European Journal of Pharmaceutics and Biopharmaceutics 75 (2010) 232–237

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

In vivo evaluation of two new sustained release formulations elaborated by one-step melt granulation: Level A *in vitro–in vivo* correlation

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ARTICLE INFO

Article history:
Received 3 December 2009
Accepted in revised form 10 February 2010
Available online 14 February 2010

Keywords:
Melt granulation
Sustained release
IVIVC
Theophylline
Binder

ABSTRACT

The objective of this study was to evaluate *in vivo* two sustained release formulations elaborated by a one-step melt granulation method using theophylline as model drug. Both formulations presented differences in the *in vitro* release profile due to the hydrophilic or lipophilic nature of the binder employed (PEG 6000 or glycerol monostearate). The formulations were administered to Beagle dogs, and plasma levels were compared. Both formulations provided a sustained plasma concentration profile after oral administration to dogs. Significant differences ($p < 0.05$) in the plasma concentration–time curves between the two formulations were found, with higher C_{max} (6.05 ± 2.00 vs. 2.55 ± 0.82 μg/mL), higher $AUC_{0-\infty}$ (70.24 ± 16.10 vs. 33.00 ± 8.96 h μg/mL) and delayed T_{max} (6.00 ± 2.12 vs. 3.17 ± 0.98 h) for the formulation containing PEG 6000. Absolute bioavailability of theophylline was 96% and 46% for the formulations containing PEG 6000 and glycerol monostearate, respectively. These results are consistent with those obtained *in vitro*, with slower release rate of theophylline from tablets elaborated with glycerol monostearate than that obtained with tablets elaborated with PEG 6000. Moreover, the formulation containing PEG 6000 provided a plasma concentration–time profile similar to that obtained with the marketed formulation Theo-Dur®. A very good Level A IVIVC was observed between dissolution and absorption profiles of the drug from both test formulations. Our results showed that one-step melt granulation in a high shear mixer allows for an easy modulation of the release profile and, consequently, of the plasma level profile of the drug by selecting the type of binder used.

1. Introduction

Sustained release (SR) delivery systems for oral dosing are effective in achieving ideal therapy with drugs that have a short biological half-life and require repeated doses to maintain efficacy in long-term treatments. Generally, the primary objectives of controlled drug delivery systems are to ensure safety and to improve drug efficacy as well as patient compliance, which can be achieved by the better control of plasma drug levels and less frequent dosing [1]. Hydrophilic matrices containing polymers such as hydroxypropylmethylcellulose (HPMC) have been widely used for oral controlled release [2–4]. This kind of polymers hydrates in the presence of a dissolution medium, forming a gel layer around the tablet which controls drug diffusion [5]. Additionally, HPMC is a pH-independent dissolving material, and the drug release rates from HPMC matrix formulations are generally independent of processing variables such as compaction pressure, drug particle size and the incorporation of lubricants [6,7].

An interesting approach to develop SR formulations is based on melt granulation in high shear mixer [8–10], which is a very short one-step technique converting fine powders into granules. For any controlled release dosage form, it is very important that both the number of excipients in the formula and the processing steps are kept to the minimum, in order to reduce tablet-to-tablet and batch-to-batch variations. Hence, melt granulation is a suitable and easily scalable technique for this purpose [11]. Powder agglomeration is promoted by the addition of a low melting point binder, which is solid at room temperature and melts at relatively low temperatures (50–80 °C). In recent years, the interest in melt granulation has increased due to the advantages of this technique over traditional wet granulation. Since it is a solvent-free process, the drying phase is eliminated and thus it becomes less consuming in terms of time and energy [12]. Moreover, this technique could be used not only to enhance the bioavailability of poorly soluble drugs [13,14], but also to retard the release rate of highly soluble drugs [15,16].

When developing a SR formulation, the establishment of a correlation between the *in vitro* dissolution profile and the *in vivo* plasma concentration profile is of great interest for pharmaceutical develop-

Abbreviations: TH, theophylline; SR, sustained release; TPE, formulation with PEG 6000; TGM, formulation with glycerol monostearate.

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doi:10.1016/j.ejpb.2010.02.008

ment. Taking into account that the release of drugs in the gastrointestinal tract is the intended rate-limiting factor in the absorption process, it is therefore desirable to use *in vitro* data to predict *in vivo* bioavailability parameters for the rational development and evaluation process of SR oral dosage forms [17,18]. For this purpose, it is necessary to establish an *in vitro* test method that can predict the process of drug release and *in vivo* absorption [19,20], particularly during the development of an innovative dosage form.

