Frontal polymerization as a new method for developing drug controlled release systems (DCRS) based on polyacrylamide

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ABSTRACT

Stimuli-responsive polymers are macromolecular materials that undergo changes in response to small external stimuli in the environmental conditions. Among stimuli-responsive hydrogels are several polyacrylamides. Frontal polymerization is a fast, easy and inexpensive polymerization technique used for the synthesis of macromolecules.

Aim of this work was the evaluation of the Frontal polymerization technique as new method for the preparation of controlled release dosage forms in which drug loading and polymer preparation occur together, as well as the possibility of obtaining more dosage units by a unique preparation. Hydrogels based on polyacrylamide containing diclofenac sodium salt were prepared using the Frontal polymerization and compared with similar systems obtained by the classic batch method. Polymers characterized by three different degree of cross-linking were prepared. The stability of the drug during the sample preparation was evaluated by IR analysis. The obtained samples were characterized in terms of drug content, morphology, in vitro drug release and swelling properties. Samples were studied also divided into disks. The results show that hydrogels based on polyacrylamide can be prepared by Frontal polymerization; these samples show similar properties to those obtained by batch polymerization. The drug is stable in the polymerization reaction conditions. Samples characterized by the lowest degree of cross-linking show drug loading values always higher than samples with the highest one regardless of the preparation method employed. The swelling ratio decreases as the degree of cross-linking increases. Loaded samples swell more than drug free ones. From a single preparation of hydrogel, three disks showing same drug content and in vitro release behaviour can be obtained and thus they can be used as three single dosage units.

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1. Introduction

Controlled drug delivery occurs when a natural or synthetic polymer is combined with a drug or other active agent in a way that the active agent is released from the material in a predesigned manner. The release of the active agent may be constant over a long period, it may be cyclic over a long period, or it may be triggered by the environment or other external events. In any case, the advantages of using controlled delivery systems can include the purpose to achieve more effective therapies by eliminating the potential for both under- and over-dosing, the maintenance of drug levels within a desired range, the need for fewer administrations, optimal use of the drug and increased patient compliance [1]. Controlled release is regulated by various mechanisms such as diffusion, erosion/degradation or swelling. Most of polymeric delivery systems which work by a swelling release mechanism are hydrogels.

Polymer hydrogels are three-dimensional, hydrophilic, macromolecular networks capable of imbibing large amounts of water or biological fluids [2,3].

Since the employment of hydrogels as soft contact lenses in the 1960s [4], hydrogels have been introduced as novel materials for pharmaceutical and biomedical applications. The work of Lim and Sun in 1980 demonstrated the successful application of calcium alginate microcapsules for cell encapsulation [5]. Later in the 1980s, Yannas and coworkers incorporated natural polymers such as collagen and shark cartilage into hydrogels for use as artificial burn dressings [6]. Recently, such hydrogels have become attractive to the new field of 'tissue engineering' for repairing and regenerating a wide variety of tissues and organs [2,7–10]. Over 30 years of research in this field resulted in the common use of hydrogels as soft contact lenses, wound dressings, drug delivery systems, superabsorbents etc.; with a number of products being commercially available, it seems that their use in the field of medicine and pharmacy may be the most successful and promising. Both natural and synthetic polymers can be used for the production of hydrogels.

In comparison to other synthetic biomaterials, hydrogels resemble living tissues closely in their physical properties because of their relatively high water content and soft and rubbery consistency. Hydrogels show minimal tendency to adsorb proteins from body fluids because of their low interfacial tension. Furthermore, the ability of molecules of different sizes to diffuse into (drug loading) and out of (drug release) hydrogels allows the possible use of dry or swollen polymeric networks as drug delivery systems for oral, nasal, buccal, rectal, vaginal, ocular and parenteral routes of administration [11,12].

Several terms have been coined for hydrogels, such as 'intelligent gels' or 'smart hydrogels' [13]. The smartness of these materials is due to their ability to receive, transmit or process a stimulus and respond by exhibiting changes in their physical or chemical behaviour resulting in the release of entrapped drug in a controlled manner [14,15].

Variations in pH are known to occur at several body sites, such as the gastrointestinal tract, vagina and blood vessels, and these can provide a suitable base for pH-responsive drug release. In addition, local pH changes can be generated by using specific substrates and used for modulating drug release. pH-responsive hydrogels are composed of polymeric backbones with ionic pendant groups. Most commonly studied ionic polymers for pH-responsive behaviour include poly(acrylamide) (PAAm), poly(acrylic acid) (PAA), poly(methacrylic acid) (PMAA), poly(diethylaminoethyl methacrylate) (PDEAEMA) and poly(dimethylaminoethyl methacrylate) (PDMAEMA) [16] which are high molecular weight organic polymers that, depending on the difference in molecular structure, can be classified as linear or cross-linked macromolecules. For instance, linear PAAM dissolves in water while cross-linked PAAM absorbs hundreds of times its weight in water without dissolving. PAAM is able to swell and gel when in contact with biological fluids and is therefore used as carrier of drugs [1,17] also in many of its copolymeric forms, which are stimulus-sensitive polymers [18–20].

