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Empirical kinetic model of propafenone release from Hot Air Coating microparticles

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Abstract

Lipid microparticles, containing 30% and 50% (w/w) propafenone hydrochloride as the active molecule and cetearyl alcohol and Pluronic® F68 as excipients, were prepared by Hot Air Coating (HAC).

The aim of the work was to identify the kinetics and the mechanism of the drug release process from these microparticulate systems. The application of the Weibull model to the release data from each single fraction of microparticles suggests that a diffusive mechanism governs drug release from microparticles. Thus, we proposed and applied a release kinetic model to the experimental data that takes into account the diffusion as the predominantly mechanism of drug release. The model proposed is a modified version of the exponential equation in which the product of the apparent release rate constant K, specific for each drug/excipient mixture, and the area-to-volume ratio of particles was used.

The K values of single fractions of HAC microparticles (coded K_{fr}) are very similar to those of the mixtures of particles obtained from the process (coded K_{pool}). Using the K_{pool} constants, the release behaviour of ensembles of different size microparticles of well-known composition was predicted. The strength of the model was proved by the good fitting of the experimental release data versus those predicted ($R^2 \geq 0.997$).

Keywords: Propafenone; Hot Air Coating; Microparticles; Release mechanism; Mathematical modelling

1. Introduction

In previous works, an innovative spray technology (Hot Air Coating) for the production of microparticles was proposed to overcome the disadvantages of conventional spray congealing technique, such as the difficulty of atomizing highly viscous and concentrated systems (Rodriguez et al., 2004; Giovannelli et al., 2005). Briefly, a mixture of solid components is forced to pass, under defined operating conditions, through a specific apparatus where the material is heated to form microparticles, which then cool during falling. To be good candidates for the Hot Air Coating (HAC) treatment, both drug and excipient must be characterized by different melting points, in particular the excipient must melt at lower temperature than the drug. In this way, the melted excipient is able to form a thin continuous solid coat around the drug particles. The active molecule is in the solid state during and even after the HAC process and its chemical and physico-chemical characteristics are not modified by the production process. The product is characterized by rounded form, smooth surface and high drug content (up to 70%, w/w); in addition the HAC microparticles are able to modify the drug release as a function of the carrier used (Pattarino et al., 2007).

In this work, lipid microparticles containing propafenone hydrochloride as the active molecule and a mixture of cetearyl alcohol and Pluronic® F68 as excipients were prepared using the HAC technique.

Propafenone is used as treatment for ventricular and supraventricular arrhythmias; it has a pronounced inhibitory effect on the fast sodium channel and a weak β-blocking effect. The daily dosing regimen recommends three oral administrations with single doses from 150 to 300 mg; this therapeutic plan reduces but does not eliminate completely the peak variations in plasma concentrations that may favour the occurrence of side effects and breakthrough paroxysms of atrial fibrillation (Giani et al., 1988). Therefore, the attention of the researchers is directed at the study and development of propafenone for-

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mulations that through the control of the drug release reduce the side effects, minimize plasma concentration fluctuations and maintain the drug levels within the desired range, increase patient compliance and improve the efficacy and safety of the therapy (Pritchett et al., 2003). Microparticulate drug delivery systems could be a good tool to achieve these important objectives. The kinetics and the mechanism of the propafenone release process from HAC microparticulate systems were evaluated.

In the literature it has been reported that the drug release behaviour of a mixture, constituted of microparticles of various size ranges, results from the contribution of each individual fraction of particles (Narayani and Panduranga Rao, 1996; Grassi et al., 2003). Starting from this consideration, the purpose of the work was to find an adequate empirical mathematical model able to predict the release behaviour of mixtures of propafenone-loaded microparticles.

2. Materials and methods

2.1. Materials

Cetearyl alcohol (an aliphatic alcohol consisting mainly of stearyl and cetyl alcohols), conforming to EP 5, was purchased from ACEF Spa (Piacenza, Italy); Pluronic® F68 was supplied by Sigma (St. Louis, MO, USA) and propafenone hydrochloride (PRF) was kindly provided by Procos Spa (Cameri, NO, Italy).

