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Spherical polymeric microparticles have been prepared by a reverse phase suspension polymerization technique. The starting polymer was α,β-poly(N-2-hydroxyethyl)-DL-aspartamide (PHEA), partially derivatized with glycidylmethacrylate (GMA). PHEA-GMA copolymer (PHG) was crosslinked in the presence of N,N′-dimethylacrylamide (DMAA) or N,N′-ethylenebisacrylamide (EBA). 5-fluorouracil was incorporated into PHG-DMAA or PHG-EBA beads both during and after the crosslinking process. Swelling studies revealed a high affinity toward aqueous medium, influenced by the presence of 5-fluorouracil. The in vitro release study showed that the release rate depends on the chemical structure of the beads and the procedure adopted to incorporate 5-fluorouracil into the microparticles.

Keywords 5-Fluorouracil, Derivatized Polyaspartamide, Drug Release, Radical Crosslinking, Swellable Beads

In recent years, significant advances have been made in the area of controlled drug delivery technology in the attempt to overcome drawbacks due to the use of the conventional dosage forms. By using drug delivery systems (DDS) it is possible to modify the rate and/or the time and/or the site of the drug release in order to reach therapeutic aims not obtainable with conventional dosage forms. This allows one to obtain several advantages including reduced toxic/side effects, improved efficacy, and patient compliance. Furthermore, and not less important, is the relatively low cost associated with the development of a DDS compared to that of the discovery of a new drug (Baker 1987; Dumitriu 1994; Kydonieus 1980; Speers and Bonanno 1999).

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Among polymeric matrices, hydrogels have been considered for use in a wide range of biomedical and pharmaceutical applications and, in particular, in the controlled release drug delivery area, mainly due to their high water content and rubbery nature (S. Kim 1985; Park 1997; Peppas 1987). Because of these properties, hydrogel materials resemble living tissue more than other synthetic biomaterials; furthermore, the high water content allows these materials to exhibit an excellent biocompatibility.

In evaluating the ability of a hydrogel to function in a particular controlled release device, two important characteristics should be considered: the network permeability and the swelling behaviour (Ritger and Peppas 1987b; Sinclair and Peppas 1984).

Drug release is due to the lowering of the glass transition temperature in the presence of the penetrating agent and the consequent relaxing of the macromolecular chains, during which time the drug diffuses through the swelling polymer (release during swelling) and subsequently diffuses through the gelled matrix (release after swelling) (Korsmeyer et al. 1983).

Many variables, such as the physicochemical properties of the drug, the water solubility of the polymer, the loading method of the drug and the cross-linking degree, control the release kinetics from these systems (Gander et al. 1989, 1990).

Hydrogels can be prepared both by physical and chemical methods; among the latter, radical polymerization through a reverse-phase suspension polymerization has some advantages compared with other techniques. It allows one to obtain spherical particles, with a narrow size distribution, which is preferred over other geometries for applications involving multiparticulate dosage forms (C. Kim and Lee 1992).

In this procedure, a water-soluble polymer with a dissolved free radical initiator is stirred in a large volume of organic solvent to form small droplets of the dispersed aqueous phase in the continuous organic phase. To minimize their interfacial free energy, these droplets adopt a strictly spherical shape, and their average size is controlled by the rate of stirring.

In a previous paper we reported the preparation of hydrogels via radical reaction employing, as starting polymer, an acryloylated polyaspartamide (Muzzalupo et al. 2001). In particular, a water-soluble and biocompatible macromolecule with a protein-like structure [i.e., α,β-poly(N-2-hydroxyethyl)-DL-aspartamide (PHEA)] was partially functionalised with glycidylmethacrylate (GMA) in order to introduce reactive vinyl groups into the side chain, thus obtaining the copolymer PHEA-GMA (PHG) (Giammona et al. 1997).

Beads with different physicochemical properties have been prepared by crosslinking of PHG alone or in the presence N,N′-ethylenebisacrylamide (EBA) or N,N′-dimethylacrylamide (DMAA) using a reverse phase suspension polymerization procedure (Muzzalupo et al. 2001).

