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Spectroscopic and chromatographic characterization of triflusal delivery systems prepared by using supercritical impregnation technologies

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Abstract

This study describes the development and evaluation of an analytical method for the characterization of triflusal (2-acetoxy-4-(trifluoromethyl) benzoic acid) dispersed in sustained delivery systems prepared using supercritical fluid impregnation technology. Characterization assays comprised the determination of the percentage of triflusal and its degradation product impregnated in polymeric supports and further monitoring of the releases of the two drug components over time in physiological conditions. Preliminary delivery profiles were monitored spectrophotometrically using a continuous-flow system. In this case, no selective wavelength for discriminating between triflusal and metabolite was found so that measurements at 225 nm provided overall profiles corresponding to the two compounds. For a more accurate study, a chromatographic method was developed for monitoring the evolution of the concentration of the two components independently. Triflusal and metabolite were separated in a C_{18} column and 25 mM acetic acid/acetate (pH 5.0) + methanol (40/60 v/v) mobile phase. Several triflusal-polymer samples were prepared under different experimental conditions and release features were evaluated. Excellent delivery systems were obtained with poly(methyl)methacrylate beads treated at 40°C and 190 bar for 48 h using supercritical carbon dioxide as a solvent. These samples showed a constant sustained release of drug for several weeks.

Keywords: Triflusal; Poly(methyl)methacrylate; HPLC analysis; Supercritical impregnation; Controlled delivery systems

1. Introduction

The development of novel pharmaceutical products dealing with drug delivery systems often involves the incorporation of active drugs into support materials through, for instance, impregnation, encapsulation of copolymerization processes [1–3]. Controlled release is especially relevant in the medical treatment of chronic diseases which commonly require a constant source of drug. This is the case of cardiovascular devices such as stents in which long-term treatment with platelet anti-aggregation drugs is required to prevent thrombi formation around the surgical implant. Novel medical strategies for tackling this issue involve the coating of the stent surface with an appropriate drug-support system compatible with *in situ* release in the target part of the body (in general inside an artery) [4,5]. The success of release systems relies in a constant, controlled and sustained delivery for reaching therapeutic levels during long periods of time (e.g., months or years).

In this study, 2-acetoxy-4-(trifluoromethyl) benzoic acid, which is known as triflusal (TRF), has been chosen as a model of active drug for preparing controlled delivery systems. Triflusal is an antithrombogenic drug structurally related to acetylsalicylic acid which is being commercialized since 1981 [6,7]. Triflusal undergoes a progressive decomposition in physiological systems yielding 2-hydroxy-4-trifluoromethy benzoic (HTB) acid as the main metabolite [8]. Despite the inevitable triflusal degradation, HTB is also highly active as platelet aggregation inhibitor so this does not represent a remarkable shortcoming from a pharmaceutical point of view [9]. The characterization of the acid–base properties of this substance is given elsewhere [10]. Various analytical methods for the determination of triflusal and HTB have been proposed based on liquid chromatography using C_{18}

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bonded silica columns and hydro-organic eluting mobile phases [11,12].

Controlled delivery systems involving triflusal have been obtained through conventional emulsion techniques involving organic solvents [13,14]. However, the interest in cleaner processes such as those based on environmentally friendly solvents is increasing. In this field, supercritical processes using carbon dioxide as a carrier medium are widely used to avoid volatile organic solvents that are usually used for the preparation of this type of systems [15–20]. Additional benefits of supercritical CO_2 technology comprise enhanced bioavailability, improved coating efficiency, lower process costs and excellent performance for dealing with labile compounds [21,22].

This paper describes the impregnation studies of triflusal in various types of poly-(methyl)methacrylate (PMMA) matrices, including bead and rod forms [23-25]. For this purpose, a supercritical procedure has been developed where temperature, pressure and contact time are among the most relevant experimental parameters. Subsequently, drug release has been monitored over time at 37 °C under continuous stirring. pH values of 2 and 7.4 have been chosen to simulate certain physiological conditions such as stomach and plasma media, respectively. The spectrophotometric monitoring using a continuous-flow system has provided release profiles in an easy and simple way. Additionally, a liquid chromatographic method has been established to obtain the kinetic profiles of the delivery processes as well as to study the evolution of drug metabolite formation by hydrolysis side reaction in a similar way as in the case of other unstable drugs [26].

