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TESIS DOCTORAL

NUEVOS SISTEMAS EXPERTOS PARA EL DISEÑO DE COMPRIMIDOS. USO DE POLÍMEROS BIODEGRADABLES PARA LIBERACIÓN MODIFICADA DE FÁRMACOS

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A Lole y mis hijos

Siempre brillante como faro en la tempestad

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ÍNDICE

INTRODUCCIÓN

En 2002, la *U.S. Food & Drug Administration* (FDA) identificó un número significativo de problemas en la fabricación farmacéutica revelando la necesidad de un enfoque riguroso, basado en la ciencia, para el diseño de formulaciones y procesos. El número de defectos era muy elevado en comparación con otros sectores, tales como la industria de fabricación de chips que había logrado reducir los errores en el proceso de fabricación a ≤ 2 ppb buscando el objetivo *"six sigma"* mientras que la eficacia en la fabricación farmacéutica era solo de *"two sigma"*, equivalente a 46.000.000.000 ppb. Por ello la FDA lanzó en agosto de 2003 la "Iniciativa PAT" para tratar de reducir la variabilidad de los procesos de fabricación en la industria farmacéutica y los altos costos asociados a dichos defectos [1].

La (FDA) fomenta los enfoques basados en el riesgo (*risk-based approaches*) y la adopción de los principios *Quality by Design* (QbD) - esbozado por primera vez por Juran en 1992 [2] - en el desarrollo, fabricación y regulación de productos farmacéuticos. El énfasis de la FDA en QbD comenzó con el reconocimiento de que el aumento del número de los análisis realizados no mejora necesariamente la calidad del producto final. La calidad debe estar integrada en el producto.

El entorno normativo actual - basado en las directrices del *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)* - para conseguir medicamentos seguros, efectivos y de calidad implican un conocimiento científico más profundo de los productos y procesos lo que comporta una aproximación basada en el concepto QbD, descrita en la guía ICH Q8 [3]. Esta metodología considera que la calidad de un producto debe ser "construida" en el producto y asegurada desde su diseño en lugar de ensayarse en la forma de dosificación final.

En la directiva ICH Q8 se define el espacio de diseño como la combinación e interacción multidimensional de variables de entrada y parámetros de proceso que han demostrado proporcionar garantía de calidad. Trabajar dentro del espacio de diseño no se considera un cambio desde el punto de vista regulatorio, ya que esto proporciona un producto final de la misma calidad, lo que supone la ventaja adicional de que no es necesario una modificación en el Expediente de Registro del Medicamento ante las autoridades regulatorias. Este espacio de diseño está limitado por puntos críticos de la formulación cuyo conocimiento es esencial para desarrollar una forma farmacéutica robusta.

Bajo este enfoque las mejores soluciones podrían obtenerse aplicando modelos mecanicistas o incluso el conocimiento de los primeros principios de la pirámide del conocimiento (Fig.1)

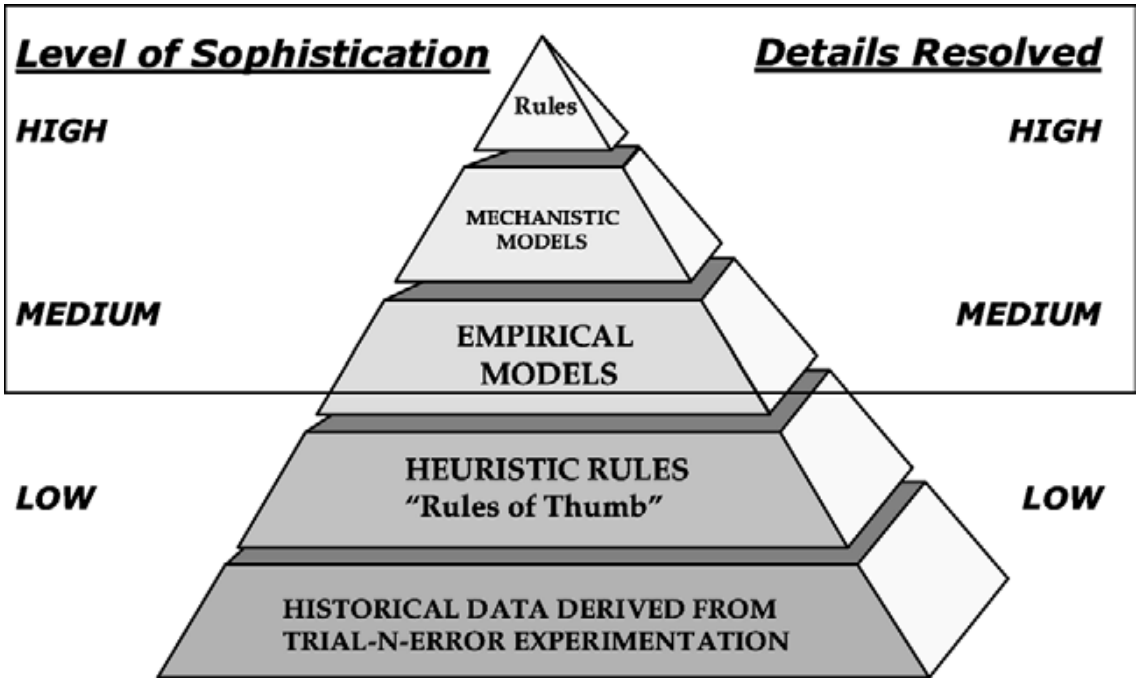

Figura 1. Pirámide del conocimiento (adaptado de Leuenberger H y Lanz M, 2005).

Ello implica aplicar un conocimiento científico profundo de los atributos de las materias primas y de los procesos de fabricación que son críticos para la calidad desde la perspectiva del paciente y los traduce a los Atributos de Calidad del Producto (CQA) y establece la relación entre las variables de formulación/fabricación para producir, de manera consistente, un medicamento con tales CQA para el paciente.

El profundo conocimiento obtenido de los estudios farmacéuticos proporciona una base científica para un establecimiento adecuado del espacio de diseño, lo que garantiza que

el proceso de fabricación conduzca a un medicamento que cumple con el Perfil de producto objetivo de calidad (QTPP) y los Atributos críticos de calidad (CQA).

Como mínimo, se deben determinar aquellos aspectos de los principios activos, excipientes, sistemas de cierre de envases y procesos de fabricación que son críticos para la calidad del producto y justificar las estrategias de control. Los atributos críticos de la formulación y los parámetros del proceso generalmente se identifican mediante una evaluación del grado en que su variación puede tener un impacto en la calidad del medicamento.

Para tener un conocimiento sólido y robusto del comportamiento de un sistema farmacéutico, es necesario conocer aquellos puntos críticos relacionados con la formulación que pueden afectar los CQAs. Estos puntos hacen que el medicamento caiga fuera del rango aceptable para ese atributo y, por lo tanto, constituyen límites naturales del espacio de diseño.

Hoy en día, los comprimidos siguen siendo la forma de dosificación farmacéutica más extendida en el mercado de medicamentos. Esta proporción incluso ha aumentado gracias a los medicamentos genéricos, ya que la fabricación de comprimidos generalmente supone un menor costo de desarrollo, así como una mayor capacidad de producción industrial [4].

Además, los comprimidos, permiten gran precisión en la dosificación, pueden enmascarar características organolépticas, son de fácil administración, gran estabilidad mecánica, química y microbiológica, fácil identificación y ofrecen la posibilidad de modular su liberación.

En las últimas décadas, se ha prestado gran atención al desarrollo de sistemas de administración de fármacos de liberación prolongada por vía oral. Estos sistemas son formulaciones farmacéuticas que liberan el fármaco lentamente y de tal manera que la velocidad de liberación se convierte en el paso limitante para controlar la llegada del fármaco a la circulación sistémica, de modo que los niveles plasmáticos del fármaco se mantienen más constantes y con menor fluctuación entre picos y valles que en el caso de las formas de dosificación convencionales. Por lo tanto, la concentración terapéutica del fármaco, se mantiene durante un período de tiempo más largo y aumenta el intervalo entre dosis [5].

De hecho mejora el cumplimiento del paciente, que es uno de los principales factores que influyen en el éxito de un tratamiento. Además, se reduce la toxicidad causada por la sobredosificación, así como los problemas de eficacia debidos a los valles en los niveles plasmáticos del fármaco [6].

No obstante, estos sistemas presentan algunos inconvenientes como la dificultad de eliminar rápidamente el fármaco en caso de efectos adversos, la variabilidad intra e interindividual de las concentraciones en el plasma del fármaco debido a la dependencia del vaciado gástrico (especialmente en el caso de sistemas monolíticos) y riesgo de liberación masiva de la dosis (*dose dumping*) causado por la rotura de los sistemas por ejemplo por defecto de fabricación o por masticación [7].

Los sistemas matriciales tienen un gran interés en la formulación de dispositivos de administración prolongada de fármacos debido a su bajo costo y facilidad de fabricación. Consisten en un fármaco disperso en una sustancia polimérica circundante. El fármaco se puede dispersar a nivel molecular, aunque más habitualmente está en forma de partículas sólidas.

A pesar de que el polímero puede sufrir procesos de hinchamiento y / o erosión, el sistema debe mantener su integridad durante todo el proceso de liberación del fármaco.

Los avances en el diseño y la ingeniería de materiales han llevado al rápido desarrollo de nuevos materiales con una complejidad y funciones crecientes. Tanto los polímeros degradables como los no degradables han encontrado amplias aplicaciones en el campo de la liberación controlada de fármacos [8–11]. Como resultado, el desarrollo de materiales que sean biocompatibles y biodegradables y libres de catalizadores metálicos tóxicos ha ganado una gran atención en los últimos tiempos [12].

Los poliésteres alifáticos han recibido especial interés ya que son potencialmente biodegradables [4]. Además, estos polímeros han encontrado aplicaciones en el campo biomédico porque son biocompatibles [13]. Dentro de los poliésteres alifáticos, han surgido los succinatos de polibutileno (PBS) [14] y poli (ε-caprolactona) (PCL) [15] junto con otros poliésteres más conocidos como el ácido poli láctico (PLA) o el ácido poli glicólico (PGA).

PBS y PCL son polímeros semicristalinos cuyas propiedades térmicas (temperatura de fusión (Tm) y temperatura de transición vítrea (Tg)) se pueden ajustar mediante

copolimerización. De hecho, se encontró que el co-poliéster de poli (succinato de butileno-co-ε-caprolactona) era cristalino para todas las composiciones y cristalizaba isodimórficamente para las composiciones intermedias [16,17].

Existen varios métodos para obtener una liberación prolongada de fármacos. La compresión directa sigue siendo el método más extendido para fabricar estas formas farmacéuticas debido al bajo costo de desarrollo y a la alta capacidad de producción industrial [11].

En algunos casos, la compresión directa no es suficiente para obtener una liberación controlada del fármaco, siendo necesarios métodos más complejos tales como las técnicas de procesamiento en caliente como por ejemplo *Hot Melt Extrusion* (HME) y Compresión Asistida por Ultrasonidos (USAC).

Estas técnicas han surgido como tecnologías de procesamiento para el desarrollo de formas farmacéuticas sólidas de liberación controlada, para administración oral y preparación de implantes [4,13].

Una de las limitaciones que presentan estas técnicas es el hecho de que los polímeros están expuestos a altas temperaturas [14,15], requiriendo una adecuada temperatura de fusión (Tm) o de transición vítrea (Tg). Además, los fármacos deben mantener la estabilidad a las temperaturas utilizadas. En el caso de HME a veces es necesaria la adición de plastificante para aumentar la capacidad de extrusión del polímero[18]. Aun así HME es una técnica ampliamente utilizada en la fabricación de formas farmacéuticas orales [19].

USAC es una tecnología que combina el proceso de compresión convencional y la irradiación por ultrasonidos produciendo el calentamiento, fusión y sinterización de materiales. Su aplicación es menos frecuente que el HME, pero puede ser útil en la preparación de formulaciones con dispersión sólida, para mejorar la biodisponibilidad de fármacos poco solubles y formulación de formas farmacéuticas de liberación prolongada, ya que proporciona un mejor control de la liberación del fármaco con un menor cantidad de excipiente [20,21].

Para explicar el beneficio de esta técnica se ha utilizado el modelo de percolación continua [22,23], así como la Eficacia del Excipiente (EE) y estudios de liberación *"in vitro"*. La EE es una herramienta para identificar la capacidad de los excipientes para

reducir la velocidad de difusión de un fármaco atrapado en una red de este excipiente [24].

La formulación de un comprimido es un sistema complejo que contiene el fármaco, generalmente un diluyente, un disgregante, un lubricante y, en algunos casos, un excipiente regulador del flujo. Desafortunadamente, la calidad de los ingredientes puede cambiar de un lote a otro, o por cambio en el proveedor de los mismos, lo que lleva a una variabilidad de las propiedades del comprimido tales como su dureza, tiempo de disgregación, perfil de disolución, etc.

En la industria farmacéutica, para la fabricación de comprimidos, se parte de materias primas que están normalmente en forma de sólidos pulverulentos. Los sistemas en forma de polvo pueden comportarse como un sólido, como un líquido y/o como un gas, por lo que en ciertos casos no obedecen las leyes físicas habituales de los sólidos [1].

Esta Tesis Doctoral aborda puntos críticos que deben tenerse en cuenta en el diseño de formas farmacéuticas sólidas.

Se ha comenzado estudiando el Sistema experto SeDeM de aplicación a sistemas pulverulentos, tanto de principios activos como de excipientes, que son el punto de partida para la fabricación de las diferentes formas sólidas de dosificación, especialmente aquellas obtenidas por Compresión Directa. Se ha tratado de profundizar en el conocimiento de dicho sistema combinándolo con la teoría de la percolación. Los resultados obtenidos se reflejan en el Capítulo 3.

Una vez estudiados aquellos parámetros que afectan a la calidad del producto final, partiendo de materias primas en forma pulverulenta, se ha procedido al estudio de formas de liberación controlada utilizando un polímero comercial, derivado de los poliuretanos, aplicando para su obtención tanto Compresión Directa como Compresión Asistida por Ultrasonidos. Se estudiaron aquellos parámetros que podrían afectar a la calidad del producto final. Los resultados obtenidos se reflejan en el Capítulo 4.1.

Al tratar de realizar un estudio de comprimidos de liberación prolongada utilizando un poliuretano comercial de grado médico con un comportamiento elástico, Tecoflex EG72®, se observó que sólo la Compresión Asistida por Ultrasonidos permitía la obtención de comprimidos de características adecuadas. Los resultados se reflejan en el Capítulo 4.2.

Por último se ha sintetizado, en colaboración con el Departament d'Enginyeria Química de la Universitat Politècnica de Catalunya (ETSEIB) de Barcelona, un copolímero de butilensuccinato con caprolactona en proporción adecuada para obtener unas temperaturas de fusión y de transición vítrea idóneas para elaborar comprimidos de liberación prolongada tanto por USAC como HME. Se han valorado parámetros que afectan a las propiedades del producto final. Los resultados se reflejan en el Capítulo 5.

OBJETIVOS

1. Evaluar la robustez y exactitud del sistema experto SeDeM, mediante la teoría de percolación**.**
2. Diseñar y elaborar sistemas matriciales de liberación prolongada con polímeros termoplásticos utilizando diferentes tecnologías de fabricación tales como compresión directa, compresión asistida por ultrasonidos y *hot melt extrusion*.
3. Avanzar en el conocimiento de la estructura interna y el comportamiento de los sistemas elaborados mediante el uso de diferentes herramientas tales como estudios cinéticos, Teoría de percolación, Teoría de Fractales y microscopía electrónica de barrido.
4. Obtención y caracterización de sistemas de liberación prolongada de fármacos utilizando un polímero biodegradable.

La presente tesis doctoral se ha desarrollado dentro de los proyectos de investigación **"Polímeros de Fuentes Renovables para Aplicaciones Farmacéuticas. Diseño de Sistemas Avanzados para Liberación Prolongada y Localizada de Fármacos" (MAT2016-77345-C3-3-P)**, financiado por el Ministerio de Economía y Competitividad, y "**Sistemas de Liberación de Fármacos Basados en Materiales Poliméricos Avanzados para el Tratamiento de Enfermedades del Tracto Gastro-Intestinal" (RTI2018-095041-B-C31)**, financiado por el Ministerio de Ciencia, Innovación y Universidades.

En ambos proyectos el doctorando ha participado como personal investigador. En el primero de ellos se ha trabajado en colaboración con el Departamento de Química Orgánica y Farmacéutica de la Universidad de Sevilla y con el Departament d'Enginyeria Química, Universitat Politècnica de Catalunya (ETSEIB) de Barcelona. En el segundo de ellos se ha trabajado en colaboración con el Departament d'Enginyeria Química, Universitat Politècnica de Catalunya (ETSEIB) de Barcelona encargado de la síntesis y caracterización química del polímero utilizado en el último artículo publicado.

Capítulo 1

First study of the evolution of the SeDeM expert system parameters based on percolation theory. Monitoring of their critical behavior.

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Research paper

First study of the evolution of the SeDeM expert system parameters based on percolation theory: Monitoring of their critical behavior

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ABSTRACT

The deep understanding of products and processes has become a requirement for pharmaceutical industries to follow the Quality by Design principles promoted by the regulatory authorities. With this aim, SeDeM expert system was developed as a useful preformulation tool to predict the likelihood to process drugs and excipients through direct compression. SeDeM system is a step forward in the rational development of a formulation, allowing the normalisation of the rheological parameters and the identification of the weaknesses and strengths of a powder or a powder blend. However, this method is based on the assumption of a linear behavior of disordered systems. As percolation theory has demonstrated, powder blends behave as non-linear systems that can suffer abrupt changes in their properties near to geometrical phase transitions of the components.

The aim of this paper was to analyze for the first time the evolution of the SeDeM parameters in drug/excipient powder blends from the point of view of the percolation theory and to compare the changes predicted by SeDeM with the predictions of Percolation theory.

For this purpose, powder blends of lactose and theophylline with varying concentrations of the model drug have been prepared and the SeDeM analysis has been applied to each blend in order to monitor the evolution of their properties. On the other hand, percolation thresholds have been estimated for these powder blends where critical points have been found for important rheological parameters as the powder flow.

Finally, the predictions of percolation theory and SeDeM have been compared concluding that percolation theory can complement the SeDeM method for a more accurate estimation of the Design Space.

1. Introduction

The new requirements imposed by regulators (ICH, EMA, FDA, etc.) for safe, effective and quality drugs imply a deeper scientific understanding of products and processes according to the Quality by Design (QbD) approach described in the guidelines of the International Conference on Harmonization (ICH Q8) [1]. Following this approach, the quality has to be "built" in the product and ensured since its design, instead of measuring it in the final product.

Successful implementation of QbD for pharmaceutical products requires an adequate determination of the design space, which must be sufficiently explored during development studies. ICH Q8 defines design space as the multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality. So, the wider the Design Space, the more robust and flexible the process is to accommodate variations.

Nowadays, tablets remain as the most widespread pharmaceutical dosage forms in drugs market. This proportion has even increased thanks to the generic drugs since tableting generally results in a lower cost of development as well as a higher industrial production capacity. Additional advantages can be obtained in the case of tablets prepared by direct compression.

With the purpose of reducing the time spent in preformulation studies, Suñé-Negre et al. [2,3] developed a new Expert System called SeDeM that provides information about the suitability of active ingredients and excipients in powder to be processed by direct compression. This tool is based on the experimental measurement and normalization of several rheological parameters followed by their appropriate mathematical and graphical treatment.

The SeDeM system allows identifying those powder properties that need to be improved in order to optimize the formulation of the end product by direct-compression. This makes possible a science-based optimization of the formulation, avoiding the trial and error method, in agreement with the QbD postulates.

On the other hand, based on the results obtained for the different normalized parameters, the SeDeM Expert System proposes three indexes to estimate whether or not the powder is acceptable for direct compression. These indexes (PI, PPI and GCI) values higher than 0.5, 5 and 5, respectively, indicate that the powder blend can be processed through direct compression.

Moreover, these authors have proposed a mathematical equation to calculate the optimal amount of an excipient to be used with a particular drug to obtain a suitable formula for direct compression [4]. This equation is based on the assumption of the linear behavior of

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powder blends of different components. However, as percolation theory has demonstrated, these blends behave as non-linear systems.

Percolation theory is a statistical discipline that studies the distribution of disordered and chaotic systems in which the components are randomly distributed in a network. This theory is been applied to several areas of knowledge like epidemiology [5], genetic disorders [6], or even transmission of information in social networks [7].

Percolation theory has been fruitfully applied in the study of pharmaceutical systems since 1987 [8]. The main aim of this theory is to study properties and parameters or predict behaviors near to the percolation threshold. Percolation threshold is the minimum concentration of a component at which there is a maximum probability of appearance of an infinite or percolating cluster of this material. A cluster is defined as a group of neighbor positions occupied by the same component in a real or virtual lattice. When a component reaches its percolation threshold, it undergoes a geometrical phase transition and starts to extend over the whole sample, having much higher influence on the properties of the system -in our case a dosage form-. In a binary system formed by a drug and an excipient, one or both components constitute a percolating cluster, depending on their relative volume ratio. The percolation threshold of the drug indicates at which concentration this substance starts dominating the system, acting in a similar way than the outer phase of an emulsion. Therefore, the general properties of the system will be, beyond this point, more similar to the properties of the drug. An important difference between solid systems and emulsions is the reduced mobility of the molecules of the first ones. As a consequence, it is possible in solid forms to observe systems in which more than one component is percolating, i.e., acting as outer phases. These systems are called bicoherent and their general properties are intermediate between the two components, for example the drug and the excipient. Therefore, in our powder blends we expect to find three situations from the point of view of percolation theory: (a) only the excipient percolates the system (i.e., acts as outer phase), (b) both drug and excipient percolate the system and (c) only the drug act as outer phase. The concentration point between situation a and b is the drug percolation threshold, and the point between situations b and c is the excipient percolation threshold. Close to the percolation thresholds, an abrupt change in the properties of the system can occur. This is known as a critical point [9,10].

From all the above it can be understood that systems close to their percolation thresholds could not meet the conditions of robustness required in the Design Space.

On the other hand, most of the tools employed by QbD approaches (for example Design of Experiments and related Analysis of Variance, different kinds of regressions, mechanistic approaches based on empirical polynomial equation…) are mathematical and statistical strategies based on a continuous behavior of the system. Nevertheless, at the percolation threshold, the distribution pattern changes, resulting in a discontinuity of the system. As a consequence, it is necessary to know the situation of the percolation thresholds, and the related critical points, to properly apply the above-mentioned QbD approaches. Leaving a critical point inside the Design Space would introduce an enormous and artificial error to the statistical estimations performed inside this space. Therefore, critical points constitute natural limits of the Design Space [10,11].

The knowledge of the behavior of blends above and below a critical point is crucial to have a deep understanding of the internal structure of the system and to properly apply the QbD approach.

The aim of the present work is to analyze, for the first time, the evolution of the SeDeM rheological parameters in powder blends from the Percolation theory point of view. Therefore, changes predicted by SeDeM method will be compared with the predictions of Percolation theory. For this purpose, powder blends of lactose and theophylline with varying concentrations of the model drug will be evaluated according to the SeDeM method in order to follow the evolution of their properties. Finally, the percolation thresholds will be estimated and the existence of critical points will be discussed.

2. Materials and methods

2.1. Materials

Anhydrous theophylline (Acofarma, Barcelona, Spain) has been used as model of Active Pharmaceutical Ingredient (API) and α-lactose monohydrate (Meggle, Wasseburg, Germany) as the excipient, both according to Eur Ph (2013) [12].

2.2. Preparation of blends

Blends of theophylline and lactose have been obtained by a Turbula mixer (WAB T2F, Willy A. Bachofen, Basel, Switzerland), during a period of 10 min, with the following concentrations: 10/90, 20/80, 30/70, 33/67, 36/64, 40/60, 50/50, 60/40, 70/30, 73/27, 76/24, 80/20, 90/10 w/w. According to our previous experience with binary powdered systems, percolation thresholds of their components are normally around 30–35% v/v [13–16]. Therefore, we have made more blends near these concentrations in order to have a more accurate estimation of the percolation thresholds.

2.3. Rheological studies using the SeDeM method

Twelve rheological tests have been performed in order to apply the SeDeM expert system (Table 1). Tests have been carried out according to the European Pharmacopeia (2013), whenever possible. When these methods were not described in the European Pharmacopeia, the methods proposed by the authors of SeDeM were applied [3].

Bulk density (ρ_{bulk}), Tapped density (ρ_{tapped}), Powder flow and Loss on drying (% LOD) were measured in accordance with the methods described in European Pharmacopoeia (sections 2.9.15, 2.9.16-2 and 2.2.32, respectively) [11,12]. All these assays were performed by three replicates.

Table 1
Parameters and equations used by SeDeM method.