The aim of our investigation is to evaluate the possibility of employing these new hydrogels as controlled release devices. For our purpose, we have chosen as a model drug, 5-fluorouracil (5-FU), which has long been used in cancer chemotherapy for the treatment of colon carcinoma by intravenous infusion or topically for the treatment of superficial basal cell epithelioma and for the treatment of keratoses, when conventional methods are ineffective (Harvey 1990). Unfortunately, its use is accompanied by toxic side effects, which include nausea and vomiting, ulcers, kidney damage, reduction in bone marrow function, and suppression of ovarian and testicular function (Chabner 1982). In addition, 5-FU is characterized by a short plasma circulation half-life as a result of its fast metabolism in liver (Fraile et al. 1980). Its administration as a hydrogel could potentially minimize the toxic side effects.

Drug loading into new hydrogels has been achieved through two different ways: by incorporation of the drug during hydrogel preparation or by soaking the hydrogel in a aqueous drug solution. All hydrogels have been characterized with regard to particle size distribution, thermal analysis, and swelling measurements in aqueous media which simulate biological fluids such as gastric, intestinal, and extracellular liquids. The effect of the two drug loading methods on the release kinetics have been investigated by in vitro studies under experimental conditions mimicking gastrointestinal fluids.

EXPERIMENTAL

Materials

All the reagents used were of analytical grade, unless otherwise stated. Anhydrous N,N-dimethylacetamide (DMA), n-hexane, CCl_4, N,N′-dimethylacrylamide (DMAA) and 5-fluorouracil (5-FU) were provided by Fluka Chemie. Glycidyl methacrylate (GMA) N,N′-ethylenebisacrylamide (EBA), 4-dimethylaminopyridine (4-DMAP) 99.9%, sorbitan trioleate (Span 85), N,N,N′,N′-tetramethylethylenediamine (TMEDA) and ammonium persulfate were purchased from Aldrich Chemical Co. α,β-poly(N-2-hydroxyethyl)-DL-aspartamide (PHEA) was prepared according to a procedure elsewhere reported (Giammona et al. 1987). The batch of PHEA used in the present study had a weight-average molecular weight of 56,900 ($M_w/M_n = 1.79$).

Derivatization of PHEA with GMA to obtain PHG copolymer was carried out in an organic phase (anhydrous DMA), using 4-DMAP as catalyst, purified and characterized according to a procedure reported elsewhere (Giammona et al. 1997). The degree of derivatization (DD) of prepared PHG, determined by ^{1}H-NMR was 28 ± 1 mol%. The weight-average molecular weight of PHG copolymer, determined by light scattering measurements, was 71,000 ($M_w/M_n = 1.86$).

Apparatus

Molecular weights of starting PHEA and PHG copolymers were determined by light scattering measurements, using a Dawn DSP-F Laser Spectra Physics Spectrometer. ^{1}H-NMR spectra were obtained with a Bruker AC-250 instrument operating at 250.13 MHz. Samples were solubilized in D_2O. FT-IR spectra were recorded as pellets in KBr in the range 4000–400 cm^{-1} using a Perkin-Elmer 1720 Fourier Transform Spectrophotometer. The resolution was 1 cm^{-1}. The number of scans was 100.

Particle size distribution and aqueous dynamic swelling measurements were carried out using an image processing and analysis system, Leica Quantimet Q 500, equipped with a Leica Wild 3D stereomicroscope. This image processor calculates the particle area and converts it to an equivalent circle diameter.

High-pressure liquid chromatography (HPLC) analyses were carried out using a Varian 9012 liquid chromatograph equipped with a Rheodyne 7125 injector (fitted with a 10 μl loop), a Kontron HPLC 432 detector, and a Hewlett-Packard 3394 integrator. A reversed-phase C_{18} column (μ Bondapak; 10 μm of 250 × 4.6 mm internal diameter, obtained from Waters) was used.

Differential scanning calorimetry (DSC) was performed on a Mettler TA 3000 calorimeter equipped with a DCS-30 cell and TC-10 processor. Samples were heated from 5°C to 180°C; the heating rate was 2°C/min. Before each test, the samples were carefully dried for 72 hours under vacuum in the presence of P_2O_5. The glass transition temperature, *Tg*, was determined as the temperature corresponding to the slope change in the specific heat-temperature plot.