The chemical and physical properties of PAAM differ significantly from those of the acrylamide (AMD) monomer, which is a neurotoxin to humans. In contrast, PAAM when used at prescribed rates is nontoxic to humans although overexposure can lead to skin irritation and inflammation of mucous membranes.

Frontal polymerization (FP) is a polymerization method that takes advantage of the exothermicity of the reaction for the propagation and self-sustaining of the reaction itself. Indeed, subsequently to an initial ignition (chemical or physical), a hot polymerization front is formed which propagates throughout the reactor in a fashion similar to a reaction wave, thus converting monomer into polymer. After reaching the steady state, no further energy supply is necessary in order for the front to sustain itself.

The first work dealing with FP dates back to the '70s: Chechilo and Enilokopyan frontally polymerized methyl methacrylate under high pressure [21]. After this first work, Pojman et al. applied FP on various typologies of monomers and reagents: epoxy resins [22], ionic liquids [23] and acrylic monomers [24–26]. Crivello et al. focused their attention on the FP of glicidyl ethers [27,28], whereas Chen et al. successfully exploited such a technique with 2-hydroxyethyl acrylate [29], and *N*-methylolacrylamide [30], moreover, they prepared epoxy resins/polyurethane networks [31] and polyurethane-nanosilica hybrid nanocomposites [32]. Our research group synthesized poly(dicyclopentadiene) [33], polyurethanes [34,35], interpenetrating polymer networks [36], unsaturated polyester/styrene resins [37], poly(diurethane diacrylates) [38], and applied FP to the consolidation of porous materials [39]. Recently, we reported on the synthesis of polymer-based nanocomposites with montmorillonite [40] and polyhedral oligomeric silsesquioxanes [41]. Besides, we proposed a new class of initiators based on ionic liquid compounds that resulted to be particularly useful in the frontal radical polymerization in that they allow for lower temperature polymerization fronts [42].

Since the nineties, FP has received a great impetus by Pojman et al. who explored macrokinetics and dynamics [21,22] and new frontally polymerizing systems [23,24].

Since 2000, our research group has been active in this field. Namely, we have studied the application of FP to the synthesis of several kind of polymers [25,27] and polymer nanocomposites [28,29]. Besides, FP was also applied to the consolidation of stone and wood [30,31].

Aims of this work were: (1) the study of the potential application of the Frontal polymerization technique as a new method for the preparation of controlled release dosage forms in which the drug loading and the polymer preparation occur simultaneously; (2) the evaluation of obtaining more dosage units by a unique preparation.

Polyacrylamide has been chosen as the polymer, also because its hydrogels are pH-sensitive and diclofenac sodium salt as a model drug.

The work has been developed by performing the following steps:

– preparation of polyacrylamide samples containing diclofenac sodium salt by Frontal polymerization and by batch polymerization as a comparison. Different poly-

mer-cross-linker ratios were used for preparing polymers characterized by two diverse degrees of cross-linking;

– evaluation of the drug stability during the sample preparation;
– determination of the monomer residue amount;
– sample characterization (drug content, morphology, and swelling properties);
– preparation and characterization of disks as single dosage units.

2. Experimental section

2.1. Materials

Diclofenac sodium (DS) was obtained from Crucianiprodotti Crual Srl (Rome, Italy). Acrylamide 97% (AAm), N,N′-methylenebisacrylamide (MBAAm), ammonium peroxodisulfate 98%, sodium hydroxide, pellets 97+% were obtained from Sigma Aldrich (Steinheim-Germany); methanol G Chromasolv, for gradient elution, and potassium phosphate monobasic were purchased from Sigma Aldrich (Seelze, Germany) and Carlo Erba SpA (Milan, Italy), respectively. All the other reagents are of analytical grade.

2.2. Sample preparation

Polymerization of acrylamide was performed using Frontal polymerizations (FP) and Batch polymerization (BP) as comparison. Various monomers to cross-linking ratios were employed to obtain polymers with different degrees of cross-linking. The composition of the produced samples is listed in Table 1.

Samples named A, B and C are characterized by an increase of cross-linking degree from A to C.

Drug free samples were also prepared by FP as a comparison (A3–C3).

2.2.1. Batch polymerizations

In a glass test tube (diameter 13 mm, length 160 mm) suitable amounts of monomer (AAm) and cross-linker (MBAAm), with or without DS, were dissolved in 1.5 g of hot water (50–60 °C) (Table 1). After manual stirring, 0.01 g of initiator (peroxodisulfate) were added to the solu-

tion. Tubes were immersed in oil bath at 70 °C and the polymerization was carried out for 4 h.

