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Preparation and *in vitro/in vivo* characterisation of a melt pelletised paracetamol/stearic acid sustained release delivery system

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Abstract. The potential of a sustained release formulation for paracetamol produced by melt pelletisation was investigated. After the production of the pellets, based on the combination of stearic acid as a melting binder and anhydrous lactose as a filler, the 3000–2000 μm size fraction was selected in the light of the promising *in vitro* dissolution results for further characterisations, including scanning electron microscopy (SEM), X-ray photoelectron spectroscopy (XPS), specific surface area and true density determination. Hence the release mechanism was analysed with the help of an appropriate mathematical model. The mathematical model was built on the hypotheses that drug diffusion and solid drug dissolution in the release environment are the key phenomena affecting drug release kinetics. Bioavailability of the developed formulation was evaluated in an *in vivo* study in eight subjects.

Keywords: Melt pelletisation, high shear mixer, paracetamol, sustained release, *in vitro* dissolution, modelling of drug-release mechanism, *in vivo* bioavailability studies

1. Introduction

The widely-used antipyretic analgesic paracetamol is normally administered in doses of 0.5 to 1 g every 3 to 4 hours. Blood levels of 10–20 μg/ml are achieved by rapid and complete release from an oral dosage form which give an effective analgesic action. Paracetamol is rapidly absorbed reaching a peak concentration in approximately 1 hour post dosing, from solutions as well as from well-formulated tablets [1]. However the absorption is incomplete, since a variable proportion, depending on the dose administered is lost through first pass hepatic metabolism. The frequency of dosing suggests that there

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is a case for developing a sustained release oral formulation tending to reduce peaks while increasing troughs compared to more frequent administration of immediate release formulations. Such an approach has been attempted by several formulation strategies. Many authors set out to achieve slow-release of paracetamol by preparing tablets or pellets: producing slow-releasing tablets combining an appropriate slow-release core with a rapid-releasing coating [2], preparing dry-coated tablets [3] or using a protein (ovoalbumin) as matrix system for oral administration [4] or coating pellets with ethyl cellulose [5,6].

Alternative methods were suggested to promote a sustained release of the drug without a coating procedure. Extended-release matrices were prepared by incorporation of the drug and some lipophilic release-modifiers (such as cetyl alcohol and paraffin) into porous cellulose matrices [7] using a simple melt method. Stella et al. [8] reported a method of preparing soft capsules and chewable gums of the hydrophobic wheat protein, crude gliadin, showing significant paracetamol controlled-release potency. Finally, Thomsen and co-workers [9,10] revealed the possibility of preparing prolonged release matrix pellets by melt pelletisation in high shear mixer, based on the combination of several hydrophobic substances as melting binders.

The objective of this work was to develop a sustained release device for paracetamol, producing in a single step, a pelletised formulation in a 10 l high shear mixer. This formulation is based on the experience acquired in a previous work dealing with the application of experimental design analysis on the evaluation of the effect of some apparatus and process variables on the final product [11]. Accordingly, the best operation conditions for the production of a combination of stearic acid, lactose and paracetamol pellets were chosen. The pellets have been characterised from the technological and the dissolution point of view. Further, a theoretical investigation on the mechanism regulating drug release from such delivery system has been carried out [12]. In this part of the research, the attention is focused on the production and subsequent *in vitro*/*in vivo* characterisation of the 3000–2000 μm pellet size fraction, which in the previous work [12] exhibited the desired sustained release of the drug. Considering paracetamol pharmacokinetic properties: short biological half-life (2–3 hours), volume of distribution (1 l/kg) and absolute bioavailability (70%) [4] it was anticipated that 1 g dose of this size fraction administered perorally would give a maximum plasma concentration of 6.5 mg/l about 2.5 hours after administration. Moreover, plasma concentrations above 2 mg/l would be maintained up to 8 hours. Pharmacokinetic simulation of the multiple dosing revealed that peaks of 15 mg/l and troughs of 5 mg/l would be reached when a dose of 2 g would be given every 8 hours (Fig. 1).