The overall aim of this paper was to evaluate *in vivo* two sustained release formulations elaborated by a one-step melt granulation method using theophylline as model drug. Both formulations presented differences in the *in vitro* release profile due to the nature, hydrophilic or lipophilic, of the binder. In order to achieve this aim, the formulations were administered orally to dogs and the plasma concentration–time profile was obtained. Secondly, we performed a comparison with a marketed sustained release formulation of theophylline, Theo-Dur®. Finally an *in vitro–in vivo* correlation (IVIVC) was established.

2. Material and methods

2.1. Materials

Anhydrous theophylline obtained from Vencaser, S.A. (Bilbao, Spain) was used as model drug and β-hydroxyethyl-theophylline (Sigma–Aldrich Chemie, Germany) as internal standard. HPMC (Methocel® K4M Premium), kindly supplied by Colorcon (UK), was used as starting material and magnesium stearate (Kirsch Pharma, Spain) as lubricant. PEG 6000 and glycerol monostearate (Vencaser, S.A., Spain) were used as meltable binders. All other solvents and reagents were of analytical or HPLC grade and used as received.

2.2. Preparation of hydrophilic matrix tablets

A laboratory scale one-step high shear mixer Rotolab® (Zanchetta, Italy) was used to prepare granules composed by PEG 6000 (TPE) or glycerol monostearate (TGM) as hydrophilic and lipophilic binder, respectively.

The granulation procedure was standardized on the basis of preliminary trials [21]. The mixture composed of theophylline (TH), HPMC K4M and the binder agent was mixed at low impeller speed (250 rpm) for 5–10 min. Afterwards, the impeller speed was increased up to 1100 rpm and the mixture was heated up to the melting point of the binder in order to obtain granules. At the end of the granulation process, the granules were cooled at room temperature by decreasing the jacket temperature and tilting the bowl to avoid agglomerate formation.

The granules obtained were sieved in order to remove lumps, mixed with 0.5% magnesium stearate for 10 min using a rotating V-blender and compressed into oblong biconvex shaped tablets (13 × 7.5 mm) on a reciprocating single punch tablet machine at a breaking strength of 70–80 N. The breaking strength was determined using a Pharma-test GmbH durometer. Tablets weighted 400 mg ±5% and contained 200 mg of TH. The tablet shape, size and hardness were held constant for both formulations.

Table 1 summarizes the components of the formulations.

2.3. In vitro dissolution studies

The drug release assay was performed using a USP type II (paddle) apparatus at 50 rpm stirring rate and 37 ± 0.5 °C. The tablets (n = 12) were placed in 750 mL HCl 0.1 N for 2 h and continued in 0.05 M sodium phosphate buffer pH 6.8 up to 24 h. The change in pH was made by the addition of 250 mL 0.2 M tribasic sodium phosphate. Additionally, four different dissolution media were used to study the influence of pH in the dissolution profile: 0.1 N HCl pH 1.2, 0.02 M acetate buffer pH 4.5, 0.05 M sodium phosphate buffer pH 6.8 and distilled water. Samples were extracted at regular time intervals and assayed spectrophotometrically at 272 nm. The UV method was validated in terms of specificity to ensure that excipients and dissolution media do not interfere in the quantification of TH. Moreover, the method was shown to be accurate and precise.

Table 1
Composition of theophylline sustained release matrix tablets.

	Formulation 1 (TPE) (%)	Formulation 2 (TGM) (%)
Theophylline	50	50
HPMC K4M	29.5	29.5
PEG 6000	20	–
Glycerol monosterate	–	20
Magnesium stearate	0.5	0.5

The similarity factor (f_2) was calculated in order to compare the release profile of each formulation in the different dissolution media with that obtained in distilled water. In this approach, a value between 50 and 100 indicates similarity between two dissolution profiles.

In order to define a model of drug release from sustained release formulations, dissolution data were analyzed by Peppas and Korsmeyer equation (Eq. (1)) [22,23] and by Weibull function (Eq. (2)).

$$M_t/M_\infty = kt^n \quad (1)$$

$$M_t/M_\infty = 1 - \exp(-\alpha t^b) \quad (2)$$

where M_t/M_∞ is the fractional drug release percentage at time t, k is the kinetic constant, n is the diffusional exponent which characterizes the drug transport mechanism and α and b are constants of Weibull function.

Experimental data were fitted to equations by using the Winnolin 4.1® Pro (Pharsight, Mountain View, CA, USA) [24].

2.4. In vivo study

The pharmacokinetic of TH sustained release formulations was studied in six Beagle dogs weighing 12 ± 1.5 kg from "Serveis de Support a la Recerca Estabulari-UB" (Barcelona, Spain). Principles in good laboratory animal care were followed, and animal experimentation was in compliance with the "Ethical committee of animal experimentation (CEEA)" of Barcelona University (UB).