2.2.2. Frontal polymerizations

The tubes containing the solution obtained as described above were locally heated at the bottom level of the solution by using a soldering iron as a heat source until the formation of a propagating front became evident. The heat released during the conversion from monomer into polymer was responsible for the formation of a hot front able to self-sustain and propagate throughout the whole tube. The polymerization process was very rapid and took just a few minutes to be performed. (Even if, due to solvent boiling, front velocity cannot precisely given, it was determined to be approximately 2–3 cm/min).

After polymerization, cross-linked polymers were removed from tubes and the hydrogels, obtained in long cylindrical shape, were allowed to dry at room temperature during 24 h.

2.3. Monomer residues determination

The amount of unreacted monomers in all hydrogels prepared, both by BP and FP, was determined by UV–Vis spectrophotometry with the aim to calculate the polymer yield and to assess whether the amount of monomer residue was low enough and, therefore, non toxic.

A dried sample of 2.0 g was added to 1000 mL purified water and stirred for 3 h at room temperature. A sample of 0.1 mL of this solution was withdrawn and diluted up to 10 mL with purified water and measured spectrophotometrically at the wavelength of 197 nm (Hitachi U2001, Hitachi Instruments Inc.). AAm concentration was calculated referring to the calibration curve previously prepared ($y = 0.2031x + 0.0306$; $R^2 = 0.999$).

Each sample was analysed in triplicate (Relative Standard Deviation, RSD, within 3.0%).

2.4. Sample characterization

2.4.1. Drug content and loading capacity

The cross-linked hydrogels (A1–C1 and A2–C2) were analysed to evaluate the actual drug content (DC) and the loading capability (LC).

A dried sample (2.0 g), transferred in 1000 mL phosphate buffer solution pH 7.4 (USP 24) and stirred for 24 h at room temperature. Samples of 1 mL were withdrawn, diluted into 25.0 mL of buffer, centrifuged for 5 min at 12,800 rpm (Spectrafuge 24D, Labnet International,Inc., Edison, USA) and the surnatant was analysed spectrophotometrically. DS concentration was determined by using a UV-spectrophotometer (Hitachi U-2001, Japan) at the wavelength of 274 nm from the calibration curve previously prepared in phosphate buffer pH 7.4 ($y = 0.3032x + 0.0042$; $R^2 = 0.999$).

The real value of drug content was calculated as the detected amount of drug with respect to the theoretical amount of drug. DC and LC, expressed as percentage, were determined in triplicate for all batches (RDS less than 0.1%) as follows:

Table 1
Composition of samples prepared by Frontal polymerization (FP) and Batch polymerization (BP).

DCRS samples	FP	BP	Monomer		Crosslinker		DS (g)
			(g)	% (w/w)	(g)	% (w/w)	
A1	+		1.9	95	0.1	5	0.5
A2		+	1.9	95	0.1	5	0.5
A3	+		1.9	95	0.1	5	0
B1	+		1.5	75	0.5	25	0.5
B2		+	1.5	75	0.5	25	0.5
B3	+		1.5	75	0.5	25	0
C1	+		1.2	60	0.8	40	0.5
C2		+	1.2	60	0.8	40	0.5
C3	+		1.2	60	0.8	40	0

$$DC\ (\%) = (d_r/EM) \times 100 \tag{1}$$
$$LC\ (\%) = (d_r/d_t] \times 100 \tag{2}$$

where d_r is the weight amount of DS found in the hydrogel sample, EM is the examined quantity of hydrogel and d_t the weight amount of DS theoretically included into the DCRS.

2.4.2. Scanning electron microscopy (SEM) observation

The surface characteristics of DS, loaded and unloaded samples (A1–A3, B1–B3 and C1–C3) were studied by SEM, (Zeiss DSM 962 Carl Zeiss Inc., Germany). Samples were placed on a double-sided tape, which had previously been secured on aluminium stubs. The samples were then analysed at 20 kV acceleration voltage after gold sputtering (25 mm thickness), under argon atmosphere.

SEM observations were also performed on dried A1, A2–B1, B2–C1, C2 after washing out with water to rinse the drug out of the system.

2.4.3. Swelling study

Morphological changes of samples A1 and C1 prepared by FP kept in contact with an aqueous medium were observed by the stereomicroscope (Olympus SZX7, Olympus, Japan) and pictures were taken.

The degree of swelling of samples A1 and C1 kept in contact with an aqueous medium was determined. The different swelling capacity of samples was determined as follows: powder particles were placed on a microscope slide and covered with a cover glass to be observed with an optical microscope (magnification 10×) (Reichert Jung Micro-Star, W. Pabish, Milano, Italy) and pictures were taken by a digital camera (time zero).

Hundred microliter of phosphate buffer pH 6.8 were added to the sample and pictures were taken after 1, 3, 5 and 10 min. The images were registered and elaborated by a suitable software (UTHSCSA Image Tool version 3.00, The University of Texas Health Science Center, USA) able to determine the particle projected area from which the degree of swelling (SD) as percentage was calculated according to the following equation:

$$SD\ (\%) = A_{(t)}/A_{(0)} \times 100 \tag{3}$$

where $A_{(t)}$ is the area registered at specific time of observation and $A_{(0)}$ is the area registered at time zero.