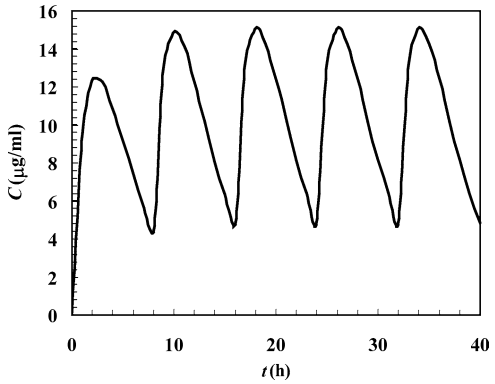

Fig. 1. Simulated plasma concentration time profile after multiple dosing of controled release formulation of paracetamol (2 g) every 8 hours.

Many studies considering paracetamol pharmacokinetics and pharmacodynamics have demonstrated that prolonged maximum antipyretic and analgesic effects are expected as long as plasma concentration is kept above 5 mg/l [4]. It was therefore expected that the developed paracetamol sustained release delivery system could improve long-term therapy.

2. Materials and methods

2.1. Materials

Paracetamol reagent-grade (ACEF, Fiorenzuola D'Arda, Piacenza, Italy), stearic acid reagent-grade (Galeno, Milano, Italy), and monohydrate lactose (Pharmatose 200 mesh, Meggle, Wasserburg, Germany) were used as starting materials and were used as received. The mean diameter ($\pm$SD) of paracetamol, determined by microscopical analysis technique as previously reported by Voinovich et al. [11], is 56 ($\pm$18) μm, while it is for lactose 16 ($\pm$11.3) μm. The melting temperature of stearic acid and PEG 6000 were estimated using the procedure described by Grassi et al. [12], 58.3°C and 65.0°C, respectively.

2.2. Granulation manufacture

The granules were prepared in the 10 l laboratory scale Zanchetta Roto J high shear mixer equipped with an electrically heated jacket (maximum temperature 100°C), already described in a previous work [13]. The temperature of the powders contained in the bowl were constantly recorded by a thermoresistance probe fixed on the bowl lid and dipped in the powder mass.

The granulation procedure was standardised on the basis of both the preliminary trials and the methodology already applied in the pelletisation of mixtures based on the combination of stearic acid and lactose [11,14]. The composition of the mixtures, totally weighing 1 kg, was paracetamol/lactose/stearic acid: 60/20/20 w/w. Paracetamol and lactose were first mixed at an impeller speed of 50 rpm while heating (using an impeller blade having an inclination angle of 30°), until their temperature had reached 55°C. The dry mixing was interrupted to add the stearic acid, and then re-started for 3 min at 100 rpm to obtain a uniform distribution of the binder. At this point, the stearic acid reached a molten state (the temperature was around 65°C). During the subsequent massing process, the impeller speed was kept constant at 289 rpm for 8 min (massing time). At the end of the granulation process the granules were cooled at room temperature by spreading them out in thin layers on trays and then stored in sealed bags for 10 days before characterisation.

2.3. Granule characterisation

The granule size fraction 3000–2000 μm was selected by sieving (vibrating apparatus Octagon 200, Endecotts, London, UK) for further characterisations and processing.

The analysis of paracetamol content was carried out, in triplicate analysis, by dissolving 100 mg of granules in 250 ml of freshly distilled water and then assaying the amount of drug spectrophotometrically (Perkin Elmer Spectrophotometer Mod. 552, Norwalk, USA) at 245 nm.

The shape and surface characteristics of the granules were observed by SEM analysis (model 500, Philips, Eindhoven, The Netherlands) using the secondary electron technique, as previously reported by Voinovich et al. [14].

The specific surface area of pellets, calculated according to the Rootare–Prenzlow equation [15], was determined with a mercury porosimeter (Autopore III 9420 system, Micrometrics Instrum. Corp., Norcross, GA, USA) following the procedure cited by Grassi et al. [12].

True density measurements were carried out in triplicate experiments in a helium pycnometer (Multipycnometer, Quantachrome Corp. Boynton Beach, USA) using a 35 cm^3 cell calibrated with a steel sphere.