All other chemicals and reagents were of analytical grade.

2.2. Methods

2.2.1. Preparation of microparticles by Hot Air Coating

Microparticles composed of cetearyl alcohol and Pluronic® F68 as the carrier and propafenone hydrochloride as the active molecule were prepared by HAC. HAC is a technological process able to produce microparticles starting from a mixture of solid components (Rodriguez et al., 2004; Giovannelli et al., 2005), which are aspirated into the HAC apparatus by the Venturi effect, accelerated in a flux of hot air and immediately returned to room temperature. Air temperature is almost 20 °C higher than the melting point of the excipient, thus the excipient melts and surrounds the drug particles forming a continuous solid coat. The composition (in particular the percentage of the excipient) and particle size of the starting material are critical elements in the selection of the optimal operating conditions (temperature and pressure).

Cetearyl alcohol and Pluronic® F68 (99:1, w/w) were mixed and melted at 60 °C. The molten mass was carried back to the solid state, milled and sieved and the fraction between 150 and 212 μm was blended with the drug, whose particle dimensions are about 75 μm. This mixture was then subjected to the HAC treatment.

In particular, two formulations with the same qualitative composition but two different drug contents were examined in this work: the first formulation contained 30% (w/w) drug (Mix OBT-30) and the second 50% (w/w) (Mix OBT-50). Air temperature and pressure were set at 91 °C and 1.75 bar respectively in the case of the formulation containing 30% drug and at 86 °C and 2.25 bar in the case of 50% drug formulation.

2.2.2. Characterization of microparticles

Once prepared, HAC microparticles were collected and separated through a set of standard sieves with apertures from 75 to 710 μm. Microparticles with dimensions smaller than 75 μm or larger than 710 μm, representing less than 10% of the total material produced, were excluded. Thus, in this study, only five size fractions were considered (fr1: 75–150 μm, fr2: 150–212 μm, fr3: 212–355 μm, fr4: 355–500 μm and fr5: 500–710 μm); the sieved fractions were individually weighed and the granulometric distribution was determined. The average diameter of each individual fraction of PRF microparticles was determined using a laser diffraction particle size analyzer (LS 32 Beckman Coulter, USA).

The drug content of the two batches of microparticles (Mix OBT-30 and Mix OBT-50) was determined: 7 and 5 mg, respectively of microparticles were dissolved in 25 mL of methanol, filtered, assayed spectrophotometrically (PerkinElmer, Lambda 35) at 250 nm and the percentage of drug loading was calculated.

Optical and scanning electron microscopy was used to investigate the shape and the morphology of the microparticles. A stereomicroscope (Seneco, Motic SMZ168 TL) equipped with a camera (Seneco, Motic MC2000) connected to an image analysis software (Seneco, Motic Image Plus, Ver. 2.0 ML) was used to carry out a preliminary evaluation of the microparticles morphology. SEM photographs were taken with a Tabletop Microscope TM-1000 (Hitachi, High-Technologies Corporation) at the required magnification before and after the release tests.

2.2.3. In vitro drug release studies

In vitro drug release studies were performed on PRF microparticles at 37 °C in 500 mL of deionised water, using a slightly modified USP dissolution apparatus 1 (basket) operating at 150 rpm (Sotax, AT7 Smart). The baskets were coated internally with a nylon gauze to allow the microparticles to come into contact with the dissolution fluid but, at the same time, to avoid particles escaping from the baskets and floating on the dissolution medium (Ganza-González et al., 1999). Accurately weighed amount of microparticles, equivalent to 35 mg of PRF, were put into the vessel; at pre-determined time intervals, 5 mL samples were withdrawn (replaced with fresh medium) and analysed spectrophotometrically at 250 nm (PerkinElmer, Lambda 35). The drug release tests were conducted on each single size fraction of microparticles and, for both formulations, on two different mixtures of microparticles, the first composed of the five size fractions in the same proportion obtained by the HAC process (Mix OBT-30 and Mix OBT-50) (Table 1) and the second constituted by a selected and pre-defined composition of particles (Mix SEL-30 and Mix SEL-50) (Table 2). All the experiments were carried out in triplicate.