Incidence	Parameter	Symbol	Unit	Equation
Dimension	Bulk density	ρ_{bulk}	g/ml	$\rho bulk = P/Va$
	Tapped density	ρ_{tapped}	g/ml	$\rho tapped = P/Vc$
Compressibility	Inter-particle porosity	IP	–	$IP = \frac{Dc-Da}{Dc \times Da}$
	Carr's index	C	%	$C = (Dc - Da/Dc) \times$
	Cohesion index	CI	N	Experimental
Flowability/ powder flow	Hausner ratio	HR	–	$HR = Dc/Da$
	Rest angle	α	°	$tg\ \alpha = h/r$
	Powder flow	t″	s	Experimental
Lubricity/ stability	Loss on drying	%LOD	%	Experimental
	Hygroscopicity	%H	%	Experimental
Lubricity/dosage	Particles ⩽ 45 μm	$\%P_{<45}$	%	Experimental
	Homogeneity index	Iθ	–	Eq. (1)

Inter particle porosity (IP); Carr's Index (C) and Hausner Ratio (HR) are derived from ρ_{bulk} and ρ_{tapped} as shown in the equations of Table 1.

Cohesion index was determined by directly compressing the product under study using an eccentric press (Bonals A-300, Barcelona, Spain) using manual feeding and applying the maximum compression force accepted by the formulation. Tablets were prepared with a weight of 1.00 g ± 0.02 using 14 mm diameter punches. In all cases, no lubricant mixture was necessary to add to compress the blends. Hardness of six tablets was determined in a Manual Tablet Hardness Tester (Sotax HT1, SOTAX AG, Aesch, Switzerland) and the mean hardness was calculated.

The rest angle was measured as the angle of the cone formed when 100 g of the sample was dropped through a funnel, according to the SeDeM method [3]. Two opposite diameters and height were measured. Sample was analyzed in six replicates.

Hygroscopicity (% H) 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 has been determined ($\%P_{<45}$), in three replicates, 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, samples were sieved employing the following sieve sizes: 0.710 mm, 0.500 mm, 0.355 mm, 0.180 mm, 0.090 mm, 0.045 mm. Sieves were vibrated during 10 min at speed 60 (Retsch, model AS 200, Germany). The percentage of product that is retained in each sieve has been calculated. Equation (1) is applied to the data obtained, Where Iθ is the relative homogeneity index, informing about the homogeneity of the particle-size distribution in the range of the fractions under study.

$$I\theta = \frac{}{(100 + (dm - dm - 1)Fm - 1 + (dm + 1 - dm)Fm + 1 + (dm -}$$

where

Fm 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.
dm 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.

The results have been converted to a scale from 0 to 10, according to the SeDeM methodology (Table 1). The normalized values were plotted in the SeDeM diagram.

To determine whether the product is acceptable for direct compression in numerical form, the following indexes are calculated based on the SeDeM method and the following indexes were calculated as:

$$\text{Parametric index PI } PI = No.p \geqslant 5/No.Pt \quad (2)$$

where

No.p ⩾ 5: Indicates the number of parameters whose value is equal to or higher than 5
No.Pt: Indicates the total number of parameters studied

The acceptability limit would correspond to PI ⩾ 0.5

$$\text{Parametric profile index PPI } PPI = mean\ r\ of\ all\ parameters \quad (3)$$

The acceptability limit would correspond to PPI ⩾ 5

$$\text{Good compression index GCI } GCI = PPI \times f \quad (4)$$

f is a reliability factor calculated from the area of the polygon formed connecting the maximum values (i.e., the value 10) of the edges in which the rheological parameters will be plotted. This area is divided by the area of a circle with radius = 10. The factor f approaches 1 as the number of rheological parameters increases, being an indicative of the reliability of the results. f is calculated as follows:

$$f = Polygon\ area/Circle\ area$$

In our case, where 12 parameters have been studied, f takes the 0.952 value.

The acceptability limit would correspond to GCI ⩾ 5.

Finally, we used the equation proposed (Eq. (5)) to calculate the amount of excipient required to compress the API, based on the SeDeM radius regarded as the minimum necessary for each incidence parameter in order to ensure successful compression.

$$CP = 100 - (RE - R)/(RE - RP) \times 100 \quad (5)$$

where

CP = percentage of corrective excipient.
RE = mean-incidence radius value of the corrective excipient.
R = mean-incidence radius value to be obtained in the blend.
RP = mean-incidence radius value of the API to be corrected.

The values in Eq. (5) have been replaced with the calculated values for theophylline and lactose in order to obtain R = 5, as the minimum value to achieve good compression.

2.4. Study of critical points according to percolation theory

According to the fundamental equation of percolation theory, if the studied parameters behave as critical properties, we can expect the following relationship for the rheological property X near to the percolation threshold p_c (Eq. (6)):

$$X \propto S(p - p_c)^q \quad (6)$$

where X is the studied rheological property, S is a proportional

constant or scaling factor; p is the occupation probability -in our case can be assimilated to the concentration in volume of the studied component-, pc is the percolation threshold or critical concentration of this component, and q is a critical exponent, which only depends on the property studied and the dimensionality of the system -in our case three dimensions-.

Therefore, at theophylline concentration p close to p_c the drug spans the whole system, and at $p > p_c$ it percolates the system changing the characteristics of the blend with respect to rheological properties.

Thus, raw values from rheological studies were plotted *versus* the% v/v of drug to observe possible discontinuities, estimating the percolation thresholds.

3. Results and discussion

3.1. Rheological results according to SeDeM method

Rheological parameters of theophylline, lactose and the blends with different proportions drug:excipient were obtained according to the described methodology. The obtained results are shown in Table 2. Drug and excipient show different values for all the parameters studied, especially for those related to flowability. It can be highlighted the abrupt change of flowability (t″) of the blends, going from 6.49 s for the powder blend with 33:67 theophylline:lactose to lack of flow (infinite time) for the blend with a 36:64 proportion. Respect to cohesion index parameter, determined by directly compressing, it is noteworthy the high values of crushing force (165–346 N) showed for all tablets obtained by different blends.

Taking into account the different rheological behavior of drug and excipient, it could be expected that increasing the drug percentage, blends would show results more similar to theophylline. However, in general, rheological parameters show a nonlinear behavior as a function of the percentage of theophylline.

These results were converted to radii using equations in Table 1, according to SeDeM method. The radii were represented in SeDeM diagrams, as shown in Fig. 1. The diagram of lactose shows their shortcomings in parameters affecting compressibility dimension, while theophylline shows a weak point in parameters affecting flowability/powder flow dimension. There is an appreciable change in parameters affecting flowability/powder flow when theophylline reaches the content of 40%, being its profile very similar to pure theophylline.

The Mean incidence and parametric indexes were calculated applying SeDeM method (Table 3). All samples meet the requirements to form tablets by direct compression based on the three Parametric Indexes (PI, PPI, GCI), which is consistent with the high Cohesion index results.

However, flowability/powder flow incidence was inadequate for blends with more than 33% of theophylline (values < 5). According to the equation proposed in the SeDeM method (Eq. (2)) and the results obtained for drug and excipient, the amount of lactose needed to improve the flowability of the API would be 74%, which means a maximum content of 26% of theophylline. However, we found good flow results for blends with 33% (34.36% v/v) of API that, as will be discussed in the following section, can be attributed to the percolation threshold of theophylline.

3.2. Estimation of percolation thresholds

In order to estimate the percolation thresholds, rheological parameters were represented as a function of their theophylline volume fraction (%). According to the percolation theory, the volume of a component, instead of its weight, determines whether this substance can percolate the sample, i.e. if there is a cluster of this component connecting all the sides of the sample [17].

In binary systems, two percolation thresholds can be expected. The first one is the percolation threshold of the drug and the second one is the corresponding to the excipient [18,19]. These thresholds correspond to geometrical phase transitions that cause a strong change in the distribution of the components. As a consequence, some properties of the system are affected, showing discontinuities.

In relation with flowability factors, rest angle and powder flow results are shown in Fig. 2(a) and (b). In the case of rest angle three linear regions were observed: (i) for low theophylline concentrations (0–31% v/v of theophylline) blends have good flow properties (angles around 25°), (ii) medium theophylline content (37–61% v/v theophylline) with rest angles between 30 and 40° and (iii) high theophylline content (74–100% v/v theophylline) showing poor flow properties and rest angles >40°.

Therefore, the results of the rest angle are indicative of a phase transition between 31 and 37% v/v of theophylline and a second one between 61 and 74% v/v of theophylline, which can be attributed to the percolation thresholds of the drug and of the excipient, respectively. The anomalous behavior of the blends containing 34.36% v/v and 71.26% v/v of theophylline reflect their vicinity to the first and to the second percolation threshold, respectively. This assay does not provide evidence enough to know whether these blends are below or above the percolation threshold.

Meanwhile, the results of the powder flow assay (Fig. 2b) show a typical divergency, going sharply to cero after the critical point. So blends with drug content up to 34.36% v/v are able to flow, whereas blends with 37.42% v/v or above do not flow when subjected to the official flow rate assay. Therefore, the flowability factors, generally considered, show a drug percolation threshold between 34.36% v/v and 37.42% v/v of theophylline.

As it was mentioned in the previous section, the amount of excipient proposed by the SeDeM method in order to improve the flowability of the API is 74% w/w, i.e., the maximum amount of drug must be 26% w/w. Based on percolation theory, in order to reduce the influence of the properties of the drug in the flowability of the blend, it would be necessary to have the API below its percolation threshold. In our case, below 33% w/w (34.36% v/v). Despite the results of both theories show the same general behavior, there is a disagreement of about 7% w/w of excipient that would be added in excess, following the SeDeM equation.

On the other hand, the results of the parameters named by SeDeM as dimension factors (bulk and tapped densities), are expressed as solid fraction and plotted as a function of the volume fraction of theophylline in Fig. 3. The solid fraction of each blend (ρ) has been calculated using the reported true densities of the materials (theophylline: 1.454 g/cm^3; lactose monohydrate: 1.545 g/cm^3) [20,21], according to the equations (Eqs. (7) and (8)):

$$\rho_{app} = \frac{apparent\ density\ of\ powder}{true\ density\ of\ powder} \tag{7}$$

$$\rho_{tap} = \frac{tapped\ density\ of\ powder}{true\ density\ of\ powder} \tag{8}$$

Table 2
Test results for different blends theophylline: lactose w/w studied with standard deviations.

Blends theophylline:lactose w/w	ρ_{bulk} (g/ml)	*ρtapped* (g/ml)	IP	C (%)	CI (N)	HR	α	t″ (s)	LOD (%)	H (%)	$\%P_{<45}$	Iθ
0:100	0.62 ± 0.01	0.70 ± 0.00	0.19 ± 0.03	11.66 ± 1.47	346 ± 12	1.13 ± 0.02	24.4 ± 0.6	5.90 ± 0.36	0.92 ± 0.26	0.10 ± 0.12	0.13 ± 0.08	0.0552 ± 0.0017
10:90	0.57 ± 0.01	0.67 ± 0.00	0.27 ± 0.04	15.24 ± 1.75	333 ± 10	1.18 ± 0.02	25.4 ± 1.4	7.20 ± 0.17	1.01 ± 0.32	0.05 ± 0.01	0.41 ± 0.01	0.0384 ± 0.0018
20:80	0.54 ± 0.01	0.64 ± 0.00	0.28 ± 0.04	14.91 ± 1.90	264 ± 34	1.18 ± 0.03	26.5 ± 0.8	6.97 ± 0.46	1.90 ± 0.35	0.03 ± 0.03	0.51 ± 0.51	0.0264 ± 0.0011
30:70	0.52 ± 0.01	0.64 ± 0.00	0.37 ± 0.02	19.15 ± 1.24	283 ± 18	1.24 ± 0.01	28.9 ± 0.9	8.07 ± 1.03	1.77 ± 0.01	0.10 ± 0.05	1.18 ± 0.72	0.0267 ± 0.0084
33:67	0.52 ± 0.01	0.63 ± 0.01	0.34 ± 0.03	17.76 ± 1.56	306 ± 17	1.22 ± 0.02	31.3 ± 1.1	6.49 ± 0.15	1.31 ± 0.24	0.07 ± 0.05	0.81 ± 0.03	0.0381 ± 0.0119
36:64	0.51 ± 0.01	0.63 ± 0.01	0.37 ± 0.01	18.90 ± 0.44	289 ± 28	1.23 ± 0.01	34.8 ± 0.7	∞	0.85 ± 0.10	0.14 ± 0.04	1.10 ± 0.75	0.0196 ± 0.0050
40:60	0.51 ± 0.01	0.63 ± 0.01	0.38 ± 0.03	19.14 ± 1.10	165 ± 17	1.24 ± 0.02	32.5 ± 1.0	∞	0.97 ± 0.23	0.07 ± 0.04	1.41 ± 0.34	0.0120 ± 0.0003
50:50	0.51 ± 0.02	0.64 ± 0.00	0.38 ± 0.08	19.28 ± 3.50	229 ± 13	1.24 ± 0.05	35.2 ± 1.1	∞	1.15 ± 0.06	0.23 ± 0.06	0.62 ± 0.01	0.0191 ± 0.0012
60:40	0.48 ± 0.02	0.59 ± 0.00	0.38 ± 0.08	18.12 ± 3.32	250 ± 20	1.22 ± 0.05	36.0 ± 1.0	∞	0.38 ± 0.06	0.29 ± 0.17	1.25 ± 0.17	0.0089 ± 0.0003
70:30	0.46 ± 0.02	0.62 ± 0.00	0.54 ± 0.08	24.81 ± 2.59	211 ± 45	1.33 ± 0.05	40.4 ± 1.0	∞	0.45 ± 0.18	0.05 ± 0.04	0.50 ± 0.05	0.0100 ± 0.0004
73:27	0.45 ± 0.00	0.61 ± 0.00	0.56 ± 0.02	25.60 ± 1.04	279 ± 20	1.34 ± 0.02	45.8 ± 1.8	∞	1.06 ± 0.23	0.15 ± 0.05	1.41 ± 0.36	0.0071 ± 0.0002
76:24	0.43 ± 0.00	0.60 ± 0.01	0.67 ± 0.02	28.71 ± 1.27	296 ± 7	1.40 ± 0.02	46.0 ± 1.0	∞	0.77 ± 0.14	0.08 ± 0.06	0.29 ± 0.32±0.72	0.0182 ± 0.0037
80:20	0.41 ± 0.01	0.53 ± 0.01	0.55 ± 0.08	22.60 ± 2.59	212 ± 16	1.29 ± 0.04	46.6 ± 2.0	∞	0.17 ± 0.08	0.09 ± 0.02	1.21 ± 0.19	0.0056 ± 0.0010
90:10	0.41 ± 0.01	0.59 ± 0.01	0.73 ± 0.05	30.13 ± 1.28	220 ± 12	1.43 ± 0.03	46.4 ± 2.0	∞	0.45 ± 0.06	0.11 ± 0.05	1.84 ± 0.32	0.0049 ± 0.0003
100:0	0.43 ± 0.02	0.57 ± 0.00	0.50 ± 0.09	24.39 ± 3.06	221 ± 13	1.32 ± 0.05	49.2 ± 0.7	∞	0.46 ± 0.08	0.05 ± 0.00	1.19 ± 0.28	0.0065 ± 0.0006

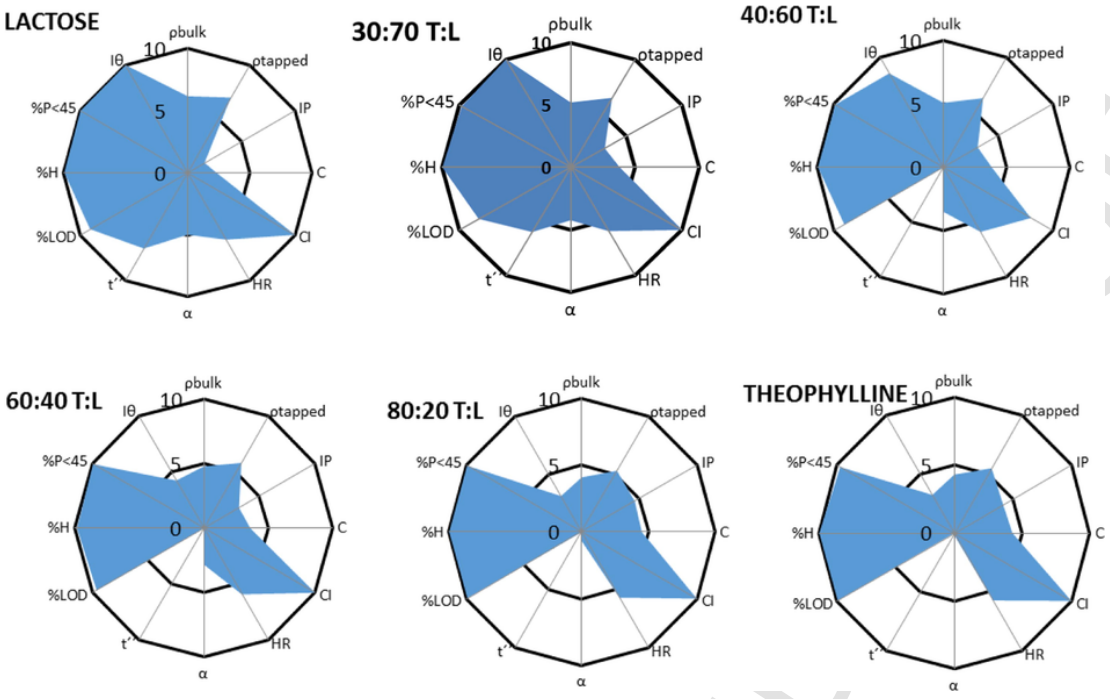

Fig. 1. SeDeM diagrams of lactose, theophylline and blends theophylline:lactose with different proportions (w/w).

Table 3
Mean incidence and parametric indexes for different blends theophylline:lactose w/w.

Blends theophylline:lactose w/w	Mean incidence					Parametric indexes		
	Dimension	Compressibility	Flowability/powder flow	Lubricity/stability	Lubricity/dosage	PI	PPI	GCI
0:100	6.56	4.64	6.09	9.52	9.99	0.75	7.04	6.70
10:90	6.22	5.09	5.79	9.24	9.96	0.75	7.00	6.66
20:80	5.91	4.87	5.77	9.95	9.96	0.75	6.86	6.53
30:70	5.82	5.63	5.36	9.09	9.88	0.75	6.88	6.55
33:67	5.75	5.46	3.99	9.33	9.92	0.67	6.53	6.22
36:64	5.70	5.62	2.97	9.54	9.89	0.67	6.34	6.03
40:60	5.69	4.98	3.13	9.46	9.21	0.67	6.04	5.75
50:50	5.74	5.67	2.94	9.37	9.71	0.67	6.29	5.99
60:40	5.32	5.60	2.91	9.74	7.11	0.50	5.82	5.54
70:30	5.39	6.48	2.49	9.76	7.45	0.58	6.01	5.72
73:27	5.32	6.60	2.12	9.43	6.64	0.58	5.74	5.47
76:24	5.15	7.11	2.04	9.60	9.52	0.75	6.33	6.03
80:20	4.70	6.38	2.13	9.94	6.53	0.50	5.65	5.38
90:10	5.00	7.38	1.98	9.75	6.03	0.67	5.80	5.53
100:0	4.91	6.16	1.97	9.97	6.50	0.50	5.59	5.32

As Fig. 3 shows, the behavior of these parameters is consistent with the observed thresholds. For example, in the case of bulk density, values of solid fraction higher than 0.34 are obtained below the drug percolation threshold, i.e., when only the excipient is percolating the system, whereas solid fractions below 0.30 are obtained above the excipient threshold (when only the drug is percolating).

With respect to Carr's index and Hausner ratio, results are in agreement with the evidence of the percolation thresholds (Fig. 4a and b). So, when excipient percolates, values of Carr's index under 20 are observed, with a decrease tendency for blends below the drug percolation, when only excipient percolates. On the other hand, blends above the excipient threshold show values higher than 20 due to the predominance of the drug, which only percolates the system. The critical point can be estimated by applying the method developed by Fuertes et al. [22], based on the Effective Medium Approximation. This method calculates the critical point as the intersection between the two regressions lines performed with the change tendency of a property *versus* the% v/v of drug. In our case, these regression lines are: $y = -0.0309x + 20.344$ and $y = 0.2105x + 11.915$. So, the intersection point of these equations is 34.9% v/v, attributed to the drug percolation threshold.

Hausner ratio results show the same behavior than Carr's index, with values higher than 1.25 when only drug percolates, and lower than 1.25 when there is an infinite cluster of excipient. In the same way, the critical point can be calculated as the intersection point of the regression lines, obtaining the value of 35.7% v/v of theophylline.

The inter-particle porosity follows exactly the same behavior than the Carr's index, whereas other SeDeM parameters as the loss on drying and the hygroscopicity show very low values (mean 0.91 and 0.11, respectively) whose variation does not reflect the changes in the

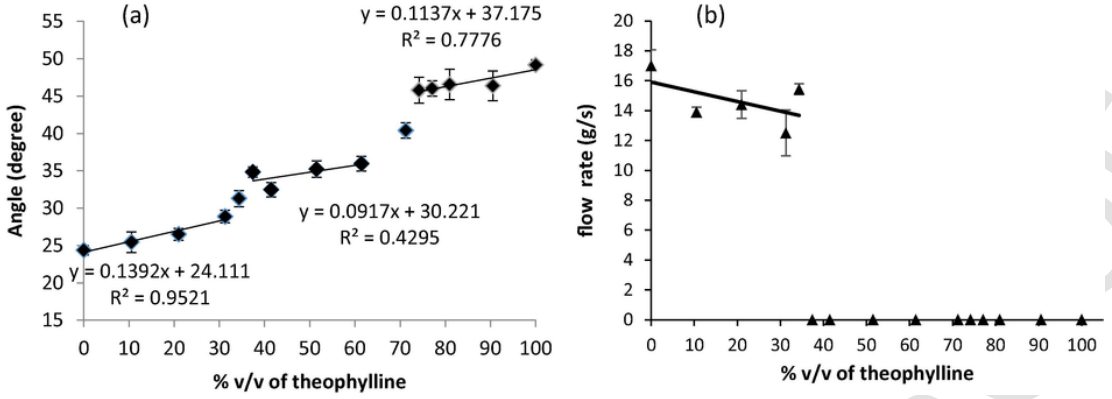

Fig. 2. Factors affecting Flowability/powder flow dimension. (a) Rest angle and (b) powder flow.

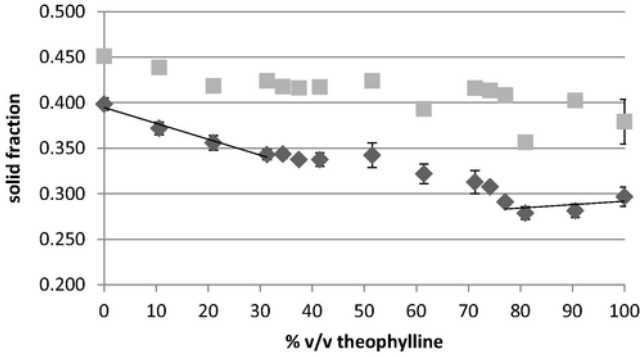

Fig. 3. Factors affecting Dimension: Bulk density (♦) and tapped density (■).

composition of the samples but the oscillation due to the experimental error.

Therefore, this study shows two critical points corresponding to theophylline and lactose percolation thresholds. So, blends with concentrations below the drug percolation thresholds (35.3% v/v) show better rheological behavior, especially affecting its flow capacity, due to the predominant effect of the excipient (these samples contain only isolated clusters of the drug). On the other hand, blends with more than 71.3% v/v of drug show higher compressibility values and poor flowability, due to the fact that the excipient will not percolate these systems, exerting a lower influence.

Following the site percolation model, different percolation thresholds are known on 3-dimensional lattices (diamond lattice, simple cubic or body-centered cubic lattice) [23]. By comparing our percolation thresholds with those reported for loose powder beds, it can be deduced that the geometrical distribution of the particles of theophylline and lactose corresponds to the simple cubic lattice [14].

4. Conclusions

Percolation theory has been successfully applied for the first time to analyze the evolution of SeDeM parameters, confirming the existence of two critical points, corresponding to the drug and excipient percolation thresholds, affecting rheological properties, especially the flow capacity.

Although SeDeM method is an adequate tool to characterize the rheological properties of materials, since this tool is based on the assumption of a linear behavior, percolation theory should be combined with this methodology, especially concerning the quantitative aspects, i.e., to calculate which concentration of a component is needed to improve the properties of a formulation. Calculations based on percolation theory have shown to be more accurate.

Therefore, percolation theory complements the SeDeM method to establish the Design Space in which the formulation is robust avoiding formulation close to phase transitions where abrupt changes in their behavior are expected.

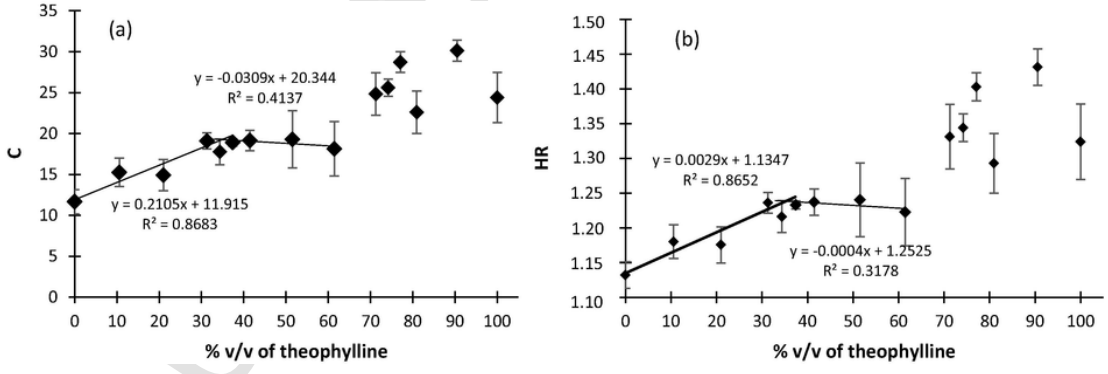

Fig. 4. (a) Carr's index and (b) Hausner ratio results.