The XPS measurements were performed in a ultra high vacuum chamber working at a base pressure of $\approx 1 \times 10^{-7}$ mbar, equipped with a conventional Mg-anode X-ray source (Physical Electronics, Eden Prairie, US, Mod. 20 095) ($h\nu = 1253.6$ eV) and a double pass Cylindrical Mirror Analyzer (PHI Physical Electronics, Eden Prairie, US, Mod. 15-255g). The samples were prepared by pressing a suitable amount of pellets onto foils of pure tantalum (99.999% purity, Goodfellow, Huntingdon, UK). The C1s, N1s and O1s concentrations were calculated from the areas of the XPS measured spectra as previously reported by Grassi et al. [12].

Paracetamol release profiles from the granulates were obtained according to USP 25 basket method (Mod. DT-1, Erweka, Heusenstamm, Germany): stirring rate of 100 rpm, temperature at 37 $\pm$ 0.1°C, 900 ml of dissolution media (pH 1.2 buffer: 0.2 M NaCl/0.2 M HCl or pH 7.4 buffer: 0.2 M KH_2PO_4/0.2 M NaOH), sink condition ($C < 0.2C_s$). Samples of 5 ml were extracted at regular time intervals (from 0.25 to 8 h), filtered and assayed spectrophotometrically at 245 nm, withdrawing the aliquot for analysis and immediately replacing it with an equal volume of fresh dissolution medium at the same temperature. The carriers did not interfere with the UV analysis. The experiments were carried out in triplicate and the SD was within 5% of mean value.

2.4. Modelling of drug release mechanism

The complexity of the developing topology (e.g., changing porosity) makes any attempt of a detailed matrix description in terms of Euclidean geometry meaningless. A fractal approach could be useful to this purpose, but it would result in a considerable complication when writing the equation ruling mass transfer [16]. Consequently, we assume that the soluble compound instantaneously dissolves and that the topology of matrix channels is not affected by drug dissolution. Moreover, although we are clearly dealing with an inhomogeneous system as drug molecules diffuse only inside the fluid filling the channels and no drug transport occurs through the insoluble channel walls, matrix homogeneity is assumed. This, of course, obliges to define an effective drug diffusion coefficient D_e characterising drug molecules motion in the matrix [17]. Additionally, we assume that matrix density does not vary due to diffusion, that we are dealing with perfectly spherical particles characterised by a determined particle size distribution and that neither erosion nor swelling affect the matrix. Although, in principle, particles are surrounded by a stagnant layer – its thickness depending on the hydrodynamic conditions imposed on the release environment-hindering drug diffusion into the dissolution medium, we assume that this resistance is negligible in comparison with drug dissolution and diffusion inside the matrix.

On the basis of these hypotheses, and supposing to deal with a poly-disperse particles system, the overall drug release process can be schematically represented by the following equations:

$$\frac{\partial C_j}{\partial t} = \frac{1}{R_j^2}\frac{\partial}{\partial R_j}\left[D_e \frac{\partial C_j}{\partial R_j} R_j^2\right] - \frac{\partial C_{dj}}{\partial t}, \quad j = 1, 2, \ldots, N_c, \tag{1}$$

$$\frac{\partial C_{dj}}{\partial t} = -K_t(C_s - C_j), \qquad j = 1, 2, \ldots, N_c, \tag{2}$$

where t is time, N_c is the number of classes in which the particle size distribution can be subdivided, C_j and C_{dj} are, respectively, the concentrations of the dissolved and not-dissolved drug fractions inside the particles of the jth class at R_j (radial co-ordinate), K_t is the dissolution constant and C_s is the drug solubility in the release fluid. Equation (1) represents the drug mass balance referred to the jth particle class, while Eq. (2) states that dissolution contribution disappears when C_j is equal to C_s or when C_{dj} vanishes [18–20].

Equation (1) has to be numerically solved (control volume method [21]) with the following initial conditions:

$$C_r = 0, \tag{3}$$

$$C_j(R_j) = 0, \qquad 0 < R_j < R_{pj}, \quad j = 1, 2, \ldots, N_c, \tag{4}$$

$$C_{dj}(R_j) = C_{d0}, \quad 0 < R_j < R_{pj}, \quad j = 1, 2, \ldots, N_c \tag{5}$$

and boundary conditions:

$$\frac{\partial C_j}{\partial R_j} = 0, \qquad R_j = 0, \qquad j = 1, 2, \ldots, N_c, \tag{6}$$

$$C_r = \frac{C_j}{K_p}, \quad R_j = R_{pj}, \quad j = 1, 2, \ldots, N_c, \tag{7}$$

$$M_0 = V_r C_r + \sum_{j=1}^{N_c} n_j \int_0^{R_{pj}} \left[C_j(R_j) + C_{dj}(R_j)\right] 4\pi R_j^2 \, \mathrm{d}R_j, \tag{8}$$

where n_j and R_{pj} are, respectively, the number and the radius of the particles belonging to the jth class, C_{d0} is the initial not-dissolved drug concentration, C_r is the drug concentration in the release environment, K_p is the drug partition coefficient, M_0 is the drug amount initially present in all the particles and V_r is the volume of the release environment.