2.2.4. Mathematical modelling of drug release data

The study of the PRF release from HAC microparticulate systems and the elucidation of the mechanism governing this

Table 1
Proportion (w/w) (ϕ_j), average diameter (d_j) and drug loading of single fractions of HAC microparticles

Size fraction	Mix OBT-30			Mix OBT-50		
	ϕ_j	d_j (mm)	Drug loading (%)	ϕ_j	d_j (mm)	Drug loading (%)
fr1 (75–150)	0.277	0.0967 ± 0.0326	30.64 ± 2.37	0.177	0.1325 ± 0.0273	45.87 ± 3.89
fr2 (150–212)	0.315	0.1653 ± 0.0416	35.24 ± 2.64	0.308	0.1778 ± 0.0457	52.54 ± 3.17
fr3 (212–355)	0.270	0.2796 ± 0.0678	35.16 ± 2.59	0.366	0.2940 ± 0.0550	53.18 ± 2.97
fr4 (355–500)	0.097	0.4258 ± 0.0539	32.19 ± 1.99	0.118	0.4785 ± 0.1140	46.20 ± 3.18
fr5 (500–710)	0.041	0.6722 ± 0.0500	32.69 ± 1.89	0.031	0.6952 ± 0.1403	50.56 ± 2.18

Table 2
Proportion (w/w) (ϕ_j) of the single fractions included in the mixture constituted of a selected and pre-defined composition of particles

Size fraction	Mix SEL-30 (ϕ_j)	Mix SEL-50 (ϕ_j)
fr1 (75–150)	0.700	0.500
fr2 (150–212)	0.180	0.400
fr1 (212–355)	0.100	0.050
fr1 (355–500)	0.020	0.040
fr1 (500–710)	–	0.010

process were carried out on the basis of the results obtained in a previous work on HAC and nifedipine (Giovannelli et al., 2005). In particular, it was demonstrated that the dimension of HAC microparticles was not substantially modified after the release experiments; the kinetic study suggested that nifedipine was primarily released by diffusion as indicated by the values of the Weibull parameters. For this reason, in the present work the Weibull function and the exponential model (Costa and Sousa Lobo, 2001; Papadopoulou et al., 2006; Dokoumetzidis et al., 2006) were chosen to describe the release behaviour of propafenone formulations. To obtain general information about the PRF release mechanism, the Weibull function was applied to the single fraction release data:

$$\left(\frac{M_t}{M_\infty}\right)_j = 1 - \mathrm{e}^{-a_j t^{b_j}} \tag{1}$$

where M_t is the amount of drug release at time t, M_∞ is the amount of drug released at infinite time, a_j is the scale parameter which defines the time scale of the process for the j fraction and b_j is the shape parameter that characterizes the shape of the release curve of the j fraction ($b = 1$ if the release curve is exponential, $b > 1$ if the curve is sigmoidal in shape and $b < 1$ if it is parabolic).

Considering that the total amount of drug released from microparticles is lower than the amount of drug in solution at the saturation point, the exponential kinetic model was also applied to the experimental data. For M_t/M_∞ values lower than 1, the equation used was:

$$\left(\frac{M_t}{M_\infty}\right)_j = 1 - \mathrm{e}^{-k_j t} \tag{2}$$

where k_j is the release rate constant of the j fraction.

In the literature it has been reported that the drug release performance of a mixture constituted of microparticles of various size ranges is different from that of every single fraction included in it and is the result of the combination of the contribution of each individual fraction (Narayani and Panduranga Rao, 1996; Grassi et al., 2003). Based on this last finding, an empirical mathematical model, able to describe the release behaviour of a mixture of different size lipid microparticles obtained by HAC process, is proposed. It is a modified version of the exponential kinetic equation that takes into account the proportion of each single fraction of microparticles included in the mixture and the release rate constant (k_j) of each dimensional class (j). The drug fraction released is related to time by the following empirical equation:

$$\frac{M_t}{M_\infty} = 1 - \phi_1 \mathrm{e}^{-k_1 t} - \phi_2 \mathrm{e}^{-k_2 t} - \cdots - \phi_n \mathrm{e}^{-k_n t} = 1 - \sum_{j=1}^{n} \phi_j e^{-k_j t} \tag{3}$$

where ϕ_j is the proportion of the j fraction in the mixture.

