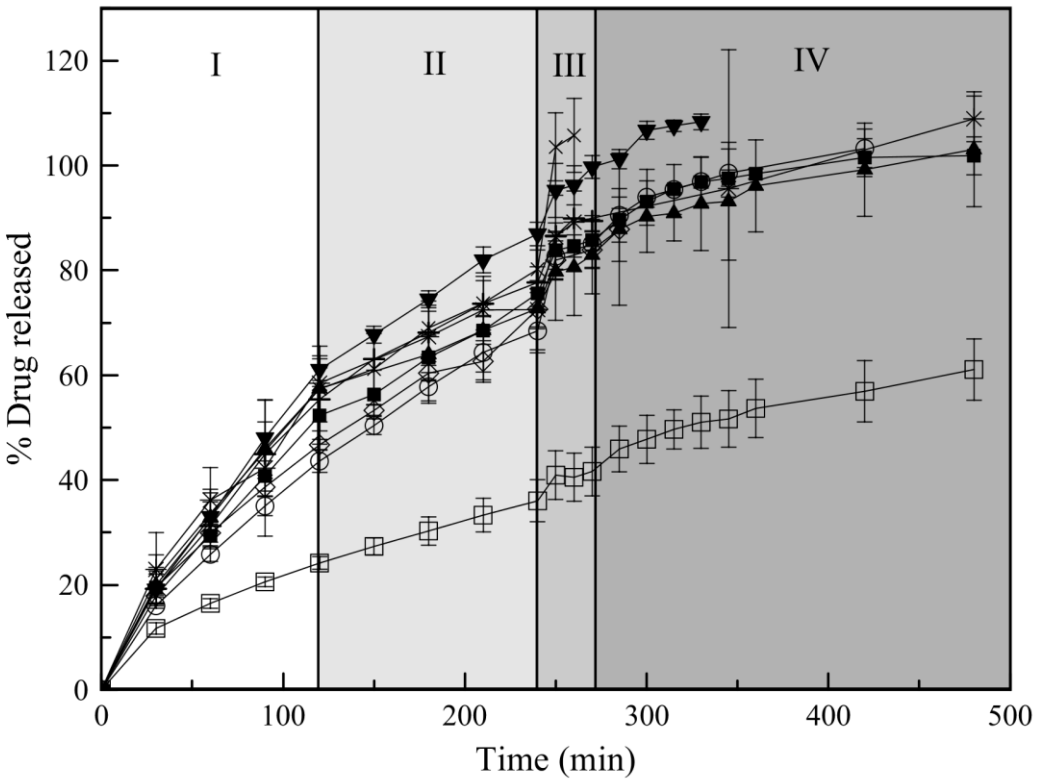

Figure 10

Table 1. Limit values accepted for the SeDeM Diagram parameters and factor applied to transform each parameter into radius values (*r*).

INCIDENCE	PARAMETER	LIMIT VALUES	FACTOR APPLIED TO *v*
Dimension	Bulk density	0-1 g/ml	10v
	Tapped density	0-1 g/ml	10v
Compressibility	Inter-particle porosity	0-1,2	10v/1,2
	Carr index	0-50 (%)	v/5
Flowability/ poder flow	Hausner ratio	3-1	(30-10v)/2
	Rest angle	50-0 (°)	10-(v/5)
	Powder flow	20-0 (s)	10-(v/2)
Lubricity/ stability	Loss on drying[a]	0-10 (%)	10-v[a]
	Higroscopicity	20-0 (%)	10-(v/2)
Lubricity/ dosage	Particles < 45 µm	50-0 (%)	10-(v/5)
	Homogeneity index	0-0,02	500v

[a]Calculated *r* for the "Loss on drying" parameter in accordance with Table 2.

Table 2. Calculation of *r*, based on the loss on drying value.

		Description	Range (a)	Range (b)	Range (c)
Range of values		Range value interval	0 to 2	3 to 10	2 to 3
		Radius (r) range to apply	0 to 10	5 to 0	10 to 0
Symbol	R_{max}	Radius top value	10	5	10
	V_{max}	Range top value	2	10	3
	V_{min}	Range minimum value	0	3	2
	V	Experimental value	V	V	V
Equations		r = Radius value calculated	$r = (R_{max}V)/(V_{max})$	$r = (R_{max}(V_{max}-V))/(V_{max}- V_{min})$	$r = (R_{max}(V_{max}-V))/(V_{max}- V_{min})$

Table 3. Compositions of the prepared formulations.