Equation (7) ensures the partitioning condition at the particle/dissolution medium interface whereas the total drug mass balance made up on the release environment and on the particles is given by Eq. (8). Such an equation substitutes the most usual flux condition at the particle/release environment interface [22], thus ensuring a more reliable and safe numerical solution for the model [23].

3. *In vivo* studies

Eight healthy volunteers, four males and four females, aged between 22 and 45 years (mean age 35.75 years) and weighing 43–105 kg (mean weight 77.63 kg) participated in this single dose cross-over study. Written informed consent was signed by each participating subject. All the volunteers had normal hepatic and renal function and were asked not to take any drugs 1 week and to fast 12 h before capsule administration. They were also not allowed to smoke, nor to take coffee or alcoholic beverages 12 h before and 48 h after drug administration. The subjects were all given a standard lunch 3.5 h after the dosing, and were allowed to drink water during the treatment period.

To verify the bioavailability, the 2000 μm size fraction pellets were inserted in a hard gelatine capsule to get a paracetamol dose of 1 g. As a reference, an Italian marketed formulation containing paracetamol (Tachipirina® tablets, Angelini, Italy – 2 tablets corresponds to 1 g) was used.

Blood samples (5 ml) were drawn at 0, 0.5, 1, 2, 3, 4, 6, 9, 12 and 24 hours following capsule administration. Each sample was collected in a heparinised tube, and plasma was immediately separated by centrifugation (at 1500 rpm for 10 min), subsequently frozen and stored at -20°C until assayed.

3.1. Analytical procedure of determination of paracetamol in plasma

The determination of unchanged paracetamol in plasma samples was performed following the method employed in our previous work [24]. Specifically, 75 μl of a 10% w/v methanol solution of 2-acetaminophenol (used as internal standard) were pipetted in a glass tube and the solvent was removed under reduced pressure in a rotary evaporator. 0.5–1 ml of plasma were subsequently added to the tube, followed by the addition of 5 ml of ethylacetate for paracetamol extraction. The mixture was vortexed for 2 min and centrifuged at 3000 rpm for 10 min. The organic phase was transferred to a clean glass tube and the solvent removed under reduced pressure. The residuum was then dissolved in 100 μl of methanol and 20 μl were injected into a reverse phase HPLC C18 column. A mixture of phosphate buffer (pH $= 4$) and acetonitrile (65 : 35 v/v) was employed as a mobile phase.

Validation for the analysis of paracetamol in plasma was carried out. The limit of quantification was approximately 0.1 μg of paracetamol per ml of plasma. The coefficient of variation of six identical samples ranging from 0.2 to 8 μg/ml did not exceed 5%. The precision of the assay method was calculated by determining the relative standard deviations of peak height ratios obtained from six replicate assays within a concentration interval of 0.15–10 μg/ml. The relative standard deviation for intra-day analysis ranged from 2.6 to 6.3% and for inter-day analysis ranged from 3.2 to 7.6%. The absolute recoveries of paracetamol and internal standard in plasma were determined by comparing the slopes of processed human plasma standard curves to standard curves prepared in methanol. The recovery of paracetamol and internal standard in plasma was $91 \pm 5\%$ and $92 \pm 6\%$, respectively.

3.2. Pharmacokinetic analysis

Non-compartmental pharmacokinetic analysis of plasma concentration-time data was performed using WinNonlin version 2.1 (Pharsight, Palo Alto, USA). Maximum plasma concentration ($C_{\max}$) and corresponding sampling time ($t_{\max}$) were recorded as observed from the individual plasma concentration–time profiles. Half-life of the terminal phase ($t_{1/2,\lambda z}$) was calculated as 0.693 divided by the slope (λz) of the linear regression line of the terminal log-linear portion of the concentration-time curve. Area under the plasma concentration versus time curve (AUC) and area under the first moment curve were calculated by the linear trapezoidal rule and extrapolated to infinite time. Mean residence time MRT was estimated as ratio of AUMC to AUC.