It seems reasonable that the k_j value is affected by the dimension of the particles of the j fraction, the particle surface available for drug release and the diffusive pathway. For this reason, it is possible to write k_j as the product of a constant, coded K, and the area-to-volume ratio of each fraction of particles ($k_j = K(3/r_j)$). The value of K constant will be the same for all the fractions included in the mixture.

Considering this assumption, Eq. (2) can be rewritten as:

$$\left(\frac{M_t}{M_\infty}\right)_j = 1 - \mathrm{e}^{-3Kt/r_j} \tag{4}$$

Therefore Eq. (3) becomes:

$$\frac{M_t}{M_\infty} = 1 - \phi_1 \mathrm{e}^{-3Kt/r_1} - \phi_2 \mathrm{e}^{-3Kt/r_1} - \cdots - \phi_i \mathrm{e}^{-3Kt/r_n} = 1 - \sum_{j=1}^{n} \phi_j \mathrm{e}^{-3Kt/r_j} \tag{5}$$

where K is the normalized apparent release rate constant and $3/r_j$ is the area-to-volume ratio for the j fraction.

The regression analyses were carried out both with the Weibull (Eq. (1)) and the exponential models (Eqs. (4) and (5)) using a non-linear cross-validated regression method and a package written with R 2.3.1 (The R Development Core Team). The K_{fr} values were calculated applying the Eq. (4) to the release data from each single fraction and K_{pool} values were obtained both for Mix OBT-30 and Mix OBT-50 applying the Eq. (5) to the respective release data.

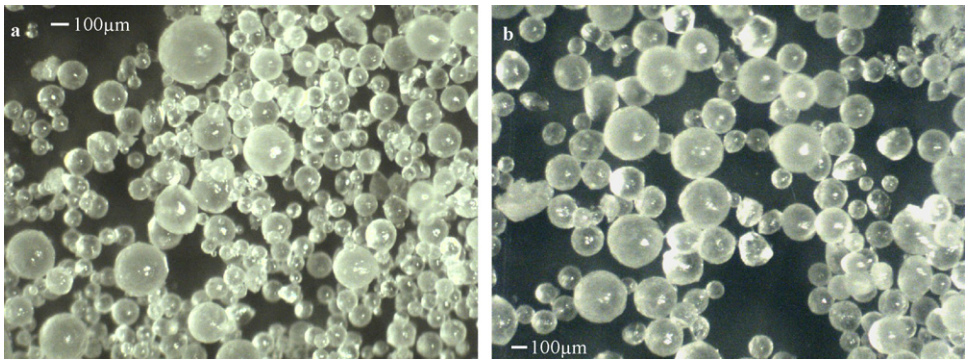

Fig. 1. Optical photographs of PRF-loaded HAC microparticles. (a) Mix OBT-30 and (b) Mix OBT-50.

3. Results and discussion

Lipid microparticles containing 30% or 50% (w/w) propafenone hydrochloride were obtained by the HAC technique: they are characterized by spherical shape and different dimensions (Fig. 1). The SEM image (Fig. 2a–b) shows that HAC microparticles have a regular, non-porous surface, characterized by the presence of some protuberances, probably due to PRF crystals embedded into the external layer. This micrograph suggests that the active molecule is almost totally included into the microparticulate system.

The granulometric distribution (ϕ_j) and the particle size of Mix OBT-30 and Mix OBT-50 microparticles are reported in Table 1. In both formulations, more than 80% of microparticles are in the size range 75–355 μm. In particular, for the Mix OBT-30 batch a large proportion of the microparticles is homogeneously distributed into the first three fractions (fr1, fr2 and fr3), while for the Mix OBT-50 formulation fr2 and fr3 portions are the richest dimensional classes.