2. Experimental

2.1. Reagents and solutions

Ultrapure water (Millipore, Milford, MA, USA) was used for the preparation of all solutions. Triflusal (2-acetoxy-4-(trifluoromethyl) benzoic acid, TRF) and 2-hydroxy-4-trifluoromethy benzoic (HTB) were kindly provided by Uriach (Barcelona, Spain). The PMMA used was either in the form of beads ($PMMA_{BP}$ from Bonar Polymers) or bars ($PMMA_{GF}$ from Good Fellow). In both cases the PMMA had a molecular weight of ~300,000 g mol^{-1}. For the supercritical impregnation, carbon dioxide (99.995%) was supplied by Carburos Metálicos (Spain). Chemicals for loading and release analysis comprised acetone (99.5%) from Fluka, 37% (w/w) hydrochloric acid solution, sodium hydroxide and sodium hydrogencarbonate (all of them from Merck, a.r.). The chromatographic eluent was prepared with ammonium acetate and acetic acid (Merck, a.r.) using methanol (Merck, HLPC grade) as the organic solvent. Fresh 1×10^{-4} M triflusal and HTB stock solutions were daily prepared in water and stored in the fridge at 4 °C. Delivery processes were characterized in water, 0.01 M HCl and 0.01 M HCO_3^-/CO_3^{2-} (pH 7.4) solutions.

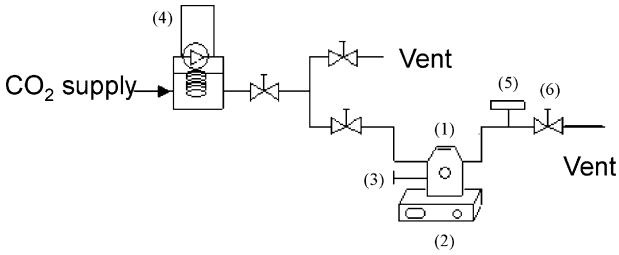

Fig. 1. Scheme of the experimental set-up for drug impregnation. (1) High pressure stainless steel reactor, (2) magnetic stirring, (3) thermocouple and resistances, (4) syringe pump, (5) pressure transducer, (6) needle valve.

2.2. Impregnation equipment and procedure

Polymer processing in $SCCO_2$ was performed in a high-pressure equipment running in the batch mode (see Fig. 1). In a typical experiment, the autoclave (70 ml, TharDesign) was charged with 3 g of polymer, a similar amount of triflusal and filled with pressurized CO_2 at the working pressure (P). Triflusal particles were wrapped inside in cylinders made of 0.45 μm pore filter paper filter and physically separated of the PMMA matrix. The amount of triflusal placed was in excess of the amount required to saturate the CO_2 in the reactor. The system was heated with resistances to the selected temperature (*T*) and stirred at 300 rpm during a fixed time period (*t*). At the end of each experimental run, the system was depressurized at *ca.* 0.2–0.4 MPa min^{-1} and led to cool to room temperature in air. Recovered samples were flushed with air and washed with ethanol in order to eliminate the excess of non-retained triflusal residue on the polymer surface. As control or blank experiment, either pure triflusal or raw PMMA was processed in $SCCO_2$ under similar experimental conditions. Series of experiments at different experimental conditions (*P*, *T* and *t*) were carried out according to Table 1.

Table 1
Summary of samples under study

Reference	Sample	Pressure (bar)	Temperature (°C)	Time (h)	TRF (%)	HTB (%)	Overall impregnation (%)
E18GF5	PMMA rod of 5mm + TRF	150	35	72	6.4	6.9	13.3
E18B	PMMA beads + TRF	150	35	72	6.8	9.5	16.3
E18GF1	PMMA rod of 1mm + TRF	150	35	72	10.5	11.2	21.7
E34GF5	PMMA rod of 5mm + TRF	200	35	96	13.7	4.5	18.2
E43GF5	PMMA rod of 5mm + TRF	190	40	48	3.9	1.1	5.0
E43B	PMMA beads + TRF	190	40	48	9.4	2.0	11.4
E45GF5[a]	PMMA rod of 5mm + TRF	190	40	48	3.7	1.0	4.7
E45B[a]	PMMA beads + TRF	180	40	48	10.6	2.3	12.9

[a] Samples pre-treated with supercritical CO_2 to try to remove the residual water.