References

[1] ICH Expert Working Group, Pharmaceutical Development Q8, ICH Harmon. Tripart. Guidel. 8 (2009) 1–28.

[2] J.M. Suñé-Negre, M. Roig Carreras, R. Fuster García, C. Hernández Pérez, R. Ruhí Roura, E. García Montoya, M. Miñarro Carmona, P. Pérez Lozano, J.R. Ticó Grau, Nueva metodología de preformulación galénica para la caracterización de sustancias en relación a su viabilidad para la compresión: Diagrama SeDeM, Cienc. y Tecnol. Pharm. 15 (2005) 125–136.

[3] P. Pérez, J.M. Suñé-Negre, M. Miñarro, M. Roig, R. Fuster, E. García-Montoya, C. Hernández, R. Ruhí, J.R. Ticó, A new expert systems (SeDeM diagram) for control batch powder formulation and preformulation drug products, Eur. J. Pharm. Biopharm. 64 (2006) 351–359.

[4] J.M. Suñé-Negre, P. Pérez-Lozano, M. Miñarro, M. Roig, R. Fuster, C. Hernández, R. Ruhí, E. García-Montoya, J.R. Ticó, Application of the SeDeM Diagram and a new mathematical equation in the design of direct compression tablet formulation, Eur. J. Pharm. Biopharm. 69 (2008) 1029–1039.

[5] W. Cai, L. Chen, F. Ghanbarnejad, P. Grassberger, Avalanche outbreaks emerging in cooperative contagions, Nat. Phys. 11 (2015) 1–13.

[6] J. Menche, A. Sharma, M. Kitsak, S.D. Ghiassian, M. Vidal, J. Loscalzo, A.-L. Barabási, Disease networks. Uncovering disease-disease relationships through the incomplete interactome, Science (80-.) 347 (2015) 1257601.

[7] J. Gao, T. Zhou, Y. Hu, Bootstrap percolation on spatial networks, Sci. Rep. 5 (2015) 14662.

[8] H. Leuenberger, B. Rohera, C. Haas, Percolation theory - a novel approach to solid dosage form design, Int. J. Pharm. 38 (1987) 109–115.

[9] Á. Aguilar-De-Leyva, C. Cifuentes, A.R. Rajabi-Siahboomi, I. Caraballo, Study of the critical points and the role of the pores and viscosity in carbamazepine hydrophilic matrix tablets, Eur. J. Pharm. Biopharm. 80 (2012) 136–142.

[10] Á. Aguilar-de-Leyva, M.D. Campiñez, M. Casas, I. Caraballo, Critical points and phase transitions in polymeric matrices for controlled drug release, In: Handb. Polym. Pharm. Technol, Scrivener Publishing LLC, 2015, pp. 125–176.

[11] M.D. Campiñez, C. Ferris, M.V. de Paz, A. Aguilar-de-leyva, J. Galbis, I. Caraballo, A new biodegradable polythiourethane as controlled release matrix polymer, Int. J. Pharm. 480 (2015) 63–72.

[12] Council of Europe. EDQM, European Pharmacopoeia, eighth ed., Strasbourg (France), 2013.

[13] M. Kuentz, A new theoretical approach to tablet strength of a binary mixture consisting of a well and a poorly compactable substance, Eur. J. Pharm. Biopharm. 49 (2000) 151–159.

[14] L.E. Holman, H. Leuenberger, The effect of varying the composition of binary powder mixtures and compacts on their properties: a percolation phenomenon, Powder Technol. 60 (1990) 249–258.

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

[16] E. Castellanos-Gil, I. Caraballo, B. Bataille, Tablet design, in: S.C. Gad (Ed.), Pharm. Manuf. Handb. Prod. Process., Wiley-interscience, New Jersey, 2008, pp. 977–1052.

[17] I. Caraballo, M. Fernández-Arévalo, M. Millán, A.M. Rabasco, H. Leuenberger, Study of percolation thresholds in ternary tablets, Int. J. Pharm. 139 (1996) 177–186.

[18] I. Fuertes, I. Caraballo, A. Miranda, M. Millán, Study of critical points of drugs with different solubilities in hydrophilic matrices, Int. J. Pharm. 383 (2010) 138–146.

[19] M. Casas, Á. Aguilar-de-Leyva, I. Caraballo, Towards a rational basis for selection of excipients: excipient efficiency for controlled release, Int. J. Pharm. 494 (2015) 288–295.

[20] M. Otsuka, K. Ibe, Y. Tokudome, H. Ohshima, Nano- and macro-geometrical structural change of caffeine and theophylline anhydrate tablets during hydration process by using X-ray computed tomography, Colloids Surf. B Biointerf. 73 (2009) 351–359.

[21] R.C. Rowe, P.J. Sheskey, W.G. Cook, M.E. Fenton, Handbook of Pharmaceutical Excipients, American Pharmacists Association, Washington, DC, 2012.

[22] I. Fuertes, A. Miranda, M. Millán, I. Caraballo, Estimation of the percolation thresholds in acyclovir hydrophilic matrix tablets, Eur. J. Pharm. Biopharm. 64 (2006) 336–342.

[23] D. Stauffer, A. Aharony, Introduction to Percolation Theory, Taylor & Francis, London, 1992.

Capítulo 2

Uso de poliuretanos como excipientes para la liberación prolongada de fármacos: estudio de parámetros para aseguramiento de la calidad

2.1. **Thermoplastic polyurethane as matrix forming excipient using direct and ultrasound-assisted compression**

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Thermoplastic polyurethane as matrix forming excipient using direct and ultrasound-assisted compression

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1. Introduction

Nowadays, polyurethanes constitutes a very interesting family of polymers utilized for a wide variety of markets due to their unique properties as adhesiveness, strength, elasticity, non-toxicity and low production price (Campiñez et al., 2016, 2015, 2013; Zia et al., 2015). Among them, thermoplastic polyurethanes (TPU) are block copolymers with great potential for controlled drug release systems thanks to their singular chemical structure composed by alternating sequences of hard (HS) and soft segments (SS) (Claeys et al., 2015; G. Verstraete et al., 2016). HS consist of isocyanates while SS are polyols as polyester or polyethers chains with a molecular weight of 1000–10.000 g/mol. The integration of the two different segments provides an elastomeric polymer with unique physicochemical characteristics such as superior tensile strength, resistance and biocompatibility. So, TPUs have been successfully employed in implants, coatings, stents or vaginal rings for years (Claeys et al., 2015). Recently, TPUs have been used in sustained release matrices manufactured by hot-processing techniques (hot-melt extrusion, twin screw melt granulation and injection molding) (Claeys et al., 2015; G Verstraete et al., 2016). However, the capacity of these polymers as matrix tablet forming excipients has been poorly studied (Campiñez et al., 2017).

Although direct compression (DC) is the preferred method of tablet manufacture, in the case of thermoplastic substances, ultrasound-assisted compression (USAC) constitutes a very interesting technology for its advantages respect to DC such as the enhanced compactibility and more

homogeneous particle distribution. Ultrasound tableting machine combines conventional compression process and ultrasound irradiation producing mechanical and thermal effects in the particles. The sonotrode applies the ultrasound energy to the powder bed producing vibration and collisions between particles increasing the temperature of the system (Millán-Jiménez et al., 2017). When the material is a thermoplastic polymer the sintering is easily achieved inducing indistinguishable limits between particles. As a consequence, these excipients can surround the drug in a more efficient way, reducing the drug release (Caraballo et al., 2000). In such a way, USAC allows the manufacture of tablets that control the drug release with very low percentages of excipient reducing the quantity of material needed in comparison with other compaction processes (Aguilar-De-Leyva et al., 2014). Due to thermoplastic deformation and sintering of particles, some researchers have described these systems as an almost continuum medium instead of a particulate one (Caraballo et al., 2000; Millán and Caraballo, 2006). The complex process involved in USAC makes convenient the application of statistical tools as the percolation theory to provide a better knowledge of the final properties of the dosage forms.

Percolation theory is a statistic physical discipline that studies the distribution of disordered and chaotic systems to analyze the behavior or predicting properties near the percolation threshold. The percolation threshold is defined as the concentration of a substance where there is the maximum probability that a geometrical phase transition occurs. At this point is expected that a component changes from being distributed in form of isolated positions to extend over the whole system, i.e. an infinite or percolating cluster is formed. When a component reaches its percolation threshold, it starts having much higher influence on the properties of the system. Close to the percolation threshold, an abrupt change in the properties of the system can occur, which is known as a critical point (Aguilar-de-Leyva et al., 2015, 2017). In this sense, it is essential to determine the critical points of the system, which represent discontinuities of the system properties and to study the behavior above and below the percolation thresholds. This theory has been successfully applied over thirty years in the pharmaceutical area since Leuenberger et al. (Leuenberger et al., 1987) firstly studied the influence of percolation theory on solid dosage forms. Thereby, percolation thresholds have been determined on different properties of the pharmaceutical systems as mechanical, rheological, conductivity, water uptake, and, especially, drug dissolution rate providing useful information about the behavior of these systems (Aguilar-de-Leyva et al., 2017; Aguilar-De-Leyva et al., 2012; Caraballo et al., 1998, 1993; Galdón et al., 2016).

The aim of this work is the development of matrices based on thermoplastic polyurethane manufactured, for the first time, by direct compression and ultrasound-assisted compression, allowing a comparison between these two methods. Technological and biopharmaceutical characteristics of TPU tablets will be evaluated, analyzing their drug release behavior by different

mathematical models. Finally, percolation theory will be applied to both systems and the existence of critical points will be discussed.

2. Materials and methods

2.1. Materials

Thermoplastic polyurethane was kindly supplied by Merquinsa (Pearlbond™ 523, Lubrizol, Ohio, USA). The chemical structure consists of polycaprolactone and 4,4´-methylene diphenyl diisocyanate at a SS/HS proportion of 140, a molecular weight of 78150 g/mol, glass transition temperature -60°C and melting point 55°C (Claeys et al., 2015). Anhydrous theophylline (batch 151209-P-1, Acofarma, Barcelona, Spain) has been used as model drug.

Pure acetone (99.8%) (Scharlab S.L, Spain) and isopropyl alcohol (99.5%) (Cosela, Spain) were used for the pulverization process of TPU.

2.2. Methods

2.2.1. Obtaining TPU powder

TPU pellets were firstly powdered in order to make matrix tablets. The process consists of dissolving the TPU polymer in acetone and slowly adding isopropyl alcohol with constant stirring until precipitation. The solid obtained was filtered and dried into an oven (40ºC) until complete solvent elimination. Finally, the TPU powder was forced to pass through a 1 mm sieve.

2.2.2. Rheological characterization of TPU by SeDeM method

Rheological studies of TPU powder were carried out according to the SeDeM method developed by Suñé-Negre et al. (Pérez et al., 2006). This method unifies several rheological parameters to provide quantitative information about the suitability of a powder in direct compression. Briefly, this expert system normalizes the rheological results from density, compressibility, flow, stability and lubricity tests giving a number in a scale from 0 to 10, allowing determining whether the product is acceptable for direct compression in numerical form. The following rheological tests have been performed: bulk density (ρ_{bulk}), tapped density (ρ_{tapped}), powder flow (t´´), loss on drying (% LOD), interparticle porosity (IP), Carr's Index (C), Hausner ratio (HR), cohesion index (CI), rest angle (α), Hygroscopicity (% H), the percentage of particles measuring <45 μm ($\%P_{<45}$) and homogeneity index (Iθ). The normalized results have been plotted in the SeDeM diagram. The Parametric index (PI), Parametric profile index (PPI) and Good compression index (GCI) were calculated based on the SeDeM approach to determine whether the polyurethane is acceptable for direct compression (Galdón et al., 2016).

In order to calculate the amount of TPU required to compress theophylline, the equation (1) proposed by the method is used, as the minimum necessary for each incidence parameter in order to ensure successful compression.

$$CP = 100 - {}^{(RE - R)}\Big/_{(RE - RP)} \times 100 \qquad (1)$$

Where CP is the percentage of theophylline.
RE = mean-incidence radius value of theophylline.
R = mean-incidence radius value to be obtained in the blend (it should be 5).
RP = mean-incidence radius value of TPU to be corrected.

2.2.3. Preparation of blends

Mixtures of theophylline and thermoplastic polyurethane were blended using a Turbula mixer (WAB T2F, Willy A. Bachofen, Basel, Switzerland) for 10 min. For direct compression matrices, blends with the following proportions were prepared: 10/90, 20/80, 30/70, 40/60, 50/50 w/w TPU/drug.

In the case of ultrasound-assisted matrix systems, the following blends were prepared: 10/90, 15/85, 20/80, 25/75 and 30/70.

2.2.4. Tablet manufacturing

2.2.4.1. Direct compression

TPU tablets were prepared by direct compression in an eccentric tableting machine (Bonals A-300, Barcelona, Spain) using manual feeding and applying the maximum compression force accepted by the formulation. The tablets have a mean weight of 600 mg and were prepared using 14 mm diameter punches and a dwell time of 0.18 s. No lubricant agents were added.

2.2.4.2. Ultrasound-assisted direct compression (USAC)

The USAC tablets were prepared using an ultrasound-assisted tableting machine with a US generator coupled to the upper punch (Tecnea Engineering Srl, Bologna, Italy). Ultrasonic energy of 600 J was applied to the powder during the compaction process at a frequency of 20 kHz. Flat cylindrical punches of 11 mm were employed. The parameters established for the proper compression were: compression pressure: 5 bar, compaction time: 5 s, cool time: 9 s and detach time: 0.5 s. USAC tablets were prepared with 250 mg of formulation.

2.2.5. Tablet characterization

TPU tablets obtained by both methods were technologically characterized. The tablet average weight and the standard deviation (SD) were obtained from 20 individually weighed (Sartorius

CP224S, Göttingen, Germany) tablets according to European Pharmacopoeia (European Pharmacopoeia, 2013).The external dimensions (height and diameter) were determined as the mean of ten tablets from each batch using the digital micrometer (VWR International, Leuven, Belgium) . The breaking force of tablets was measured in a Manual Tablet Hardness Tester (Sotax HT1, SOTAX AG, Aesch, Switzerland). Tablet friability (European Pharmacopoeia, 2013) was calculated as the percentage weight loss of 20 tablets after 4 min at 25 rpm in an Erweka TA (Heusenstamm, Germany) friability tester. Disintegration testing (European Pharmacopoeia, 2013) was performed at 37 ºC in distilled water (800 ml), using an Erweka ZT3 (Heusenstamm, Germany) apparatus. The disintegration times reported are averages of six determinations.

2.2.6. Dissolution studies

Drug release studies were carried out in a USP apparatus 2 Sotax AT7 Smart, (Allschwil, Switzerland) using 900 ml of deaerated water maintained at 37± 0.5 ºC, during 12 h at 50 rpm. The percentage of drug released was measured with an UV–vis spectrophotometer Agilent 8453 (California, USA) at a wavelength of 272 nm (Casas et al., 2010). The assay was performed for six tablets from each batch. Sink conditions were met throughout the dissolution test.

2.2.7. Kinetic studies

Drug release data ($M_t/M_\infty < 0.6$) were analyzed according to zero order, Higuchi (1963) (Higuchi, 1963) Korsmeyer et al. (1983) (Korsmeyer et al., 1983) and Peppas and Sahlin (1989) (Peppas and Sahlin, 1989) equations (2-5):

$$\frac{M_t}{M_\infty} = k_0 t \qquad (2)$$

$$\frac{M_t}{M_\infty} = b t^{1/2} \qquad (3)$$

$$\frac{M_t}{M_\infty} = k_k t^n \qquad (4)$$

$$\frac{M_t}{M_\infty} = k_d t^m + k_r t^{2m} \qquad (5)$$

where M_t/M_∞ is the drug released fraction at time t (the drug loading was considered as M_∞), k_0 is the zero-order release kinetic constant, b is the Higuchi's release rate constant, k_k is the Korsmeyer's kinetic constant, t is the release time, n is the release exponent that depends on the release mechanism and the shape of the matrix tested (Ritger and Peppas, 1987), k_d and k_r are the diffusion and relaxation rate constants, respectively, and m is the purely Fickian diffusion exponent for a device of any geometrical shape which exhibits controlled release.

2.2.8. Estimation of the Excipient Efficiency

The Excipient Efficiency was calculated for the different batches by applying the following equation (6) according to Casas et al. (Casas et al., 2015):

$$EE = \frac{\varepsilon}{b} \cdot \frac{1}{(1.43 - 0.00244d)} \cdot \frac{1}{(1.963 - 0.246 \ln C_s)} \qquad (6)$$

where ε is the total porosity of the matrices, b is the Higuchi's release rate constant, d is the mean particle size of excipient (μm) and C_s is drug solubility in mg/ml. The total porosity is calculated with the known values of volume and weight of tablets according to the following equation:

$$\varepsilon = \frac{V_{real} - V_{theor}}{V_{real}} \text{ x } 100$$

where V_{real} is the real volume of the tablets and V_{theor} the theoretical volume of the tablets, obtained as the TPU volume calculated from its real density. Drug volume was not taken into account due to its soluble behavior.

2.2.9. Estimation of the excipient percolation threshold

According to the percolation theory, critical points represent discontinuities of the system properties, due to geometrical phase transitions of the components. In order to estimate percolation thresholds, kinetic parameters were represented as a function of their theophylline volume fraction (%).

3. Results and discussion

Rheological parameters of TPU Pearlbond™ 523 powder were obtained according to the SeDeM methodology. This preformulation tool has been chosen as it provides very useful information about the suitability of substances to be directly compressed. Table 1 shows the results of the studies with normalized values and the mean of each incidence. According to SeDeM methodology, powders with values above 5 are considered acceptable for direct compression. Except for lubricity/stability properties, this polyurethane show moderate characteristics for direct compression. With respect to the cohesion test, TPU powder could be directly processed in tablet machine without any excipient added, but the tablet hardness could not be measured due to the markedly ductile behavior of the polyurethane. So, tablets were deformed instead of being broken when diametrical force is applied. Figure 1 shows the SeDeM diagram where these rheological results become evident.

Table 1. Normalized results of rheological parameters for TPU powder with the mean incidence values.

Incidence Factor	Parameter	Symbol	Unit	Normalized Result	Mean incidence
Dimension	Bulk density	ρ_{bulk}	g/ml	2.10	2.19
	Tapped density	ρ_{tapped}	g/ml	2.28	
Compressibility	Inter-particle Porosity	IP	-	3.13	2.35
	Carr Index	C	%	1.58	
	Cohesion Index	CI	N	-	
Flowability/ Powder Flow	Hausner Ratio	HR	-	9.57	4.63
	Angle of Repose	α	º	4.31	
	Powder flow	t´´	s	0.00	
Lubricity/Stability	Loss on Drying	%LOD	%	9.87	9.43
	Hygroscopicity	%H	%	9.00	
Lubricity/Dosage	Particles ≤45µm	%P<45	%	10.00	5.75
	Homogeneity Index	Iθ	-	1.50	

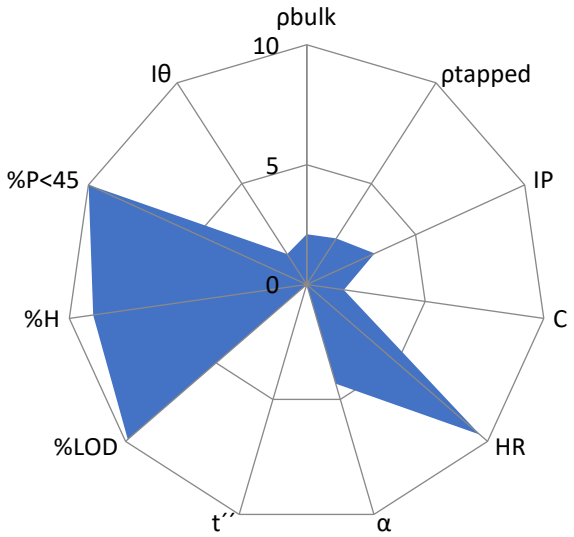

Figure 1. SeDeM diagram of thermoplastic polyurethane Pearlbond™ 523.

The SeDeM Expert System proposes three indexes (PI, PPI and GCI) to determine whether a powder is acceptable for direct compression: parametric index (PI), parametric profile index (PPI) and good compression index (GCI). Values higher than 0.5, 5 and 5, respectively, indicate that the substance can be processed through direct compression (Pérez et al., 2006; Suñé-Negre et al., 2005). The three indexes were calculated according to the method and the results were very close to the acceptable values (PI: 0.36; PPI: 4.85; GCI: 4.57). In general, TPU powder shows similar

rheological values to commercial excipients widely used in direct compression as hydroxypropylmethylcellulose (GCI= 4.52) or ethylcellulose (GCI=5.57)(Saurí et al., 2014) but fulfilling only two of the five incidence factor of the method. The polythiourethane PTU (DTT-HMDI) studied by Campiñez et al. (Campiñez et al., 2015) also showed GCI values of 4.59. The identification of weaknesses and strengths referred to rheological properties of the TPU contributes to the deeper knowledge of the polymer and provides a scientific basis to an adequate establishment of the compression operation knowledge space and its associated design space (Liu et al., 2018). Therefore, results from this preformulation tool allow one to formulate based on the concept of Quality by Design proposed by the ICHQ8 (ICH Expert Working Group, 2009).

SeDeM method allows identifying those powder characteristics that should be improved by adding other substances and, also, provides and estimation of the quantity of material to be added by applying a mathematical equation (Suñé-Negre et al., 2008). The model drug used -theophylline- has been previously characterized by SeDeM method showing a GCI value of 5.32 and good dimensional and compression properties, thus complementing the weaknesses of the polymer (Galdón et al., 2016). According to the equation (1) proposed by SeDeM, the mean quantity of theophylline to add to have a blend with suitable properties for direct compression is 81.46% w/w. However, blends with a lower content of theophylline were successfully compressed, confirming the complementary characteristics of the components. The discrepant results can be attributed to some limitations of the preformulation tool to predict the quantities of API and excipients needed to obtain direct compressible blends. In this sense, Scholtz et al. (Scholtz et al., 2017) found out some shortcomings of the method to adequately evaluate several physicochemical properties such as the elasticity or the cohesiveness of a drug, or to analyze the rheological characteristics of some novel excipients. Moreover, in the SeDeM method, the calculation of the quantity of excipient needed to prepare a suitable formulation is based on the assumption of a linear behavior of the systems. As percolation theory has demonstrated, disordered systems behave as non-linear systems so, in the vicinity of the percolation threshold, the SeDeM estimation shows a certain deviation (Galdón et al., 2016).

All matrix tablets manufactured with blends of TPU and theophylline fulfilled the guidelines specified in European Pharmacopoeia (European Pharmacopoeia, 2013) related to weight uniformity test and friability test, except for the case of 10% USAC, with values higher than 1% (Table 2). With respect to breaking force results, differences were found between tablets depending on the manufacturing method used. So, matrices prepared by direct compression showed hardness values between 80-120 N, while tablets by USAC have a ductile behavior that prevented to measure the tablet hardness, as occurs in cohesion index with 100% TPU tablets. Only matrices from 10% USAC batch could be measured, but obtaining a very low value. Therefore, the excipient exerts more influence in the mechanical behavior of the system when is

compressed by USAC than by DC. Even USAC batches with a very low proportion of TPU (15%) showed this ductile behavior. This fact can be explained by the difference between the continuum medium obtained by the sintering process involved in USAC or the particulate one by DC. Finally, all matrices maintained their physical integrity after 30 minutes in disintegration test.

Table 2. Technological characterization of TPU matrix tablets obtained by DC and USAC.

Batch	Weight (mg)	Diameter (mm)	Thickness (mm)	Hardness (N)	Friability (%)	Disintegration (min)
10% DC	0.598 ± 0.001	14.088 ± 0.018	3.085 ± 0.023	106 ± 11	0.42	>30
20% DC	0.596 ± 0.007	14.057 ± 0.024	3.096 ± 0.0506	113 ± 13	0.18	>30
30% DC	0.599 ± 0.0016	14.065 ± 0.023	3.308 ± 0.0563	85 ± 6	0.08	>30
40% DC	0.589 ± 0.014	14.026 ± 0.007	3.327 ± 0.0127	91± 3	0.98	>30
50% DC	0.601 ± 0.004	14.027 ± 0.018	3.595 ± 0.055	110 ± 9	0.03	>30
10% USAC	0.243 ± 0.002	11.06 ± 0.05	2.31 ± 0.06	21 ± 7	1.41	>30
15% USAC	0.241 ± 1.94	11.06 ± 0.05	2.26 ± 0.06	-	0.89	>30
20% USAC	0.235 ± 0.008	11.05 ± 0.04	2.01 ± 0.17	-	0.73	>30
25% USAC	0.241 ± 2.88	11.07 ± 0.05	2.07 ± 0.07	-	0.28	>30
30% USAC	0.233 ± 0.012	11.13 ± 0.08	2.06 ± 0.10	-	0.73	>30

Drug dissolution studies from matrices with the TPU are shown in Figure 2. Blends with higher content of 30% TPU were not analyzed as the drug release was minimal. In order to compare the results of tablets with different weights and geometries, dissolution results have been normalized taking into account the surface/volume ratio. All the matrices, even with only 10% of TPU, showed a prolonged drug release, confirming the ability of this polymer as matrix forming excipient. As expected, tablets obtained by USAC have theophylline release profiles lower than traditional tablets. In fact, USAC matrices with 25% of TPU have similar profiles than DC tablets with 50% polymer. This can be explained by the improvement in the compaction process thanks to the sintering at the interparticle contact points resulting in strong solid bridges and, consequently, a less porous system and better coating of the drug particles by the excipient (Casas et al., 2015).