The mean radius value of each fraction (r_j), obtained by laser diffraction analysis, was used in the application of the empirical mathematical model proposed.

Moreover, Table 1 shows the PRF content of each dimensional class of particles: for the two formulations, the drug loading of the mixtures of microparticles (Mix OBT 30 and Mix OBT-50) is very high and, above all, approaches the theoretical

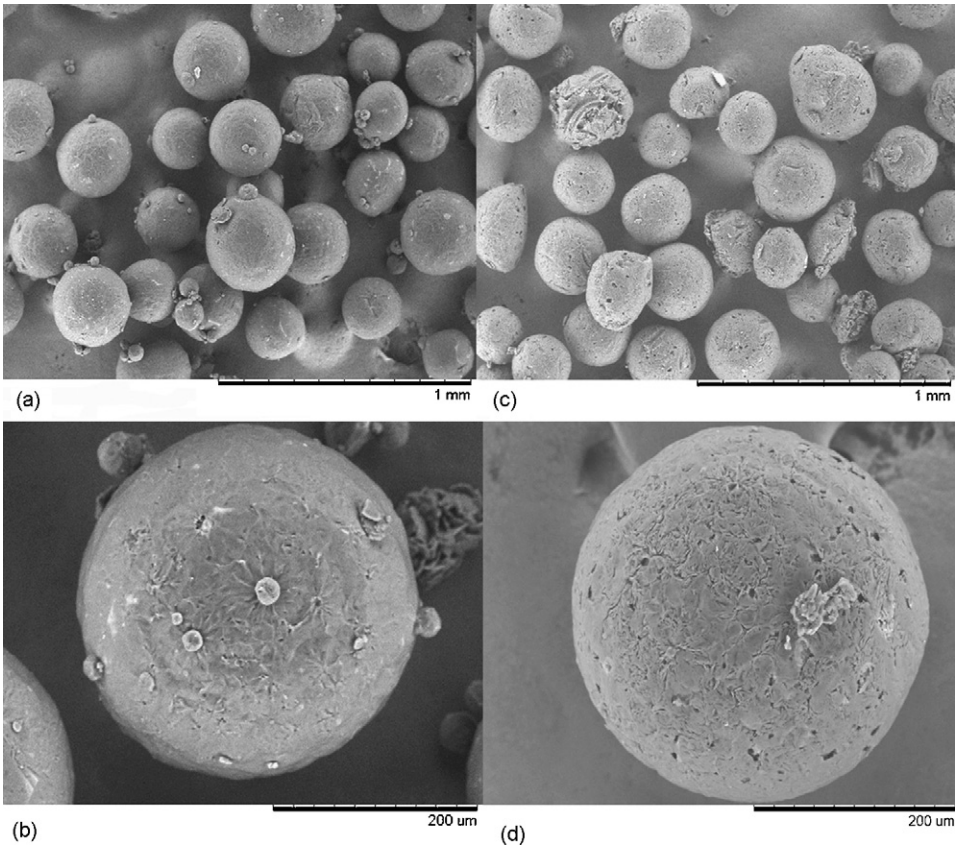

Fig. 2. SEM pictures of Mix OBT-30 microparticles obtained by HAC technique before (a, b) and after (c, d) the drug release test.

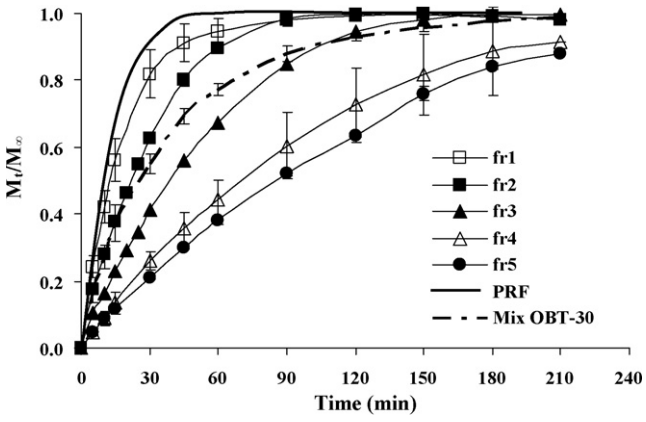

Fig. 3. *In vitro* propafenone release profiles from each size fraction of Mix OBT-30 microparticles and from the mixture of all of the fractions. As a reference, the dissolution curve of the free drug is reported.

