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European Journal of Pharmaceutics and Biopharmaceutics 54 (2002) 75–81

European Journal of Pharmaceutics and Biopharmaceutics

www.elsevier.com/locate/ejphabio

Research paper

A novel approach for the preparation of highly loaded polymeric controlled release dosage forms of diltiazem HCl and diclofenac sodium

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Received 3 August 2001; accepted in revised form 31 January 2002

Abstract

In this investigation, modified-release dosage forms of diltiazem HCl (DT) and diclofenac sodium (DS) were prepared. The development work comprised two main parts: (a) loading the drug into ethylene vinyl acetate (EVA) polymer, and (b) generation of a non-uniform concentration distribution of the drug within the polymer matrix. Phase separation technique was successfully used to load DT and DS into the polymer at significantly high levels, up to 81 and 76%, respectively. Size diameter of the resultant microspheres was between 1.6 and 2.0 mm. Controlled-extraction of loaded microspheres and high vacuum freeze-drying were used to generate the non-uniform concentration distribution and to immobilize the new drug distribution within the matrix. Parameters controlling the different processes were investigated, and hence optimal processing conditions were used to prepare the dosage forms. Rates of drug release from the two dosage forms in water and in media having different pH were found to be constant for an appreciable length of time (>8 h) followed by a slow decline; a characteristic of a non-Fickian diffusion process. Scanning electron microscopy studies suggested that the resultant release behavior was the outcome of the combined effects of the non-uniform distribution of the drug in the matrix and the apparent changes in the pores and surface characteristics of the microspheres. Comparison of release rate–time plots of dissolution data of marketed products with the newly developed dosage forms indicated the ability of the latter to sustain more zero order release.

Keywords: Diclofenac sodium; Diltiazem HCl; Controlled release dosage forms

1. Introduction

Attempts to prepare controlled release devices by dispersing an active agent in a polymer matrix are reported in the literature. In these systems, the drug particles were either dissolved or uniformly dispersed within the matrix. Release from such systems, which presumably have uniform drug concentration distribution, typically starts initially high then eventually reaches a plateau. The observed release behavior is a consequence of increased diffusional path length and decreased area at the penetrating diffusion front. The increase in diffusional distance results from the fact that drug leaching starts at the surface, then at the layers just beneath the surface until the core. As a result, these systems failed to exhibit zero-order release [1–3]. Several approaches were investigated to circumvent this difficulty [1–4]. The attempts included use of specific matrix geometry and introduction of a constant rate of surface erosion or a constant rate of solvent front penetration. However, the applicability of these approaches was limited by the need to maintain a constant surface area at the solvent front.

Lee and co-workers explored a different concept to achieve zero-order drug release from a glassy polymer matrix. In their approach, drug distribution within the matrix was manipulated in such a manner that drug concentration increases toward the core; thus, creating a non-uniform drug distribution. The initial drug concentration profile is theorized to be sigmoidal in shape with an inflection point [1–3]. This procedure subjects the drug-loaded polymer to a controlled-extraction process, followed by a high vacuum freeze-drying step. The latter process rapidly removes the swelling solvent and immobilizes the non-uniformly distributed drug in the matrix. The resultant non-uniform drug distribution compensates for the increase in the aforementioned diffusional distance and generally causes the product to exhibit a constant release rate for a reasonably long period of time.

Ethylene vinyl acetate (EVA) copolymer has been used in the formulation of monolithic devices for the controlled delivery of macromolecule drugs such as insulin [5],

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0939-6411/02/$ - see front matter
PII: S0939-6411(02)00035-8

heparin and enzymes [6]. It is also used as a rate controlling membrane in Alza Ocusert, Progestasert IUD, Transderm-Nitro, and Estraderm [6]. EVA copolymer is Federal Drug Administration (FDA) approved, biocompatible, safe, stable and heat-sealable [7]. Diltiazem hydrochloride (DT) is a calcium antagonist used in cases of hypertension and angina. Diclofenac sodium (DS) is a non-steroidal anti-inflammatory drug used for chronic treatment of osteoarthritis and rheumatoid arthritis. Both drugs are administered orally and could induce various side effects. It is desirable to formulate these drugs as controlled release dosage forms, hence, alleviating some of the associated problems and afford better management of plasma levels through the course of treatment [8–10].