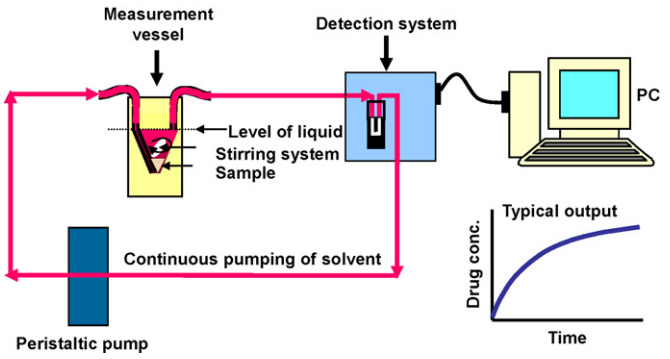

Fig. 2. Scheme of the continuous-flow system for the characterization of drug delivery processes.

2.3. Apparatus

A PerkinElmer Lambda-19 spectrophotometer equipped with a Helma flow-cell of 10 mm path length and 60 μl volume was used for spectral measurements over time at a working wavelength of 225 nm. Spectroscopic data were acquired with a PC using the standard PerkinElmer software. A magnetic stirrer IKA® RCT basic (safety control) equipped with a temperature probe was used for controlling the release conditions. A CyberScan model 2500 potentiometer (precision of ±0.1 mV) with a combined pH electrode ORION 9103SC was used for pH measurements. The chromatographic system consisted of an Agilent 1100 Series instrument equipped with a G1311A quaternary pump, a G1379A degasser, a G1315B diode-array detector furnished with a 13-μl flow-cell and an Agilent Chemstation for data acquisition and analysis (Rev. A 10.02), all of them from Agilent Technologies (Waldbronn, Germany). Samples were injected with a six-port rotary valve Rheodyne 7725(i) (Rohnert Park, CA, USA) with a 20 μl sample loop. A Hitachi S570 scanning electron microscope (SEM) was used for the analysis of the PMMA morphology after supercritical treatment.

2.4. Analytical methods

2.4.1. Spectroscopic continuous-flow procedure

The continuous-flow system depicted in Fig. 2 was used for spectroscopic measurements of release processes. A peristaltic pump (Watson Marlow 505DU) was used for continuous recirculation of the solution through the system at a flow-rate of 3 ml min^{-1}. Standard Tygon tubing was used for pumping the solution. PTFE connection pieces and tubing were used for the construction of the manifold. The sample solution continuously circulated through the system. The evolution of the drug concentration in the solution was recorded as a function of time at 225 nm as explained in section 2.6 to obtain overall release profiles corresponding to the total amount of TRF and HTB. The absence of selective wavelength for TRF and HTB hindered the individual monitoring of each compound.

2.4.2. Chromatographic procedure

The chromatographic method for the determination of TRF and HTB was based on the separation of components on a Synergy Hydro-RP C_{18} column from Phenomenex (150 mm × 4.6 mm i.d., particle size 4 μm, 80 Å) using isocratic elution. The mobile phase consisted of 25 mM acetic acid/acetate aqueous solution (pH 5.0) + MeOH (40/60, v/v). The flow rate was 1 ml min^{-1} and the injection volume 20 μl. Analytes were detected spectrophotometrically at 280 nm. This procedure was used in the determination of the percentage of impregnation (Section 2.5) and in the monitoring of the drug release (Section 2.6).

2.5. Determination of the percentage of impregnation

The amount of TRF and HTB impregnated in the matrix of PMMA was determined by liquid chromatography. For this purpose, 5 mg of sample were treated with 50 ml of acetone for swelling and dissolving the polymeric support while quickly releasing the drug components to the solution. Subsequently, the solvent was evaporated under nitrogen current and the dry residue was re-dissolved in 20 ml of mobile phase. The mobile phase was chosen as a solvent to avoid the formation of undesired peaks that may appear in the presence of other solvents. 20 μl of the resulting solution was injected into the chromatographic system for the quantification of TRF and HTB in each sample as explained in Section 2.4.

2.6. Drug release monitoring

The drug delivery process was evaluated via desorption experiments in which solutes were lixiviated with appropriate solvents including water, 10 mM HCl and 10 mM HCO_3^-/CO_3^{2-} (pH 7.4) solutions. A proper amount of sample varying from 5 to 25 mg was placed in the center of a vessel containing the desired volume of solvent. Both stirring rate and temperature were fixed at 70 rpm and 37 °C, respectively. The kinetic process was monitored spectrophotometrically or chromatographically to obtain the corresponding delivery profiles (see Section 2.4). The spectrophotometric procedure provided overall drug profiles corresponding to TRF and HTB in a simple and rapid manner. This method was appropriate for studying processes over a sort period of time (e.g., several hours) but it was less recommendable for longer studies involving various days. The chromatographic method provided additional information about the evolution of both TRF and HTB contents in the system. This procedure was also appropriate for long-term studies lasting several months since analyses were carried out off-line by collecting discrete volumes of sample at desired times to be further injected into the chromatograph.