The dogs did not receive food but had free access to water for 12 h before and after drug administration. Each animal received the new SR formulations (TPE and TGM), Theo-Dur® and an intravenous solution of TH in a crossover experimental design. The dose of theophylline was 200 mg orally and 8 mg/kg intravenously. A washout period of 7 days was allowed between the different treatments. Serial blood samples were collected from the cephalic vein at predetermined time points up to 12 h in the case of intravenous administration and up to 24 h after oral administrations. All blood samples were taken in heparinized tubes, and plasma was separated by centrifugation at 3000 rpm and immediately stored at −80 °C until analysis.

2.5. HPLC determination of theophylline in plasma

Determination of TH plasma concentrations was performed by high-performance liquid chromatography with a Waters (Waters Corp., Milford, USA) apparatus coupled to an UV detector. A reversed-phase HPLC column was used at room temperature (Symmetry® C18 5 μm, 4.6 mm × 150 mm). The mobile phase contained acetonitrile:acetate buffer (0.01 M) pH 4 (9.7:0.3 v/v) and was delivered at a flow rate of 0.8 mL/min. The wavelength for UV detection was 272 nm.

In order to analyze samples, 100-μL aliquot of plasma was placed in an eppendorf tube and spiked with 100 μL of methanol containing $ZnSO_4$ (12 mg/mL) as precipitant agent and β-hydroxyethyl-theophylline (10 μg/mL) as internal standard. The mixture was vigorously mixed in vortex for 30 s and then centrifuged at 4 °C at 15,000 rpm for 10 min. A 20-μL aliquot of supernatant was injected onto the column for HPLC analysis.

The analytical method was previously validated according to FDA and ICH Guidelines [25,26]. The assay was linear over plasma concentrations ranging from 0.25 to 30 μg/mL. The intraday and interday coefficients of variation ranged from 2.24% to 6.20% at the three concentrations tested (0.75, 12, 24 μg/mL). The bias at these concentrations ranged from 0.14% to 11.93%. The limit of quantification was considered the lowest level included in the calibration curve (0.25 μg/mL) and measures of intraday and interday coefficient of variation ranged from 3.10% to 7.10% with a bias ranging from 0.60% to 11.88%. No interfering peaks were detected with the assay. TH plasma samples stored at −80 °C were stable for at least 2 months.

2.6. Pharmacokinetic analysis

Plasma levels of TH in dogs were plotted against time, and pharmacokinetic parameters were calculated by a non-compartmental method using WinNonlin 4.1. The area under the plasma concentration vs. time curve up to the last quantifiable time point, AUC_{0-t} was obtained by the linear and log-linear trapezoidal method. The AUC_{0-t} was extrapolated to infinity ($AUC_{0-\infty}$) by adding the quotient C_{last}/K_{el}, where C_{last} represents the last measured concentration and K_{el} represents the apparent terminal rate constant. K_{el} was calculated by the linear regression of the log-transformed concentrations of the drug in the terminal phase. The half-life of the terminal elimination phase was obtained using the relationship $t_{1/2} = 0.693/K_{el}$. The C_{max} and T_{max} were obtained directly from the data. Oral clearance (Cl/F) was calculated as dose divided by $AUC_{0-\infty}$. The apparent volume of distribution was obtained from the equation $Vdz/F = D/(AUC_{0-\infty} \times K_{el})$. Mean residence time (MRT) was determined by division of AUMC (area under the first moment curve) by $AUC_{0-\infty}$. Absolute oral bioavailability (F) was calculated from plasma data using the relationship F = [dose IV × $AUC_{0-\infty}$ oral/dose oral × $AUC_{0-\infty}$ IV] × 100.

Deconvolution of plasma data was attempted using intravenous bolus data parameters. WinNonlin 4.1 was used to perform the numerical deconvolution procedure. A plot of percent dissolved *in vitro* vs. percent absorbed *in vivo* input at various time points up to 12 h was constructed. These plots allowed us to develop an *in vitro–in vivo* correlation (IVIVC) that could be used to establish a relationship between i*n vivo* behavior of a dosage form and the *in vitro* performance, which would allow *in vitro* data to be used as a surrogate for *in vivo* behavior.

2.7. Statistical analysis

Statistical analyses were performed with SPSS 15 software for Windows® (SPSS® Inc., Chicago, USA). The Shapiro–Wilks test [27] was used to verify normality, and the Levene test [28] was used to verify homogeneity of variances. ANOVA followed by Scheffe test was used to determine statistical comparisons. The Wilcoxon test was used to analyze the data of T_{max}. Statistical significance was assessed at $p < 0.05$.

3. Results and discussion

3.1. In vitro dissolution studies

In a previous work we studied the physical and rheological characteristics of various formulations based on melt granulation with different binders and HPMC grades [21]. The results obtained showed the suitability of this technique for the development of SR formulations, and, therefore, two different binders, a hydrophilic one (PEG 6000) and a lipophilic one (glycerol monostearate) were selected for a further *in vitro* characterization and a pharmacokinetic study in Beagle dogs.