Scanning electron microscopy (SEM) photographs were obtained with a Leo stereoscan 420; the sample surface was made conductive by the deposition of a layer of gold in a vacuum chamber.

Drug Loading During Crosslinking Reaction (Samples a′ and b′)

In a typical experiment, a mixture of hexane and carbon tetrachloride was placed in a round-bottomed cylindical glass reaction vessel fitted with an anchor-type stirrer and thermostated at 35°C, then treated, after 30 min of N_2 bubbling, with a solution of PHG, 5-FU, co-monomer (DMAA, for the sample a′) or cross-linker (EBA, for the sample b′) and ammonium persulfate in H_2O. The density of the organic phase was adjusted by

TABLE 1
Amounts of reagents, solvents, and initiators employed in the crosslinking reaction

Dispersed phase		Continuous phase		Initiators	
Reagents (mg)	Solvent (ml)	Solvents (ml)	Surfactant (μl)	$(NH_4)_2S_2O_8$ (mg)	TMEDA (μl)
PHG (352) DMAA (144) 5-FU (80)	H_2O (3)	CCl_4/Hexane (18/25)	Span 85 (150)	(80)	(160)
PHG (356) EBA (130) 5-FU (81)	H_2O (3.5)	CCl_4/Hexane (20/22)	Span 85 (150)	(70)	(150)

addition of CCl_4 so that the aqueous phase sank slowly when stirring stopped. With stirrers at 1000 rpm, the mixture was treated with Span 85 and, after 10 min with TMEDA, stirring was continued for another 60 min. All reagents and the amounts used in these experiments are reported in Table 1.

Each matrix so obtained was filtered, washed with 100-ml portions of 2-propanol, ethanol, and acetone, then dried at 10^{-1} mmHg in the presence of P_2O_5 to contant weight.

In order to verify the absence of chemical alteration of 5-fluorouracil under the conditions of radical polymerization, a preliminary test was performed without PHG, EBA, and DMAA, and the reaction mixture was analysed by HPLC. In particular, the solution, at a known concentration in 5-fluorouracil, was analysed after different times of reaction and the recorded chromatograms showed that the drug concentration was constant.

Drug Loading by Soaking Procedure after Crosslinking Reaction (Samples a″ and b″)

Empty microparticles of PHG/DMAA (sample a) and PHG/EBA (sample b) have been prepared following the above procedure but in the absence of drug. Then they were immersed in a concentrated aqueous solution of 5-fluorouracil and soaked for 5 days at room temperature. During this time, the mixture was continuously stirred and then the solvent was removed and microparticles (samples a″ and b″ based on PHG/DMAA/5-FU and PHG/EBA/5-FU respectively) were dried at 10^{-1} mmHg in the presence of P_2O_5 to contant weight.

Determination of Drug Amount Entrapped in the Beads

Aliquots of 50 mg of samples a′, b′, a″, and b″ were extensively extracted at 60°C with 60 ml of water/methanol (1:1 v/v) mixture. The liquids of extraction were collected and evaporated under vacuum at 40°C. The obtained residue, dissolved in methanol, was assayed by HPLC for the quantitative determination of the 5-FU.

Swelling Studies

Aliquots, weighed exactly, of the prepared microparticles were kept in contact with double-distilled water, HCl 0.1 N (pH 1), and phosphate buffers (NaCl, Na_2HPO_4, KH_2PO_4) at pH 6.8 and 7.4 until swelling equilibrium was reached; each swollen sample was filtered, blotted with paper, and weighed. Water content (WC %) was calculated as follows:

$$\mathrm{WC}(\%) = (W_s - W_d)/W_s \times 100$$

where W_s and W_d are the weights of the swollen and dry microparticles, respectively.

Aqueous dynamic swelling was determined by observing through an optical stereomicroscope equipped with an image processor, the variation of microparticle diameter in distilled water, pH 1, pH 6.8, and pH 7.4 aqueous solutions, at room temperature until the microparticles achieved the full swollen equilibrium with a diameter d_∞. The values of normalized diameter, d_t/d_0 have been determined, d_t being the diameter of swollen microparticle at time t and d_0 the diameter of dry microparticle.