3. Results and discussion

3.1. Study of chromatographic conditions

Solvent (methanol) percentage and pH consisted of the principal factors influencing on the separation of triflusal-related compounds. The pH of the mobile phase was varied from 2.3 to 5.0 using various formic acid/formate and acetic acid/acetate solutions. The most acid buffers led to too wide peaks due to the

partial deprotonation of triflusal and HTB as they have low pK_a values. As a result, a 25 mM acetic acid/acetate (pH 5.0) solution was chosen as a buffering medium. In these circumstances, sharp chromatographic peaks were obtained.

The percentage of methanol in the mobile phase was first studied with a pH gradient ranging from 10 to 90% (v:v). Analytes were eluted at concentrations around 60–80% so that these values were further checked under isocratic conditions. The selected elution consisted of 25 mM acetic acid/acetate (pH 5.0) + methanol (40:60, v:v) at a constant flow rate of 1 ml min^{-1}. Fully resolved analyte peaks were obtained with retention times of 2.5 and 3.4 min for HTB and triflusal, respectively.

Figures of merit established for both triflusal and HTB at 280 nm were as follows: the response was linear at least up to 2.5×10^{-4} M with excellent correlation coefficients of 0.9997 and 0.9999 for triflusal and HTB, respectively. Detection limits estimated for a signal-to-noise ratio of 3 were 2.0×10^{-6} and 2.4×10^{-6} M. The repeatability (%R.S.D.) in retention time calculated from 8 replicates was around 0.4%. Repeatabilities for peak areas established at a concentration level of 5×10^{-5} M and 8 replicates were 1.4% and 2.3% for triflusal and HTB, respectively.

3.2. Preliminary characterization of triflusal degradation in aqueous solutions

As a preliminary step, the decomposition of the triflusal in water, hydrochloric (pH 2) and hydrogencarbonate (pH 7.4) solutions was characterized spectrophotometrically and chromatographically as described in Section 2.5. The amounts of unaltered triflusal and the resulting metabolite were calculated from the corresponding chromatographic peaks. Fig. 3 summarizes the results obtained in various release conditions. In the three cases, triflusal solutions progressively decomposed although the process was faster in water and hydrogencarbonate solution (pH 7.4) in which the degradation to HTB was completed in 10 days, approximately. Acid solutions were more stable and, after 14 days, a significant amount of triflusal (≈30%) was still present in the solution. In order to extract reliable conclusions in further experiments, this decomposition should be taken into account as parallel side reactions may overlap the release process.

3.3. Impregnation studies

Several impregnation experiments were carried out to ascertain the optimal conditions for preparing the sample specimens. The total impregnated amount of drug (including both triflusal and HTB contributions) was considered as a relevant objective in this optimization. At the same time that high percentages of impregnation were searched, the delivery process should be sustained with progressive release over an extended period of time. Note that either too rapid or too slow release may not be efficient to attain the desired therapeutic parameters.

The definition of the experimental variables that influenced the loading was also important for the optimization process.