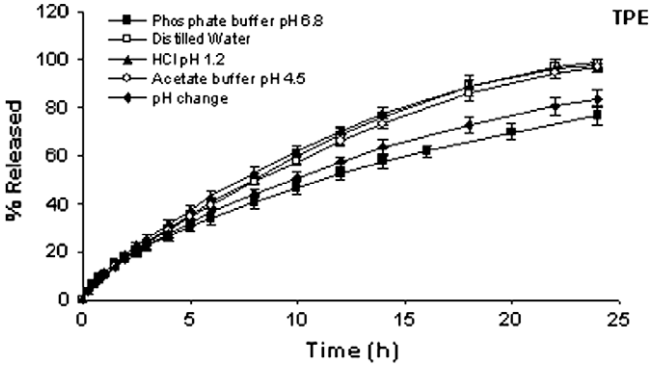

Fig. 1. *In vitro* dissolution profiles of TH from TPE formulation in different dissolution media. Bars represent the standard deviation obtained from the individual data (n = 12).

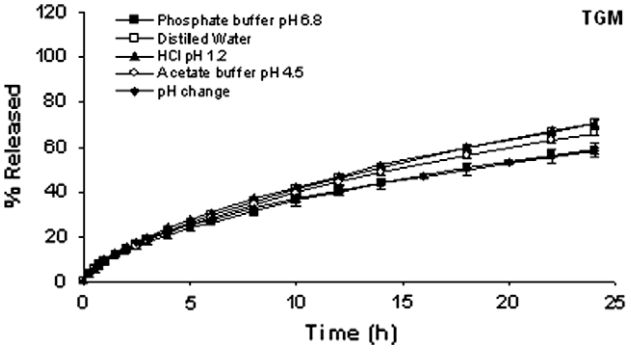

Fig. 2. *In vitro* dissolution profiles of TH from TGM formulation in different dissolution media. Bars represent the standard deviation obtained from the individual data (n = 12).

In order to test the influence of the binder and the dissolution medium pH on the release of TH from the tablets, dissolution test was carried out at various pH values. Figs. 1 and 2 feature the TH release profile from the two formulations (TPE and TGM) in the different media.

In vitro dissolution results showed that both TPE and TGM formulations provided a sustained release of the drug for a period of 24 h.

The similarity factor (f_2) was used to compare the dissolution profile in different dissolution media (HCl pH 1.2, acetate buffer pH 4.5, phosphate buffer pH 6.8 and pH change media) with that obtained in distilled water. For TPE formulation, f2 values were 85.52, 87.36, 55.61 and 58.84, for each pH value, respectively. The values obtained for TGM formulation were 84.56, 95.21, 61.35 and 63.74, respectively. These results indicate that TH release from the two matrix systems, TPE and TGM, was independent of the pH value of the release medium.

However, we detected differences in the release rate of TH depending on the formulation. The nature of the binder contained in the tablets could explain this behavior. The formulation containing glycerol monostearate presented a slower TH release rate. At 24 h, total TH released was around 65% and higher than 80% from TGM and TPE, respectively, in all pH studied.

This behavior could be explained by the hydrophobic nature of glycerol monostearate which could probably delay wetting of the

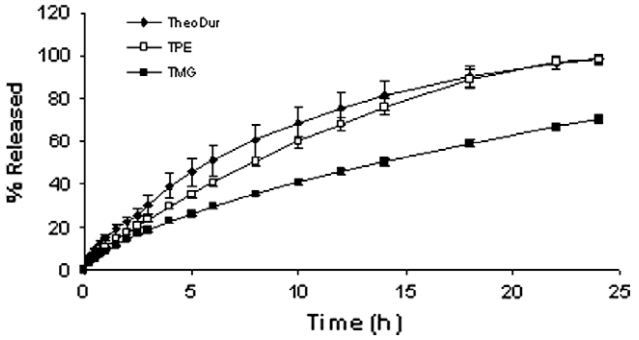

Fig. 3. In vitro release profile of TPE, TGM and Theo-Dur® in distilled water. Bars represent the standard deviation obtained from the individual data ($n = 12$).