	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Batch 6	Batch 7	Batch 8	Batch 9
PU4	10%	20%	30%	-	-	-	-	-	-
PU5	-	-	-	10%	20%	30%	-	-	-
PU5'	-	-	-	-	-	-	10%	20%	30%
API	90%	80%	70%	90%	80%	70%	90%	80%	70%
Total	100%	100%	100%	100%	100%	100%	100%	100%	100%
Mean weight (mg)	240.6	241.9	242.1	245.43	243.24	246.66	246.84	247.1	248
SD (mg)	1.52	1.7	0.36	0.51	1.07	0.73	1.57	0.97	0.65

Table 4. Specifications of the four phases of in vitro dissolution assays

Phase	GI- segment	Time (min)	pH
I	Stomach	0-120	1.2
II	Jejunum	120-240	6.8
III	Ileum (distal)	240-270	7.5
IV	Colon (proximal)	270-480	6

Table 5. Results obtained for the characterization of the PU4 and PU5.

Incidence	Parameter	Symbol	U	Experimental Value				(r)		Mean incidence	
				PU4	SD	PU5	SD	PU4	PU5	PU4	PU5
Dimensions	Bulk density	ρ_{bulk}	g/ml	0.256	0.005	0.335	0.009	2.56	3.35	3.05	3.22
	Tapped density	ρ_{tapped}	g/ml	0.354	0.001	0.448	0.009	3.54	4.48		
Compressibility	Inter-particle porosity	*Ie*	-	1.077	0.061	0.753	0.123	8.97	6.27	7.24	5.23
	Carr index	*IC*	%	27.57	1.09	25.16	3.44	5.51	5.03		
Flowability/ powderflow	Hausner ratio	*IH*	-	1.38	0.02	1.33	0.06	5.40	8.33	3.07	3.30
	Rest angle	*α*	°	30.96	3.09	24.95	1.8	3.80	5.01		
	Powder flow	*t"*	*S*	∞	0	∞	0	0	0		
Lubrication/ stability	Loss on drying	*%HR*	%	1.73	0.20	0.12	0.003	8.27	9.88	8.97	6.15
	Hygroscopicity	*%H*	%	0.63	0.115	6.49	0.004	9.68	6.75		
Dosage/ lubrication	Particles< 45µm	*%Pf*	*µm*	0.052	0.05	1.35	0.94	9.99	9.73	5.35	7.20
	Homogenity Index	*Iθ*	-	0.001	0.005	0.009	0.004	0.72	4.8		
								PU4	**PU5**		
						Parametricindex		0.54	0.54		
						Parametricprofile (mean radius)		5.31	5.78		
						Goodcompressionindex (IGC)		5.00	5.45		

Table 6. Kinetic parameters.

	Zero Order				Higuchi				Korsmeyer						Peppas&Sahlin					
	Stomach/ jejunum	**r^2**	**Ileum/ colon**	**R**	**Stomach/ jejunum**	**R**	**Ileum/ colon**	**R**	**n (Stomach/ jejunum)**	**k**	**R**	**n (Ileum/ colon)**	**k**	**R**	**k1 (Stomach/ jejunum)**	**k2**	**R**	**k1 (Ileum/ colon)**	**k2**	**R**
PU 410 %/ API 90 %	0,252	0,989	-	-	0,054	0,997	-	-	0,711	0,014	0,999	-	-	-	0,039	0,00007	0,9999	-	-	-
PU 420 %/ API 80 %	0,245	0,994	0,193	0,897	0,052	0,995	0,063	0,89111	0,655	0,020	0,997	1,375	5,23E-05	0,6445	0,048	0,00002	0,995	-1,640	0,05518	1
PU 430 %/ API 70 %	0,114	0,991	0,126	0,960	0,024	0,998	0,044	0,96778	0,543	0,018	0,999	3,9863	1,31E-11	0,9116	0,017	0,00004	1	0,163	-0,00035	0,9711
PU 510 %/ API 90 %	0,277	0,967	-	-	0,059	0,994	-	-	0,645	0,024	0,994	-	-	-	0,076	-0,00008	0,996	-	-	-
PU 520 %/ API 80 %	0,271	0,957	0.28	-	0,056	0,981	0.089	-	0,569	0,034	0,9778	4.367	5.E-12	*	0,069	-0,00006	0,9822	-	-	-
PU 530 %/ API 70 %	0,238	0,9223	0.236	0,9447	0,052	0,974	0.077	0.9443	0,665	0,022	0,8443	5.997	2.7E-16	0,9711	0,106	-0,00025	0,9991	-1.793	0.057	0.999
PU 5' 10 %/ API 90 %	0,319	0,962	-	-	0,069	0,994	-	-	0,736	0,016	0,9889	-	-	-	0,093	-0,00011	0,996	-	-	-
PU 5' 20	0.277	0.95	0.332	-	0,073	0,98	0.106	-	0.685	0.01	0.98	8.098	3.38E-	-	0.088	-0,00	0.99	-	-	-

%/ API 80 %		5				0				9	9		21			13	5			
PU 5' 30 %/ API 70 %	0,262	0,976	0.165	0.930	0,079	0,976	0.054	0.925	0,660	0,021	0,994	4.062	1.43E-11	0,952	0,056	-3E-06	0,995	-1.446	0.046	0.997

Graphical abstract