2.5. Stability of the drug during DCRS preparation

With the aim to assess the integrity of the drug during the polymerization reactions employed to prepare the DCRS, samples were investigated by IR spectrophotometric analysis (Jasco FT/IR-460 PLUS Fourier Transform Infrared Spectrometer).

Tests were performed on pure drug, DS, on A3 (unloaded PAAm with low cross-linking degree, produced by FP) and on samples A1 and A2 (drug loaded delivery systems based on PAAm with low cross-linking degree and produced by FP and BP, respectively).

The IR analysis was carried out using the KBr method: pulverized dried sample (2.0 mg) was mixed with 150 mg of KBr with a pestle and mortar. From this mixture, 100 mg was taken for the preparation of KBr tablet at 9 tons of pressure under vacuum for 1 min. The spectra were scanned in the mid-IR region from 4000 to 600 cm^{-1}.

2.6. Preparation and characterization of single dosage units (disks)

In order to obtain from a unique preparation several single dosage units of small dimension and more suitable to a pharmaceutical use, after the preparation, the cylinders A1 and C1 were divided by a bistoury into three disks (upper, middle and lower disks) of similar size which were dried in oven till constant weight.

2.6.1. Drug content

Each disk coming from the sectioned hydrogels A1 and C1 (characterized by different cross-linking degree) was analysed to evaluate the actual drug content.

A dried sample (200 mg), transferred in 100 mL of phosphate buffer solution pH 7.4 (USP 24) and stirred for 24 h at room temperature. Samples of 1 mL were withdrawn, diluted into 25.0 mL of buffer, centrifuged for 5 min at 12,800 rpm (Spectrafuge 24D, Labnet International,Inc., Edison, USA) and analysed spectrophotometrically.

DS concentration was determined using a UV-spectrophotometer (Hitachi U-2001, Japan) at the wavelength of 274 nm from the calibration curve previously prepared in phosphate buffer pH 7.4.

The real value of drug content was calculated as reported above.

Measurements were performed in triplicate (RDS less than 0.2%).

2.6.2. In vitro release study

The in vitro drug release from powder (200 mg) was carried out in 1000 mL phosphate buffer, pH 7.4 using the USP 24 apparatus no. 1, at 37 ± 0.5 °C and 100 rpm (Erweka DT 70; Erweka GmbH, Heusenstamm, Germany). Filtered samples (1 mL) were withdrawn at different time intervals up to 6 h (5, 10, 20, 60, 120, 180, 240 and 360 min), spectrophotometrically at 274 nm (Hitachi spectrophotometer U-2001; Hitachi Instruments, Tokyo, Japan) using the calibration curve previously calculated to determine the amount of drug released. The in vitro drug release under acid condition was evaluated using HCl 0.1N at 37 ± 0.5 °C and 100 rpm along 2 h.

Triplicate measurements were performed (RDS less than 0.01%).

2.7. Statistical analysis

Data are presented as mean values ± RSD. Differences were assessed by using One way ANOVA followed by Dunnett's test and the nonparametric Kruskal–Wallis test; individual differences were evaluated using a post-hoc Dunn's test (GraphPad Prism, version 2.01; GraphPad software Incorporated). A value of $P < 0.05$ was considered statistically significant.

3. Results and discussion

3.1. Sample preparation

Samples obtained are characterized by a cylindrical shape, length of 3 ± 0.5 cm and diameter of 10 mm. The Fig. 1a shows A1, chosen as an example.

The cylindrical sample was sectioned into three units called disks (upper, middle and lower disk) with similar size (Fig. 1b).

3.2. Monomer residue determination

The amount of unreacted monomer was evaluated on DCRS samples, obtained by FP and by BP, characterized by the lower and the highest cross-linking degree, respectively.

The results, listed in Table 2, show that the percentage of monomer residue is generally very low and depends on the cross-linking degree: in particular, it increases when high cross-linking is employed, being 0.88% in case of A3 and 1.20% in case of C3 which are comparable with respect to monomer conversion occurring by BP.

3.3. Sample characterization

3.3.1. Drug content and loading capacity
DC and LC values (from 19.2 and 96%, in case of samples C, to 19.9 and 99% as concerning samples A) are very close to theoretical values (20 and 100%, respectively). Data show that no differences in loading capability are found ($P > 0.05$) relating to the polymerization technique employed but the highest DC and LC values are established in the samples A characterized by the lowest cross-linking degree.

3.3.2. Scanning electron microscopy (SEM) observation
SEM observations were performed on DS pure drug and on A1–A3, B1–B3, C1–C3. Pictures of the observed samples are reported as Figs. 2–5.
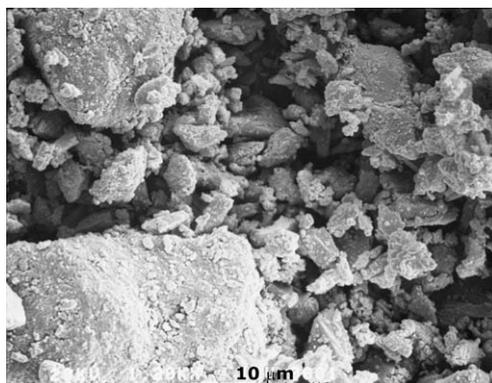
Table 2
Percentage of unreacted monomer found in the DCRS samples after the polymerization reaction.