This research investigates the development of highly loaded modified-release dosage forms of DT and DS using the concept of generating a non-uniform drug distribution in an EVA matrix. The work also comments on release from the developed dosage forms as compared to those of marketed products.

2. Materials and methods

2.1. Materials

De-ionized double distilled water was used. DT and DS were kindly supplied by the Arab Pharmaceutical Manufacturing Company, Salt, Jordan. Methylene chloride and EVA copolymer pellets with vinyl acetate content of 40% were purchased from Janssen Chimica, Belgium. Acetone and ethanol of analytical grade were purchased from Lab-Sacan, Ireland. Potassium dihydrogen phosphate, sodium hydroxide and hydrochloric acid were purchased from Merck, Germany. White opaque hard gelatin capsules (Size 3) were kindly supplied by the Arab Center for Pharmaceuticals and Chemicals, Amman, Jordan.

2.2. Drug loading of polymer

The drug–polymer microspheres were prepared using a non-solvent phase separation technique. A 10% w/v solution of EVA copolymer was prepared in methylene chloride. Weighed amounts of DT (7.6 g) or DS (9.2 g) were suspended in 30 or 25 ml of the polymer solution, respectively, then vortexed to form a uniform suspension. The suspension was then pumped, in a drop-wise manner using a peristaltic pump (S035 issue; Watson-Marlow, Famouth, Cornwall), into 20 ml of cold unstirred absolute ethanol or acetone at −70°C, for DT and for DS, respectively [11]. The mixture gelled immediately upon contact with the cold solvent forming nearly spherical shaped droplets. After warming to room temperature, the solvent medium was replaced with a fresh solvent and left standing overnight. The microspheres were removed from the solvent and dried for 5 h in a vacuum oven at room temperature. The diameters of 20 beads were measured using both a zone reader (Pool Bioanalysis Italiana, Italy) and a micrometer (W and F company, England) and the average diameter was calculated. To determine percentage of loading of the treated DT beads, an exact weight was dissolved in methylene chloride and the absorbance was measured at 240 nm using Beckman DU-7HS spectrophotometer (Beckman, USA). In case of DS, an exact weight of loaded microspheres was dissolved in methylene chloride then extracted with distilled water and the concentration of the aqueous portion was determined spectrophotometrically at 275 nm.

2.3. Modification of drug distribution in the loaded microspheres

To achieve the non-uniform distribution of the drug in the matrix, the dry loaded microspheres were suspended for 70 min in 1:1 ethanol–water solvent mixture at 37°C with constant stirring at 250 rpm using USP XXIII dissolution Apparatus II (Erweka 6D, Germany). The microspheres were then removed from the extracting solvent mixture and subjected to vacuum freeze-drying (Alpha Chrisp, Germany) under reduced pressure of 0.4 atm. for 10 h. In the subsequent discussion, these microspheres are designated as treated microspheres or beads otherwise they are called untreated. In an attempt to optimize the controlled-extraction and the freeze-drying of the loaded beads, variables controlling the two processes were investigated. Extraction time, extraction solvent, extraction temperature, stirring rate of the extraction process, and freeze drying time were specifically investigated for their effects on release of the drug from treated DT beads. Table 1 summarizes experimental conditions investigated and corresponding evaluation criteria used to arrive at an optimized experimental procedure. Experimental conditions used in this section were based on results obtained from these studies.

2.4. Release studies

Release of the drugs from the loaded microspheres was studied using USP XXIII, Dissolution Apparatus II (PTWSC, Pharma test, Hainburg, Germany, connected to auto-sampler 98-100-064, Hanson research, Chatsworth, CA, USA). In the case of DT, 135 mg beads loaded at 67% level, equivalent to 90 mg DT, was placed in 900 ml distilled water at 37°C and stirred at 100 rpm. In the case of DS, 130 mg beads loaded at 76% level, equivalent to 100 mg DS was placed in 900 ml distilled water or 0.3% Tween 80 aqueous solution at 37°C and stirred at 50 rpm. The 0.3% Tween 80 solution was used as a potentially more differentiating dissolution medium to compare with the release in water. Samples were withdrawn at fixed time intervals and replaced with fresh release media. The drug concentration in each sample was then determined spectrophotometrically at 240 and 275 nm for DT and DS, respectively. Release from brand name products; Dilzem 90 mg SR tablets and Cardizem 90 mg capsules and the newly developed DT dosage form filled in hard gelatin capsules,