Moreover, one-compartment model with first order absorption and elimination, Eq. (9), was simultaneously fitted to plasma concentration profiles C of the sustained release and reference formulation, sharing the elimination rate constant k_{el} [25].

$$C = \frac{FDk_a}{V(k_a - k_{\text{el}})}\left[\mathrm{e}^{-k_{\text{el}}t} - \mathrm{e}^{-k_a t}\right]. \tag{9}$$

Apparent volumes of distribution V, divided by bioavailable fractions F of the dose D and absorption rate constants k_a for the sustained release formulation and reference Tachipirina tablets and common elimination rate constant k_{el} were identified.

4. Results and discussion

The optimal size fraction for the purpose of the research, that is, a sustained release of the drug has been previously found to be the 3000–2000 μm size fraction [12]. Hence, this pellet size fraction was selected and extensively characterised with the aim of describing the mechanism of drug release from this device. An overview of the results of its characterisation is reported in Table 1.

These pellets, representing the prevalent size fraction of the produced batch of granulates and having a drug content correspondent to the theoretical one a specific superficial area of 1.7 $m^2 10^3/g$ and a true density of 1.33 g/cm^3, exhibited the complete release ($t_{90\%}$) of the paracetamol after about 6 h, depending on the pH of the buffer. The photomicrograph of the granulates, shown in Fig. 2, indicates that they mainly consisted of spherical particles having a satisfactory regular surface.

Table 1
Characterisation of 2000 μm granule size fraction

Analysis	Results		
Yield (% w/w)	49.40		
Drug content[a] (%)	60.2 ± 0.1		
Specific superficial partial area ($m^2\ 10^3/g$)[a]	1.7 ± 0.2		
True density (g/cm^3)[a]	1.33 ± 0.05		
	C1s	N1s	O1s
Superficial atomic composition (%)	3	15	82
	pH 1.2 buffer	pH 7.4 buffer	
t_{10}% (min)[a]	4	5	
t_{50}% (min)[a]	90	110	
t_{90}% (min)[a]	330	360	

[a]mean $\pm$ SD; $n = 3$.

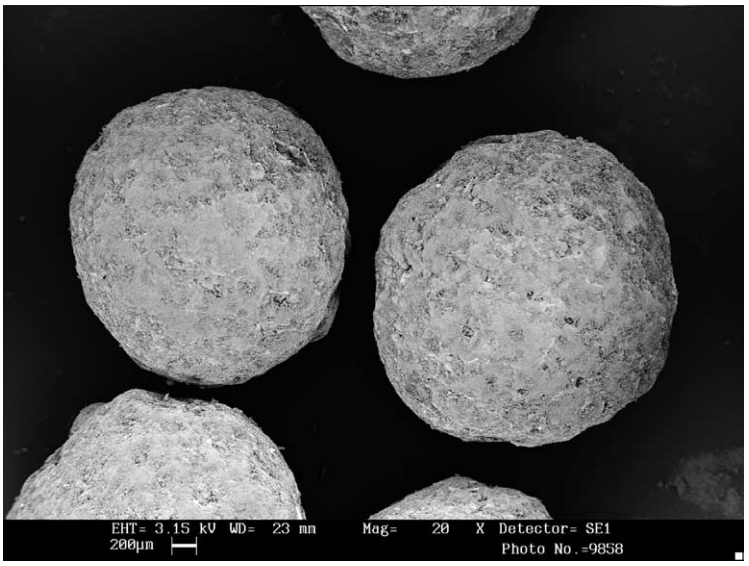

Fig. 2. SEM photograph 2000 μm size fraction pellets.