The experiment analysed twenty microparticles of each sample and the results were in agreement within ±2% standard error.

Drug Release at pH 1.0 and 6.8 from Beads

Samples a′, b′, a″, or b″ (10 mg) were dispersed in flasks containing HCl 0.1 N (pH 1.0, simulated gastric fluid) and maintaned at 37 ± 0.1°C in a water bath for 2 h with magnetic stirring (100 rpm). To the samples a′ and b′, for which drug release was not complete after 2 h incubation at pH 1.0, a solution of 0.2 M tribasic sodium phosphate was added to adjust the pH to 6.8 (simulated intestinal fluid), according to the method reported in USP XXII (drug-release test, method A for enteric-coated particles). Sink conditions were maintained throughout the experiment. At suitable time intervals, samples were filtered and analysed by HPLC. Each experiment was carried out in triplicate and the results were in agreement within ±5% standard error.

RESULTS AND DISCUSSION

Aqueous solutions of PHG were crosslinked by radical polymerization through a reverse phase suspension polymerization technique in the presence of a co-monomer (DMAA) or a crosslinking agent (EBA) following a prodecure elsewhere reported (Muzzalupo et al. 2001). In order to determine the

ability of PHG/DMAA and PHG/EBA matrices to release drug molecules, beads loaded with 5-fluorouracil, chosen as a model drug, have been prepared. In particular, to evaluate the effect of the loading method on 5-fluorouracil release rate, drug was incorporated during the crosslinking reaction (samples a′ and b′ based on PHG/DMAA and PHG/EBA, respectively) or after the crosslinking reaction (samples a″ and b″ based on PHG/DMAA and PHG/EBA, respectively) as described in the experimental section.

The incorporation of drug during the crosslinking process was possible because 5-fluorouracil was unaltered under the reaction conditions as demonstrated by performing a preliminary stability test of the drug in the reaction mixture but in the absence of PHG, DMAA, and EBA.

For samples a′ and b′, the amount of drug incorporated was 2.58 and 2.73% w/w, respectively; no significant difference in the loaded drug amount occurred by varying the chemical structure of the beads. The soaking method has been carried out in such a way as to produce an amount of drug incorporated corresponding to 2.7% w/w for both the samples a″ and b″, (i.e., a value drug loading near to that obtained for samples a′ and b′) (see Table 2). The comparable value of drug loading allows correlation of the possible differences of behaviour of samples a′, b′, a″, and b″ to the different drug loading procedure.

All beads containing 5-fluorouracil were characterized by dimensional analysis using a stereomicroscope equipped with image processing. There is an asymmetric particle distribution with a maximum value of equivalent diameter in the range 5–10 μm for samples based on PHG/EBA (samples b′ and b″) and 15–20 μm for samples based on PHG/DMAA (samples a′ and a″), apart from the loading method. This is similar to data previously found for microparticles prepared in the absence of drug (Muzzalupo et al. 2001) and according to the hypothesis that the degree of crosslinking should increase in the following order PHG/DMAA < PHG/EBA.

The image processor used for the determination of particle size distribution, also calculates the roundness index, which was always near 1. The roundness index is a parameter that gives information about particle shape. It has been calculated by the following ratio: $(\text{Perimeter})^2/(4 \times \pi \times \text{Area} \times 1.064)$ were 1.064 is a correction factor for the angles produced by the image digitalisation. Values of roundness index corresponding to 1 indicate a spherical shape.

TABLE 2
Drug loading microparticles

Components	Sample name	Drug loading (w/w %)
PHG/DMAA + 5-FU (i)*	a′	2.58
PHG/EBA + 5-FU (i)*	b′	2.73
PHG/DMAA + 5-FU (ii)**	a″	2.60
PHG/EBA + 5-FU (ii)**	b″	2.71

*(i) Incorporation during crosslinking; **(ii) Soaking after crosslinking.