Table 1
Effects of changing the conditions of controlled-extraction and freeze-drying processes on the release of diltiazem HCl from treated microshpheres

Profile criterion	Variables studied											
	Extraction time (min)			Extraction solvent				Extraction temperature		Stirring rate (rpm)		Freeze-drying time (h)	
	10	30	70	Eth:H_2O	H_2O	pH2	pH7	29°C	37°C	150	250	15	25
k[a](mg/h)	5.74 ± 0.156	5.62 ± 0.223	5.03 ± 0.175	3.33 ± 0.091	4.16 ± 0.107	4.83 ± 0.359	4.62 ± 0.273	4.63 ± 0.137	4.16 ± 0.107	5.26 ± 0.349	4.16 ± 0.107	4.16 ± 0.107	4.46 ± 0.130
L[b](h)	8	8.5	9.5	15	12	9	9	9	12	9	12	12	12
O[c](mg)	60.51	58.64	55.93	37.89	48.30	55.27	51.17	52.19	48.30	58.34	48.30	48.30	51.54
R[d]	0.998	0.997	0.997	0.996	0.997	0.992	0.994	0.997	0.997	0.994	0.997	0.997	0.997

[a] k is zero-order release rate constant, as determined from the linear segment of the curve.
[b] L is duration of constant release (h).
[c] Q is the amount (mg) released in 12 hours.
[d] R is correlation coefficient for the linear segment of the curve.

was investigated in 900 ml water at 37°C and 100 rpm. Release from the brand name product; Voltaren XR 100 mg tablets and the newly developed DS dosage form filled in hard gelatin capsules, was investigated in 900 ml buffer of pH 6.8 at 37°C and 50 rpm.

2.5. Scanning electron microscope studies

The shape and characteristics of the micro-surface of treated and untreated microspheres were examined and photographed using a digital scanning electron microscope (DSM 950, Zeiss, Germany). Four to five microspheres loaded with the drug were placed on the sample holder whose surface was coated with liquid carbon. The samples were then dried with a gentle stream of air. Samples were examined at suitable magnifications using a voltage of 10 kV. Processing parameters were optimized to obtain the best possible micrographs. Electron photomicrographs of treated and untreated microspheres after being subjected to dissolution for 4 and 22 h in the case of DS, and only for 4 h in the case of DT, were similarly prepared.

3. Results and discussion

3.1. Drug loading and preparation of microspheres

Equilibration of EVA pellets with excess amount of DT in appropriate solvent mixture to load the drug into the polymer, resulted in beads with very low drug content. Release of DT from these beads was almost undetectable. Consequently, this approach was judged unsuitable and the non-solvent-phase separation method was used to load the polymer with the desired amount of the drug and to generate microspheres of the desired characteristics and particle size. Using this technique, high percentages of drug loading were achieved; up to 81% in the case of DT and up to 76% in the case of DS. The success in achieving such a high a percentage of loading could be due to the high drug loading-capacity that EVA offers and the ability of the phase separation process to have the drug particles engulfed by the polymer without disruption of the matrix structure. The resultant beads were quite reasonably spherical in shape with particle size diameter ranging from 1.6 to 2.0 mm. The relatively narrow range of particle size suggests reasonably controlled loading and sphere generation processes. Moreover, microspheres obtained by this technique were non-tacky and non-sticky. They were also freely flowing regardless of the percentage of drug loading. Furthermore, changing the drug/polymer ratio in the drug–polymer suspension changed the percentage of drug loading. Rates of drug release increased with increasing drug loading. The increase in release rates could be due to the associated increase in the fluid-filled cavities created by dissolution and diffusion of the drug particles near the surface, which in turn resulted in an increase in the permeability of the drug [4]. Release data of untreated DT beads with different percentage of loading,

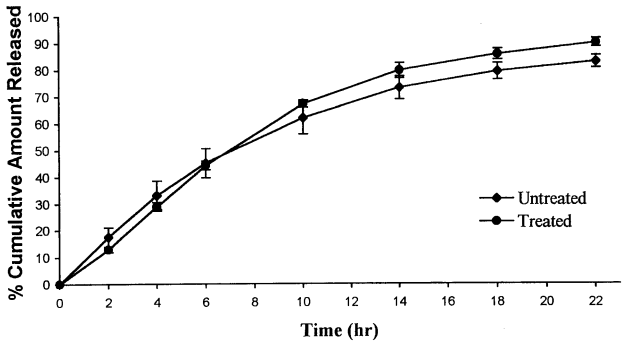

Fig. 1. Comparison of cumulative amount of Diltiazem HCl released from treated and untreated microspheres in water at 100 rpm and 37°C.

when plotted according to a modified Higuchi equation [4,12] describing release from monolithic matrix devices, showed applicability of the model up to 70% release. These results support the conclusion that the untreated microspheres belong to the monolithic matrix dispersion type. A similar conclusion was reached regarding the untreated DS microspheres.