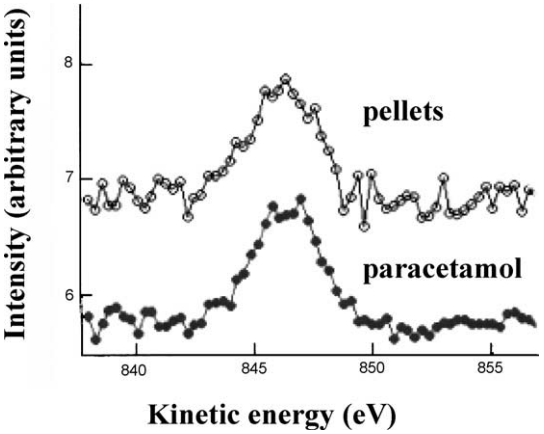

Fig. 3. Superficial atomic composition (%) of the pellets.

The surface atomic composition of the surface of the pellets, derived from XPS analysis as suggested by [26] and already applied in our previous work [14], attested the presence of paracetamol on pellet surface and justifies the rapid drug release in the early stages of the *in vitro* dissolution of these pellets (see $t_{10\%}$ Table 1). In particular, the nitrogen peak present in the paracetamol molecule at about 405 eV and still present in the spectrum of the pellets was taken as a confirmation of the presence of the drug on their surface layer (Fig. 3).

4.1. In vitro test

Drug release from this kind of delivery systems is a complex phenomenon ruled by different and concurrent mechanisms. When the aqueous dissolution medium wets the system, the soluble compound (lactose) and the drug (paracetamol) present in the outer matrix layers begin dissolving however with very different kinetics proportional to their aqueous solubility (at 37°C 0.28 g/ml for lactose, 0.018 g/ml at pH 1.2 and 0.033 at pH 7.4 for paracetamol). Accordingly, two solid–liquid interfaces (lactose–dissolution medium and drug–dissolution medium) move inward with very different speeds. This process gives origin to a porous matrix characterised by a series of interconnecting channels developing inside the insoluble compound (stearic acid) and hosting the dissolved drug and soluble compound molecules that diffuse outward due to the concentration gradient. The release process terminates when the thermodynamic equilibrium between the matrix and the dissolution medium is attained.

The developed mathematical model is tested on the release data performed at both pH (1.2, 7.4). Regardless the fact that the particles certainly constitute a poly-dispersed system, we assume that they can be represented by their mean diameter ϕ_m (=2500 μm). Accordingly, the effective diffusion coefficient D_e and the dissolution constant K_t represent model fitting parameters.

Figures 4a and 4b show, respectively, the comparison between model best fitting (solid line) and experimental data (filled circles, pH = 7.4; open circles, pH = 1.2).

This fitting is performed knowing that the volume of the dissolution medium V_r is equal to 900 cm^3, while all other parameters are reported in Table 2 for both pH.

While the agreement between experimental data and model best fitting is satisfactory for the pH = 1.2 case (Fig. 4a) as model fitting never differs from experimental data more than standard deviation (vertical bars), this is no more true for the pH = 7.4 case (Fig. 4b). This is surely due to the fact that while in the pH = 1.2 case no particles swelling/erosion takes place during drug release, in the pH = 7.4 an

Table 2

Fitting parameters (D_e, K_t) and physical parameters relative to both pH conditions (W_0 = amount of pellets considered, M_0 = paracetamol amount contained in W_0; C_s paracetamol solubility at 37°C)

pH	W_0 (mg)	M_0 (mg)	C_{d0} (μg/cm^3)	D_e (cm^2/min)	K_t (cm/min)	C_s (μg/cm^3)
1.2	15.7	9.4	741,528	1.7×10^{-4}	12	18,000
7.4	21.4	19.9	741,528	0.8×10^{-4}	10	32,585