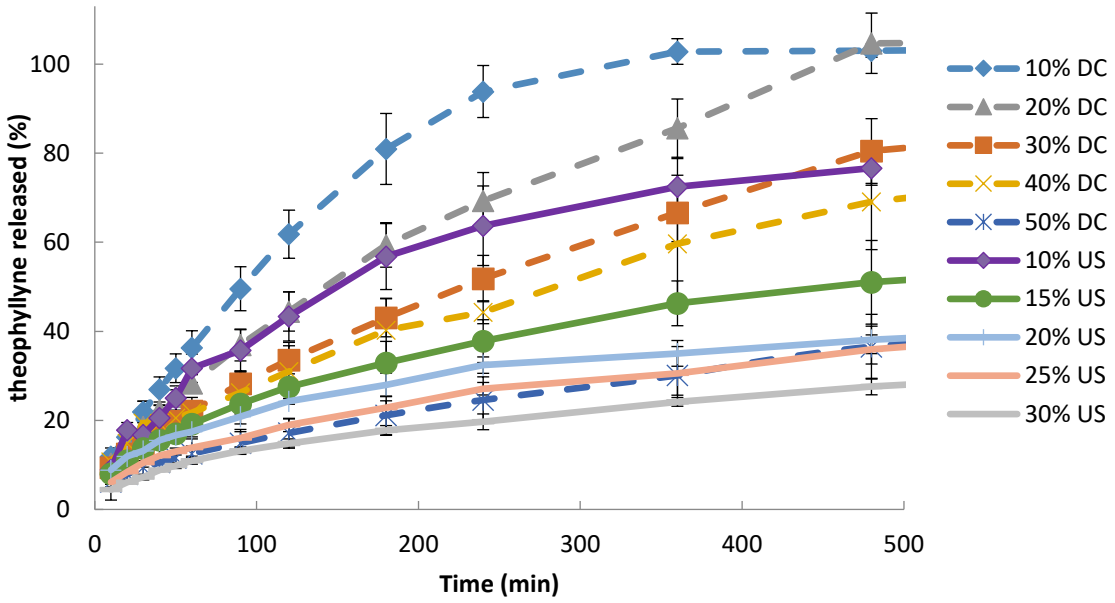

Figure 2. Normalized dissolution profiles for TPU matrix tablets obtained by direct compression (discontinued lines) and ultrasound-assisted compression (continuous lines). Normalization was carried out to take out the different geometries of matrices.

In all cases, except for batch 10% DC, matrix tablets keep their shape and dimensions after the dissolution test, confirming the inert behavior of these matrices. The standard deviation values of USAC batches lower than those from DC matrices can be indicative of the higher robustness of the process.

With respect to kinetic studies, drug release profiles from TPU DC tablets seems to fit Peppas and Sahlin model, according to kinetic parameters shown in Table 3. The release exponent values oscillate between 0.45-0.68, which means that matrices with lower content of TPU (10, 20%) show a drug release behavior with a certain contribution of the erosion mechanism, confirmed by the higher K_r values and the complete disintegration of batch 10%, while matrices with higher content of TPU have a drug release mechanism mainly controlled by diffusion. On the other hand, USAC matrices show a drug release behavior controlled by diffusion, according to the *n* values and the clear predominance of k_d with respect to k_r.

Table 3. Drug release kinetic parameters and Excipient Efficiency from TPU matrix tablets.

	Zero order	Higuchi		Korsmeyer		Peppas & Sahlin			EE ($min^{1/2}$ x mg^{-1}x ml)
Batch	r^2	b	r^2	n	r^2	k_d	K_r	r^2	
10 DC	0.9977	0.0608	0.9830	0.6799	0.9909	0.0152	0.0032	0.9995	9.93
20 DC	0.9916	0.0445	0.9905	0.6092	0.9966	0.0217	0.0014	0.9999	12.01
30 DC	0.9842	0.0325	0.9930	0.5494	0.9914	0.0199	0.0006	0.9995	14.71
40 DC	0.9824	0.0261	0.9836	0.4565	0.9811	0.0136	0.0006	0.9934	15.82
50 DC	0.9639	0.015	0.9920	0.4590	0.9936	0.0104	0.0001	0.9998	24.81
								Mean EE	**15.46**
10 USAC	0.9674	0.0559	0.9808	0.6149	0.9702	0.0389	0.001	0.9840	10.36
15 USAC	0.9545	0.0303	0.9995	0.4931	0.9994	0.0316	-0.00006	0.9996	19.05
20 USAC	0.8943	0.0218	0.9823	0.3868	0.9952	0.0342	-0.0005	0.9964	24.26
25 USAC	0.9460	0.0208	0.9967	0.4509	0.9977	0.0230	-0.00009	0.9972	23.97
30 USAC	0.9409	0.0163	0.9974	0.4734	0.9977	0.0192	-0.0001	0.9988	28.51
								Mean EE	**21.23**

b, Higuchi kinetic constant; n, release exponent; k_d, Peppas diffusion kinetic constant; k_r, peppas relaxation kinetic constant; r^2, determination coefficient.

According to the parameter *Excipient Efficiency,* developed to quantify the ability of an excipient to control the drug release, the thermoplastic polyurethane has a mean value of 15.46 $min^{½}·mg^{-1}·ml$ when processed by direct compression. This value is similar to those obtained for commercial inert and hydrophilic matrix forming excipients (Ethocel® 10FP: 9.54; Methocel® K4M: 20.73). In the case of matrices manufactured by USAC, as they have shown a higher drug release control, *Excipient Efficiency* increases up to 21.23 $min^{½}·mg^{-1}·ml$. Casas et al.(Casas et al., 2015) also reported a higher value of *Excipient Efficiency* for Eudragit RS matrices obtained by USAC (12.43 $min^{½}·mg^{-1}·ml$), respect to direct compression (4.52 $min^{½}·mg^{-1}·ml$), attributed to the lower porous structure and the better coating of drug particles by this manufacturing method.

Regarding the estimation of the excipient percolation threshold, kinetic parameters (from Higuchi, Korsmeyer or Peppas and Sahlin equations) have been plotted as a function of the volumetric fraction of TPU % (v/v) in order to observe possible discontinuities (Figure 3). In the case of direct compression, it can be observed a change tendency of K_d and K_r respect to the volumetric fraction of TPU, and a critical point can be calculated as the intersection point of linear regressions, based on the method developed by Fuertes et al. (Fuertes et al., 2006). So, the percolation threshold of TPU can be between 25-27% v/v. That means that this proportion will

constitute a limit in the Design Space to achieve a robust formulation, according to the requirements of ICH Q8 guideline (ICH Expert Working Group, 2009).

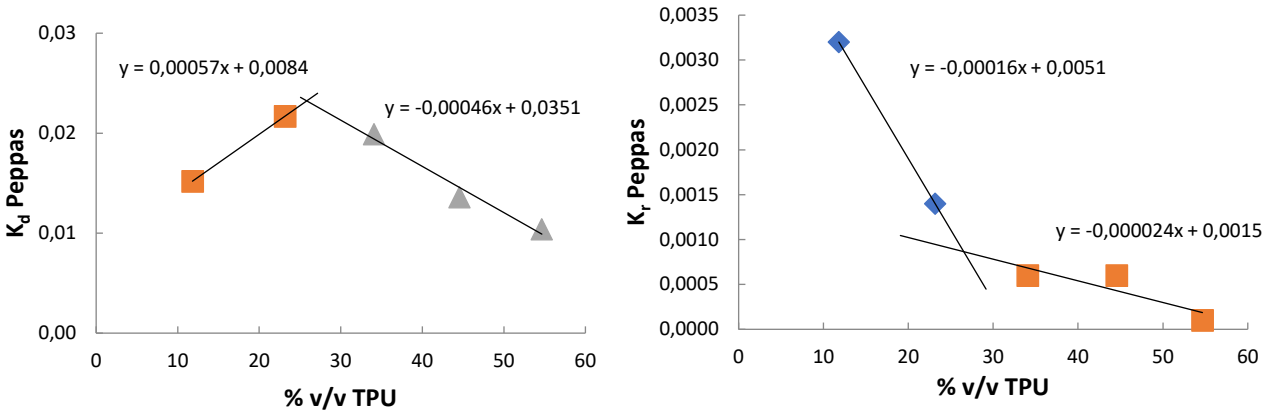

Figure 3. Estimation of the drug percolation threshold in TPU tablets by direct compression.

In the case of USAC tablets, the plots of the kinetic constants show decreasing values of Higuchi kinetic constant and K_d as the TPU % increases. On the other hand, with respect to relaxation behavior, all matrices show negative values, except for the batch with 10%. This batch has also shown different physical and technological characteristics: the fastest drug release profile, the highest friability and being the only one whose tablets are broken instead of deformed when subjected to the crushing strength assay. Since these systems constitute an almost continuum medium instead of a particulate one, continuum percolation models can be applied. In this case, the percolation threshold of a substance is estimated at 16% v/v (Caraballo et al., 2000). According to the densities of the two components, the batch with 10 and 15% TPU w/w are equivalent to a volumetric fraction of 11.81 and 17.54 % v/v, respectively. Therefore, based on the differences shown by the batch with 10% of TPU, it can be estimated a TPU percolation threshold between 11.8-17.5 % v/v.

4. Conclusions

The thermoplastic polyurethane evaluated has shown excellent technological and biopharmaceutical characteristics to be a matrix tablet forming excipient. Matrix tablets with TPU and high drug loads (up to 90 % w/w) have been successfully manufactured for the first time by two methods: direct compression and ultrasound assisted compression. The application of USAC to the thermoplastic polymer results, very profitably, in a drastic reduction of 50% of the excipient needed to obtain a similar drug release rate in direct compression. Excipient efficiency calculated from porosities and kinetic constants shows the high ability of this polymer to control the drug release. The estimation of the percolation threshold of the thermoplastic polyurethane

(Pearlbond™ 523) for both manufacture methods allows defining the Design Space of a formulation, according to the requirements of ICH Q8 guideline.

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References

Aguilar-de-Leyva, A., Campiñez, M.D., Casas, M., Caraballo, I., 2015. Critical Points and Phase Transitions in Polymeric Matrices for Controlled Drug Release, Handbook of Polymers for Pharmaceutical Technologies. doi:10.1002/9781119041375.ch4

Aguilar-de-Leyva, Á., Campiñez, M.D., Casas, M., Caraballo, I., 2017. Design space and critical points in solid dosage forms. J. Drug Deliv. Sci. Technol. doi:10.1016/j.jddst.2017.06.004

Aguilar-De-Leyva, Á., Cifuentes, C., Rajabi-Siahboomi, A.R., Caraballo, I., 2012. Study of the critical points and the role of the pores and viscosity in carbamazepine hydrophilic matrix tablets. Eur. J. Pharm. Biopharm. 80, 136–142. doi:10.1016/j.ejpb.2011.09.007

Aguilar-De-Leyva, Á., Gonçalves-Araujo, T., Daza, V., Caraballo, I., 2014. A new deferiprone controlled release system obtained by ultrasound-assisted compression. Pharm. Dev. Technol. 19, 728–734.

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., Benito, E., Romero-Azogil, L., Aguilar-de-Leyva, Á., García-Martín, M. de G., Galbis, J.A., Caraballo, I., 2017. Development and characterization of new functionalized polyurethanes for sustained and site-specific drug release in the gastrointestinal tract. Eur. J. Pharm. Sci. 100, 285–295. doi:10.1016/j.ejps.2017.01.017

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., 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

Caraballo, I., Alvarez-Fuentes, J., Melgoza, L., Millán, M., Holgado, M., Rabasco, A., Fernández-

Arévalo, M., 1998. Validation study of the conductometrical analysis. Application to the drug release studies from controlled release systems. J. Pharm. Biomed. Anal. 18, 281–285. doi:10.1016/S0731-7085(98)00180-0

Caraballo, I., Fernández-Arévalo, M., Holgado, M.A., Rabasco, A.M., 1993. Percolation theory: application to the study of the release behaviour from inert matrix systems. Int. J. Pharm. 96, 175–181.

Caraballo, I., Millán, M., Fini, A., Rodriguez, L., Cavallari, C., 2000. Percolation thresholds in ultrasound compacted tablets. J. Control. Release 69, 345–355.

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

Casas, M., Ferrero, C., Jiménez-Castellanos, M.R., 2010. Graft tapioca starch copolymers as novel excipients for controlled-release matrix tablets. Carbohydr. Polym. 80, 71–77. doi:10.1016/j.carbpol.2009.10.065

Claeys, B., Vervaeck, A., Hillewaere, X.K.D., Possemiers, S., Hansen, L., De Beer, T., Remon, J.P., Vervaet, C., 2015. Thermoplastic polyurethanes for the manufacturing of highly dosed oral sustained release matrices via hot melt extrusion and injection molding. Eur. J. Pharm. Biopharm. 90, 44–52. doi:10.1016/j.ejpb.2014.11.003

European Pharmacopoeia, 2013. European Pharmacopoeia, 8th ed. Strasbourg (France).

Fuertes, I., Miranda, A., Millán, M., Caraballo, I., 2006. Estimation of the percolation thresholds in acyclovir hydrophilic matrix tablets. Eur. J. Pharm. Biopharm. 64, 336–42. doi:10.1016/j.ejpb.2006.05.009

Galdón, E., Casas, M., Gayango, M., Caraballo, I., 2016. First study of the evolution of the SeDeM expert system parameters based on percolation theory: Monitoring of their critical behavior. Eur. J. Pharm. Biopharm. 109, 158–164. doi:10.1016/j.ejpb.2016.10.004

Higuchi, T., 1963. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci. 52, 1145–1149.

ICH Expert Working Group, 2009. Pharmaceutical Development Q8. ICH Harmon. Tripart. Guidel. 8, 1–28.

Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P., Peppas, N.A., 1983. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm. 15, 25–35.

Leuenberger, H., Rohera, B., Haas, C., 1987. Percolation theory - a novel approach to solid dosage

form design. Int. J. Pharm. 38, 109–115. doi:10.1016/0378-5173(87)90105-0

Liu, J., Dai, S., Zhang, Z., Xu, B., Qiao, Y., Shi, G., Shi, X., 2018. SeDeM expert system for directly compressed tablet formulation: A review and new perspectives. Powder Technol. 342, 517–527. doi:10.1016/j.powtec.2018.10.027

Millán-Jiménez, M., Galdón, E., Ferrero, C., Caraballo, I., 2017. Application of ultrasound-assisted compression in pharmaceutical technology. Design and optimization of oral sustained-release dosage forms. J. Drug Deliv. Sci. Technol. 1–7. doi:10.1016/j.jddst.2017.05.016

Millán, M., Caraballo, I., 2006. Effect of drug particle size in ultrasound compacted tablets. Continuum percolation model approach. Int. J. Pharm. 310, 168–74. doi:10.1016/j.ijpharm.2005.12.005

Peppas, N.A., Sahlin, J.J., 1989. A simple equation for the description of solute release. III. Coupling of diffusion and relaxation. Int J Pharm. 57, 169–172.

Pérez, P., Suñé-Negre, J.M., Miñarro, M., Roig, M., Fuster, R., García-Montoya, E., Hernández, C., Ruhí, R., Ticó, J.R., 2006. A new expert systems (SeDeM diagram) for control batch powder formulation and preformulation drug products. Eur. J. Pharm. Biopharm. 64, 351–9. doi:10.1016/j.ejpb.2006.06.008

Ritger, P.L., Peppas, N.A., 1987. A simple equation for description of solute release I. Fickian and non-fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. J Control. Release. 5, 23–36.

Saurí, J., Millán, D., Suñé-Negre, J.M., Colom, H., Ticó, J.R., Miñarro, M., Pérez-Lozano, P., García-Montoya, E., 2014. Quality by Design approach to understand the physicochemical phenomena involved in controlled release of captopril SR matrix tablets. Int. J. Pharm. 477, 431–441. doi:10.1016/j.ijpharm.2014.10.050

Scholtz, J.C., Steenekamp, J.H., Hamman, J.H., Tiedt, L.R., 2017. The SeDeM Expert Diagram System: Its performance and predictability in direct compressible formulations containing novel excipients and different types of active ingredients. Powder Technol. 312, 222–236. doi:10.1016/j.powtec.2017.02.019

Suñé-Negre, J.M., Pérez-Lozano, P., Miñarro, M., Roig, M., Fuster, R., Hernández, C., Ruhí, R., García-Montoya, E., Ticó, J.R., 2008. Application of the SeDeM Diagram and a new mathematical equation in the design of direct compression tablet formulation. Eur. J. Pharm. Biopharm. 69, 1029–39. doi:10.1016/j.ejpb.2008.01.020

Suñé-Negre, J.M., Roig Carreras, M., Fuster García, R., Hernández Pérez, C., Ruhí Roura, R.,

García Montoya, E., Miñarro Carmona, M., Pérez Lozano, P., Ticó Grau, J.R., 2005. Nueva metodología de preformulación galénica para la caracterización de sustancias en relación a su viabilidad para la compresión: Diagrama SeDeM. Cienc. y Tecnol. Pharm.

Verstraete, G., Mertens, P., Grymonpré, W., Bockstal, P.J. Van, Beer, T. De, Boone, M.N., Hoorebeke, L. Van, Remon, J.P., Vervaet, C., 2016. A comparative study between melt granulation / compression and hot melt extrusion / injection molding for the manufacturing of oral sustained release thermoplastic polyurethane matrices. Int. J. Pharm. 513, 602–611. doi:10.1055/s-2003-38483

Verstraete, G., Van Renterghem, J., Van Bockstal, P.J., Kasmi, S., De Geest, B.G., De Beer, T., Remon, J.P., Vervaet, C., 2016. Hydrophilic thermoplastic polyurethanes for the manufacturing of highly dosed oral sustained release matrices via hot melt extrusion and injection molding. Int. J. Pharm. 506, 214–221. doi:10.1016/j.ijpharm.2016.04.057

Zia, F., Zia, K.M., Zuber, M., Kamal, S., Aslam, N., 2015. Starch based polyurethanes: A critical review updating recent literature. Carbohydr. Polym. 134, 784–798. doi:10.1016/j.carbpol.2015.08.034

2.2. **Achieving High Excipient Efficiency with Elastic Thermoplastic Polyurethane by Ultrasound Assisted Direct Compression**

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Achieving High Excipient Efficiency with Elastic Thermoplastic Polyurethane by Ultrasound Assisted Direct Compression

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Abstract: Ultrasound assisted compression (USAC) is a manufacturing technique which applies thermal and mechanical energy to the powder bed, producing tablets with improved characteristics compared to the direct compression process. This technology is ideal for thermoplastic materials, as polyurethanes, whose particles usually undergo a sintering process. Thermoplastic polyurethanes are widely used in sustained drug release systems but rarely seen in tablets due to their elastic properties. The aim of this work is to investigate the ability of USAC to manufacture sustained release matrix tablets based on elastic thermoplastic polyurethanes (TPU), overcoming the limitations of direct compression. The technological and biopharmaceutical characteristics of the TPU matrices have been evaluated, with special focus on the porous structure due to the implications on drug release. For the first time, USAC has been successfully employed for manufacturing elastic thermoplastic polyurethanes-based matrices. TPU tablets show an inert character with a sustained drug release governed by a diffusional mechanism. Initial porosity of matrices was similar in all batches studied, with no influence of drug particle size, and a fractal nature of the pore network has been observed. SEM microphotographs show the continuum medium created by the sintering of the polymer, responsible for the high excipient efficiency.

Keywords: ultrasound assisted direct compression; polyurethanes; prolonged-release tablets; percolation theory; porosity; fractal dimension

1. Introduction

Nowadays, tablets remain as the most common dosage form in the pharmaceutical market. This proportion has even increased thanks to the generic drugs since tableting generally results in a lower cost of development as well as a higher industrial production capacity [1]. However, in the majority of cases, either wet or dry granulation has to precede the compaction step to obtain suitable properties for industrial processing and to achieve the targeted properties of the finished drug product.

Ultrasound-assisted compression (USAC) is a manufacturing technology which combines a conventional compression process with ultrasound irradiation. Ultrasound energy causes mechanical and thermal effects which lead to heating and sintering of materials, improving the compression process [2]. Thus, ultrasounds increase the interparticle bonds resulting in stronger and less porous tablets at lower pressures as compared to conventional tableting [3–5]. Moreover, the use of intermediate processes as granulation is also avoided with USAC.

This technology has been successfully employed for different applications as the amorphization of active pharmaceutical ingredients, production of solid dispersions to enhance the bioavailability of poorly soluble drugs and formulation of sustained drug release forms [3,6–10]. In the case of prolonged

release systems, USAC appears as a promising technique, decreasing the cost and the quantity of excipient needed for the control of the drug release [8], which usually constitutes an important drawback in the formulation of sustained-release systems.

This process is particularly suitable when the excipient exhibits a thermoplastic deformation, allowing the formation of a framework that holds the non-thermoplastic particles together. In this way, the polymer will form an inert skeleton avoiding the disintegration of the matrix, surrounding more efficiently the drug, and consequently controlling the drug release with a low quantity of excipient.

Thermoplastic polyurethanes (TPU) have stood out as a very interesting group of excipients for controlled release dosage forms, being successfully used in vaginal rings, stents, coatings, and implants due to favorable properties as its inert, non-ionic, and water-insoluble character. They also exhibit a high tensile strength, crack resistance, inherent lubricity, and highly elastomeric character. Recently, TPU have been researched for the manufacturing of oral sustained drug release forms obtained by hot-processing techniques, such as hot melt extrusion or injection molding [11,12]. However, the manufacture of TPU tablets by direct compression has been very limited due to their poor plastic/elastic balance at room temperature [13].

Due to the water insoluble character of TPU, the porosity of the inert matrices obtained plays an important role in their performance as it directly affects the liquid uptake rate and influences the drug release kinetics. Normally, the pore structure is complex and randomly distributed with different sizes, shapes, and orientations, which makes it difficult to accurately describe it [14]. Therefore, different techniques have been employed to determine macroscopic and microscopic pore parameters, since its analysis becomes necessary for the deeper knowledge of these systems.

The aim of this work is to investigate the ability of USAC to overcome the undesirable elastic properties of thermoplastic polymers, allowing one to obtain tablets by direct compression. An additional objective is the study of the properties of the obtained tablets.

For this purpose, we employed the elastic thermoplastic polyurethane (TPU) Tecoflex^{TM} EG-72D as the matrix forming excipient in tablets obtained by USAC. The main properties of the obtained high drug content TPU matrices have been evaluated, including the study of their porous system through fractal dimension and the influence of drug particle size.

2. Materials and Methods

2.1. Materials

Anhydrous theophylline (batch151209-P-1, Acofarma, Barcelona, Spain) was used as model drug. Medical grade elastomer thermoplastic polyurethane Tecoflex^{TM} EG-72D (TPU) was used as matrix forming excipient, which was kindly supplied by Lubrizol Advanced Materials Spain S.L. (Bacelona, Spain). The TPU chemical structure consists of polytetrahydrofuran (soft segment) and hydrogenated methylene diphenyl diisocyanate (hard segment) at a molar ratio of 3.5. The molecular weight is 59,000 g/mol and its melting point is 53° [11]. TPU ultimate tensile strength and elongation at break are 55.8 MPa and 310%, respectively.

2.2. Methods

2.2.1. Blends Preparation

Tecoflex^{TM} EG-72D pellets were frozen in liquid nitrogen and subsequently milled with a Restch ZM 200 equipment (Haan, Germany), using a 1.0 mm output sieve. Three fractions of drug particle size (<90 μm, 90–150 μm and 150–355 μm) were obtained by sieving in order to evaluate the influence of this factor on the technological and biopharmaceutical behavior of the systems.

Blends of theophylline and polymer powder (70/30 *w*/*w* proportion) have been mixed during 15 min (Turbula mixer, Willy A. Bachofen, Basel, Switzerland). The optimum blend time was calculated based on the drug content of 5 representative samples at different times tested. The quantity of drug

was determined by UV–Vis spectrophotometry (Agilent 8453 (California, CA, USA)) at 272 nm [15]. Variation coefficient values lower than 5% were considered as appropriate.

2.2.2. Preparation of TPU Tablets by Direct Compression

An eccentric tableting machine (Bonals A-300, Barcelona, Spain) was used to compact 300 mg of blends, using manual feeding and applying the maximum compression force accepted by the formulation.