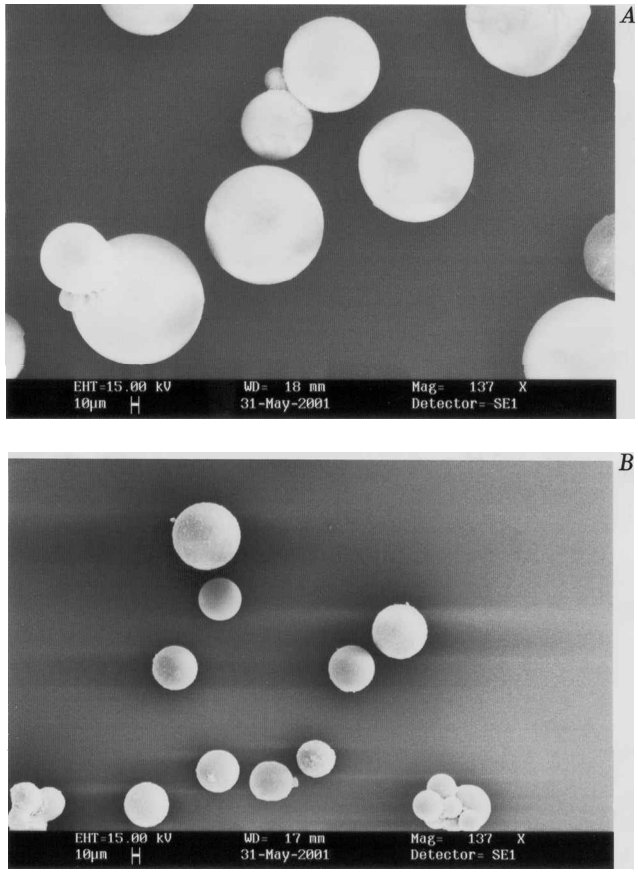

FIG. 1. Scanning electron micrographs of samples a′ (A) and b′ (B).

This result suggests that the incorporation of 5-fluorouracil into the prepared beads does not modify the distribution profile of microparticles. Scanning electron microscopy has confirmed the sperical geometry of all prepared samples and their uniform size.

As an example in Figure 1, the SEM micrographs of the samples a′ and b′ are reported. Analogous results have been obtained for samples a″ and b″. In addition, it is evident in Figure 2 the presence of micropores in the inside surface of samples b′ (similar results have been obtained for all other samples) according to the formation of a network structure.

Drug presence and loading method influence the values of glass transition temperature (*Tg*). *Tg* values of microparticles containing 5-fluorouracil are lower than those of empty beads (samples a and b) (see Table 3), thus suggesting a plasticizer effect of the drug molecules, which probably reduce the interaction between polymeric chains, and consequently, the rigidity of network. Obviously this effect is more marked when the drug is incorporated during the crosslinking process (drug molecules are tightly entrapped in the polymer network) than when it is introduced by the soaking procedure.

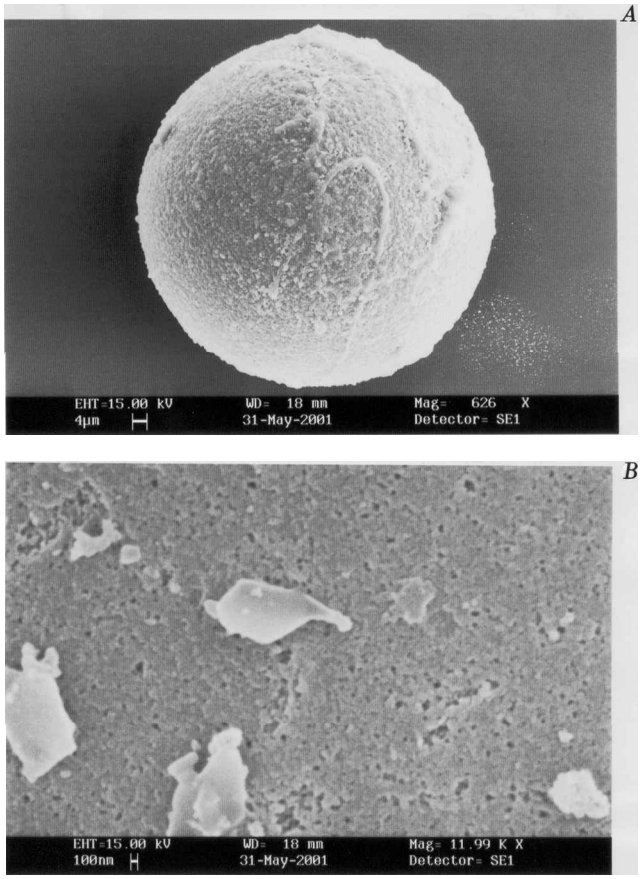

FIG. 2. Scanning electron micrographs. Outside surface of sample b′ (A). Inside surface of sample b′ (B).