DCRS samples	Mean weight of the sample (g)	Monomer residue (%) ± SD[a]
A3	2.02	0.88 ± 2.99
C3	1.86	1.20 ± 1.24
A3[b]	2.16	0.90 ± 2.71
C3[b]	2.00	1.33 ± 0.24

[a] Mean ± standard deviation, SD; n = 3.
[b] Samples prepared by bulk polymerization.


Fig. 2. SEM picture of DS pure drug. Magnification: 1200×.

As illustrated in Figs. 3–5 there are differences between the loaded (A–C1 and A–C2) and unloaded (A3–C3) DCRSs which have smoother and more compacted surface if compared with the loaded samples in which is possible to see particles of drug powder inhomogeneously dispersed.

DCRSs with diverse cross-linked degree are characterized by different morphological properties: C3 structure is more compact, regular and smooth.

After rinsing the drug out of the DCRSs A1–C1 and A2–C2 with water, SEM analysis was performed. These samples were named: A1r, A2r–B1r, B2r–C1r, C2r.
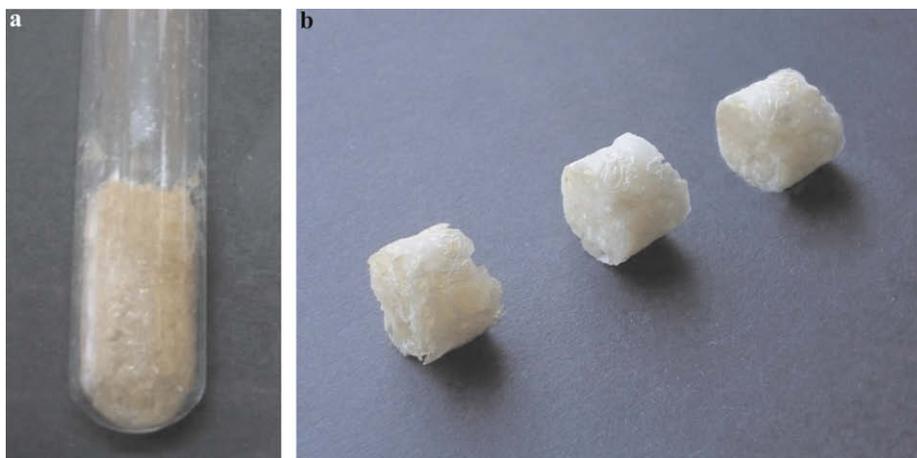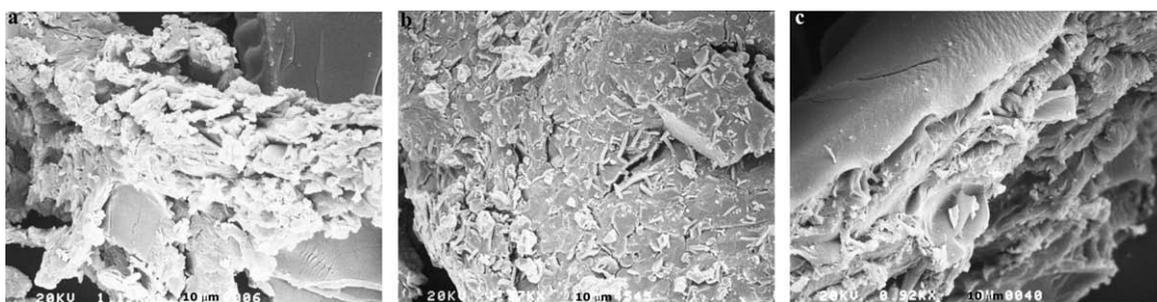

Fig. 1. A1 produced by FP.

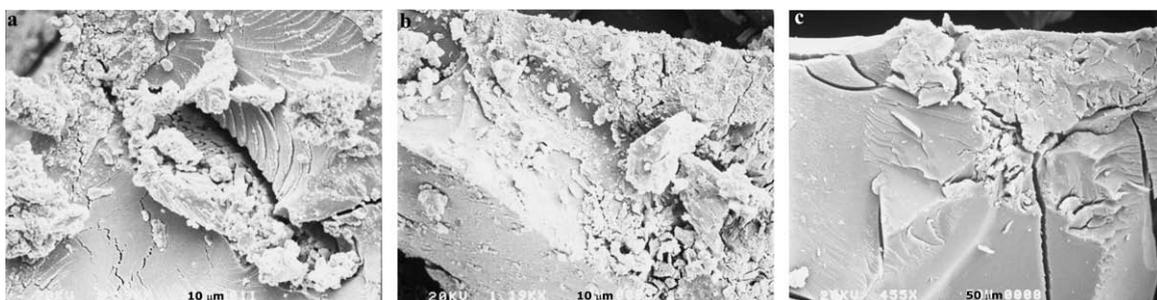**Fig. 3.** SEM picture of (a) A1, (b) A2 and (c) A3. Magnification: (a and b) 1200×, (c) 900×.