2.2.3. Preparation of TPU Tablets by Ultrasound-Assisted Direct Compression

Tablets of 300 mg weight for each lot were obtained using an ultrasound-assisted tableting machine (Tecnea Engineering, Casale Monferrato, Italy). An ultrasonic energy of 650 J was applied to the mixture at 20 kHz frequency. Flat cylindrical punches of 11 mm were employed. The parameters established for the proper compression were: compression pressure 0.3 MPa, compaction time 6 s, cool time 9 s and detach time 0.5 s.

2.2.4. Physical Characterization of TPU Tablets

The weight (EP214, Ohaus Corporation, Parsippany, NJ, USA), thickness and diameter (VWR International, Leuven, Belgium) of the TPU tablets were determined as the mean of 10 tablets for each lot.

2.2.5. Dissolution Testing of TPU Tablets and Modelling

Drug release studies were carried out using a USP Apparatus II Sotax AT7 smart (Allschwil, Switzerland) with 900 mL of deionized water at 37 ± 0.5 °C and 50 rpm. Samples were withdrawn at specific interval times and filtered through 0.45 mm filters (Millipore Ltd., Cork, Ireland). The percentage of drug released was measured in a UV–Vis spectrophotometer Agilent 8453 (California, CA, USA) at 272 nm [15]. The assay was performed in triplicate and sink conditions were met throughout the dissolution test.

Drug release data ($M_t/M_\infty \leq 0.6$) were analyzed according to Higuchi (1963) [16], Korsmeyer et al. (1983) [17] and Peppas and Sahlin (1989) [18] Equations (1)–(3):

$$\frac{M_t}{M_\infty} = kt^{\frac{1}{2}}, \quad (1)$$

$$\frac{M_t}{M_\infty} = k_k t^n, \quad (2)$$

$$\frac{M_t}{M_\infty} = k_d t^m + k_r t^{2m}, \quad (3)$$

where M_t/M_∞ is the drug released fraction at time t (the drug loading was considered as M_∞), k is the Higuchi's release rate constant, k_k is the Korsmeyer's kinetic constant, t the release time, n the release exponent that depends on the release mechanism and the shape of the matrix tested [19], k_d and k_r are, respectively, the diffusion and relaxation rate constants, and finally m which is the purely Fickian diffusion exponent for a device of any geometrical shape which exhibits controlled release.

2.2.6. Mercury Porosimetry Measurements

Mercury porosimetry runs were undertaken using an Autopore IV 9510 (Micromeritics, Madrid, Spain) porosimeter with a 3 cm^3 penetrometer. An adequate number of tablets per tested formulation was used in order to obtain a stem volume between 25% and 90% of the penetrometer capacity. Working pressures covered the range 0.1–60,000 psi. Total porosity and pore size distribution of tablets were determined before and after the drug release study in duplicate and for each tested batch.

In the case of leached tablets, the porosity results have been normalized by subtracting the initial mercury intrusion, in order to perform a clearer comparison of the structure of the pore network inside these systems.

2.2.7. Measurement of Fractal Dimension

Volume fractal dimension D_v of TPU matrices has been estimated according to the idealized model of the Menger sponge [20,21]. This model correlates the relative density of the system with the pore diameter filled with mercury at a certain intrusion pressure through the following equation (Equation (4)):

$$\log \rho_r = (3 - D_v) log d + c, \quad (4)$$

where the relative density ρ_r is obtained by the pore volume fraction filled with mercury intrusion pressure $\rho_r = 1 - \varepsilon$ and c is a constant.

Volume fractal dimension can be calculated by the slope of the straight line obtained by plotting the relative density of the system ρ_r as a function of diameter in a double logarithmic plot.

2.2.8. Scanning Electron Microscopy (SEM)

The surface of TPU matrices were evaluated at the Microscopy Service of the CITIUS in the University of Seville by using Scanning Electron Microscopy (SEM) with a FEI TENEO electronic microscope (FEI Company, Hillsboro, OR, USA), operating at 5 kV. Tablets were coated with a 10 nm thin Pt layer with Leica EM SCD500 high vacuum sputter coater.

2.2.9. Estimation of the Excipient Efficiency

The Excipient Efficiency is a parameter to quantify the ability of an excipient to control the drug release from a pharmaceutical formulation [15]. This parameter has been calculated for TPU according to the following equation (Equation (5)):

$$E = \frac{\varepsilon}{b} \frac{1}{(1.43 - 0.00244d)} \frac{1}{(1.963 - 0.246 ln C_s)}, \quad (5)$$

where ε is the total porosity of the matrices, b is the Higuchi's release rate constant, d is the mean particle size of excipient (μm) and C_s is the drug solubility in mg/mL.

3. Results and Discussion

Tablets of TPU and theophylline were successfully obtained by USAC for all batches. Conversely, when the same blends of TPU and theophylline were processed through a standard eccentric tableting machine, the obtained tablets do not show suitable technological characteristics, mainly due to their elastic properties leading to a crumbling of tablets during the relaxation step (in less than 24 h). Therefore, all the following sections, devoted to the characterization of the obtained tablets, are referred to the USAC tablets.

3.1. Characterization of TPU Tablets Obtained by USAC

Physical characteristics of tablets were consistent with the established compression conditions, obtaining an average weight, diameter, and thickness of 297.3 ± 1.0 mg, 11.247 ± 0.000 mm, and 2.856 ± 0.034 mm, respectively. Tablet hardness or tensile strength of tablets could not be measured due to the elastic nature of the system. Tablets were deformed instead of broken when they were subjected to the crushing strength tester.

3.2. Dissolution Testing of TPU Tablets and Modelling

Drug release profiles of TPU tablets are shown in Figure 1. Matrices made with different particle size of drug display similar biopharmaceutical behavior, achieving a prolonged theophylline release during more than 8 h. The integrity of tablets was maintained in all cases at the end of the study.

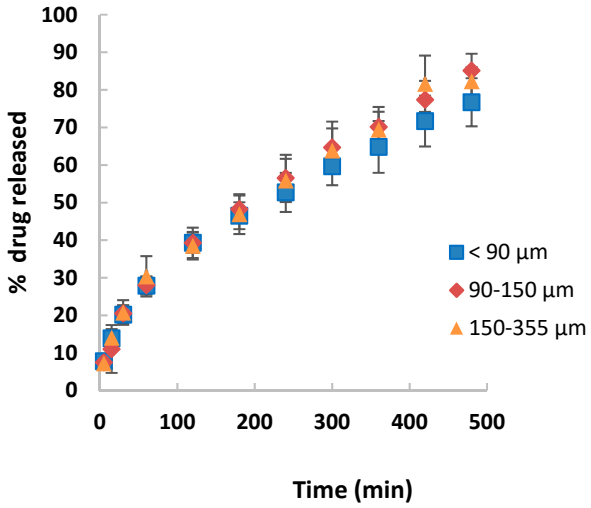

Figure 1. Drug release profiles of thermoplastic polyurethanes (TPU) tablets with different drug particle size.

On the basis of percolation theory, pharmaceutical systems can be described as randomly distributed materials where geometrical phase transitions can occur [22,23]. When a component reaches its percolation threshold, it starts to extend over the whole sample, having much greater influence on the properties of the system.

In our case, as the excipient undergoes thermoplastic deformation, the continuum percolation model can be used to predict the changes in the system. This model considers a continuum distribution function of the components and the percolation threshold of a substance is situated at approximately 16% v/v of occupation probability [2]. According to the densities of the components, TPU constitutes 37.5% v/v, being therefore above its percolation threshold. This is consistent with the inert matrix formed and the controlled drug release obtained. With respect to the drug, being at a proportion of 62.5% v/v is also clearly above its percolation threshold. That ensures the complete release of the drug dose.

Drug release data have been analyzed according to different kinetic models: Higuchi, Korsmeyer and Peppas and Sahlin (Table 1). The good determination coefficients for the diffusional model (Higuchi), the Korsmeyer n values close to 0.5, and the predominance of k_d over k_r in the Peppas and Sahlin equation reveal a drug release mechanism predominantly controlled by drug diffusion.

Table 1. Main kinetic parameters from TPU tablets.

TPU Tablets with Different Drug Particle Size (µm)	Higuchi		Korsmeyer		Peppas & Sahlin		
	b ($min^{-0.5}$)	r^2	n	r^2	k_d ($min^{-0.5}$)	k_r (min^{-1})	r^2
<90	0.0339	0.9986	0.4915	0.9988	0.0387	-2.10^{-4}	0.9994
90–150	0.0373	0.9966	0.5366	0.9896	0.0361	9.10^{-5}	0.9974
150–355	0.0354	0.9947	0.513	0.9938	0.0361	-2.10^{-6}	0.9957

b, Higuchi kinetic constant; n, release exponent; k_d, Peppas diffusion kinetic constant; k_r, Peppas relaxation kinetic constant; r^2, determination coefficient.

3.3. Mercury Porosimetry Measurements

As TPU tablets are inert matrix systems, the knowledge of total porosity—the sum of the initial pores plus the pores that appear once the drug is dissolved—is critical to ensure the complete drug

leaching and plays an important role in the release kinetics. TPU tablets showed initial porosity values between 17.1%–19.8% with a median pore diameter around 2 µm (Table 2). Figure 2A shows the cumulative mercury intruded by the matrices at different pressures, where no difference of porosity has been found as a function of drug particle size. Porosity of matrices after dissolution testing (total porosity) was measured since the integrity of tablets was maintained in all cases at the end of the assay.

Table 2. Porosity and fractal dimension D_v of TPU matrices obtained by ultrasound assisted compression (USAC), containing three different fractions of theophylline.

Drug Fraction	TPU Matrices	Porosity (%)	Median Pore Diameter (µm)	D_v (and range in µm)
	<90 µm	17.9 ± 0.7	2.1	2.883 (3.2–1.1)
	90–150 µm	19.8 ± 2.9	1.8	2.882 (2.5–1.1)
	150–355 µm	17.1 ± 1.9	1.7	2.899 (2.5–0.8)
	TPU Matrices after Dissolution Testing			
Drug Fraction	<90 µm	59.1 ± 0.4	33.7	2.9203 (17.2–90.6)
	90–150 µm	58.6 ± 1.8	41.1	2.9344 (21.3–90.3)
	150–355 µm	60.3 ± 0.1	40.5	2.9542 (13.9–90.5)

In the case of leached tablets, the obtained results showed different porosity patterns depending on particle size, as shown in Figure 2B. Matrices containing larger drug particle size have higher mercury intrusion at atmospheric pressure, due to the presence of higher pores left by the coarser drug particles after leaching [24]. Normalized porosity results, in which the initial mercury intrusion value has been subtracted, have been represented in the same Figure 2B in order to study the pore network. A more extensive pore network can be observed for the case of matrices with smaller particle size.

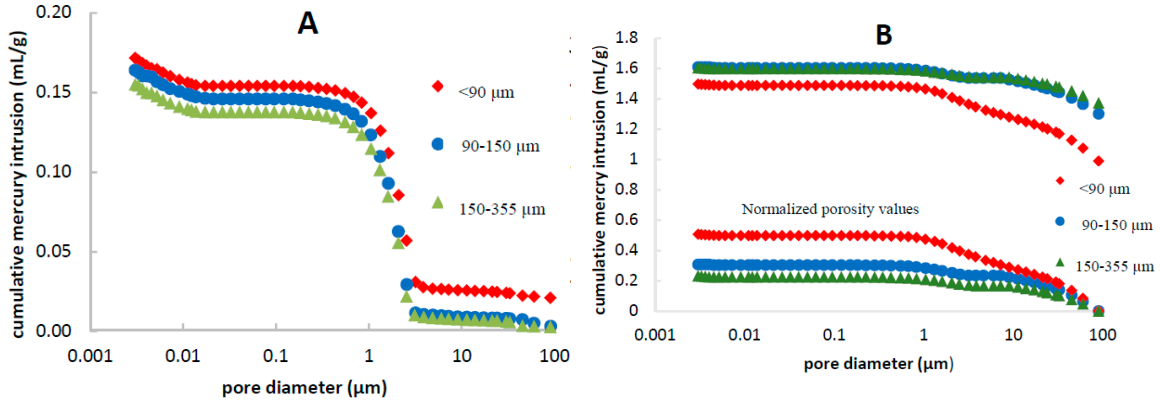

Figure 2. Cumulative mercury intrusion of USAC tablets with different drug particle sizes, before (**A**) and after drug release study (**B**), with normalized porosity values—without initial mercury intrusion—represented at the bottom of the image.

As indicated in previous sections, the influence of drug particle size on the release profiles was sparingly significant. This can be due to the existence of two opposite influences. On one hand, the wider pores left by the coarser particles favor a faster diffusion through a reduction of the thickness of the diffusion layer. On the other, the matrices containing finer particles are expected to have a lower drug percolation threshold [25]. Therefore, they have a higher distance to the drug percolation threshold and consequently, they are expected to contain a more extended drug network than the coarser particles. The first one of these opposite phenomena is reflected in the absolute values of mercury intrusion, and the second one in the behavior of the normalized porosity results (Figure 2B).

The elastic nature of the TPU was evidenced since the extrusion curves follow the same plotted path as the intrusion curves (Figure 3). In contradistinction to non-elastic materials that show a typical

pore retention hysteresis at extrusion process, TPU tablets seems to return to its original shape after being elastically compressed at the highest pressures, expelling the mercury [14,26].

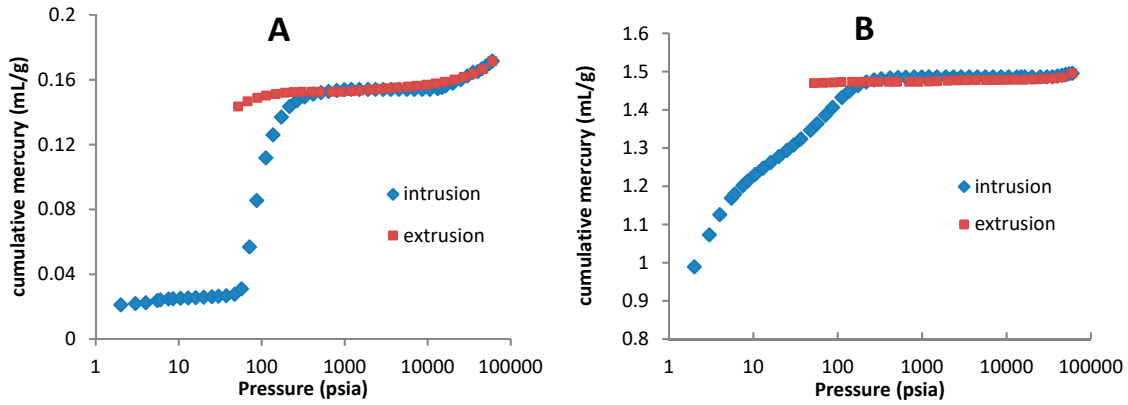

Figure 3. Mercury intrusion and extrusion curves from TPU tablets (**A**) and leached tablets (**B**).

3.4. Measurement of Fractal Dimension

Fractal analysis, based on the concept of self-similarity, contributes to the knowledge of these porous systems, assigning them a fractional number which provides information about their structural complexity [27–29]. Volume fractal dimensions have been calculated for all matrices according to equation 4. Table 2 shows the obtained D_v values, which are in the range of 2.88–2.95, similar to previously reported values for sustained release matrices [20]. Higher D_v values have been obtained for matrices after drug dissolution test. In our study, self-similarity, which is characterized by a constant fractal dimension, was restricted to relatively narrow pore ranges: around 0.5 to 5, and around 10–100 micrometers for initial pores and pores formed after drug leaching, respectively (see Figure 4). Comparing the values for the different theophylline particle sizes studied, higher fractal nature was found when decreasing drug particle size, as observed by other researchers [20].

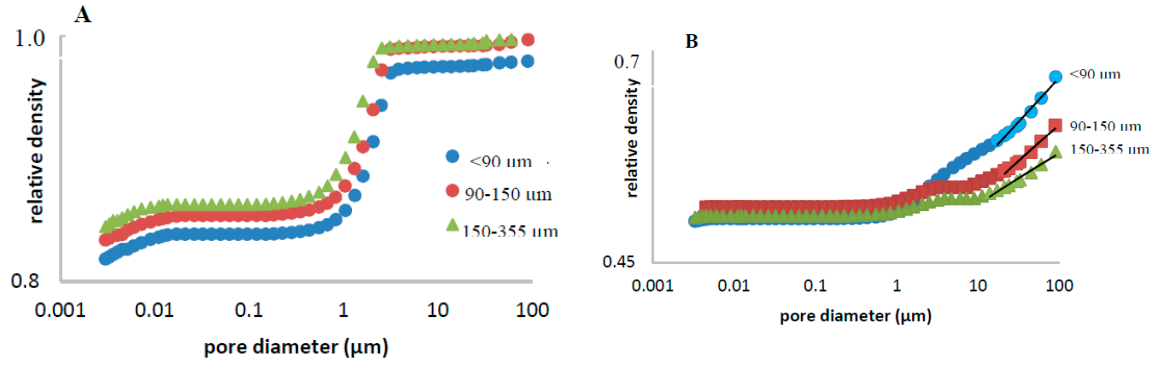

Figure 4. Determination of the volume fractal dimension of TPU matrices containing three different size fractions of theophylline, before (**A**) and after drug release study (**B**).

3.5. Scanning Electron Microscopy (SEM)

Microphotographs obtained by SEM contributed to analyze the behavior of the polymer in the matrices. Images were taken before and after drug release studies, showing the continuum medium created by the thermoplastic excipient with only 30% weight fraction (Figure 5). This continuum medium of the polymer has been formed thanks to the ultrasounds applied by the upper punch-sonotrode which lead to the movement of the powder particles increasing the friction and collisions between them and rising the temperature of the system [2]. So, the boundaries between particles become indistinguishable causing the sintering of the system. Some researchers have also confirmed the sintering process obtained with USAC by SEM [5–7,30]. It can be highlighted that

acicular drug particles tend to be distributed in parallel thus offering the lowest porosity previously measured, and how TPU works binding these particles (Figure 5A,B). SEM images of matrices after drug release study show the inert skeleton of TPU on which the fingerprints of theophylline particles are patent (Figure 5D,E).

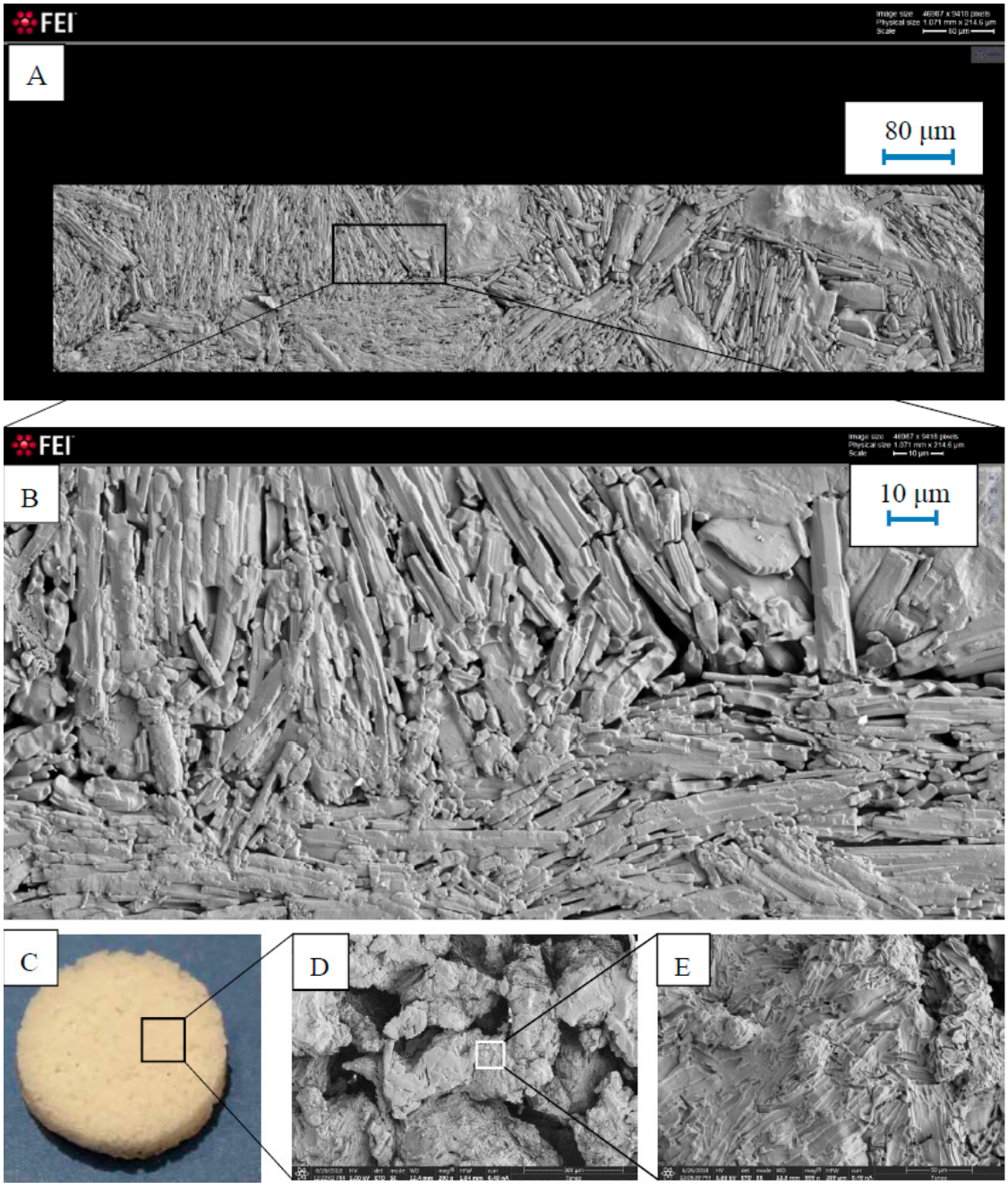

Figure 5. SEM images of USAC tablets before (**A**,**B**) and after drug dissolution (**D**,**E**). (**C**) is a digital photograph of the matrix after dissolution testing. Microphotograph 5A was obtained by Microsoft HD View 3.3 software. Magnifications of microphotographs 5B, 5D, and 5E are 5920×, 200×, and 800×, respectively.

3.6. Estimation of the Excipient Efficiency

Considering the current regulatory framework, which encourages the application of the "Quality by Design" approach in pharmaceutical product development, we have estimated the

parameter Excipient Efficiency (EE), in order to quantify the capability of Tecoflex^{TM} EG-72D for controlling the drug release. The mean EE value for the studied elastic thermoplastic polyurethane is 13.41 $min^{1/2} \cdot mg^{-1} \cdot mL$, according to the total porosity and the Higuchi's release constant from the inert matrices. The obtained value is higher than those previously reported for inert matrix forming excipients as Ethocel® (9.54–9.89) or Eudragit® (5.59) [15]. This fact may be due to the compression process since the sintering process caused by USAC has been reported to increase the EE [7].

The capability of TPU for controlling drug release has been estimated for theophylline, which is slightly soluble in water. Obviously, in the case of lipophilic drugs, much lower release rates are expected. Taking into account the biocompatibility of this polymer, it would be possible to develop drug loaded implant devices using this technology.

4. Conclusions

Ultrasound-assisted compression (USAC) has demonstrated its ability to compress elastic materials, overcoming the traditional limitations of these materials for compression. For the first time, an elastic thermoplastic polymer has been successfully compressed by USAC, resulting in inert matrices with a semi-continuum excipient structure formed by the sintering process of these elastic TPU particles. This technology allows manufacturing matrices with low quantity of polymer (30%) showing high excipient efficiency. A fractal nature has been found in the pore structure. Porosity analysis has contributed to the understanding of the drug release behavior of TPU matrices, confirming the robustness of the obtained USAC matrices for varying drug particle size fractions.