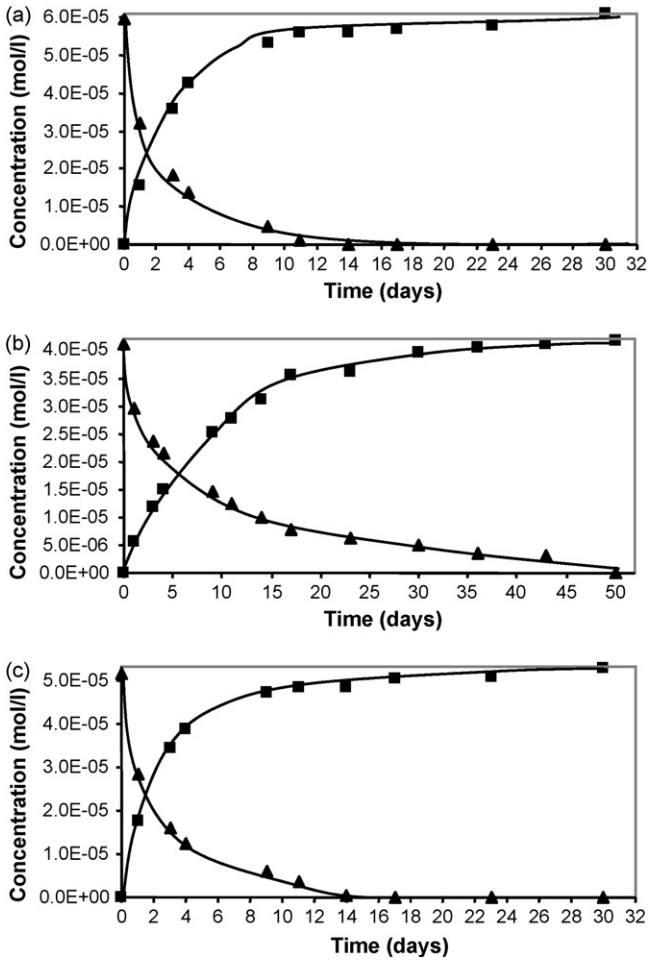

Fig. 3. Results of the degradation of triflusal in aqueous solutions: (a) water, (b) 10 mM HCl and (c) 10 mM HCO_3^-/CO_3^{2-} (pH 7.4) solutions. Symbols: triangles = triflusal, squares = HTB.

The most significant variables in the supercritical process were temperature, pressure and time. The initial drug/PMMA ratio in the performed series was fixed to 1:1 in weight. At the same time, temperature was set to 35–40 °C as higher temperatures may enhance the triflusal hydrolysis during impregnation. Pressures in the runs ranging from 100 to 200 bar were applied for process times ranging from 24 to 96 h. A summary of samples with the most relevant features is given in Table 1.

SEM technique was used for the study of morphology modification of the polymeric materials as a consequence of swelling and further impregnation. As an example, Fig. 4 shows the pictures of raw and impregnated PMMA rods as well as SEM images of sample E43GF5. Significant morphologic changes in the treated samples were observed. Visually, the initially transparent bars became opaque as a result of swelling and further hole formation during decompression. As shown in the pictures, the selected exposure time was not enough to swell the entire sample homogeneously and a boundary propagating inside the polymer samples was observed. The diffusion front was an interface between glassy and plasticized regions. The impregnated sample increased the diameter of the bar in 2 mm approximately as a consequence of the process and big pores of 20–50 μm of

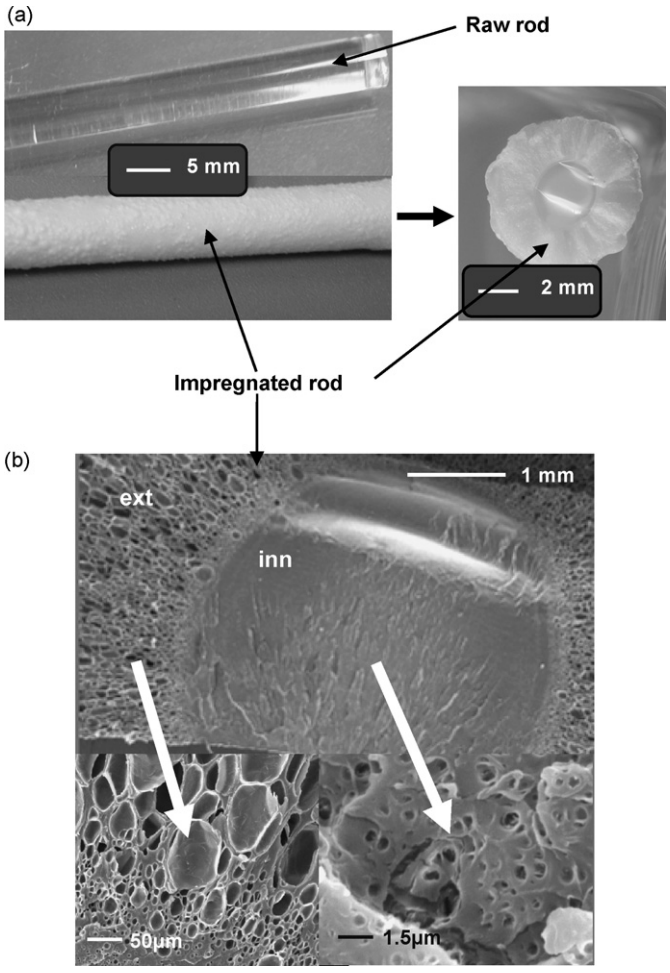

Fig. 4. Pictures of raw and impregnated PMMA rods (a) and SEM micrograph of the cross-section of sample E43GF5 (b).

diameter were formed in the outer part. The cross-sectional analysis indicated that, apparently, a portion of the inner part of the sample was not swelled.