Fig. 4. SEM picture of (a) B1, (b) B2 and (c) B3. Magnification: (a) 1600×, (b) 1200×, (c) 455×.

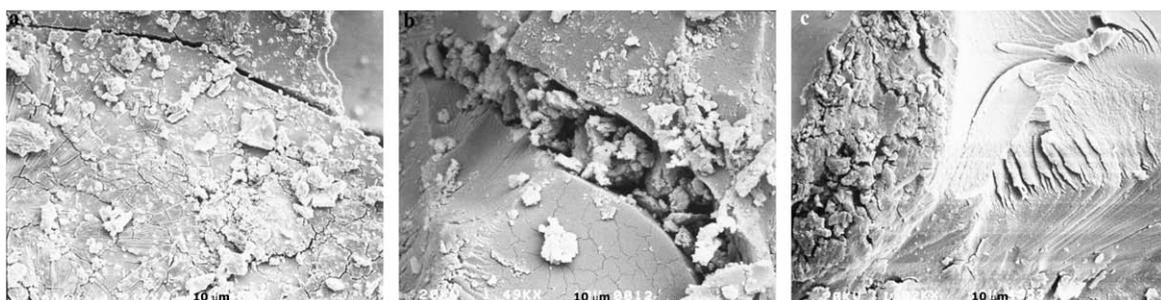**Fig. 5.** SEM picture of (a) C1, (b) C2 and (c) C3. Magnification: (a) 1200×, (b) 1500×, (c) 1000×.

The results show that the cleaned samples have smooth and compacted surface similar to the corresponding unloaded A3–C3 (Fig. 6) and that the dispersed powder observed before washing disappear while some cavities become visible.

No variation in surface characteristics is observed between DCRSs with regard to the polymerization method and cross-linking degree.

3.3.3. Swelling study

Samples A1 and C1, obtained by FP, were put in contact with phosphate buffer pH 6.8 and photostereomicroscopy observation was performed. Pictures were taken after 1 h. Fig. 7 shows the gelled samples. The images evidence the different structure of the samples, prepared by FP, with regard to the degree of cross-linking.

The water uptake capability of all samples prepared was also determined and the results are expressed as degree of swelling percentage (SD), calculated applying the Eq. (3), and illustrated in Fig. 8.

The results show that the samples A, characterized by the lowest degree of cross-linking, have the highest swelling capacity ($P < 0.05$): the SD rapidly increases to about 100% after 1 min and reaches values of 190% after 10 min.

By increasing the degree of cross-linking the swelling capability remarkably decreases and only 50–65% of swelling degree is obtained at the end of the test; however, there are not differences between samples B and C. The expected reduced swelling properties can be due to the rigidity of the structure of these samples.

By comparing the swelling capability of drug free samples A3 and B3 with the corresponding loaded ones A1, A2 and B1, B2, it can be seen that the drug presence influences the SD causing an improvement of the water uptake and thus higher percentages of swelling are obtained. On the
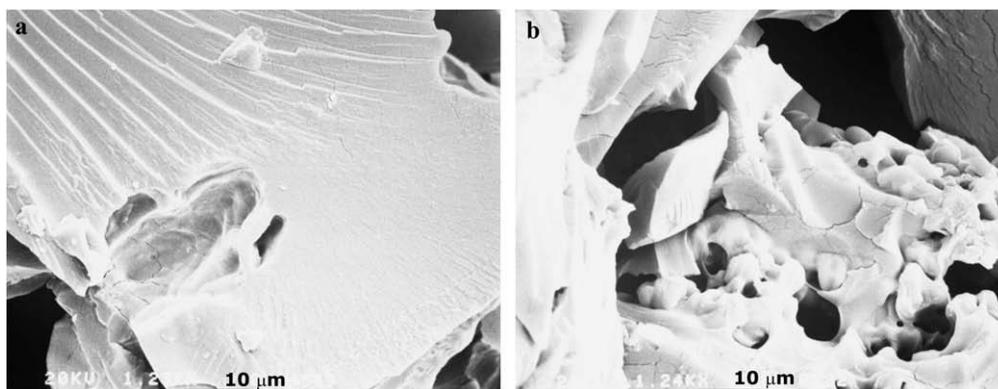
Fig. 6. SEM pictures of samples (a) A1r and (b) A2r, chosen as examples, washed out with water. Magnification: (a) 1200×, (b) 1240×.
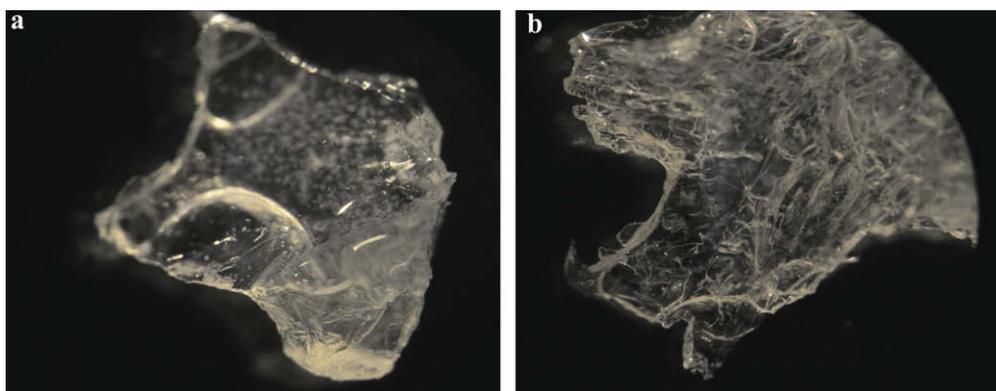