In order to evaluate the affinity of prepared beads towards aqueous medium, the value of water content percentage (WC%) was determined and dynamic swelling measurements were carried out in aqueous media which simulate some biological fluids, such as gastric (pH 1), intestinal (pH 6.8), and extracellular (pH 7.4) liquids as well as in distilled water. In order to understand how the drug presence, depending on loading process, influences their swelling behaviour, we have compared the results from beads containing 5-fluorouracil with those from beads prepared in the absence of drug (samples a and b).

TABLE 3
Values of the glass-transition temperature (*Tg*) of unloaded and drug loaded microparticles

Sample	*Tg* (°C)
a	73
b	83
a′	43
b′	60
a″	55
b″	66

TABLE 4
Water content (%) of drug loaded and unloaded microparticles in various media

	Water content (WC %)			
Sample	H_2O	pH 7.4	pH 6.8	pH 1
a	80.5	78.8	77.3	73.7
b	58.8	58.3	52.4	42.8
a′	87.4	81.6	81.7	81.7
b′	76.2	74.3	74.9	71.0
a″	81.3	80.1	79.3	77.0
b″	60.5	63.9	57.5	56.2

Data reported in Table 4 show that the values of water content percentage (WC%) are the highest in double-distilled water, while in other liquids, the swelling was lower because of the osmotic pressure and ionic strength of media. In addition, the swelling ability of PHG/DMAA (sample a) beads is greater than that of PHG/EBA (sample b) for all investigated media, according to the different crosslinking degree (greater for sample b) and hydrophilic/hydrophobic balance of the microparticles.

It is evident that 5-fluorouracil affects the value of WC%, especially for samples a′ and b′. In particular, the presence of drug causes an increase of water uptake, probably because drug molecules act as a plasticizer reducing the interaction between polymeric chains thus causing a greater interaction with aqueous medium. According to the *Tg* values, the effect of drug presence on WC% is more marked for samples a′ and b′. In order to have information about the processes that occur during swelling, we have performed dynamic swelling measurements. In particular, we have evaluated, through an optical stereomicroscope equipped with an image processor, the variation of microparticle diameter as a function of time, when the samples were kept in contact to the media reported above.

The diameter of unloaded microparticles increases monotonically towards the equilibrium swollen value (d_∞), according to the different crosslinking degree and the nature of penetrant medium following the trend discussed above for WC% values. On the contrary, loaded beads swell until the diameter reached maximum value before a gradual approach to a lower equilibrium value. This behaviour is due to the combination of both matrix swelling and drug diffusion. Water absorption increases and drug diffusion decreases the microparticle dimensions (Lee 1985). During the process both phenomena take place. However, when water absorption predominates over drug diffusion, the microparticle diameter increases, reaching the maximum swollen value. When drug diffusion prevails, the microparticle diameter decreases toward the lower equilibrium swollen value.

Dynamic swelling measurements confirm that loaded samples (especially samples a′ and b′) have an affinity towards