3.2. In vitro release of drugs from untreated and treated microspheres

After the controlled extraction of loaded beads, it could be seen that the core section was rich in drug content which decreased towards the outer layers. Freeze-drying immediately caused immobilization of the drug and fixation of the new drug concentration profile within the beads. Fig. 1 shows the cumulative amounts of DT released from treated and untreated beads. It is apparent that the release profile of the treated product assumed a linear trend up to 10 h. The data shown in Fig. 1 were further processed and presented as plots of the rates of release versus time plots as shown in Fig. 2. This type of plot helps in delineating the kinetics controlling release mechanisms. From Fig. 2, it is obvious that, while release from the untreated beads was controlled by a first order or Higuchi type kinetics, release from treated beads obeyed zero-order kinetics up to more than 70% release. These findings are in harmony with the expected release profiles from polymer matrices with uniform and non-uniform drug distribution, respectively [1,2]. The

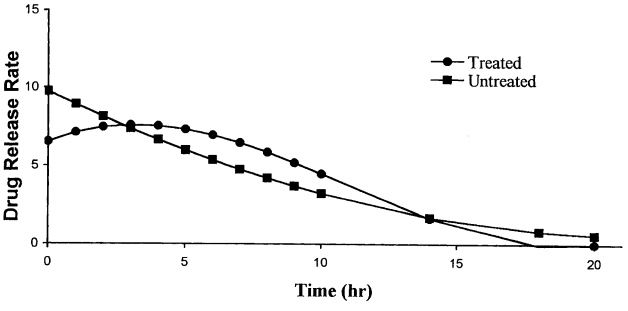

Fig. 2. Comparison of rates of release of Diltiazem HCl (mg/h) from treated and untreated microspheres in water at 100 rpm and 37°C.

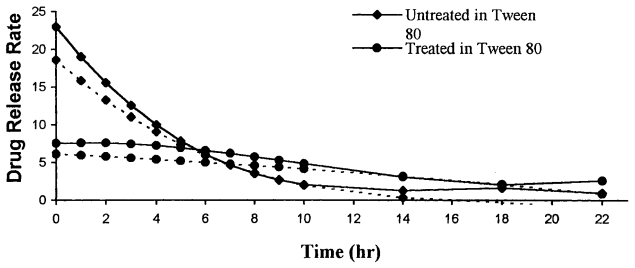

Fig. 3. Comparison of Diclofenac sodium release rates (mg/h) from treated and untreated microspheres in 0.3% Tween 80 aqueous solution (-) and Water (---) at 100 rpm and 37°C.

constant release obtained from the treated beads could be explained in light of the fact that the non-uniform drug distribution within the beads helped to compensate for the increase in the diffusional path length. Similar conclusions regarding DS are drawn from Fig. 3, which depicts the rate–time profiles of treated and untreated beads of the drug in two different release media.

3.3. Scanning electron microscope studies

Shown in Figs. 4 and 5are digital scanning electron microscope pictures of treated and untreated beads of DS and DT, before and after dissolution, respectively. From these pictures, it seems that before dissolution, the morphology of surfaces of treated and untreated beads were quite similar. However, after dissolution, surfaces of the untreated beads showed a significant number of relatively large irregular pores penetrating deep into the surface layer. On the other hand, the surfaces of the treated leached beads were covered with small, more or less uniformly distributed pores. Therefore, it is reasonable to assume that the combined controlled-extraction/freeze-drying process not only affected the drug distribution within the beads but also influenced their surface characteristics. As demonstrated earlier, release profiles of untreated beads exhibited high initial rates of release which declined with time. From the scanning electron micrographs, the presence of large, non-uniform, deep pores on the surfaces of untreated