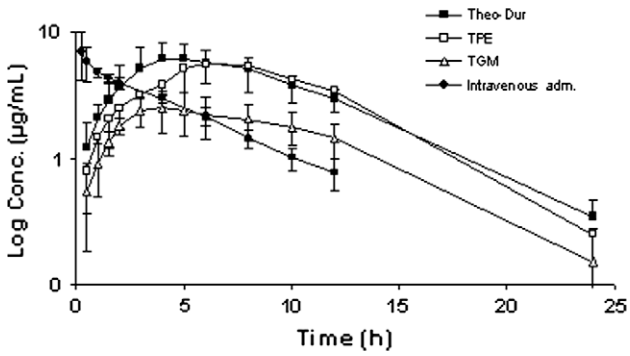

Fig. 4. Plot of mean (± SD) plasma TH concentration–time curves following intravenous administration of TH in solution and the test SR formulations and commercial tablets.

solid HPMC matrix and, consequently cause a slower release rate. Therefore, the choice of binder proves crucial when using a one-step melt granulation process to elaborate SR formulations: the *in vitro* release profile of the drug can be modulated with only a change in the nature of the binder.

The release profile of TH from Theo-Dur® was not affected by the pH of the medium (data not shown). For this formulation, the f_2 values at each pH compared to distilled water were found to be higher than 55, indicating similarity between the different dissolution profiles. Since pH does not affect the release profile, distilled water was selected as dissolution medium to study the behavior of the two new formulations in comparison with a marketed TH SR formulation, Theo-Dur®. Fig. 3 shows the release profile of the three sustained release formulations in distilled water.

The formulation containing the hydrophilic binder PEG 6000 (TPE) showed a similar release profile than the marketed Theo-Dur® ($f_2 = 60.54$). Theo-Dur® is an extended used marketed formulation that is composed of a part of TH presented in a matrix and the remainder is contained in small cores which are embedded in the matrix [29].

Table 2 summarizes the release kinetic parameters calculated with Weibull and Korsmeyer–Peppas equations from the drug dissolution data in distilled water. Both TPE and TGM formulations showed a very good correlation with the power law equation ($r^2 \geqslant 0.999$). The release exponent n was 0.709 for the TPE formulation, 0.641 for the TGM formulation and 0.561 for Theo-Dur®, suggesting a non-Fickian diffusion kinetics ($0.5 < n < 1$) [22].

Table 2
Release kinetic parameters calculated with Weibull and Korsmeyer–Peppas equations from the drug dissolution data in distilled water.

	Weibull		Korsmeyer–Peppas		
	r^2	b (SD)	r^2	n	K (h^{-n}) (SD)
TPE	0.996	1.10 (0.04)	0.999	0.709	0.621 (0.05)
TGM	0.999	0.84 (0.01)	0.999	0.641	0.668 (0.02)
Theo-Dur®	0.998	0.97 (0.03)	0.995	0.561	1.767 (0.24)

The Korsmeyer–Peppas equation is confined to the description of the first 60% of the release curve [30,31]; however, Weibull function is used to describe the drug release mechanism of the entire drug release curve. The fitting of release values to Weibull equation showed a good correlation ($r^2 \geqslant 0.996$) for the three formulations. A b value ranging from 0.75 to 1 was obtained for TGM and Theo-Dur®, which is indicative of diffusion in normal Euclidian substrate together with another release mechanism. In the case of TPE, a $b > 1$ indicates that a complex mechanism governs the release process, with an initial non-linear increase up to an inflection point and, thereafter, an asymptotic decrease. These results are in line with previous studies that provide experimental evidence for the successful use of the Weibull function in the entire drug release studies [31,32].

3.2. In vivo study

The formulations were administered orally to Beagle dogs, and the plasma concentration–time profiles were obtained. Fig. 4 and Table 3 summarize the mean plasma TH concentration–time curves and pharmacokinetics parameters following intravenous administration of TH in solution and the test SR formulations and commercial tablets.

As Fig. 4 shows, the matrix tablets (TPE and TGM) presented sustained plasma level profiles. Significant differences ($p < 0.05$) in the plasma concentration–time curves between the two formulations were found, with higher C_{max} (6.05 ± 2.00 vs. 2.55 ± 0.82 µg/mL), higher $AUC_{0-\infty}$ (70.24 ± 16.10 vs. 33.00 ± 8.96 h µg/mL) and delayed T_{max} (6.00 ± 2.12 vs. 3.17 ± 0.98 h) for the TPE formulation. These results are consistent with those obtained *in vitro*, with slower release rate of TH from TGM than from TPE. These results support the use of lipophilic binders for the development of SR formulations with highly soluble drugs [33]. The addition of fatty

Table 3
Mean (± SD) pharmacokinetic parameters of TH following an IV Bolus injection and single oral administration of the sustained release formulations to dogs ($n = 6$).