The percentage of impregnation was determined chromatographically for all samples listed in Table 1. Samples were treated with acetone as described in the Section 2 for a rapid swelling of the polymer and dissolution of the active components. Results indicated that under similar experimental conditions triflusal impregnation was more efficient for PMMA beads, while lower yields were obtained for PMMA rods. The effect of time was clearly evidenced in the series of rod samples where the percentage of impregnation increased significantly with processing time.

Significant amounts of degradation product were detected in all samples studied, with percentages ranging from 20% to 60% depending on the experimental conditions. As shown in Fig. 5, the presence of HTB was noticeable even in recently prepared samples and its percentage increased with ageing. For instance, in the case of sample E43GF5, contents of HTB increased from 23% to 50% in 85 days (i.e., the percentage of TRF decreased from 77% to 50% in the same period). A similar behavior was found for bead sample E43B as the HTB percentage varied from 18% to 44% when ageing for 85 days under ambient conditions (see data in Fig. 5b). The formation of HTB was attributed to side reactions and interactions between polymer and drug, possibly associated to the existence of residual water in the polymer. A supercritical drying procedure to remove the traces of water from the polymer material was investigated to try to minimize this degradation. The strategy was based on a preliminary treatment of polymer with a continuous flow of supercritical CO_2. Here, for instance, samples E45B and E45GF5 were pre-treated with supercritical CO_2 and were further subjected to the impregnation treatment as indicated in Table 1. The percentages of HTB in these samples were similar to those found in the case of E43B and E43GF5 (obtained without pre-treatment in the same impregnation conditions). As a result, the process assayed for decreasing degradation was inefficient so that it was not considered anymore for the preparation of impregnations.

The penetration of triflusal inside the rod material (i.e., the distribution profile of drug in depth) depended on the degree of swelling of the polymer. This factor was investigated for sample E34GF5. As commented in the SEM analysis, the diameter of impregnated rod sample after the process was 7.0 mm (i.e., 2 mm wider than the raw material). The surface of the rod was eroded progressively and fractions of the recovered powder were chromatographically analyzed. The resulting profile has been plotted in Fig. 6 (the 3.5 mm scale depicted in this figure corresponded to the depth measured in a radial direction). The higher impregnation percentages were found in the more external zones of the rod while the inner range was almost unaltered so that the amount of triflusal present in this region found was negligible.

Complementary studies were focus on detecting the origin of the metabolite HTB. The supercritical processing of pure

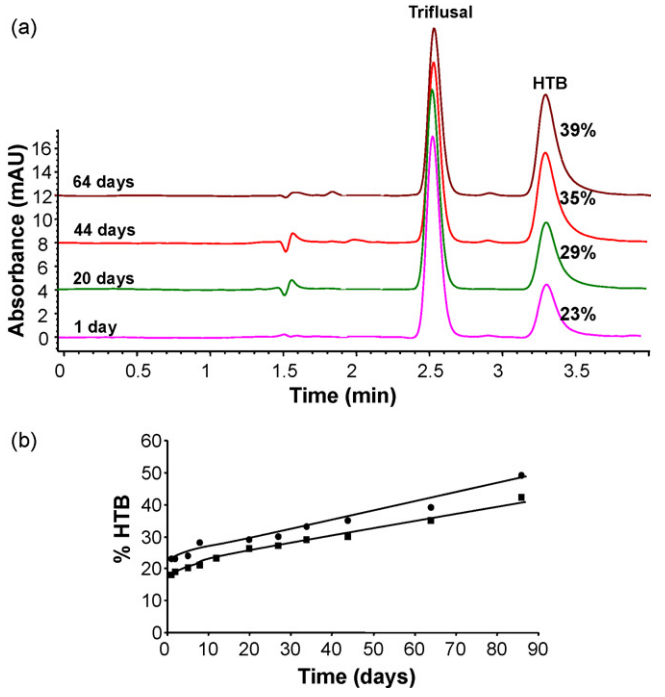

Fig. 5. Evolution of the triflusal degradation in impregnated samples as a function of sample ageing. (a) Selected chromatograms of the evaluation of E43GF5 taken over the ageing period. (b) Variation of the HTB percentage over time of samples E43GF5 (circles) and E43B (squares).