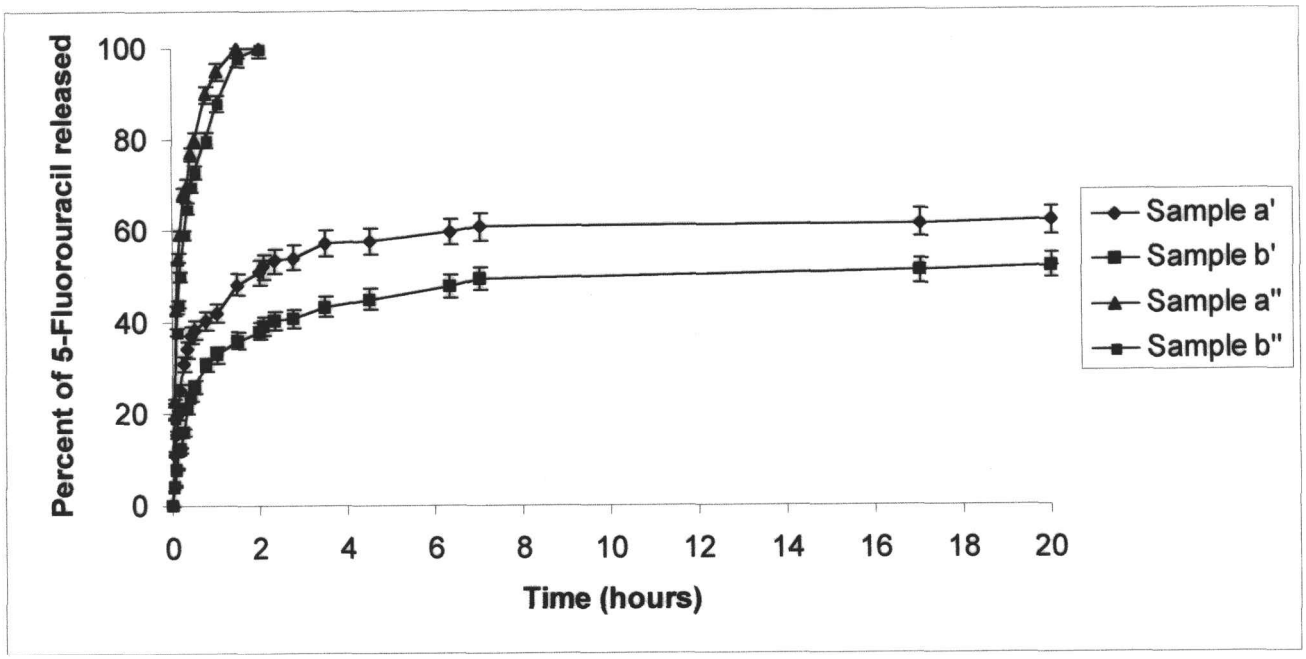

FIG. 3. Release of 5-fluorouracil at pH 1 from 0 to 2 hours (samples a′, b′, a″, and b″) and at pH 6.8 from 2 to 20 hours (samples a′ and b′).

aqueous medium greater than unloaded samples, according to WC% values reported in Table 3. The fast swelling and the high values of water content percentage suggest a potential biocompatibility of beads and allow one to suppose that the prepared matrices have a good ability to release entrapped drug molecules in a physiological medium.

In order to confirm this supposition, we have carried out in vitro release studies at 37°C at pH 1 (simulated gastric fluid) and pH 6.8 (simulated intestinal fluid) using the pH change method. Experimental data have shown that the release rate depends on the chemical structure of beads and the procedure adopted to incorporate 5-fluorouracil into the microparticles. Figure 3 depicts drug release, expressed as the percent of drug (related to the entrapped total dose) delivered as a function of time.

The experimental data revealed a more rapid release of drug from the samples a″ and b″, prepared by soaking procedure, than that obtained from the samples a′ and b′ in which the drug was incorporated during crosslinking process. In particular, the drug is completely released at pH 1.0 from the samples a″ and b″ within 2 hours, probably because in the soaking method the drug molecules are not tightly entrapped in the network. The initial burst effect is due probably to drug molecules adsorbed on the surface of particles, which present a large surface area of contact with the release medium due to their small dimensions. For the samples a′ and b′ the initial burst effect is more reduced than samples a″ and b″, and after 2 hours of incubation at pH 1 only the about 50% of drug was released from sample a′ and 38% from sample b′. For this reason, we have continued the experiment by changing pH from 1.0 to 6.8 and the release was followed for 20 hours. However, in this condition, which simulates the intestinal fluid, drug release is not complete (i.e., the crosslinked structure of the matrix reduces the mobility of drug which consequently is released in a prolonged way).