Fig. 7. Pictures of (a) A1 and (b) C1 hydrogels analysed by photostereo microscopy.
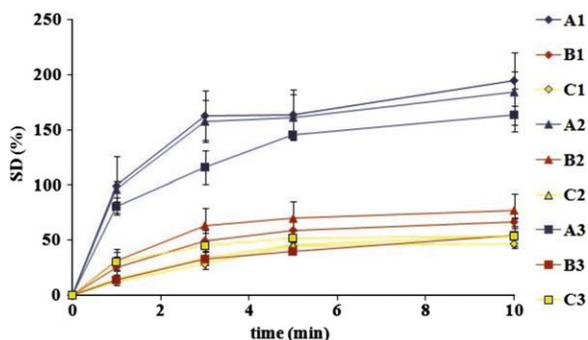

Fig. 8. Swelling percentage of A–C1, A–C2, A–C3 obtained by different preparation methods and characterized by different cross-linking degree; $P < 0.05$ for samples A versus samples C.

contrary there are not differences in SD between loaded and unloaded C samples ($P > 0.05$).

Nevertheless, the swelling capability does not depend on the polymerization techniques employed regardless of the degree of cross-linking ($P > 0.05$).

3.4. Stability of the drug during DCRS preparation

The integrity of the drug during the polymerization reactions was investigated by IR spectrophotometric anal-ysis. Tests were performed on pure drug, and on samples A1, A2 and A3. The IR spectrum in Fig. 9a is referred to the pure drug. The following signals are considered as ref-erence to the loaded samples:

Cl: 746, 317 cm^{-1}

C=O carboxylic: 1574, 1559 cm^{-1}.

IR spectrum of the unloaded A3 is reported in Fig. 9b.

Despite the different preparation method, the spectra of loaded samples A1 and A2 are superimposable: the peaks of the drug are recognised indicating that the drug stays unmodified inside the produced systems regardless of the kind of polymerization used.

The spectrum concerning the sample A1, is reported in Fig. 9c as an example.

3.5. Preparation and characterization of single dosage units (disks)

3.5.1. Drug content

The amount of drug loaded in each disk was determined to verify the distribution of the drug during the DCRS prep-aration and to evaluate the possibility to obtain three sin-gle dosage units with comparable properties. The results show that the drug is almost uniformly distributed along the whole sample and the disks are able to load about the same amount of drug without significant differences between the two hydrogels A1 and C1 analysed ($P > 0.05$).
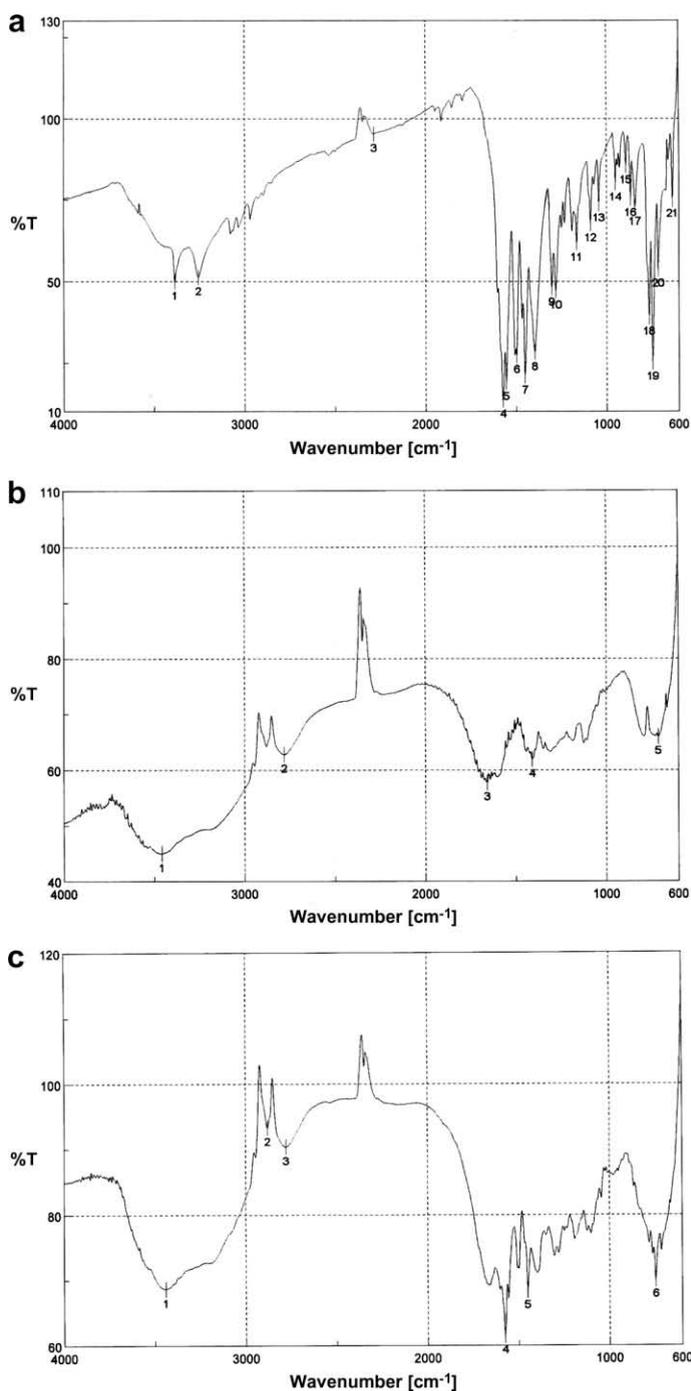
Fig. 9. IR spectra of (a) raw drug, DS, (b) A3 and (c) A1.