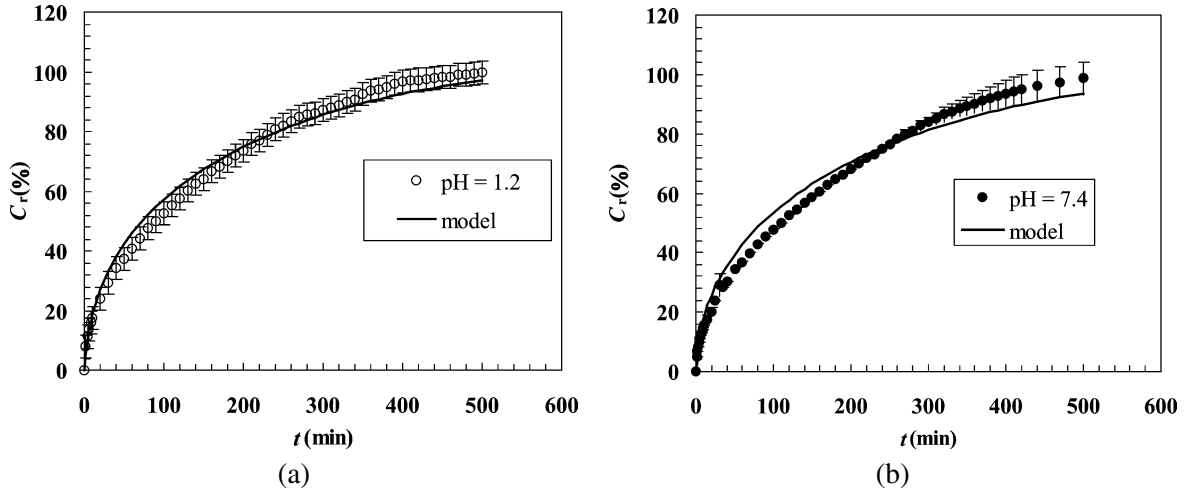

Fig. 4. (a) Paracetamol concentration (C_r) increase in the release environment at pH = 1.2 (symbols correspond to experimental data; solid line corresponds to model best fitting; vertical bars indicate data standard deviation). (b) Paracetamol concentration (C_r) increase in the release environment at pH = 7.4 (symbols correspond to experimental data; solid line corresponds to model best fitting; vertical bars indicate data standard deviation).

although limited swelling process happens. Accordingly, the hypotheses on which the model was build (neither particles erosion, nor swelling) are not fully attained. Nevertheless, this is not so problematic as, in the light of the *in vivo* application of our delivery system, what we are mainly interested in is the evaluation of the order of magnitude of drug diffusion and dissolution on pH variations. In this optic, Table 2 shows that while drug dissolution constant K_t is not significantly affected by pH, apparent drug diffusion coefficient D_e becomes one half passing from pH = 1.2 to 7.4. Nevertheless, the D_e decreasing is compensated by drug solubility increase passing from pH = 1.2 to 7.4. Indeed, Figures 4a and 4b underline that the variation of pH does not sensibly affect release kinetics. This, in turn, should reflect in a uniform drug release kinetics along the whole gastro-intestinal tract whose pH approximately ranges between 1.2 and 7.4. Finally, it is interestingly noticing that our analysis evidences how release kinetics is mainly affected by drug diffusion rather than drug dissolution being K_t, at both pH, very high.

4.2. In vivo test

Parameters of the non-compartmental pharmacokinetic analysis are summarized in Table 3. Mean plasma concentration profiles are presented in Fig. 5.

Table 3

Non-compartmental pharmacokinetic parameters for paracetamol following peroral administration of 1000 mg sustained release pellets in hard gelatine capsule and reference immediate release 2×500 mg Tachipirina® tablets (mean $\pm$ standard deviation)

Parameter	Sustained release pellets	Tachipirina® tablets
t_{max} (h)	3.0 ± 0.0	0.9 ± 0.1
C_{max} (μg/ml)	6.0 ± 2.6	14.4 ± 8.3
λ_z (h^{-1})	0.1 ± 0.0	0.3 ± 0.1
$t_{1/2,\lambda z}$ (h)	7.4 ± 2.7	2.2 ± 0.5
AUC (μg h/ml)	71.2 ± 30.2	46.6 ± 17.5
AUMC (μg h^2/ml)	889.5 ± 599.9	157.4 ± 27.7
MRT (h)	11.9 ± 4.3	3.5 ± 0.7