The effect of different chemical structure and crosslinking degree of investigated samples on release rate is evident, especially for samples a′ and b′ (i.e., samples based on PHG/DMAA release the drug with a greater rate than the samples based on PHG/EBA).

Since the microparticles have a well-defined geometry and a narrow dimensional distribution, we have determined the mechanism of drug release (Fickian or non-Fickian). In particular, the kinetics of 5-FU release were analysed using the power law expression (Korsmeyer et al. 1983)

$$M_t/M_{\text{inf}} = K t^n \qquad [1]$$

for $M_t/M_{\text{inf}} \leq 0.6$. M_t/M_{inf} is the drug fraction released at time t, K and n are a constant and the kinetic exponent of drug release, respectively. Although the use of this equation requires detailed statistical analysis, the calculated exponent, n, gives an indication of the release kinetics [for spherical matrices it ranges from Fickian ($n = 0.43$) to Case II transport ($n = 0.85$), while it is anomalous for intermediate values)] (Ritger and Peppas 1987a). The n values reported in Table 5 indicate that the kinetics of 5-FU release are anomalous, as expected for swellable microparticles. A more informative analysis can be obtained by

TABLE 5
Fitting of release data with Equations 1, 2, and 3

Sample	$K\ 10^3$ (min^{-n})	Exponent n	r
	$M_t/M_{inf} = Kt^n$	(1)	
a′	122.16	0.50	0.994
b′	54.34	0.65	0.991
a″	155.28	0.61	0.982
b″	138.95	0.56	0.981
	$K_1\ 10^3$ ($min^{-1/2}$)	$K_2\ 10^3$ (min^{-1})	
	$M_t/M_{inf} = K_1t^{1/2} + K_2t$	(2)	
a′	131.28	−4.77	0.984
b′	94.35	−2.48	0.992
a″	219.62	−12.72	0.991
b″	186.96	−9.63	0.995
	$D_i 10^{12}$ ($cm^2\ s^{-1}$)		
	$1-M_t/M_{inf} = (6/\pi^2)\exp -(\pi^2\ D_i t/r^2)$	(3)	
a′	13.69		
b′	0.83		
a″	26.87		
b″	4.37		

fitting the data with the model proposed by Peppas and Sahlin (1989). The equation for this model is:

$$M_t/M_{inf} = K_1t^{1/2} + K_2t \quad [2]$$

with $M_t/M_{inf} \leq 0.95$. In this equation, the first term is the Fickian contribution and the second term is the Case II relaxational contribution. Table 5 reports K_1 and K_2 values calculated according to equation 2. The term $K_1t^{1/2}$ is greater than the term K_2t, for all investigated samples, indicating that the predominant mechanism for 5-FU release is Fickian diffusion through the swollen microparticles.

Finally, in order to calculate the apparent diffusion coefficient, D_i, the final portion of the release profiles ($0.6 \leq M_t/M_{inf} < 1$) was analysed by means of the approximative diffusion equation for spherical matrices (Baker and Lonsdale 1974; Gander et al. 1988):

$$1 - M_t/M_{inf} = (6/\pi^2)\exp - (\pi^2\ D_i t/r^2) \quad [3]$$

where r is the mean radius of the swollen microparticles. The calculated D_i values reported in Table 5, confirm that the drug diffusion from samples a″ and b″ is faster than from samples a′ and b′.

Release data suggest that samples a′ and b′ offer good potential as systems for the sustained release of bioactive molecules.

CONCLUSION

Spherical microparticles have been obtained by reverse phase suspension polymerization using, as a starting polymer, a polyaspartamide functionalized with glycidylmethacrylate in the presence of dimethylacrylamide or N,N′-ethylenebisacrylamide. The suitability of these matrices as drug delivery systems has been evaluated by using 5-fluorouracil as a model drug. Beads are able to trap the bioactive agent during or after the crosslinking reaction by a soaking procedure. The presence of the drug increases the swelling ability in media which simulate some biological fluids and reduce the rigidity of the network as revealed by calorimetric measurements. Both these effects facilitate drug release, where the mechanism is essentially controlled by diffusion. Release data showed that the soaking procedure produces beads that give a fast release whereas samples in which drug was incorporated during the crosslinking process are suitable for prolonged drug release.

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