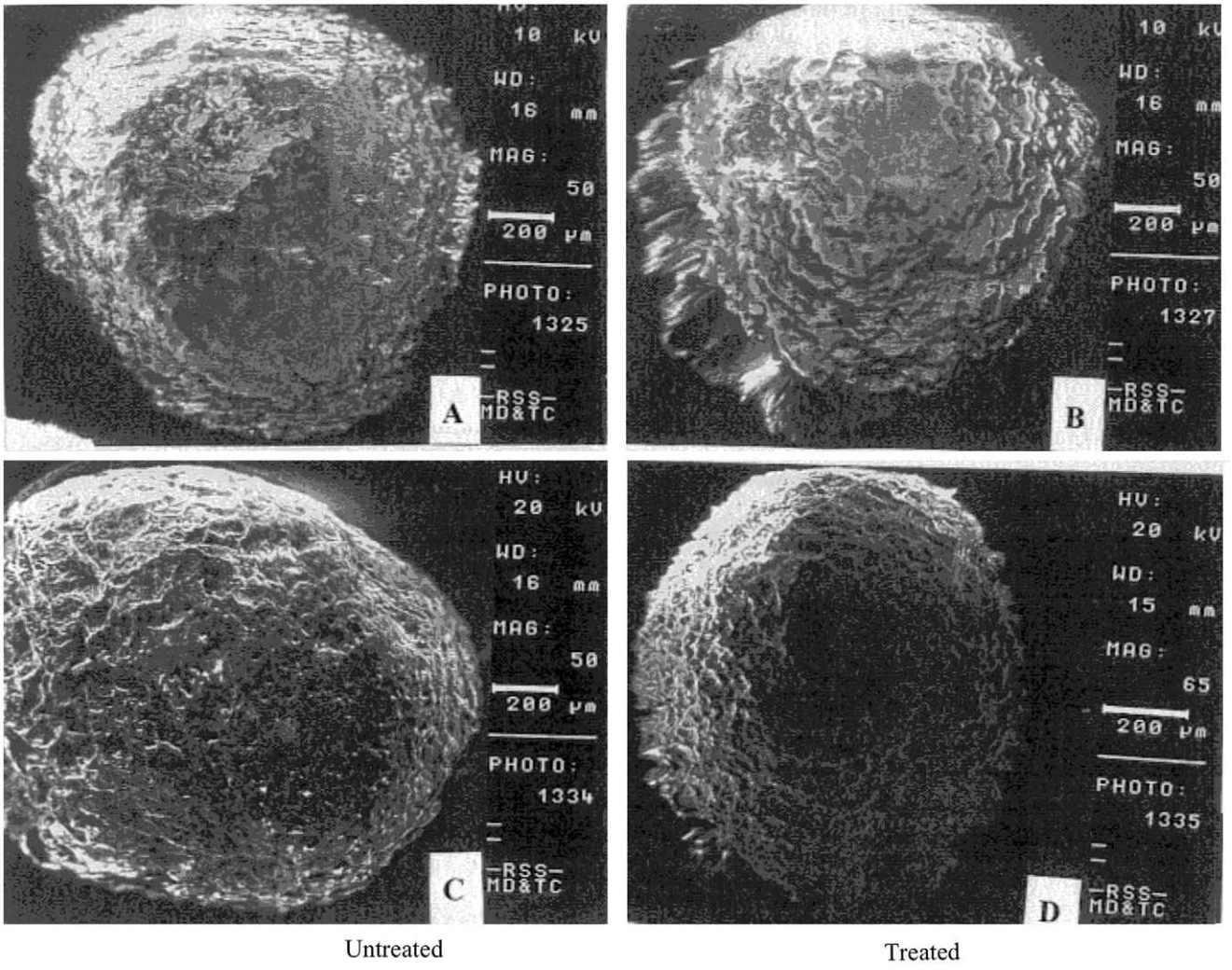

Fig. 4. Scanning electron micrographs of treated and untreated microspheres of diclofenac sodium. (A, B): before dissolution; (C, D): after dissolution.