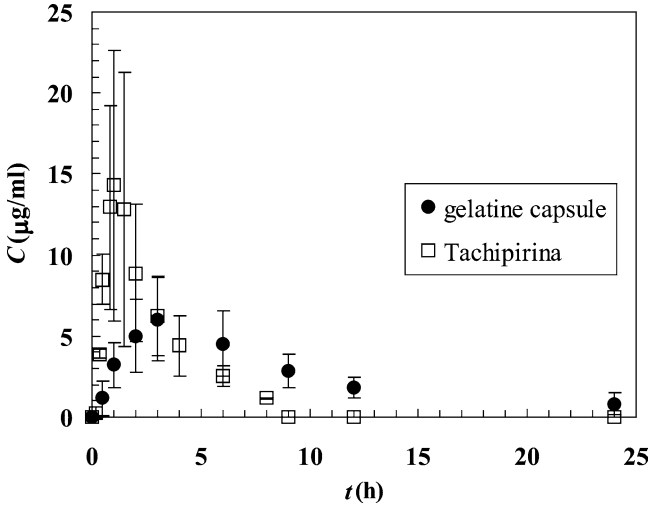

Fig. 5. Mean paracetamol plasma concentration (C) profiles of sustained release formulation (gelatine capsules, black circles) and the reference immediate release formulation (Tachipirina®, open squares) (vertical bars indicate data standard deviation).

Observed plasma concentration–time course was very close to the predicted one, which was based on paracetamol pharmacokinetic properties and *in vitro* dissolution profile. By comparison of the t_{max}, C_{max} and MRT values, it is evident that significant decrease in the paracetamol absorption rate was achieved by melt pelletization. Moreover, the AUC values (46.6 μg h/ml^3, Tachipirina®; 71.2 μg h/ml^3, sustained release formulation) clearly indicate that paracetamol bioavailability was increased compared to Tachipirina®. Comparison of the terminal slopes of the pharmacokinetic profiles (λ_z) reveals the existence of the flip-flop situation. It is clear that sustained release formulation displays absorption rate limited elimination. The terminal portion of the curve therefore reflects the absorption rate constant.

A simple one compartment model adequately described the experimental data (Fig. 6). The following parameters of the pharmacokinetic model were identified by simultaneous fitting of both pharmacokinetic profiles, sharing a common elimination rate constant: $(V/F) = 60.45$ l, $k_a = 0.34$ h^{-1}, for the sustain release formulation and $(V/F) = 56.60$ l, $k_a = 1.57$ h^{-1}, for the reference immediate release formulation. Elimination rate constant k_{el} was 0.35 h^{-1}. The identified parameters are in agreement with the results of the non-compartmental analysis. Paracetamol absorption rate from the developed formulation is significantly decreased, while its bioavailable fraction is increased.

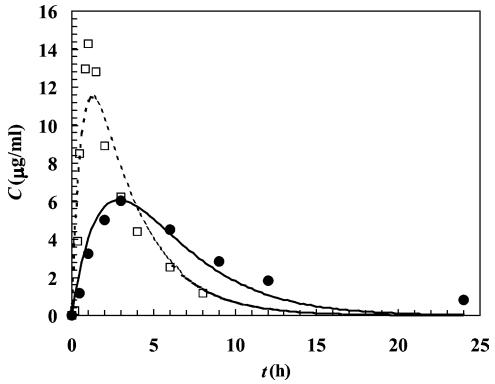

Fig. 6. Observed and model predicted paracetamol plasma concentration profiles of sustained release formulation (gelatine capsules, black circles) and the reference immediate release formulation (Tachipirina®, open squares).

It is expected that effective steady state plasma concentrations would be achieved by multiple dosing of 2 g paracetamol in the developed sustained release formulation every 8 hours and that such a formulation could be convenient to patients on long term paracetamol therapy.

5. Conclusion

We concluded that melt pelletisation technique in high shear mixer is a viable method to develop a sustained-release device for paracetamol in a single step, without any coating procedure, even including a high drug loading. Besides the release prolonging features, the formulation based on the combination of stearic acid and lactose, had favourable technological properties. In fact, the characterisation proved the ability of the adopted technique to give a product with homogeneous composition. Pellets mainly having spherical shape and satisfactory regular surface were obtained in the 2000 μm size fraction, which exhibited the slowest *in vitro* drug release. The best-fit mathematical model on experimental data allows to conclude that drug diffusion rather than drug dissolution rules release kinetics at both pH. Comparison between the behaviour of our sustained release formulation and that of the reference (Tachipirina®) evidences that our formulation yields a sustained release behaviour increasing paracetamol bioavailability. Simulation of the multiple dosing revealed that effective steady state plasma concentrations would be achieved by administration of 2 g paracetamol in the developed sustained release formulation every 8 hours. Such a formulation could be convenient to patients on long term paracetamol therapy.

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