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References

1. Galdón, E.; Casas, M.; Gayango, M.; Caraballo, I. First study of the evolution of the SeDeM expert system parameters based on percolation theory: Monitoring of their critical behavior. *Eur. J. Pharm. Biopharm.* **2016**, *109*, 158–164. [CrossRef] [PubMed]
2. Millán-Jiménez, M.; Galdón, E.; Ferrero, C.; Caraballo, I. Application of ultrasound-assisted compression in pharmaceutical technology. Design and optimization of oral sustained-release dosage forms. *J. Drug Deliv. Sci. Technol.* **2017**, *42*, 119–125. [CrossRef]
3. Fini, A.; Holgado, M.A.; Rodriguez, L.; Cavallari, C. Ultrasound-compacted indomethacin/polyvinylpyrrolidone systems: Effect of compaction process on particle morphology and dissolution behavior. *J. Pharm. Sci.* **2002**, *91*, 1880–1890. [CrossRef]
4. Fini, A.; Cavallari, C.; Ospitali, F. Effect of Ultrasound on the Compaction of Ibuprofen/Isomalt Systems. *Pharmaceutics* **2009**, *1*, 3–19. [CrossRef]
5. Levina, M.; Rubinstein, M.H.; Rajabi-Siahboomi, A.R. Principles and application of ultrasound in pharmaceutical powder compression. *Pharm. Res.* **2000**, *17*, 257–265. [CrossRef]
6. Aguilar-De-Leyva, A.; Goncalves-Araujo, T.; Daza, V.; Caraballo, I. A new deferiprone controlled release system obtained by ultrasound-assisted compression. *Pharm. Dev. Technol.* **2014**, *19*, 728–734. [CrossRef]
7. Caraballo, I.; Millán, M.; Fini, A.; Rodriguez, L.; Cavallari, C. Percolation thresholds in ultrasound compacted tablets. *J. Control. Release* **2000**, *69*, 345–355. [CrossRef]
8. Levina, M.; Rubinstein, M.H. The Effect of Ultrasonic Vibration on the Compaction Characteristics of Paracetamol. *J. Pharm. Sci.* **2000**, *89*, 705–723. [CrossRef]
9. Millán, M.; Caraballo, I. Effect of drug particle size in ultrasound compacted tablets. Continuum percolation model approach. *Int. J. Pharm.* **2006**, *310*, 168–174. [CrossRef] [PubMed]

10. Sancin, P.; Caputo, O.; Cavallari, C.; Passerini, N.; Rodriguez, L.; Cini, M.; Fini, A. Effects of ultrasound-assisted compaction on Ketoprofen/Eudragit®S100 mixtures. *Eur. J. Pharm. Sci.* **1999**, *7*, 207–213. [CrossRef]
11. Claeys, B.; Vervaeck, A.; Hillewaere, X.K.D.; Possemiers, S.; Hansen, L.; De Beer, T.; Remon, J.P.; Vervaet, C. Thermoplastic polyurethanes for the manufacturing of highly dosed oral sustained release matrices via hot melt extrusion and injection molding. *Eur. J. Pharm. Biopharm.* **2015**, *90*, 44–52. [CrossRef]
12. Verstraete, G.; Samaro, A.; Grymonpré, W.; Vanhoorne, V.; Van Snick, B.; Boone, M.N.; Hellemans, T.; Van Hoorebeke, L.; Remon, J.P.; Vervaet, C. 3D printing of high drug loaded dosage forms using thermoplastic polyurethanes. *Int. J. Pharm.* **2018**, *536*, 318–325. [CrossRef]
13. Campiñez, M.D.; Benito, E.; Romero-Azogil, L.; Aguilar-de-Leyva, Á.; de Gracia García-Martín, M.; Galbis, J.A.; Caraballo, I. Development and characterization of new functionalized polyurethanes for sustained and site-specific drug release in the gastrointestinal tract. *Eur. J. Pharm. Sci.* **2017**, *100*, 285–295. [CrossRef]
14. Markl, D.; Strobel, A.; Schlossnikl, R.; Bøtker, J.; Bawuah, P.; Ridgway, C.; Rantanen, J.; Rades, T.; Gane, P.; Peiponen, K.E.; et al. Characterisation of pore structures of pharmaceutical tablets: A review. *Int. J. Pharm.* **2018**, *538*, 188–214. [CrossRef] [PubMed]
15. Casas, M.; Aguilar-de-Leyva, Á.; Caraballo, I. Towards a rational basis for selection of excipients: Excipient Efficiency for controlled release. *Int. J. Pharm.* **2015**, *494*, 288–295. [CrossRef]
16. Higuchi, T. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J. Pharm. Sci.* **1963**, *52*, 1145–1149. [CrossRef] [PubMed]
17. Korsmeyer, R.W.; Gurny, R.; Doelker, E.; Buri, P.; Peppas, N.A. Mechanisms of solute release from porous hydrophilic polymers. *Int. J. Pharm.* **1983**, *15*, 25–35. [CrossRef]
18. Peppas, N.A.; Sahlin, J.J. A simple equation for the description of solute release. III. Coupling of diffusion and relaxation. *Int. J. Pharm.* **1989**, *57*, 169–172. [CrossRef]
19. Ritger, P.L.; Peppas, N.A. A simple equation for description of solute release I. Fickian and non-fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. *J. Control. Release* **1987**, *5*, 23–36. [CrossRef]
20. Bonny, J.; Leuenberger, H. Determination of fractal dimensions of matrix-type solid dosage forms and their relation with drug dissolution kinetics. *Eur. J. Pharm. Biopharm.* **1993**, *39*, 31–37.
21. Usteri, M.; Bonny, J.; Leuenberger, H. Fractal dimension of porous solid dosage forms. *Pharm. Acta Helv.* **1990**, *65*, 55–61.
22. Aguilar-de-Leyva, Á.; Campiñez, M.D.; Casas, M.; Caraballo, I. Design space and critical points in solid dosage forms. *J. Drug Deliv. Sci. Technol.* **2017**, *42*, 134–143. [CrossRef]
23. Leuenberger, H.; Rohera, B.; Haas, C. Percolation theory - a novel approach to solid dosage form design. *Int. J. Pharm.* **1987**, *38*, 109–115. [CrossRef]
24. Caraballo, I.; Fernández-Arévalo, M.; Holgado, M.A.; Rabasco, A.M. Percolation theory: Application to the study of the release behaviour from inert matrix systems. *Int. J. Pharm.* **1993**, *96*, 175–181. [CrossRef]
25. Caraballo, I.; Millán, M.; Rabasco, A.M. Relationship between drug percolation threshold and particle size in matrix tablets. *Pharm. Res.* **1996**, *13*, 387–390. [CrossRef] [PubMed]
26. Ridgway, C.; Bawuah, P.; Markl, D.; Zeitler, J.A.; Ketolainen, J.; Peiponen, K.E.; Gane, P. On the role of API in determining porosity, pore structure and bulk modulus of the skeletal material in pharmaceutical tablets formed with MCC as sole excipient. *Int. J. Pharm.* **2017**, *526*, 321–331. [CrossRef] [PubMed]
27. Mahamud, M.M.; Novo, M.F. The use of fractal analysis in the textural characterization of coals. *Fuel* **2008**, *87*, 222–231. [CrossRef]
28. Pippa, N.; Dokoumetzidis, A.; Demetzos, C.; Macheras, P. On the ubiquitous presence of fractals and fractal concepts in pharmaceutical sciences: A review. *Int. J. Pharm.* **2013**, *456*, 340–352. [CrossRef]
29. Xianwen Shen; Longjian Li; Wenzhi Cui; Ya Feng Improvement of fractal model for porosity and permeability in porous materials. *Int. J. Heat Mass Transf.* **2018**, *121*, 1307–1315. [CrossRef]
30. Rodriguez, L.; Cini, M.; Cavallari, C.; Passerini, N.; Fabrizio Saettone, M.; Fini, A.; Caputo, O. Evaluation of theophylline tablets compacted by means of a novel ultrasound-assisted apparatus. *Int. J. Pharm.* **1998**, *170*, 201–208. [CrossRef]

Capítulo 3

A Biodegradable Copolyester, Poly(butylene succinate-co-ϵ-caprolactone), as a High Efficiency Matrix Former for Controlled Release of Drugs

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Article

A Biodegradable Copolyester, Poly(butylene succinate-*co*-ε-caprolactone), as a High Efficiency Matrix Former for Controlled Release of Drugs

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Abstract: A biodegradable copolyester, poly(butylene succinate-*co*-ε-caprolactone) (PBS_CL), was used for first time as an excipient for pharmaceutical dosage forms using direct compression and hot processing techniques (ultrasound-assisted compression (USAC) and hot melt extrusion (HME)). Robust binary systems were achieved with hot processing techniques, allowing a controlled release of the drug. With only 12% *v*/*v* of PBS_CL, controlled release forms were obtained using USAC whereas in HME over 34% *v*/*v* of excipient is necessary. Amounts over 23% *v*/*v* allowed a long-extended release for more than 72 h following diffusional kinetic. Thanks to the high melting point of theophylline and the physicochemical properties of PBS_CL selected and synthesized, the structure of the excipient inside the USAC tablets and HME filaments corresponds to a continuum medium. A percolation threshold around 23% *v*/*v* was estimated, which agrees with a continuum percolation model. The polymer shows a high excipient efficiency value using HME and USAC. A nanostructured matrix with wall thicknesses lower than 0.1 μm was obtained. This leads to a very effective coating of the drug particles by the excipient, providing a slow and reproducible release. The present study therefore supports the use of PBS_CL, for the preparation of controlled release dosage forms using hot processing techniques.

Keywords: poly(butylene succinate-*co*-ε-caprolactone); biodegradable polymer; ultrasound-assisted compression; hot melt extrusion; controlled release; nanostructured matrices

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1. Introduction

Advances in material design and engineering have led to the rapid development of new materials with increasing complexity and functions. Both degradable and non-degradable polymers have found wide applications in the field of controlled drug delivery [1–4]. As a result, the development of materials that are biocompatible and biodegradable and free from toxic metallic catalysts has gained great attention in recent years [5].

Aliphatic polyesters have received much attention since they are potentially biodegradable [6]. Moreover, these polymers have found applications in the biomedical field because they are biocompatible [7]. Within the aliphatic polyesters, poly(butylene succinate) (PBS) [8] and poly(ε-caprolactone) (PCL) [9] have emerged together with other more well-known polyesters such as poly(lactic acid) (PLA) or poly(glycolic acid) (PGA). PBS and PCL are semicrystalline polymers whose thermal properties (melting temperature (T_m) or glass transition temperature (T_g)) can be tuned by copolymerization. In fact, it has been found that poly(butylene succinate-*co*-ε-caprolactone) copolyester is crystalline for all compositions and crystallized isodimorphically for intermediate compositions [10].

Controlled release pharmaceutical forms provide a slow release rate of the drug, which becomes the rate limiting step in the arrival of the drug to the systemic circulation [11]. The reasons, among others, that have led to the formulation of controlled or sustained release drug delivery systems stem from the wish to decrease the number of daily administrations, improve compliance, and minimize side effects [12].

There are several methods to obtain the prolonged release of drugs. Direct compression remains the most widespread method to manufacture pharmaceutical dosage forms due to low cost of development as well as a high industrial production capacity [13].

In some cases, direct compression is not enough to obtain controlled release of the drug, with more complex methods being needed like hot processing techniques such as, for example, hot melt extrusion (HME) and ultrasound-assisted compression (USAC).

These techniques have emerged as processing technologies for the development of controlled release solid pharmaceutical forms, for oral administration, and for implant preparation [14,15].

One of the limitations presented by these techniques is the fact that the polymers are exposed to high temperatures [16,17], requesting an adequate melting (T_m) or glass transition temperature (T_g). Additionally, the drugs should keep stability at the temperatures used. In the case of HME, the addition of plasticizer is sometimes necessary to increase the extrusion capacity of the polymer [18]. Even so, HME is a widely used technique in the manufacture of oral dosage forms [19].

USAC is a technology that combines the conventional compression process and ultrasound irradiation producing the heating, melting, and sintering of materials. Its application is less frequent than HME, but it can be useful in the preparation of formulations with solid dispersion to improve the bioavailability of poorly soluble drugs and formulation of sustained-release pharmaceutical forms, since it provides a better control of drug release with a smaller amount of excipient [20,21].

To explain the performance of this technique, the continuous percolation model [22,23] has been used, as well as the excipient efficiency (EE) and the slope of the Higuchi constant. EE provides a path to identify the ability of excipients to reduce the diffusion rate of a drug trapped in a network of this excipient [24].

In this study, drug delivery systems were prepared by direct compression, ultrasound-assisted compression and hot melt extrusion using, for the first time, the biodegradable copolyester, poly(butylene succinate-*co*-ε-caprolactone) with a selected feed composition (70/30 butylene succinate/ε-caprolactone) and theophylline as the model drug. This 70/30 composition of the copolyester was chosen because its thermal properties were found to be suitable for USAC and HME processing techniques.

These systems were characterized from the physicochemical point of view. Furthermore, in vitro release studies were performed, in order to investigate the capacity of controlling the drug release of this new chemical entity processed with different technologies.

2. Materials and Methods

2.1. Materials

Anhydrous theophylline (Acofarma, Barcelona, Spain) was used as the model drug. Theophylline is a natural alkaloid derivative of xanthine (Figure 1) used as bronchodilator agent. It has experienced a renaissance due to preparations for oral use as a gradual release preparation [25]. It has been chosen as a model drug not only for its pharmacological characteristics but for its physicochemical and technological properties.

It is a drug with low solubility (7.36 mg/L at 25 °C in water) [26] and an intermediate partition coefficient (XLogP3 $\simeq$ 0). As its pKa is 8.81, the main form in the gastrointestinal tract is the ionized form (Figure S1). From the point of view of pharmaceutical technology, it is a relatively complex drug due to the acicular shape of its crystalline form and its high capacity to charge electrostatically.

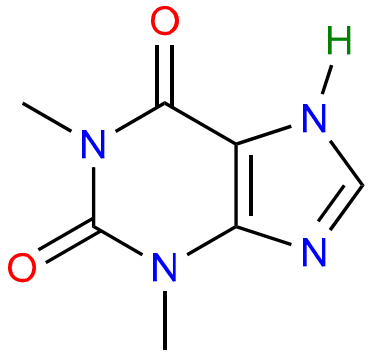


Figure 1. Structural formula of theophylline.

Anhydrous theophylline was milled in a hammer mill and a fraction of drug particles size <500 μm was selected by sieving.

Dimethyl succinate (DMS), 1,4-butanediol (BD), titanium tetraisopropoxide (TTP) catalyst, and ε-caprolactone (CL) were purchased from Aldrich Co. All materials were used as received.

2.2. Methods

2.2.1. Synthesis and Characterization of Poly(butylene succinate-co-ε-caprolactone)

Random copolyester with a feed molar ratio 70/30, butylene succinate/ε-caprolactone, (PBS_CL) has been synthesized by ring opening polymerization/polycondensation in the melt phase using the procedure previously reported [10]. The final polymer was taken from the reactor and used without further purification.

^{1}H and ^{13}C NMR spectra were recorded in a Bruker AMX-300 NMR instrument. The sample was dissolved in $CDCl_3$ and spectra were referenced to the signal of the TMS internal reference. About 10 and 50 mg of sample were used for ^{1}H and ^{13}C NMR, respectively. Sixty-four scans were acquired for ^{1}H and 5000–10,000 for ^{13}C with 32-K and 64-K data points, respectively.

Molecular weight analysis was performed by GPC on a Waters equipment equipped with RI and UV detectors. A total of 100 μL of 0.1% (w/v) sample solution in 1,1,1,3,3,3-Hexafluoro-2-propanol was injected and chromatographed with a flow of 0.5 mL min^{-1}. HR5E and HR2 Waters linear Styragel columns (7.8 mm × 300 mm, pore size 103–104 Å) packed with crosslinked polystyrene and protected with a precolumn were used. Molar mass average and distributions were calculated against PMMA standards.

The thermal behavior of PBS_CL copolyester was examined by differential scanning calorimetry (DSC), using a Perkin-Elmer DSC 8500. The thermograms were recorded from a 5 mg sample at heating and cooling rates of 10 °C·min^{-1} under a nitrogen flow of 20 mL·min^{-1}. Indium and zinc were used as standards for temperature and enthalpy calibration. The glass transition temperature (T_g) was taken as the inflection point of the heating DSC traces recorded at 20 °C·min^{-1} from melt-quenched sample, and the melting temperature (T_m) was taken as the maximum of the endothermic peak appearing on the second heating trace. Thermogravimetric analysis was performed on a Mettler-Toledo TGA/DSC 1 Star System under a nitrogen flow of 20 mL·min^{-1} at a heating rate of 10 °C·min^{-1} and within a temperature range of 30 to 600 °C.

Flattened PBS_CL particles were frozen in liquid nitrogen and subsequently milled with a Restch ZM 200 equipment (Haan, Germany), using a 1.0 mm output sieve. Later they were sieved with a 500 μm sieve.

2.2.2. Rheological Characterization of PBS_CL by SeDeM Method

Rheological studies of PBS_CL powder were carried out according to the SeDeM method developed by Suñé-Negre et al. [27]. This method unifies and standardizes several rheological parameters to provide quantitative information about the suitability of processing a powder through direct compression. Briefly, this expert system normalizes the

rheological results from density, compressibility, flow, stability and lubricity tests leading to a result on a scale from 0 to 10. A value of 5 indicates that the product is acceptable for direct compression.

The following rheological tests were performed: bulk density (ρbulk), tapped density (ρtapped), powder flow (t''), loss on drying (% LOD), interparticle porosity (IP), Carr's Index (C), Hausner ratio (HR), cohesion index (CI), rest angle (α), percentage of particles measuring <45 μm (%p < 45), and homogeneity index (Iθ). The normalized results have been plotted in the SeDeM diagram [28]. The parametric index (PI), parametric profile index (PPI) and good compression index (GCI) were calculated based on the SeDeM approach to determine whether the PBS_CL is acceptable for direct compression.

2.2.3. Preparation of Matrix Systems

Blends of PBS_CL powder and theophylline at 12/88, 23/77, 34/66 and 47/53% v/v ratios have been mixed during 10 plus 10 min (Turbula mixer, Willy A. Bachofen, Basel, Switzerland). The optimum mixing time was calculated based on the drug content of five samples withdrawn at different time points. The drug content of the samples was determined by UV–Vis spectrophotometry (Agilent 8453, Agilent Technologies, Santa Clara, CA, USA) at 272 nm. Variation coefficient values lower than 5% were considered as appropriate.

Direct compression PBS_CL tablets were prepared in an eccentric tableting machine (Bonals A-300, Barcelona, Spain) using manual feeding and applying the maximum compression force accepted by the formulation. The tablets have a mean weight of 250 mg. They were prepared using 12 mm diameter flat punches with a dwell time of 0.18 s.

USAC tablets were prepared using an ultrasound-assisted tableting machine with a US generator coupled to the upper punch (Tecnea Engineering Srl, Bologna, Italy). An ultrasonic energy of 650 J was applied to the powder during the compaction process at a frequency of 20 kHz. The tableting machine was equipped with flat cylindrical punches of 11 mm. The parameters established for the proper compression were compression pressure 0.3 MPa, compaction time 6 s, cool time 9 s, and detach time 0.5 s. USAC tablets were prepared with 250 mg of formulation.

Hot melt extrusion filaments were prepared in order to test the suitability of the polymer to be processed with this technological method. The polymer and the anhydrous theophylline were studied in different proportions (34/67 and 45/55% v/v). The physical mixtures were extruded using a co-rotating twin screw extruder (Haake MiniLab, Thermo Electron, Karlsruhe, Germany), operating at a screw speed of 50 rpm and the extrusion temperature was set to 125 °C for both formulations. Uniform strands of extrudate were collected during steady state extrusion only for the 45/55 ratio. On the other hand, the strand with the proportions 34/67 did not have adequate characteristics to be used.

2.2.4. Matrix Systems Characterization

The tablets and filaments obtained were characterized as follows:

Physical dimensions. The tablet average weight and the standard deviation (SD) were obtained from six individually weighed tablets (Sartorius CP224S, Gottingen, Germany). The external dimensions (height and diameter) were determined as the mean of six tablets from each batch using the digital micrometer (VWR International, Leuven, Belgium). The multidimensional image analysis software Nis-elements BR (Nikon Corporation, Chiyoda-ku, Tokyo, Japan) was used to calculate the lateral surface area of the filaments.

Drug release assays were carried out in a USP apparatus 2 Sotax AT7 Smart, (Sotax, Allschwil, Switzerland) using 900 mL of deaerated water maintained at 37 ± 0.5 °C, during 24 h at 50 rpm. The percentage of drug released was measured with an UV–vis spectrophotometer Agilent 8453 (Agilent, CA, USA) at a wavelength of 272 nm. The test was performed in triplicate for each batch. Sink conditions were met throughout the dissolution test.

Kinetic adjustments. Drug release data ($M_t/M_\infty \leq 0.6$) were analyzed according to zero order, Higuchi [29], Korsmeyer et al. [30], and Peppas and Sahlin [31]. Equations (1)–(4):

$$\frac{M_t}{M_\infty} = k_0 t \quad (1)$$

$$\frac{M_t}{M_\infty} = k t^{1/2} \quad (2)$$

$$\frac{M_t}{M_\infty} = k_k\, t^n \quad (3)$$

$$\frac{M_t}{M_\infty} = k_d t^m + k_r t^{2m} \quad (4)$$

where M_t/M_∞ is the fraction of drug released at time t (the drug loading was considered as M_∞). k is the Higuchi's release rate constant. k_k is the Korsmeyer's kinetic constant, t the release time, n the release exponent that depends on the release mechanism and the shape of the matrix tested [32], k_d and k_r are, respectively, the diffusion and relaxation rate constants, and finally m, which is the purely Fickian diffusion exponent for a device of any geometrical shape that exhibits controlled release.

Estimation of the excipient efficiency. The excipient efficiency was calculated for the different batches by applying the following Equation (5) according to Caraballo [33]:

$$EE = \frac{\varepsilon}{b} \quad (5)$$

where ε is the total porosity of the matrices, b is the Higuchi's release rate constant. The total porosity is calculated with the known values of volume and weight of tablets according to the following Equation (6):

$$\in = \frac{Vreal - Vtheor}{Vreal} \times 100 \quad (6)$$

where Vreal is the real volume of the tablets and Vtheor the theoretical volume of the tablets, obtained as the PBS_CL volume calculated from its true density obtained by Helium picnometry, Pentapycnometer 5200E (Quantachrome Instruments, Boynton, FL, USA). Drug volume was not taken into account due to its soluble behavior.

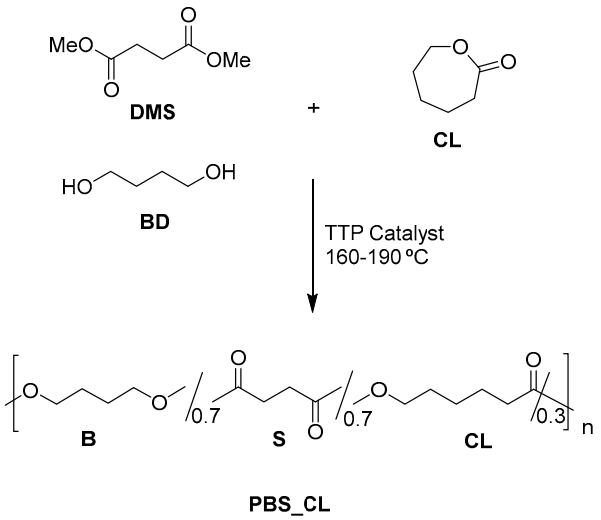
Scanning electron microscopy. The surface of samples, tablets obtained by USAC, and DC and HME filaments were evaluated at the Microscopy Service of the CITIUS in the University of Seville by using scanning electron microscopy (SEM) with a FEI TENEO electronic microscope (FEI Company, Hillsboro, OR, USA), operating at 5 kV. Tablets were previously coated with a 10 nm thin Pt layer with Leica EM SCD500 high vacuum sputter coater.

3. Results and Discussion

3.1. PBS_CL Characterization

PBS_CL copolyester with a BS/CL feed molar 70/30 was synthesized using the synthetic method reported by Safari et al. [10] (Scheme 1). This composition of the copolyester was chosen because its thermal properties could be suitable for USAC and HME processing techniques (solid polymer at room temperature with melting point around 90 °C and a crystallization temperature around 35 °C in order to obtain a rapid recrystallization of the filament, once extruded). A polymer with high molecular weight was obtained (M_n= 24.300 g·mol^{-1} and $Đ$ = 2.1). The infrared spectrum of PBS_CL copolyester is depicted in Figure S2. It shows the characteristic bands associated with the carbonyl ester groups as a broad peak centered at 1714 cm^{-1} and C-O stretching absorption at 1160 cm^{-1}. Other absorption bands corresponding to the stretching and bending of methylene groups are observed at 2949 and 1421 cm^{-1}, respectively. Moreover, Figure 2 shows the ^{1}H NMR spectrum with peak assignments. The composition of the copolyester was calculated by integration of the signals corresponding to methylene next to the carbonyl of the capro-

lactone unit (e) and the methylene signals of the succinate unit (k). It was observed that the calculated composition was very near to feed composition (73/27). On the other hand ^{13}C NMR was used to determine the microstructure of the copolymer. Some signals of the spectra split into three or four peaks due to sequence distributions. By deconvolution of these peaks, the degree of randomness could be determined. It was very close to 1, proving that the copolyester had a random microstructure (Figure S3).



Scheme 1. Synthesis route to PBS_CL copolyester.

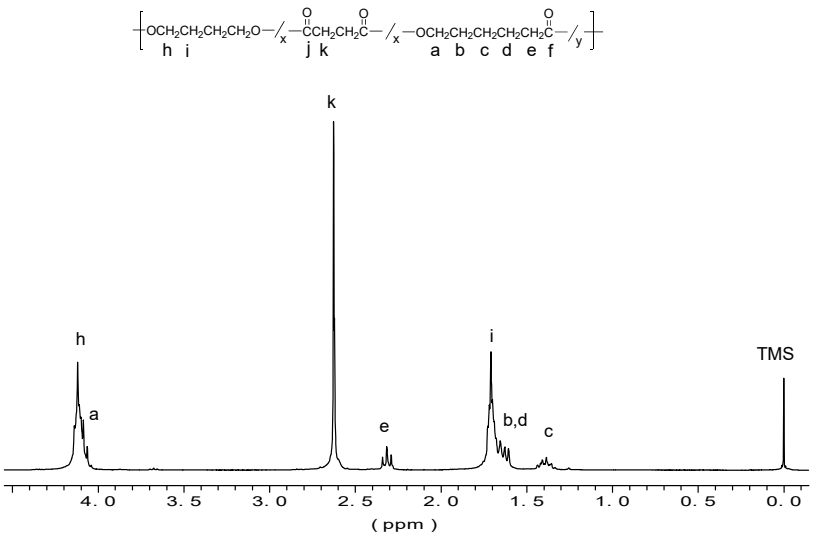


Figure 2. ^{1}H NMR spectrum of PBS_CL copolyester with peak assignments.