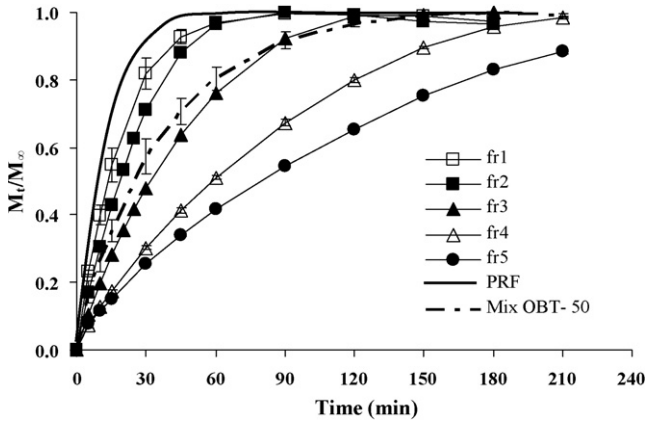

Fig. 4. *In vitro* propafenone release profiles from each size fraction of Mix OBT-50 microparticles and from the mixture of all of the fractions. As a reference, the dissolution curve of the free drug is reported.

value. In particular, the drug content is 32.67% ± 2.18 for Mix OBT-30 and 50.22 ± 3.25 for Mix OBT-50. In the case of the drug content of the single size fractions, there are small but not substantial differences compared to the theoretical values. This testifies the good entrapment efficiency obtained by the HAC manufacturing process.

To get information about the kinetics and mechanism that govern the drug release process from these microparticles, the PRF release profiles were constructed; the drug release test was performed for both formulations on each size fraction and on the unfractionated mixtures (Mix OBT-30 and Mix OBT-50), and the results are illustrated in Figs. 3 and 4. All of the release curves obtained are concave downward and no significant burst effect is present in accordance with the presence of a small number of PRF crystals in the external layer of the shell. Thus, the absence of a burst release and the results of microscopic analysis indicate that HAC microparticles are microcapsules, that is, systems in which there is an internal core composed of the active molecule and a coating layer constituted of the lipid excipient.

It is well known that the drug release performance can be influenced by the physico-chemical characteristics of microparticles, by the formulation composition and manufacturing process (production method and operating conditions) (Bhardwaj et al., 1995; Karasulu et al., 2003; Haznedar and Dortunç, 2004). In particular, the size of microparticles is one of the most critical factors affecting drug release rate (Bezemer et al., 2000; Berkland et al., 2002; Berkland et al., 2003; Siepmann et al., 2004). For both formulations, the fractions constituted of large particles exhibit slower drug release compared to small particle fractions. This is expected due to the decrease in surface-to-volume ratio with increasing size.

The mixtures consisting of all the size fractions, both Mix OBT-30 and Mix OBT-50, show a release profile characterized by an intermediate trend compared to those of the individual size fractions (Figs. 3 and 4) and this could be due to the different size of the particles included in the mixture.

As exemplified by the SEM image of the Mix OBT-30 system (Fig. 2), microparticles are unbroken after contact with the dissolution fluid and their shape appears unmodified (Fig. 2, c and d) compared to that of particles before the release test (Fig. 2, a and b). Moreover the particle dimension is unchanged even if, on the external layer of the shell, some minute openings due to the solubilization of the PRF crystals can be observed.

On the basis of these findings, the release data from each single size fraction of the two batches were analysed by the Weibull function to acquire general information about the PRF release mechanism. Applying the Weibull model to each fraction of both formulations, values of the b_j parameter close to 1 were obtained (Table 3), indicating that, in all the considered cases, the shape of the release curves is exponential and the drug release follows a diffusive mechanism. Moreover, the values of the a_j parameter, related to the rate of the release process, decrease with increasing particle dimension.