3.5.2. In vitro dissolution test

The release rate of the drug from each disk was determined. The release profiles are illustrated in the Fig. 10 from which it is evident that samples A and C have the same behaviour: 100% of the drug is released in the dissolution medium after about 2 h. Moreover there are not significant differences in the drug release rate concerning the disk chosen ($P > 0.05$). Thus, the results coming from the drug content and in vitro dissolution experiments indicate that disks obtained by sectioning the originally prepared hydrogel cylinder can be indiscriminately employed as three dosage units.

Furthermore, each disk was able to control the drug release in acidic medium.
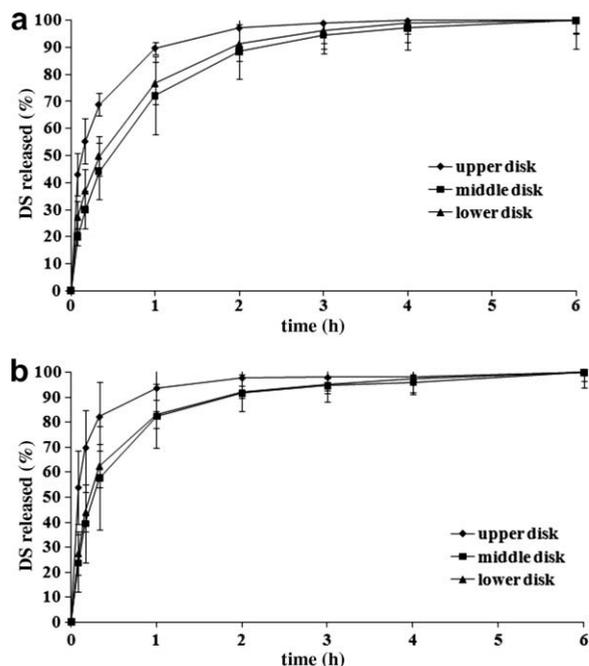
Fig. 10. The in vitro dissolution profiles of diclofenac sodium from disks obtained by dividing the whole samples (a) A1 and (b) C1.

4. Conclusions

Frontal polymerization is a fast, easy and economically convenient technique which has been applied to the preparation of an ever increasing number of polymer systems. Specifically, in the present work it was exploited for the production of drug controlled release systems based on gelling polymers such as PAAm.

The amount of monomer remaining in the samples depends on the cross-linking degree of the polymer; on the other hand, the values are always very low and far from the toxic concentrations.

The drug is not damaged during the hydrogel preparation regardless of the polymerization technique chosen. The amount of drug loaded is almost 100% and no differences were revealed between FP and BP indicating that the FP can furnish DCRS with properties similar to those obtained by BP but it is less time consuming and characterized by easier protocols. The loading of the drug does not modify the swelling aptitude of PAAm even if the degree of cross-linking seems to have influence on the swelling degree of the systems.

When the whole hydrogel is divided into three disks, they show similar amount of drug and in vitro drug release profiles. From these preliminary data it might be concluded that by a unique preparation of a hydrogel based on PAAm containing diclofenac sodium, using the FP, three single dosage units with matching in vitro release behaviour can be obtained and the polymer with different cross-linking degree can be chosen depending on the release time required.

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