It was thermally stable up to 250–300 °C as observed by TGA analysis (Figure 3).

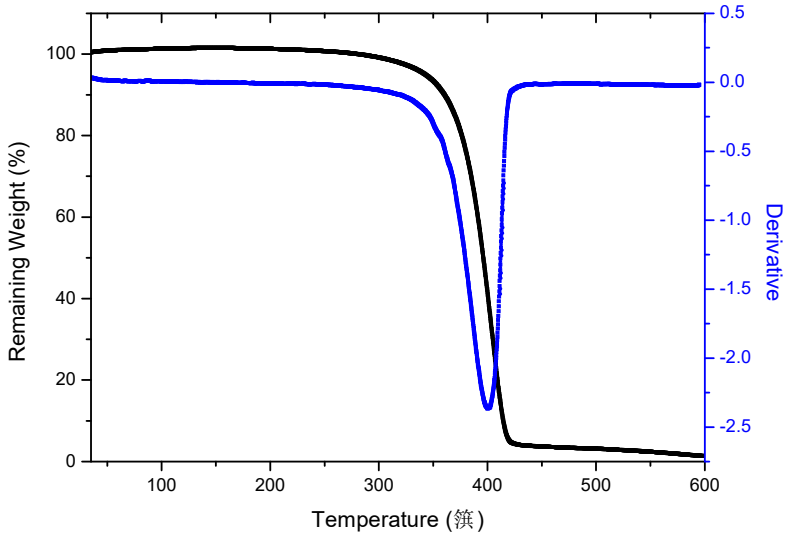


Figure 3. TGA thermograms of PBS_CL copolyester recorded under nitrogen atmosphere.

This thermal stability was high enough for ensuring the used processing techniques without deterioration of properties. On the other hand, the copolyester was observed to be semicrystalline with a melting temperature and enthalpy of 90.2 °C and 51.5 $J \cdot g^{-1}$, respectively. Full data of PBS_CL characterization are reported in Supplementary Materials.

The hydrolytic/enzymatic degradation of PBS_CL results in 1,4-butanediol, hexanoic acid, and butanedioic acid that are biocompatible and non-toxic [34–36].

3.2. Matrix Systems Characterization

Tablets of PBS_CL and theophylline were successfully obtained by USAC and DC for all the prepared blends.

However, HME filaments were only obtained for PBS_CL contents higher than 34% v/v. This is in agreement with the results previously obtained by Verstraete et al. for different polymers [32,33] and with past unpublished research by our group. Furthermore, Viidik et al. [34], using polycaprolactone and theophylline blends, reported difficulties obtaining filaments by HME at 60 to 80% w/w of drug without the use of a plasticizer.

The physical characterization of the different batches is summarized in Table 1. The differences in physical dimensions are a consequence of the methods used during the preparation. Weights were maintained constant for all systems.

Table 1. Dimensions of PBS_CL tablets obtained by DC and USAC and HME filaments.

Batch	PBS_CL Content (%vol)	Theophylline Content (%vol)	Total Weight (mg)	Diameter (mm)	Thickness (mm)	Volume (mm^3)	Initial Porosity (ε_0)
12:88 DC	12	88	246.1 ± 4.9	12.10 ± 0.01	2.001 ± 0.244	218.79	23.37
23:77 DC	23	77	242.6 ± 2.1	12.13 ± 0.08	1.869 ± 0.224	205.26	17.77
34:66 DC	34	66	240.4 ± 0.8	12.25 ± 0.23	1.764 ± 0.010	204.57	16.58
47:53 DC	47	53	238.9 ± 1.6	12.14 ± 0.03	1.827 ± 0.023	211.39	18.09
12:88 USAC	12	88	241.2 ± 1.7	11.15 ± 0.03	2.132 ± 0.022	208.89	21.33
23:77 USAC	23	77	246.9 ± 0.2	11.25 ± 0.03	2.114 ± 0.019	210.81	18.52
34:66 USAC	34	66	241.8 ± 2.7	11.21 ± 0.02	2.109 ± 0.028	208.24	17.86
47:53 USAC	47	53	248.1 ± 3.0	11.19 ± 0.04	2.008 ± 0.009	197.33	9.18
				Lenght (mm)	Section (mm^2)		
45:55 HME	45	55	242.5 ± 6.1	47.22 ± 1.18	4.16 ± 0.00	196.48	10.92

Results are expressed in $v/v\%$ to facilitate the interpretation of the behavior of the systems, especially on the basis of excipient efficiency and percolation theory approaches.

3.3. Rheological Results According to SeDeM Method

Rheological parameters of PBS_CL were obtained according to the described methodology. This preformulation tool has been chosen as it provides very useful information about the suitability of substances to be directly compressed. Moreover, this method provides information about industrial processing of powdery substances.

Table 2 shows the obtained results of the studies with normalized values as well as the mean of each incidence, and Figure 4 shows the SeDeM diagram where these rheological results have been plotted.

Table 2. Normalized results of rheological parameters for PBS_CL powder with the mean incidence values.

Incidence Factor	Parameter	Symbol	Unit	Normalized Result	Mean Incidence
Dimension	Bulk density	ρbulk	g/mL	4.19	4.70
	Tapped density	ρtapped	g/mL	5.20	
Compressibility	Inter-particle Porosity	IP	-	3.83	3.85
	Carr Index	C	%	3.86	
Flowability/ powder flow	Hausner Ratio	HR	-	2.42	4.37
	Angle of Repose	α	º	2.88	
	Powder flow	t″	s	7.80	
Lubricity/ stability	Loss on Drying	%LOD	%	5.50	5.50
Lubricity/ dosage	Particles ≤45 µm	Pf	%	9.98	6.50
	Homogeneity Index	Iθ	-	3.25	
Parametric Index (PI)		**0.40**			
Parametric Profile Index (PPI)		**4.89**			
Good Compression Index (GCI)		**5.29**			

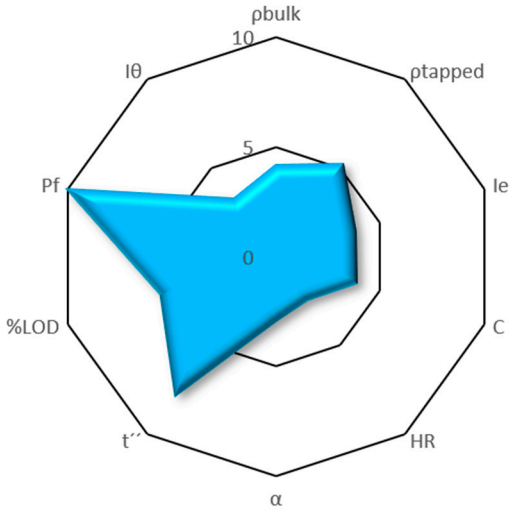


Figure 4. SeDeM diagram of PBS_CL.

PBS_CL shows moderate characteristics for direct compression in all the studied properties. The SeDeM Expert System proposes three indexes to determine whether a powder is acceptable for direct compression: parametric index (PI), parametric profile index (PPI) and good compression index (GCI). Values higher than 0.5, 5, and 5, respectively, indicate that the substance can be processed through direct compression [27,37]. The

three indexes were calculated according to this method. The good compressibility index (IGC) of PBS_CL, 5.29, is similar to other excipients used in direct compression [38] and overcame the acceptable value. PI and PPI results were very close to the acceptable values (PI: 0.4; PPI: 4.89). The obtained results confirm that the polymer has adequate compression properties, even in the range of direct compression tableting excipients.

3.4. Drug Release Results

Drug dissolution studies from tablets obtained by the direct compression method with PBS_CL are shown in Figure 5. A rapid dissolution profile can be observed for tablets with 12% v/v of PBS_CL (less than 240 min for 100% released). The release profiles of tablets with higher amounts of PBS_CL (23, 34 and 47% v/v) were very similar between them and showed a higher capacity for the prolonged release of the drug (300 min for 100% theophylline released). The integrity of the tablets was lost in all cases during the dissolution test.

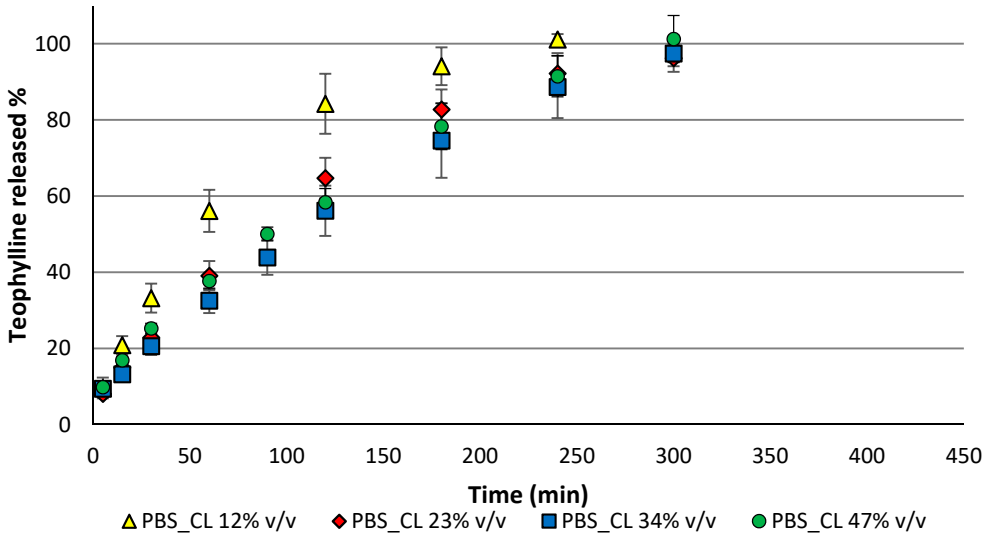


Figure 5. Dissolution profiles for PBS_CL tablets obtained by direct compression.

Drug dissolution studies from tablets obtained by the ultrasound-assisted compression method with PBS_CL are shown in Figure 6. It A prolonged release dissolution profile can be observed for tablets even with only 12% v/v of PBS_CL (360 min for 100% released). The integrity of these tablets was also lost during the dissolution test. When the amount of PBS_CL increases to 23% v/v, the release profile of theophylline drops significantly, releasing only 67% of the drug after 420 min. The drug release drops again significantly for concentrations above 23% v/v, releasing only 42% of the drug in 420 min while keeping their shape and dimensions after the dissolution test.

For concentrations higher than 23% v/v of excipient, an incomplete drug release is observed and a coherent skeleton of the insoluble excipient appears that provides integrity to the tablet. This indicates the existence of an excipient infinite cluster able to develop mechanical resistance to the disintegration, controlling the release of the drug.

This result is in agreement with the critical point previously reported by Caraballo et al. based on a continuum percolation model. The excipient percolation threshold was estimated to be in the range of 13.4 to 20.2% v/v of polymer (Eudragit RS) for systems compacted by USAC [22].

In a conventional sustained release tablet, the limited accessibility of many drug particles to the dissolution medium can be assumed since they are encapsulated by polymeric materials [39]. This effect is clearly increased when the excipient particles undergo a sintering process and are transformed in a quasi-continuum medium. In this case, the coating of the drug is much more effective.

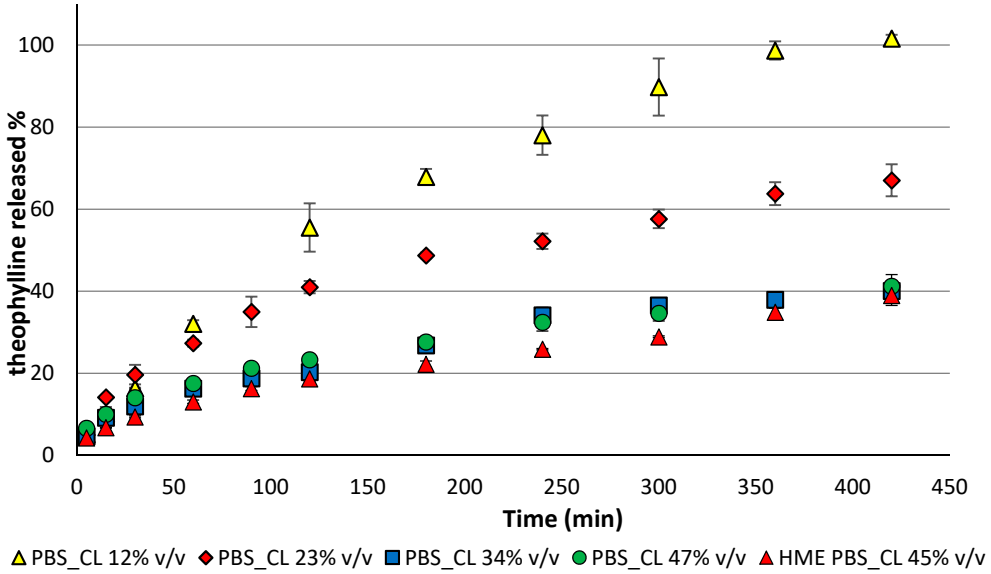


Figure 6. Dissolution profiles for PBS_CL tablets obtained by ultrasound-assisted compression and HME filaments.

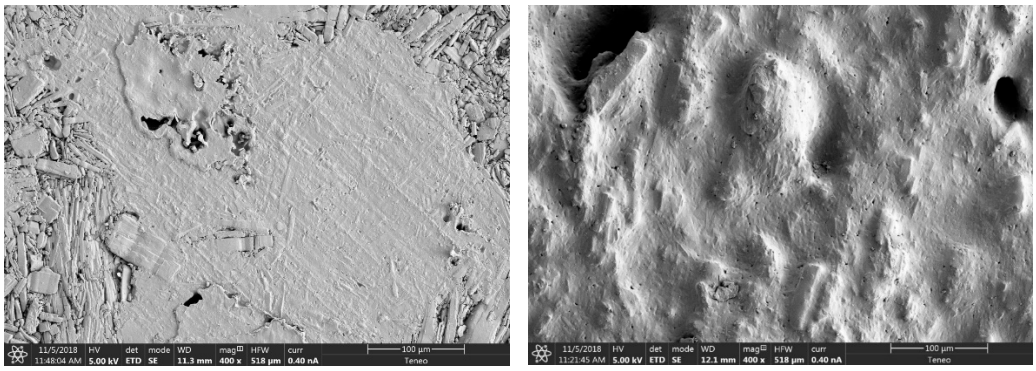
In order to perform a better characterization of the obtained drug delivery systems, the excipient efficiency has been calculated for all of them. The excipient efficiency is a parameter developed to quantify the ability of an excipient to control the drug release [40]. As can be observed in Table 3, PBS_CL USAC tablets show a higher EE value than PBS_CL direct compression tablets. This is attributed to the sintering process that particles usually undergo with the USAC technique [28].

Table 3. Drug release kinetic parameters and Excipient Efficiency from PBS_CL tablets and filaments. B = Higuchi kinetic constant; n = release exponent; kd = Peppas diffusion kinetic constant; kr = Peppas relaxation kinetic constant; r2 = determination coefficient.

Batch	Zero Order		Higuchi		Korsmeyer		Peppas y Sahlin			EE
	k0	r2	b (min^{-1})	r2	n	r2	kd (min^{-5})	kr (min^{-1})	r2	($min^{1/2}$)
12:88 DC	0.0083	0.9945	0.0844	0.9911	0.7065	0.9996	0.0844	0.1086	0.9911	12.23
23:77 DC	0.0056	0.9982	0.0563	0.9832	0.6277	0.9941	0.0563	0.0596	0.9832	
34:66 DC	0.0041	0.9992	0.0538	0.9742	0.5724	0.9724	0.0538	0.0637	0.9742	
47:53 DC	0.0042	0.986	0.0566	0.9951	0.5672	0.9973	0.0566	0.0451	0.9951	
12:88 USAC	0.0062	0.9894	0.0730	0.9477	0.8393	0.987	0.0758	0.1695	0.9682	25.47
23:77 USAC	0.0016	0.8902	0.0330	0.9867	0.5699	0.971	0.039	0.0112	0.9859	
34:66 USAC	0.0009	0.9468	0.0202	0.9885	0.4812	0.9921	0.0204	0.0041	0.9889	
47:53 USAC	0.0007	0.9432	0.0185	0.9985	0.4116	0.9983	0.0185	0.0313	0.9985	
45:55 HME	0.0008	0.9783	0.0167	0.9848	0.4886	0.9948	0.0205	−0.0001	0.9904	27.43

Hot melt extrusion filaments were prepared to study the suitability of the PBS_CL for the HME method. The release profile corresponding to 45% v/v is shown in Figure 6. The obtained filaments show a great ability to control drug release despite their thin shape. This is reflected by the high excipient efficiency obtained for systems prepared by hot melt extrusion (see Table 3). They released only 40% of theophylline in 480 min while

maintaining their shape and dimensions. Compared to PBS_CL USAC systems with similar polymer contents (see HME PBS_CL 45% v/v versus USAC PBS_CL 47% v/v in Figure 6), the filaments obtained by HME show a slightly lower release rate in the first 30 min. This can be attributed to a better coating of the drug particles situated on the outer surface of the system, as can be clearly observed in Figure 7.



(**a**) (**b**)

Figure 7. SEM images, magnification 400×, of PBS_CL tablets obtained by USAC (47/53% v/v) (**a**) and filaments obtained by HME (45/55% v/v) (**b**) before release of drug.

These results are concordant with those previously reported by Galdón et al. [28].

3.5. Kinetic Analysis

Regarding kinetic studies, drug release profiles from PBS_CL DC tablets for concentrations above 34% v/v seem to fit the Zero order model, according to the kinetic parameters shown in Table 3. The significant difference between k_0 values reflects the rapid dissolution rate of tablets with 12% v/v of PBS_CL compared with tablets with higher concentrations. Moreover, kr values in the Peppas and Sahlin models show a certain contribution of the erosion mechanism. This agrees with the loss of integrity of these tablets during the dissolution test.

According to Peppas and Sahlin kd and kr values for HME filaments and USAC tablets with concentrations above 12% v/v PBS_CL, diffusion seems to be the main release mechanism whereas relaxation-erosion mechanism is almost non-existent (see Table 3). This is in agreement with the fact that these tablets behave as inert matrices, keeping their integrity during drug dissolution.

The n value in the Korsmeyer model indicates which is the main release mechanism depending on the geometric shape of the systems, based on the aspect ratio parameter [30]. As the aspect ratio value of our system ranges from 5 to 9, n values around 0.45 (see Table 3), this confirms that diffusion is the main release mechanism of our systems.

Therefore, both release kinetics studies demonstrate that polymer hydrolysis does not significantly influence the release kinetics nor the tablet integrity. Therefore, the release of the model drug is driven by a diffusion-controlled mechanism.

On the other hand, USAC tablets with a PBS_CL concentration of 23% v/v do not fit any kinetic model, suggesting that this concentration of PBS_CL is very close to a critical point, i.e., a geometrical phase transition causing a high variability and erratic release profiles.

3.6. Internal Structure Study

To explain the release behaviour of the obtained systems, the structure of the matrices was studied by SEM.

Due to the sintering of the polymer in USAC and the fusion process in HME, a very tight scaffold is formed (Figure 8).

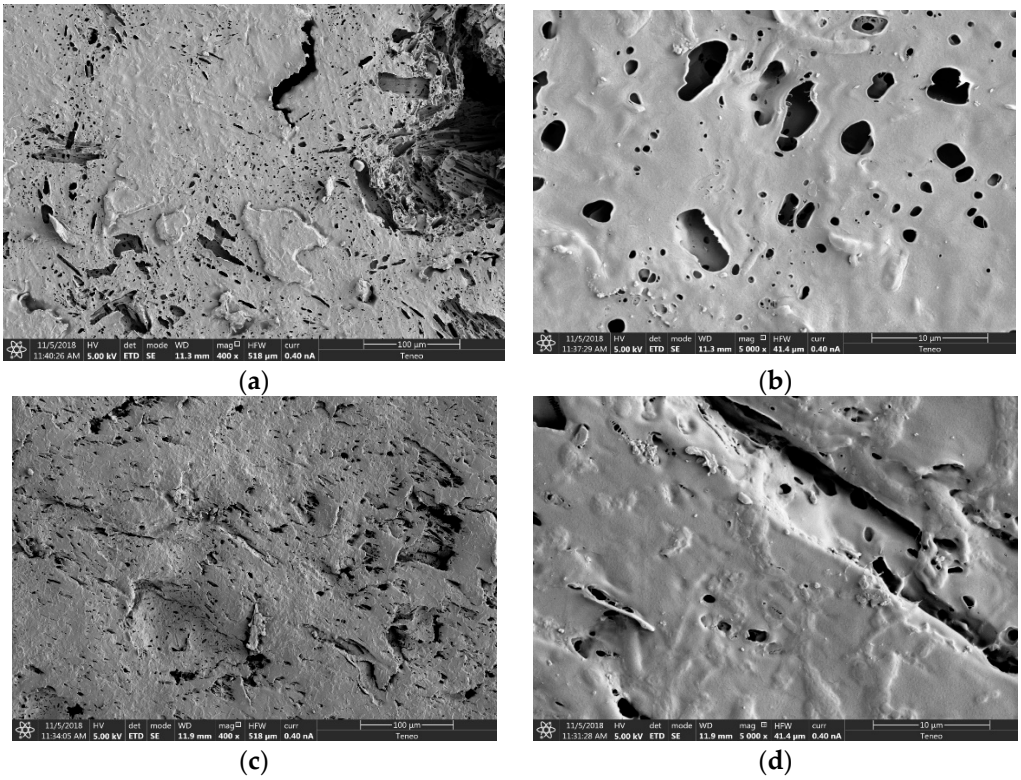


Figure 8. SEM images of PBS_CL tablets obtained by USAC (47/53% v/v) and filament obtained by HME (45/55% v/v) after drug release. (**a**,**b**) USAC tablets at 400× and 5000×; (**c**,**d**) HME filament at 400× and 5000×.

In order to reveal the inner structure of the matrix, we studied tablets obtained by USAC at 23:77% v/v after the drug was released for 72 h (Figure 9). It has been found that the excipient has a great efficacy coating the drug with layers less than 0.1 µm thick, forming what we have called a nanostructured matrix system.

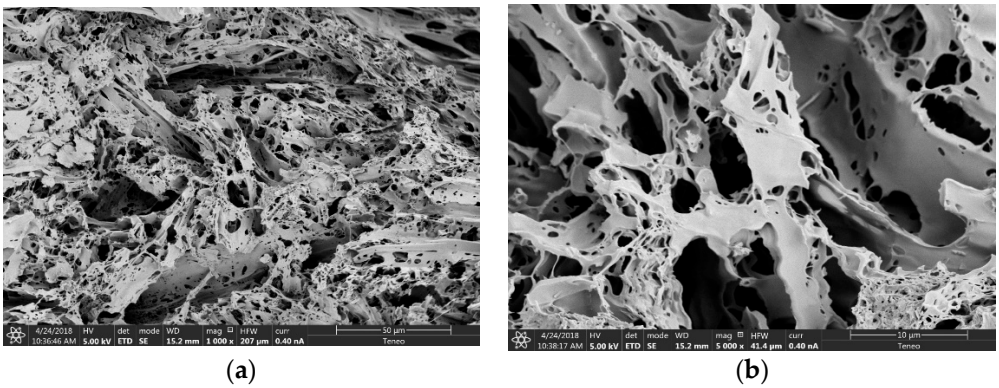


Figure 9. SEM images of PBS_CL tablets obtained by USAC (23:77% v/v) after drug release. Detail of the nanostructured matrix (**a**) 1000× (**b**) 5000×.

Previous studies have used microporous films and nanostructured matrices prepared by thermally induced phase separation. Unfortunately, most biocompatible materials useful for the preparation of such microporous films are sub-optimal for drug delivery due to poor processability and/or drug encapsulation properties [41–43]. In the systems studied in the present paper, the drug is incorporated into the polymer before the preparation of the nanostructured matrix and, thanks to the properties of PBS_CL, the obtained nanostructure matrices can load a high amount of drug, controlling its release rate without a burst effect.

4. Conclusions

The results of this study demonstrate the suitability of the biodegradable polymer PBS_CL for preparing sustained release systems in proportions as low as 12% by volume (10% by weight) of excipient, using hot processing techniques (USAC and HME).

The high excipient efficiency showed by the polymer using USAC and HME derives from the formation of a nanostructured matrix capable of containing high drug loads. This structure also results in a very high ability to control drug release. On the basis of percolation theory, this is due to a decrease in the critical point of the excipient from 30–35% v/v, which corresponds to a particulate system, to a range of 13.4 to 20.2% v/v of polymer, corresponding to a continuum percolation model.

The behavior of the nanostructured matrices introduced in the present work has been explained based on the study of the release kinetics, the excipient efficiency, the direct observation of their structures before and after drug leaching, and the percolation thresholds of the systems. This may be of help in the estimation of the design space for these new formulations, in line with the ICH Q8 Guidelines and the quality by design concept [44].