The use of the Weibull model for the description of the release profiles is often criticized because of the lack of kinetic basis and for the non-physical nature of its parameters (Dokoumetzidis et

Table 3
Weibull model parameters (b_j, a_j) for drug release from each single size fraction of propafenone-loaded HAC microparticles (statistical significance of the coefficients: $p < 10^{-7}$)

Size fraction	Mix OBT-30		Mix OBT-50	
	b_j	a_j	b_j	a_j
fr1 (75–150)	1.0372 ± 0.0211	0.0551 ± 0.0032	1.0634 ± 0.0314	0.0451 ± 0.0041
fr2 (150–212)	1.0781 ± 0.0236	0.0259 ± 0.0020	1.1627 ± 0.0435	0.0242 ± 0.0033
fr3 (212–355)	1.1201 ± 0.0276	0.0120 ± 0.0012	1.1120 ± 0.0319	0.0154 ± 0.0018
fr4 (355–500)	1.1830 ± 0.0380	0.0055 ± 0.0009	1.1127 ± 0.0238	0.0077 ± 0.0008
fr5 (500–710)	1.1412 ± 0.0332	0.0046 ± 0.0007	1.0480 ± 0.0288	0.0077 ± 0.0010

Table 4
Average radius (r_i) and normalized apparent release rate constant (K_{fr}) of each single size fraction of HAC PRF microparticles

Size fraction	r_j (mm)	K_{fr} (mm min^{-1}) $\times 10^{-4}$	R^2
Mix OBT-30			
fr1 (75–150)	0.0486	9.836 ± 0.139	0.9973
fr2 (150–212)	0.0827	9.217 ± 0,149	0.9948
fr3 (212–355)	0.1398	8.811 ± 0.182	0.9927
fr4 (355–500)	0.2129	8.636 ± 0.258	0.9875
fr5 (500–710)	0.3361	9.885 ± 0.214	0.9899
		$\bar{K}_{fr}$ 9.277 ± 0.188	
Mix OBT-50			
fr1 (75–150)	0.0663	11.381 ± 0.239	0.9948
fr2 (150–212)	0.0889	11.948 ± 0.040	0.9943
fr3 (212–355)	0.1470	11.361 ± 0.283	0.9967
fr4 (355–500)	0.2393	10.514 ± 0.181	0.9931
fr5 (500–710)	0.3476	11.189 ± 0.175	0.9937
		$\bar{K}_{fr}$ 11.279 ± 0.184	

al., 2006). For this reason and to confirm the suggestions from the Weibull model, the exponential kinetic equation (Eq. (2)) was fitted to experimental data (results not reported); the successful fittings obtained proved that a diffusive mechanism is mostly involved in the drug release from HAC microparticles.

The experimental release data from each single fraction of microparticles were then fitted to the mathematical model proposed (Eq. (4)) and the normalized apparent release rate constants (K_{fr}) were calculated (Table 4). It has to be noted that K_{fr} has a very similar value for all of the fractions: the different release pathway, that depends on the coating thickness and on the amount of propafenone in microparticles, accounts for the slight discrepancy in the K_{fr} values obtained for the two formulations.

The empirical model proposed in the Eq. (5) was applied to the experimental release data from the mixtures consisting of all the five size fractions (Mix OBT-30 and Mix OBT-50). The values of the normalized apparent release rate constant (K_{pool}) were determined: $(9.115 \pm 0.152) \times 10^{-4}$ mm min^{-1} for Mix OBT-30 and $(11.515 \pm 0.274) \times 10^{-4}$ mm min^{-1} for Mix OBT-50. The fitting of the model was extremely good for both the formulations ($R^2 = 0.999$ for Mix OBT-30 and $R^2 = 0.998$ for Mix OBT-50). The K_{pool} values are not statistically different from the average of the release rate constants ($\bar{K}_{fr}$) obtained from the analysis of single fraction data. These findings confirm the strength of the model and the presence of a mostly diffusive release mechanism; moreover they support the proposition done by other authors (Narayani and Panduranga Rao, 1996; Grassi et al., 2003) that the release of a drug from microparticulate systems is due to the additive contribution of each dimensional class of particles.