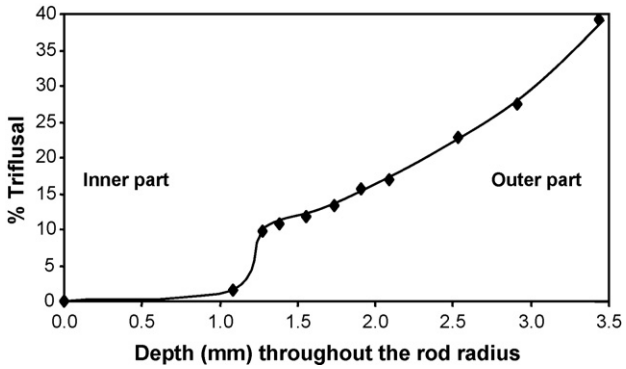

Fig. 6. Evolution of the content of triflusal as a function of depth in rod sample E34GF5.

triflusal in the absence of PMMA, under similar experimental conditions than the impregnation runs, showed that the hydrolysis was almost negligible (below 2%). As a result, the formation of HTB was attributed to side reactions and interactions between polymer and drug, possibly associated to the existence of residual water in the polymer.

From the therapeutic point of view, the progressive triflusal hydrolysis in the impregnated samples did not represent any serious shortcoming due to the analogous activity of triflusal and metabolite, displaying both excellent anti-aggregation properties.

3.4. Drug release monitoring

The set of samples given in Table 1 was pre-evaluated as described in Section 3.3 in order to select the most appropriate candidates for a more thoroughly characterization of release behavior. E43B and E43GF5 were here chosen as representative examples of bead and rod samples as they displayed the lowest percentage of degradation product. Drug delivery processes were preliminarily characterized using the continuous-flow procedure described in the Section 2. Profiles recorded at 225 nm provided an estimation of the simultaneous release of the two components. Results of the monitoring of the delivery processes of E43B and E43GF5 in 0.01 M HCl are shown in Fig. 7. The overall concentration of TRF and HTB in the assays increased progressively during the period studied and, after 24 h, approximately, 1.2% and 3.4% of active compounds were solubilised from bead and bar samples, respectively. It was also found that releases at pH 7.4 (not shown here) were faster and about a 9% of TRF species were dissolved after 24 h of process. As an operational disadvantage of the continuous-flow spectrophotometric monitoring, note that the spectrophotometer was constantly switched on during measurement period so that this procedure was only recommendable for monitoring during a short time (typically for several hours). Additionally, despite being extremely simple, another drawback of the continuous-flow monitoring studies was the difficulty to distinguish between TRF and HTB. This shortcoming cannot be solved spectrophotometrically due to the lack of selectivity so that the chromatographic procedure was thus required.

In order to examine more deeply the release process of the triflusal/PMMA samples, special attention was paid on the discrimination between triflusal and HTB through HPLC analysis. The performance of the HPLC method was compared with spectrophotometric procedure. As shown in Fig. 7, the concordance in the overall amount of TRF + HTB was satisfactory. However, in the case of chromatographic results, the contributions of TRF and HTB to the release process were also obtained.

The chromatographic procedure was also appropriate for long-term monitoring of delivery kinetics so that this method was chosen for an evaluation of characteristics of samples during several weeks. Examples of the evaluation of E43B (beads) and E43GF5 (rods) samples at pH 7.4 are shown in Fig. 8. For impregnated bead samples, a sustained delivery following a zero-order kinetic was found which indicated that the increase in the concentration of the active substances was almost linear. Half-life times $t_{1/2}$, corresponding to a release of 50% of the active principle to the medium, were 41.1 and 34.2 days at pH 2 and 7.4, respectively. Again, it is shown that the delivery rate was significantly faster in basic medium. The evaluation of the release features of impregnated PMMA bars showed a biphasic behavior. A faster release was observed within the first 2 days of study while a slower quasi-linear release was found after this initial period. The corresponding $t_{1/2}$ values were 54.9 and 38.9 days in acid and basic media, respectively. From this characterization, it was concluded that impregnated samples had an excellent potential for the preparation of pharmaceutical formulations. Delivery profiles were consistent with keeping stable