Pharmacokinetic parameters	Intravenous formulation	Theo-Dur®	TPE (PEG 6000)	TGM (glycerol Monost.)
$t_{1/2}$ (h)	4.08 ± 0.74	4.24 ± 0.90	3.73 ± 0.82	4.45 ± 1.14
C_{max} (µg/mL)	8.42 ± 4.65	7.16 ± 1.78	6.05 ± 2.00	2.55 ± 0.82*
$AUC_{0-\infty}$ (h ug/mL)	34.92 ± 4.16	74.27 ± 10.17	70.24 ± 16.10	33.00 ± 8.96*
T_{max} (h)	–	5.00 ± 1.79	6.00 ± 2.12	3.17 ± 0.98*
MRT (h)	3.93 ± 0.38	8.17 ± 0.65	8.40 ± 1.10	8.34 ± 2.38
Cl (L/h)	0.23 ± 0.03	2.78 ± 0.35	2.73 ± 0.37	2.77 ± 0.36
Vdz (L)	1.35 ± 0.17	16.87 ± 3.43	14.65 ± 3.43	18.55 ± 4.17
F	–	103.44 ± 18.83	95.55 ± 22.84	46.35 ± 14.85*

* Significant differences ($p < 0.05$) between TPE, TGM and Theo-Dur®.

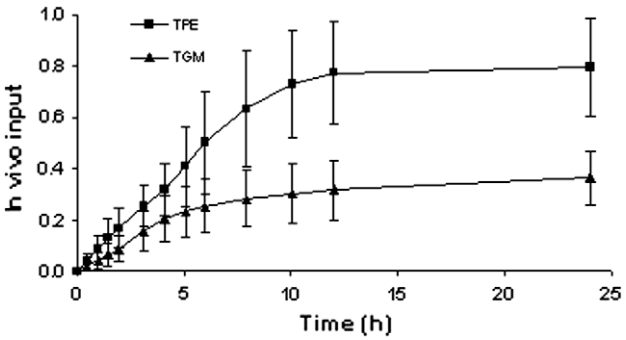

Fig. 5. Plots of mean (± SD) percent absorbed *in vivo* vs. time for both new SR formulations. Bars represent the standard deviation obtained from the individual data ($n = 6$).

excipients like glycerol monostearate may retard the dissolution, and consequently decrease the *in vivo* absorption of hydrophilic drugs, whereas the addition of hydrophilic excipients could be used to improve the absorption of slightly soluble drugs [34].

Moreover, a very similar profile was obtained with TPE and the commercial formulation Theo-Dur®. No significant differences ($p > 0.05$) in plasma levels nor in pharmacokinetic parameters were found between the two formulations.

3.3. IVIV correlation development

An important step in the dosage form development process is exploring a relation between the *in vitro* drug release and the *in vivo* absorption from a sustained release dosage form [35,36]. Fig. 5 showed the percent absorbed *in vivo* vs. time for both new SR formulations.

Fig. 5 shows that a prolonged and slow absorption was consistent with the *in vitro* release in the dissolution profiles. Moreover, the lower release of TH from the TGM formulation is in line with a lower absorption of the drug, which is reflected in a poor bioavailability ($F < 0.5$). The TPE formulation showed a very high bioavailability ($F > 0.95$) due to a good release and absorption profiles of TH from this formulation.

Level A IVIV correlation is the most informative and very useful from a regulatory perspective since it represents a point-to-point relationship between *in vitro* dissolution and the *in vivo* input rate of the drug from the dosage form [37]. Fig. 6 presents an example of Level A IVIVC with linear correlation plots for percentage of *in vitro* dose released and percentage of *in vivo* dose absorbed.

It is known that a Level A correlation obtained with a single formulation can be useful only when the formulation under study is shown to be independent of dissolution conditions (e.g., pH, ionic strength, agitation conditions). In our study, *in vitro–in vivo* correlation was also obtained with the release profile obtained at different media with different pH values of dissolution media. In all cases a very good correlation was obtained for both formulations with $r > 0.995$ for TPE and $r > 0.975$ for TGM, respectively. This was expected since, as we have shown above, that pH does not affect the release profile of TH from the matrices.

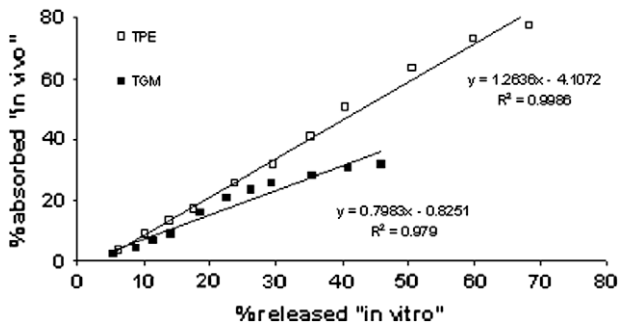

Fig. 6. Example of IVIVC plots for TPE and TGM formulations in distilled water as dissolution medium.

It is important to note that, a good IVIV correlation suggest the possibility to predict *in vivo* pharmacokinetic behavior from the observed *in vitro* drug release profiles. Validation of IVIV correlation would be the next step. For this purpose it is convenient to evaluate a significant number of formulations.