To verify the predictive ability of the mathematical model, two formulations with a pre-defined composition of microparticles (Mix SEL-30 and Mix SEL-50, Table 2) were submitted to the release test and their release profiles were constructed. The release behaviour of these two mixtures was also predicted using Eq. (5), in which the above determined K_{pool} values (9.115×10^{-4} mm min^{-1} for 30% mixture and 11.515×10^{-4} mm min^{-1} for 50% mixture) and the average

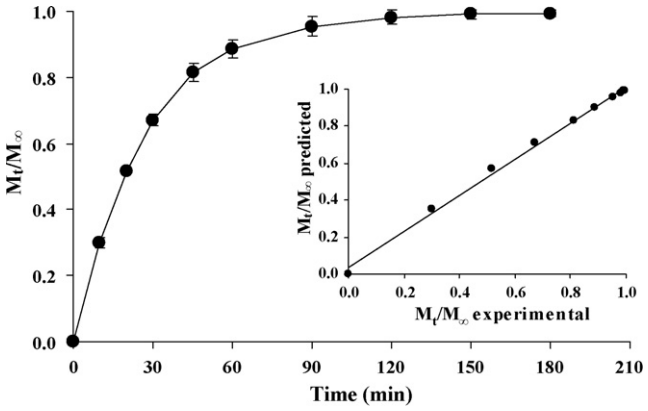

Fig. 5. Propafenone release profile and predicted vs. experimental correlation plot (small panel) of Mix SEL-30.

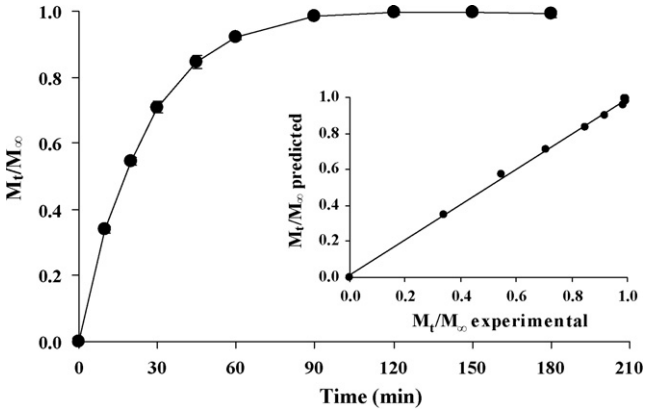

Fig. 6. Propafenone release profile and predicted vs. experimental correlation plot (small panel) of Mix SEL-50.

radius (r_j) of each single fraction (Table 4) were introduced. Figs. 5 and 6 report the experimental release curves obtained for Mix SEL-30 and Mix SEL-50 respectively: the fitting of the experimental versus predicted data is totally satisfactory (R^2 Mix SEL-30 = 0.997 and R^2 Mix SEL-50 = 0.999) and establishes the capability of the model to adequately describe the PRF release process.

4. Conclusions

Hot Air Coating proves to be a good technique to produce lipid microparticles with spherical shape, smooth surface and high drug content. The rate of propafenone release from the investigated Mix OBT-30 and Mix OBT-50 HAC microparticles is affected by drug loading and by the dimensions of the microparticles. The drug release process is mostly controlled by diffusion; in fact, for both formulations, a successful fitting was obtained when the exponential kinetic equation was applied to the experimental release data from the single dimensional class of particles.

An empirical mathematical model able to describe the release behaviour of a mixture of microparticles of different sizes was proposed and validated. This model allows the prediction of the release from an ensemble of microparticles of specific and well-

known composition. The results of the present work represent a good starting point to future development of HAC microparticles as controlled release propafenone delivery system.

The capability of the model to describe the release behaviour of a specific mixture of microparticles is extremely good and this finding leads us to consider the applied model as a valuable tool for the selection of appropriate mixtures able to generate precise and desired drug release profiles.

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