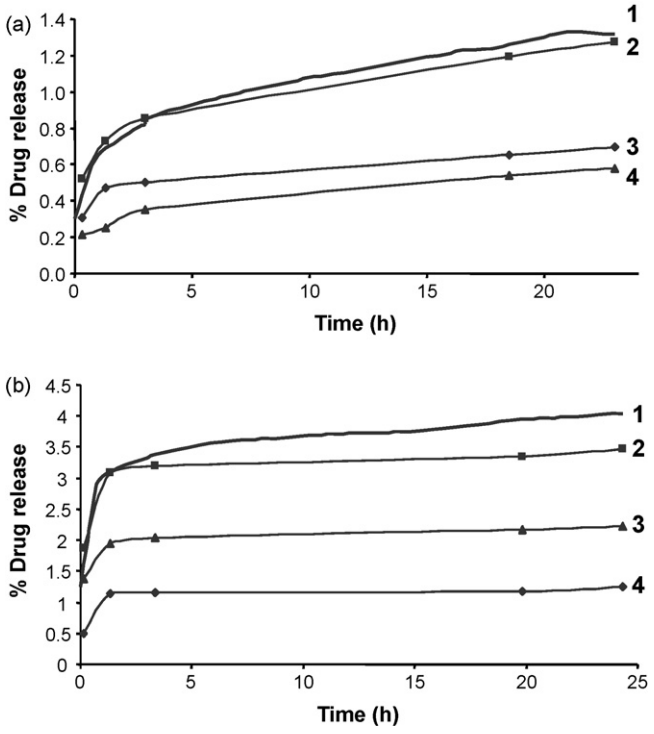

Fig. 7. Comparison of release profiles obtained with the continuous-flow spectrophotometric and chromatographic procedures. (a) Characterization of bead sample E43B; (b) characterization of rod sample E43GF5. Identification: 1, overall profile (spectrophotometric); 2, overall profile (chromatographic); 3, TRF profile (chromatographic); 4, HTB profile (chromatographic).

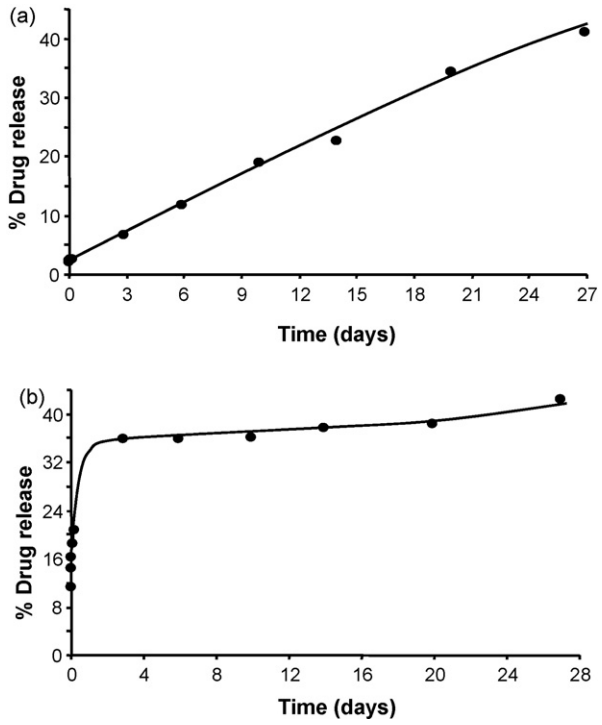

Fig. 8. Drug release profiles obtained chromatographically for drug/PMMA bead (a) and rod (b) systems in aqueous solution at pH 7.4.

levels of the drug over a long period of time, reducing the number of administrations and, in the case of bead samples, avoiding the initial sharp increase in drug concentration. Finally, the reported $t_{1/2}$ values were compatible with a sustained delivery for a period longer than 2 or 3 months.

4. Conclusions

The characterization of triflusal release from supercritically impregnated polymeric systems has been successfully accomplished by spectroscopic and chromatographic methods. Spectrophotometric monitoring at 225 nm resulted in a straightforward way for a preliminary evaluation of release processes focused on selecting candidate samples. However, this method is unable to discriminate among triflusal and metabolite so that only overall profiles of the two components can be obtained. The chromatographic method can be used for a more accurate study of the release behavior of the prepared samples. Also, the chromatographic approach provided additional information regarding the presence of triflusal hydrolysis product and its evolution over long periods of time. From the set of samples prepared in different experimental conditions, the best behavior from a pharmaceutical point of view corresponded to the case of poly(methyl methacrylate) beads impregnated according to the supercritical procedure for 48 h at 190 bar and 40 °C. In these samples, the amount of triflusal impregnated corresponded to an 11.4% and a constant release in aqueous media was expected to be longer than 2 months.

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