4. Conclusions

In summary, two sustained release formulations of theophylline were elaborated by one-step melt granulation in a high shear mixer. Each formulation contained a different binder (PEG 6000 or glycerol monostearate, as hydrophilic or lipophilic binder, respectively) and presented different *in vitro* release profiles. Both formulations provided a sustained plasma concentration profile after oral administration to dogs, and the formulation containing PEG 6000 (TPE) achieved a similar plasma profile than Theo-Dur®. Furthermore, a very good Level A IVIV correlation was observed between dissolution profiles and absorption profiles of the drug for both test formulations.

We can conclude that one-step melt granulation in high shear mixer could be an easy and more cost-effective technique for sustained release formulation development. This technique allows for an easy modulation of the release profile and, consequently, of the plasma level profile of the drug by selecting the type of binder used.

Acknowledgement

Thanks go to the University of Basque Country for the Grant given to L. Ochoa.

References

[1] V.H.K. Li, J.R. Robinson, Fundamentals of controlled release drug delivery, in: J.R. Robinson, V.H.L. Lee (Eds.), Controlled Drug Delivery: Fundamentals and Applications, Marcel Dekker, New York, 1987, pp. 3–11.
[2] M.A. Bayomi, S.A. Al-Suwayeh, A.R. El-Helw, Excipient–excipient interaction in the design of sustained-release theophylline tablets: in vitro and in vivo evaluation, Drug Dev. Ind. Pharm. 27 (2001) 499–506.
[3] I.J. Hardy, A. Windberg-Baarup, C. Neri, P.V. Byway, S.W. Booth, S. Fitzpatrick, Modulation of drug release kinetics from hydroxypropyl methyl cellulose matrix tablets using polyvinyl pyrrolidone, Int. J. Pharm. 337 (2007) 246–253.
[4] S. Zuleger, R. Fassihi, B.C. Lippold, Polymer particle erosion controlling drug release. II. Swelling investigations to clarify the release mechanism, Int. J. Pharm. 247 (2002) 23–37.
[5] J. Heller, Fundamentals of controlled release drug delivery, in: J.R. Robinson, V.H.L. Lee (Eds.), In Controlled Drug Delivery: Fundamentals and Applications, Marcel Dekker, Inc., New York, 1987, pp. 140–174.
[6] J.L. Ford, M.H. Rubinstein, J.E. Hogan, Formation of sustained release promethazine hydrochloride tablets using hydroxypropylmethylcellulose matrix, Int. J. Pharm. 24 (1985) 327–338.
[7] B.J. Lee, S.G. Riu, S.H. Cui, Formulation and release characteristics of hydroxypropyl methylcellulose matrix tablet containing melatonin, Drug Dev. Ind. Pharm. 25 (1999) 493–501.
[8] J. Goole, F. Vanderbist, K. Amighi, Development and evaluation of new multiple-unit levodopa sustained-release floating dosage forms, Int. J. Pharm. 334 (2007) 35–41.
[9] B. Perissutti, F. Rubessa, M. Moneghini, D. Voinovich, Formulation design of carbamazepine fast-release tablets prepared by melt granulation technique, Int. J. Pharm. 256 (2003) 53–63.
[10] A. Royce, J. Suryawanshi, U. Shah, K. Vishnupad, Alternative granulation technique: melt granulation, Drug Dev. Ind. Pharm. 22 (1996) 917–924.
[11] I.N. Bjorn, A. Jansson, M. Karlsson, S. Folestad, A. Rasmuson, Empirical to mechanistic modelling in high shear granulation, Chem. Eng. Sci. 60 (2005) 3795–3803.
[12] J. Hamdani, A.J. Moes, K. Amighi, Development and evaluation of prolonged release pellets obtained by the melt pelletization process, Int. J. Pharm. 245 (2002) 167–177.