On the other hand, PBS_CL would also be adequate for the preparation of other kinds of drug delivery systems for the controlled release of drugs, e.g., implants, 3D printed dosage forms, etc.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/pharmaceutics13071057/s1, Figure S1: Theophylline distribution of ionized/non ionized form, Figure S2: FTIR spectrum of PBS_CL copolyester with main absorption bands assigned to stretching (υ) and bending (δ) modes of different functional groups, Figure S3: ^{13}C NMR spectrum of PBS_CL copolyester with peak assignments and expanded signals used for the determination of the degree of randomness, Figure S4: DSC thermograms of PBS_CL copolyester, Figure S5: High resolution SEM image of PBS_CL tablets obtained by USAC after drug release Detail of the nanostructured matrix at 1000×, Figure S6: High resolution SEM image of PBS_CL tablets obtained by USAC after drug release Detail of the nanostructured matrix at 5000×, Table S1: Molecular weights of PBS_CL copolyester, Table S2: Composition and microstructure of PBS_CL copolyester, Table S3: TGA parameters of PBS_CL copolyester, Table S4: Thermal properties of PBS_CL copolyester after the first heating run.

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References

1. Anselmo, A.C.; Mitragotri, S. An overview of clinical and commercial impact of drug delivery systems. *J. Control. Release* **2014**, *190*, 15–28. [CrossRef]
2. Englert, C.; Brendel, J.C.; Majdanski, T.C.; Yildirim, T.; Schubert, S.; Gottschaldt, M.; Windhab, N.; Schubert, U.S. Pharmapolymers in the 21st century: Synthetic polymers in drug delivery applications. *Prog. Polym. Sci.* **2018**, *87*, 107–164. [CrossRef]
3. Fu, Y.; Kao, W.J. Drug release kinetics and transport mechanisms of non-degradable and degradable polymeric delivery systems. *Expert Opin. Drug Deliv.* **2010**, *7*, 429–444. [CrossRef]
4. Mozafari, M.; Chauhan, N.P.S. *Advanced Functional Polymers for Biomedical Applications*; Elsevier: Amsterdam, The Netherlands, 2019; ISBN 9780128163498.

5. Papadimitriou, S.A.; Papageorgiou, G.Z.; Bikiaris, D.N. Crystallization and enzymatic degradation of novel poly(ε-caprolactone-co-propylene succinate) copolymers. *Eur. Polym. J.* **2008**, *44*, 2356–2366. [CrossRef]
6. Albertsson, A.C.; Varma, I.K. Aliphatic polyesters: Synthesis, properties and applications. *Adv. Polym. Sci.* **2002**, *157*, 1–40.
7. Manavitehrani, I.; Fathi, A.; Badr, H.; Daly, S.; Shirazi, A.N.; Dehghani, F. Biomedical applications of biodegradable polyesters. *Polymers* **2016**, *8*, 20. [CrossRef] [PubMed]
8. Gigli, M.; Fabbri, M.; Lotti, N.; Gamberini, R.; Rimini, B.; Munari, A. Poly(butylene succinate)-based polyesters for biomedical applications: A review in memory of our beloved colleague and friend Dr. Lara Finelli. *Eur. Polym. J.* **2016**, *75*, 431–460. [CrossRef]
9. Malikmammadov, E.; Tanir, T.E.; Kiziltay, A.; Hasirci, V.; Hasirci, N. PCL and PCL-based materials in biomedical applications. *J. Biomater. Sci. Polym. Ed.* **2018**, *29*, 863–893. [CrossRef] [PubMed]
10. Safari, M.; Martínez De Ilarduya, A.; Mugica, A.; Zubitur, M.; Muñoz-Guerra, S.; Müller, A.J. Tuning the Thermal Properties and Morphology of Isodimorphic Poly[(butylene succinate)- ran-(ε-caprolactone)] Copolyesters by Changing Composition, Molecular Weight, and Thermal History. *Macromolecules* **2018**, *51*, 9589–9601. [CrossRef]
11. Campiñez, M.D.; Ferris, C.; de Paz, M.V.; Aguilar-de-Leyva, Á.; Galbis, J.A.; Caraballo, I. A new biodegradable polythiourethane as controlled release matrix polymer. *Int. J. Pharm.* **2015**, *480*, 63–72. [CrossRef]
12. Maderuelo, C.; Zarzuelo, A.; Lanao, J.M. Critical factors in the release of drugs from sustained release hydrophilic matrices. *J. Control. Release* **2011**, *154*, 2–19. [CrossRef]
13. Galdón, E.; Casas, M.; Gayango, M.; Caraballo, I. First study of the evolution of the SeDeM expert system parameters based on percolation theory: Monitoring of their critical behavior. *Eur. J. Pharm. Biopharm.* **2016**, *109*, 158–164. [CrossRef]
14. Bode, C.; Kranz, H.; Fivez, A.; Siepmann, F.; Siepmann, J. Often neglected: PLGA/PLA swelling orchestrates drug release: HME implants. *J. Control. Release* **2019**, *306*, 97–107. [CrossRef]
15. Bisharat, L.; Alkhatib, H.S.; Abdelhafez, A.; Barqawi, A.; Aljaberi, A.; Qi, S.; Berardi, A. Hot melt extruded zein for controlled delivery of diclofenac sodium: Effect of drug loading and medium composition. *Int. J. Pharm.* **2020**, *585*, 119503. [CrossRef]
16. Goyanes, A.; Robles Martinez, P.; Buanz, A.; Basit, A.W.; Gaisford, S. Effect of geometry on drug release from 3D printed tablets. *Int. J. Pharm.* **2015**, *494*, 657–663. [CrossRef]
17. Kempin, W.; Domsta, V.; Brecht, I.; Semmling, B.; Tillmann, S.; Weitschies, W.; Seidlitz, A. Development of a dual extrusion printing technique for an acid- and thermo-labile drug. *Eur. J. Pharm. Sci.* **2018**, *123*, 191–198. [CrossRef] [PubMed]
18. Desai, D.; Sandhu, H.; Shah, N.; Malick, W.; Zia, H.; Phuapradit, W.; Vaka, S.R.K. Selection of solid-state plasticizers as processing aids for hot-melt extrusion. *J. Pharm. Sci.* **2018**, *107*, 372–379. [CrossRef] [PubMed]
19. Patil, H.; Tiwari, R.V.; Repka, M.A. Hot-Melt Extrusion: From Theory to Application in Pharmaceutical Formulation. *AAPS PharmSciTech* **2016**, *17*, 20–42. [CrossRef] [PubMed]
20. Levina, M.; Rubinstein, M.H. The Effect of ultrasonic vibration on the compaction characteristics of Paracetamol. *J. Pharm. Sci.* **2000**, *89*, 705–723. [CrossRef]
21. Millán-Jiménez, M.; Galdón, E.; Ferrero, C.; Caraballo, I. Application of ultrasound-assisted compression in pharmaceutical technology. Design and optimization of oral sustained-release dosage forms. *J. Drug Deliv. Sci. Technol.* **2017**, *42*, 119–125. [CrossRef]
22. Caraballo, I.; Millán, M.; Fini, A.; Rodriguez, L.; Cavallari, C. Percolation thresholds in ultrasound compacted tablets. *J. Control. Release* **2000**, *69*, 345–355. [CrossRef]
23. Millán, M.; Caraballo, I. Effect of drug particle size in ultrasound compacted tablets: Continuum percolation model approach. *Int. J. Pharm.* **2006**, *310*, 168–174. [CrossRef]
24. Caraballo, I. Prices of the Controlled Release Society. In Proceedings of the 28th Symposium in San Diego, Controlled Release Society, San Diego, CA, USA, 23–24 June 2001.
25. Theophylline | C7H8N4O2-PubChem. Available online: https://pubchem.ncbi.nlm.nih.gov/compound/2153 (accessed on 23 June 2021).
26. Yalkowsky, S.H.; He, Y.; Jain, P. *Handbook of aqueous solubility data*; CRC Press: Boca Raton, FL, USA, 2010; Volume 125, p. 395. ISBN 0-8493-1532-8.
27. Pérez, P.; Suñé-Negre, J.M.; Miñarro, M.; Roig, M.; Fuster, R.; García-Montoya, E.; Hernández, C.; Ruhí, R.; Ticó, J.R. A new expert systems (SeDeM diagram) for control batch powder formulation and preformulation drug products. *Eur. J. Pharm. Biopharm.* **2006**, *64*, 351–359. [CrossRef]
28. Galdón, E.; Casas, M.; Caraballo, I. Achieving high excipient efficiency with elastic thermoplastic polyurethane by ultrasound assisted direct compression. *Pharmaceutics* **2019**, *11*, 157. [CrossRef]
29. Higuchi, T. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J. Pharm. Sci.* **1963**, *52*, 1145–1149. [CrossRef] [PubMed]
30. Korsmeyer, R.W.; Gurny, R.; Doelker, E.; Buri, P.; Peppas, N.A. Mechanisms of solute release from porous hydrophilic polymers. *Int. J. Pharm.* **1983**, *15*, 25–35. [CrossRef]
31. Peppas, N.A.; Sahlin, J.J. A simple equation for the description of solute release. III. Coupling of diffusion and relaxation. *Int. J. Pharm.* **1989**, *57*, 169–172. [CrossRef]
32. Ritger, P.L.; Peppas, N.A. A simple equation for description of solute release I. Fickian and non-fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. *J. Control. Release* **1987**, *5*, 23–36. [CrossRef]
33. Caraballo, I. Newsletter Controlled Release Society. *Control. Release Soc.* **2001**, *18*, 12.

34. Pubchem 1,4-Butanediol | HO(CH2)4OH-PubChem. Available online: https://pubchem.ncbi.nlm.nih.gov/compound/8064#section=Toxicity&fullscreen=true (accessed on 28 June 2021).
35. Hexanoic acid | C6H12O2-PubChem. Available online: https://pubchem.ncbi.nlm.nih.gov/compound/8892#section=Toxicity&fullscreen=true (accessed on 28 June 2021).
36. Succinic acid | C4H6O4-PubChem. Available online: https://pubchem.ncbi.nlm.nih.gov/compound/1110#section=Toxicity&fullscreen=true (accessed on 28 June 2021).
37. Nardi-Ricart, A.; Nofrerias-Roig, I.; Suñé-Pou, M.; Pérez-Lozano, P.; Miñarro-Carmona, M.; García-Montoya, E.; Ticó-Grau, J.R.; Boronat, R.I.; Suñé-Negre, J.M. Formulation of sustained release hydrophilic matrix tablets of tolcapone with the application of sedem diagram: Influence of tolcapone's particle size on sustained release. *Pharmaceutics* **2020**, *12*, 674. [CrossRef]
38. Suñé-Negre, J.M.; Roig, M.; Fuster, R.; Hernández, C.; Ruhí, R.; García-Montoya, E.; Pérez-Lozano, P.; Miñarro, M.; Ticó, J.R. New classification of directly compressible (DC) excipients in function of the SeDeM Diagarm Expert System. *Int. J. Pharm.* **2014**, *470*, 15–27. [CrossRef]
39. Crowley, M.M.; Schroeder, B.; Fredersdorf, A.; Obara, S.; Talarico, M.; Kucera, S.; McGinity, J.W. Physicochemical properties and mechanism of drug release from ethyl cellulose matrix tablets prepared by direct compression and hot-melt extrusion. *Int. J. Pharm.* **2004**, *269*, 509–522. [CrossRef]
40. Casas, M.; Aguilar-de-Leyva, Á.; Caraballo, I. Towards a rational basis for selection of excipients: Excipient efficiency for controlled release. *Int. J. Pharm.* **2015**, *494*, 288–295. [CrossRef] [PubMed]
41. Ageitos, J.M.; Pulgar, A.; Csaba, N.; Garcia-Fuentes, M. Study of nanostructured fibroin/dextran matrixes for controlled protein release. *Eur. Polym. J.* **2019**, *114*, 197–205. [CrossRef]
42. Zhou, J.; Han, S.; Dou, Y.; Lu, J.; Wang, C.; He, H.; Li, X.; Zhang, J. Nanostructured poly(l-lactide) matrix as novel platform for drug delivery. *Int. J. Pharm.* **2013**, *448*, 175–188. [CrossRef] [PubMed]
43. Hsu, S.-H.; Huang, S.; Wang, Y.-C.; Kuo, Y.-C. Novel nanostructured biodegradable polymer matrices fabricated by phase separation techniques for tissue regeneration. *Acta Biomater.* **2013**, *9*, 6915–6927. [CrossRef] [PubMed]
44. ICH Expert Working Group. *Pharmaceutical Development Q8 (R2)*; European Medicine Agency: London, UK, 2009; Volume 8.

RESUMEN GLOBAL DE LOS RESULTADOS Y DISCUSIÓN

- Para evaluar la exactitud del sistema experto SeDeM, mediante la teoría de percolación, se prepararon mezclas de lactosa y teofilina en polvo en distintas proporciones y se aplicó el Sistema experto SeDeM a cada mezcla para controlar la evolución de sus propiedades. Por otro lado, se han estimado umbrales de percolación para estas mezclas donde se han encontrado puntos críticos para parámetros reológicos importantes tales como el ángulo de reposo o el flujo. Finalmente se han comparado las predicciones de Método SeDeM y las de la teoría de percolación, concluyendo que la teoría de percolación puede complementar el método SeDeM para una estimación más exacta del Espacio de Diseño. Esto es debido a que el método SeDeM hace una aproximación lineal al comportamiento de las mezclas de sustancias en polvo frente al tratamiento de discontinuidades que aporta la teoría de la percolación.
- Las matrices de TPU han mostrado un comportamiento inerte y una liberación sostenida del fármaco con una cantidad relativamente baja de excipiente. El mejor control de la liberación de fármacos de las matrices obtenido por la USAC se ha explicado en base a la sinterización de las partículas de TPU, dando como resultado estructuras con porosidad menor y un medio cuasi-continuo en lugar de sistemas particulados. Los valores de eficiencia del excipiente muestran la alta capacidad de este TPU para controlar la liberación del fármaco mediante ambos métodos. Finalmente, la estimación del umbral de percolación de TPU por ambos métodos ha contribuido a un conocimiento más profundo de los sistemas lo que permitiría definir el Espacio de Diseño de una formulación.
- Por primera vez se ha empleado con éxito la Compresión Asistida por Ultrasonidos (USAC) para fabricar matrices para la liberación controlada de fármacos a base de poliuretanos termoplásticos elásticos. Los comprimidos de TPU muestran un carácter inerte con una liberación sostenida del fármaco, gobernada por un mecanismo de difusión. La porosidad inicial de las matrices fue similar en todos los lotes estudiados, sin influencia del tamaño de las partículas del fármaco, y se ha observado una naturaleza fractal de la red de poros. Las microfotografías SEM muestran el medio continuo creado por la sinterización del polímero lo que consigue la alta eficiencia del excipiente.

- Se ha utilizado como excipiente, por primera vez para formas farmacéuticas, un copoliéster biodegradable de butilensuccinato y ε-caprolactona (PBS_CL), en proporción 70/30 para conseguir una temperatura de fusión próxima a 90ºC, utilizando técnicas de compresión directa y procesamiento en caliente (compresión asistida por ultrasonido (USAC) y extrusión de fusión en caliente (HME)). Con las técnicas de procesamiento en caliente se han logrado sistemas binarios robustos permitiendo una liberación controlada del fármaco. Con tan solo un 12% v/v de PBS_CL, se obtuvieron formas de liberación controlada usando USAC mientras que en HME es necesario más del 34% v/v de polímero. Cantidades superiores al 23% v/v permitieron una liberación prolongada durante más de 72 h. Gracias a las propiedades fisicoquímicas del PBS_CL sintetizado, la estructura del excipiente dentro de los comprimidos obtenidos por USAC y los filamentos de HME se corresponde con un medio continuo. Se estimó un umbral de percolación entre el 12 y el 23% v/v, lo que es compatible con un modelo de percolación continua. El polímero muestra una alta eficiencia de excipiente usando HME y USAC. Se obtuvo una matriz nanoestructurada con espesores de pared inferiores a 0,1 μm. Esto conduce a un recubrimiento muy eficaz de las partículas de fármaco por el excipiente, proporcionando una liberación lenta y reproducible. Por lo tanto, los resultados del presente estudio muestran que el PBS_CL sería un candidato adecuado para la preparación de formas de dosificación de liberación prolongada utilizando técnicas de procesamiento en caliente.

CONCLUSIONES GENERALES

1. La complementación con la Teoría de la Percolación del Método experto SeDeM facilita establecer los puntos críticos de mezclas binarias de fármaco y excipiente, proporcionando un conocimiento más profundo del comportamiento de dichas mezclas en la elaboración de comprimidos por compresión directa. Esto favorece el establecimiento del Espacio de Diseño de acuerdo con la ICH Q8.

2. Se han elaborado comprimidos matriciales con un poliuretano termoplástico comercial, tanto por compresión directa como por compresión asistida por ultrasonidos, consiguiendo en ambos casos una alta carga de fármaco (hasta el 90% peso/peso). La elaboración de los comprimidos mediante USAC permite una reducción de un 50% en la necesidad de excipiente para controlar la liberación, que se refleja en la Eficacia del Excipiente. La estimación de los umbrales de percolación permite ayudar a definir el espacio de diseño de acuerdo con los requerimientos de la Norma ICH Q8.

3. Se han conseguido elaborar comprimidos con un poliuretano termoplástico elástico mediante USAC superando la limitación de este tipo de materiales para su compresión. Con esta técnica se han conseguido comprimidos matriciales para liberación prolongada. Una vez liberado el fármaco, se ha encontrado una naturaleza fractal de la estructura porosa. El análisis de la dimensión fractal permite un mejor conocimiento del comportamiento de liberación del fármaco confirmando la robustez de los comprimidos obtenidos para diferentes tamaños de partícula del fármaco.

4. Escogiendo las proporciones de monómeros para la síntesis de un co-poliéster de poli (butilensuccinato-co-ϵ-caprolactona) se ha conseguido un polímero biodegradable adecuado como excipiente para la elaboración de matrices para liberación prolongada de fármacos. Usando técnicas de procesado en caliente para la elaboración de los sistemas, se ha conseguido una liberación prolongada del fármaco con tan sólo un 12% en volumen del excipiente. La alta eficacia del polímero deriva de la formación de matrices nanoestructuradas.

BIBLIOGRAFÍA GENERAL:

[1] Leuenberger H, Lanz M. Pharmaceutical powder technology — from art to science: the challenge of the FDA's Process Analytical Technology initiative. Adv Powder Technol 2005;16:3–25. https://doi.org/10.1163/1568552053166683.

[2] Juran JM. Juran on quality by design: the new steps for planning quality into goods and services. Simon and Schuster; 1992.

[3] ICH. PHARMACEUTICAL DEVELOPMENT Q8 (R2). vol. 8. 2009.

[4] Galdón E, Casas M, Gayango M, Caraballo I. First study of the evolution of the SeDeM expert system parameters based on percolation theory: Monitoring of their critical behavior. Eur J Pharm Biopharm 2016;109:158–64. https://doi.org/10.1016/j.ejpb.2016.10.004.

[5] Pacheco RM. Tratado de Tecnología Farmacéutica, Volumen III: Formas de Dosificación. vol. III. Madrid, ES: Síntesis; 2017.

[6] Aguilar-de-Leyva A, Campiñez MD, Casas M, Caraballo I. Critical Points and Phase Transitions in Polymeric Matrices for Controlled Drug Release. In: Thakur VK, M.K T and, editors. Handb. Polym. Pharm. Technol., Hoboken, NJ, USA: John Wiley & Sons, Inc.; 2015, p. 101–41. https://doi.org/10.1002/9781119041375.ch4.

[7] Nokhodchi A, Raja S, Patel P, Asare-Addo K. The role of oral controlled release matrix tablets in drug delivery systems. BioImpacts 2012;2:175–87. https://doi.org/10.5681/bi.2012.027.

[8] Anselmo AC, Mitragotri S. An overview of clinical and commercial impact of drug delivery systems. J Control Release 2014;190:15–28. https://doi.org/10.1016/j.jconrel.2014.03.053.

[9] Englert C, Brendel JC, Majdanski TC, Yildirim T, Schubert S, Gottschaldt M, et al. Pharmapolymers in the 21st century: Synthetic polymers in drug delivery applications. Prog Polym Sci 2018;87:107–64. https://doi.org/10.1016/j.progpolymsci.2018.07.005.

[10] Fu Y, Kao WJ. Drug release kinetics and transport mechanisms of non-degradable and degradable polymeric delivery systems. Expert Opin Drug Deliv

2010;7:429–44. https://doi.org/10.1517/17425241003602259.

[11] Mozafari M, Chauhan NPS. Advanced Functional Polymers for Biomedical Applications. Amsterdam, The Netherlands: Elsevier; 2019. https://doi.org/10.1016/C2018-0-00041-9.

[12] Papadimitriou SA, Papageorgiou GZ, Bikiaris DN. Crystallization and enzymatic degradation of novel poly(ε-caprolactone-co-propylene succinate) copolymers. Eur Polym J 2008;44:2356–66. https://doi.org/10.1016/j.eurpolymj.2008.05.004.

[13] Bode C, Kranz H, Fivez A, Siepmann F, Siepmann J. Often neglected: PLGA/PLA swelling orchestrates drug release: HME implants. J Control Release 2019;306:97–107. https://doi.org/10.1016/j.jconrel.2019.05.039.

[14] Bisharat L, Alkhatib HS, Abdelhafez A, Barqawi A, Aljaberi A, Qi S, et al. Hot melt extruded zein for controlled delivery of diclofenac sodium: Effect of drug loading and medium composition. Int J Pharm 2020;585:119503. https://doi.org/10.1016/j.ijpharm.2020.119503.

[15] Goyanes A, Robles Martinez P, Buanz A, Basit AW, Gaisford S. Effect of geometry on drug release from 3D printed tablets. Int J Pharm 2015;494:657–63. https://doi.org/10.1016/j.ijpharm.2015.04.069.

[16] Safari M, Mugica A, Zubitur M, Martínez de Ilarduya A, Muñoz-Guerra S, Müller AJ. Controlling the Isothermal Crystallization of Isodimorphic PBS-ran-PCL Random Copolymers by Varying Composition and Supercooling. Polymers (Basel) 2019;12:17. https://doi.org/10.3390/polym12010017.

[17] Safari M, Martínez De Ilarduya A, Mugica A, Zubitur M, Muñoz-Guerra S, Müller AJ. Tuning the Thermal Properties and Morphology of Isodimorphic Poly[(butylene succinate)- ran-(ϵ-caprolactone)] Copolyesters by Changing Composition, Molecular Weight, and Thermal History. Macromolecules 2018;51:9589–601. https://doi.org/10.1021/acs.macromol.8b01742.

[18] Kempin W, Domsta V, Brecht I, Semmling B, Tillmann S, Weitschies W, et al. Development of a dual extrusion printing technique for an acid- and thermo-labile drug. Eur J Pharm Sci 2018;123:191–8. https://doi.org/10.1016/j.ejps.2018.07.041.

[19] Desai D, Sandhu H, Shah N, Malick W, Zia H, Phuapradit W, et al. Selection of Solid-State Plasticizers as Processing Aids for Hot-Melt Extrusion. J Pharm Sci 2018;107:372–9. https://doi.org/10.1016/j.xphs.2017.09.004.

[20] Patil H, Tiwari R V, Repka MA. Hot-Melt Extrusion: from Theory to Application in Pharmaceutical Formulation. AAPS PharmSciTech 2016;17:20–42. https://doi.org/10.1208/s12249-015-0360-7.

[21] Levina M, Rubinstein MH. The Effect of Ultrasonic Vibration on the Compaction Characteristics of Paracetamol. J Pharm Sci 2000;89:705–23. https://doi.org/10.1081/DDC-120003446.

[22] Caraballo I, Millán M, Fini A, Rodriguez L, Cavallari C. Percolation thresholds in ultrasound compacted tablets. J Control Release 2000;69:345–55. https://doi.org/10.1016/S0168-3659(00)00307-2.

[23] Millán M, Caraballo I. Effect of drug particle size in ultrasound compacted tablets: Continuum percolation model approach. Int J Pharm 2006;310:168–74. https://doi.org/10.1016/j.ijpharm.2005.12.005.

[24] Caraballo I. Prices of the Controlled Release Society. In: Controlled Release Society, editor. 28th Symp. San Diego, San Diego, Cal.: 2001.

LISTADO DE ABREVIATURAS

CQA - Atributos críticos de calidad (Critical Quality Attribute)

EE - Eficacia del Excipiente

ETSEIB - Departament d'Enginyeria Química de la Universitat Politècnica de Catalunya

FDA - Administración de Alimentos y Medicamentos de EE.UU. (U.S. Food and Drug Administration)

HME - Hot-Melt Extrusion

ICH - Conferencia Internacional sobre armonización de requisitos técnicos para el registro de productos farmacéuticos para uso humano (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use)

PBS – Poli butilensuccinato

PBS_CL - Copoliéster de poli (butilensuccinato-co-ϵ-caprolactona)

PCL - Poli (ε-caprolactona)

PGA - Ácido poli glicólico

PLA - Ácido poli láctico

QbD - Calidad por diseño (Quality by Design)

QTTP - Perfil de producto objetivo de calidad (Quality Target Product Profile)

SEM - Microscopia electrónica de barrido (Scanning Electron Microscopy)

Tg - Temperatura de transición vítrea

Tm - Temperatura de fusión

USAC - Compresión Asistida por Ultrasonidos (Ultrasound Assisted Compression).