[13] D. Yang, R. Kulkarni, R.J. Behme, P.N. Kotiyan, Effect of the melt granulation technique on the dissolution characteristics of griseofulvin, Int. J. Pharm. 329 (2007) 72–80.
[14] J. Goole, P. Deleuze, F. Vanderbist, K. Amighi, New levodopa sustained-release floating minitablets coated with insoluble acrylic polymer, Eur. J. Pharm. Biopharm. 68 (2008) 310–318.
[15] D.J. Hauss, Oral lipid-based formulations, Adv. Drug Deliv. Rev. 59 (2007) 667–676.
[16] S. Shimpi, B. Chauhan, K.R. Mahadik, A. Paradkar, Preparation and evaluation of diltiazem hydrochloride-gelucire 43/01 floating granules prepared by melt granulation, AAPS PharmSciTech 5 (3) (2004).
[17] N. Sirisuth, L.L. Augsburger, N.D. Eddington, Development and validation of a non-linear IVIVC model for a diltiazem extended release formulation, Biopharm. Drug Dispos. 23 (2002) 1–8.
[18] Z. Hussein, M. Friedman, Release and absorption characteristics of novel theophylline sustained release formulations: in vitro–in vivo correlation, Pharm. Res. 7 (1990) 1167–1171.
[19] J. Varshosaz, T. Ghafghazi, A. Raisi, M. Falamarzian, Biopharmaceutical characterization of oral theophylline and aminophylline tablets. Quantitative correlation between dissolution and bioavailability studies, Eur. J. Pharm. Biopharm. 50 (2000) 301–306.
[20] L. Shan-Yang, K. Yuh-Horng, C. Hsiao-Ning, Preliminary evaluation of the correlation between in vitro release and in vivo bioavailability of two aminophylline slow-release tablets, J. Pharm. Sci. 79 (1990) 326–330.
[21] L. Ochoa, M. Igartua, R.M. Hernandez, A.R. Gascon, J.L. Pedraz, Preparation of sustained release hydrophilic matrices by melt granulation in a high-shear mixer, J. Pharm. Pharm. Sci. 8 (2005) 132–140.
[22] N.A. Peppas, Analysis of Fickian and non-Fickian drug release from polymers, Pharm. Acta Helv. 60 (1985) 110–111.
[23] R.W. Korsmeyer, R. Gurny, E. Doelker, P. Buri, N.A. Peppas, Mechanism of solute release from porous hydrophilic polymers, Int. J. Pharm. 15 (1983) 25–35.
[24] Winnolin 4.1, Pharshigt Corporation, Mountain View, California, 2003.
[25] Food and Drug Administration: Guidance for Industry, Bioanalytical Methods Validation for Human Studies, US Department of Health and Human Services/Food and Drug Administration/Center for Drug Evaluation and Research, Rockville, MD, 1998.
[26] ICH, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Q2/R1 Validation of Analytical Procedures. Text and Methodology, 1995.
[27] S.S. Shapiro, M.B. Wilk, An analysis of variance test for normality (complete samples), Biometrika 52 (1965) 591–611.
[28] H. Levene, Robust tests for equality of variances, in: I. Olkin, S.G. Ghurye, W. Hoeffding, W.G. Madow, H.B. Mann (Eds.), Contribution to Probability and Statistics, 1960, pp. 278–292.
[29] D.L. Munday, A.R. Fassihi, In vitro-in vivo correlation studies on a novel controlled release theophylline delivery system and on Theo-Dur tablets, Int. J. Pharm. 118 (1995) 251–255.
[30] K. Kosmidis, P. Argyrakis, P. Macheras, A reappraisal of drug release laws using Monte Carlo simulations: the prevalence of the Weibull function, Pharm. Res. 20 (2003) 988–995.
[31] V. Papadopoulou, K. Kosmidis, M. Vlachou, P. Macheras, On the use of the Weibull function for the discernment of drug release mechanisms, Int. J. Pharm. 309 (2006) 44–50.
[32] J. Siepmann, A. Streubel, N.A. Peppas, Understanding and predicting drug delivery from hydrophilic matrix tablets using the "sequential layer" model, Pharm. Res. 19 (2002) 306–314.
[33] G.A. Abdelbary, M.I. Tadros, Design and in vitro/in vivo evaluation of novel nicorandil extended release matrix tablets based on hydrophilic interpolymer complexes and a hydrophobic waxy polymer, Eur. J. Pharm. Biopharm. 69 (2008) 1019–1028.
[34] N. Passerini, B. Albertini, B. Perissutti, L. Rodriguez, Evaluation of melt granulation and ultrasonic spray congealing as techniques to enhance the dissolution of praziquantel, Int. J. Pharm. 318 (2006) 92–102.
[35] R.M. Hernández, A.R. Gascón, M.B. Calvo, C. Caramella, U. Conte, A. Domínguez-Gil, J.L. Pedraz, Correlation of 'in vitro' release and 'in vivo' absorption characteristics of four salbutamol sulphate formulations, Int. J. Pharm. 139 (1996) 45–52.
[36] Y. Qiu, H.S. Cheskin, K.R. Engh, R.P. Poska, Once-a-day controlled-release dosage form of divalproex sodium I: formulation design and in vitro/in vivo investigations, J. Pharm. Sci. 92 (2003) 1166–1173.
[37] Food and Drug Administration: Guidance for Industry. Extended Release Solid Oral Dosage Forms. Development, Evaluation and Application of In Vitro/In Vivo Correlations, US Department of Health and Human Services/Food and Drug Administration/Center for Drug Evaluation and Research, Rockville, MD, 1997.