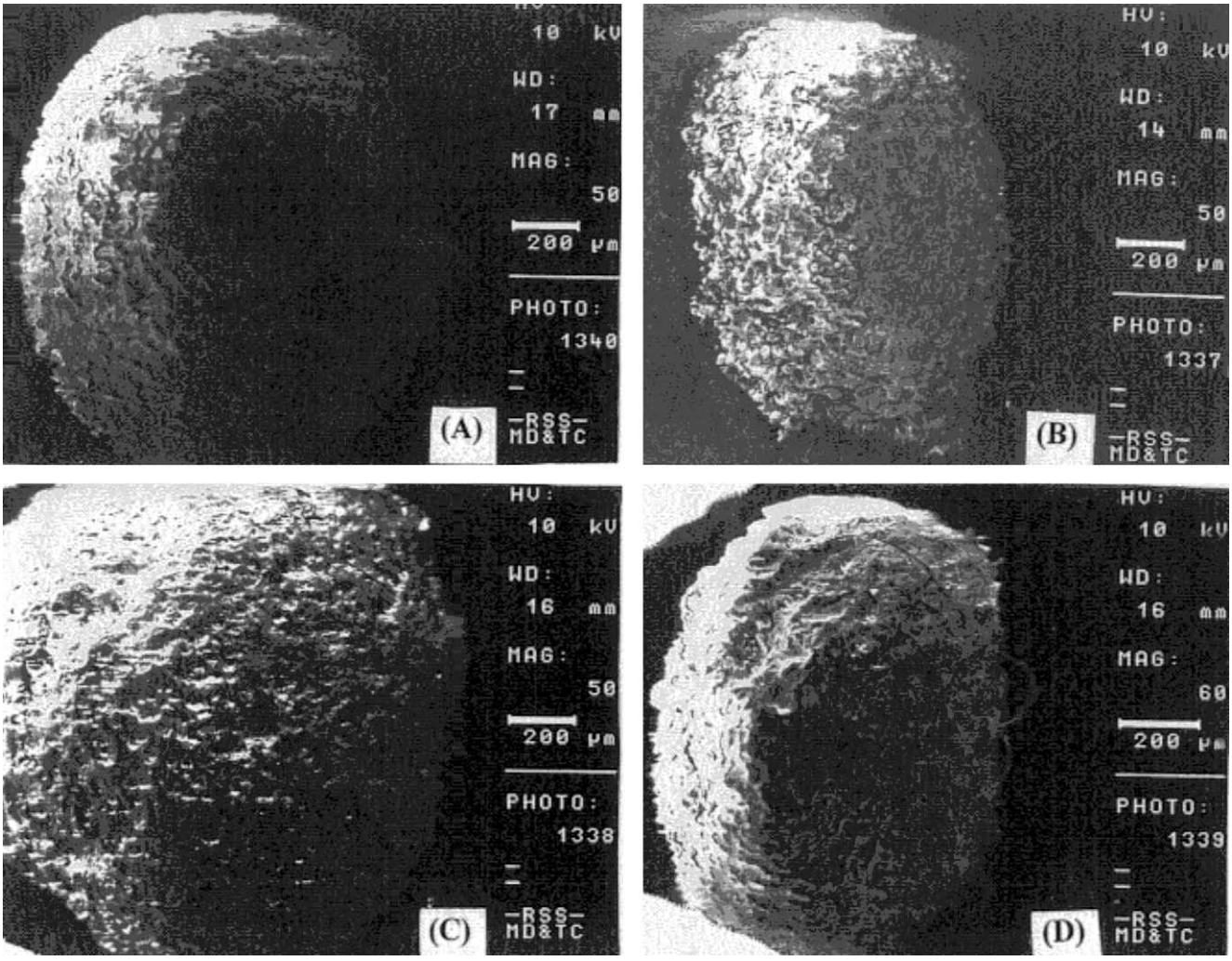

Fig. 5. Scanning electron micrographs of treated and untreated microspheres of Diltiazem HCl, (A, B): before dissolution, (C, D): after dissolution.

beads, suggests initial unhindered release from the surface layer of these beads. This release became more difficult with time as it proceeded from deeper layers. The suggested release behavior correlates well with the determined release profiles of the untreated beads. Meanwhile, in the case of the treated beads, the controlled-extraction process was accompanied by formation of a saturated solution of drug within the pores and only partial depletion of the drug from the outer layers of the beads. The abrupt application of high-vacuum freeze-drying at this point in time resulted in the removal of imbibed solvent and the fixation of a new drug distribution within the beads with a concomitant change in pore/surface characteristics. These two outcomes apparently helped to sustain a constant release for an appreciable length of time.

3.4. Effects of pH of release media

Effects of pH of the receiving medium on release from treated beads were investigated in the pH range 1.3–7.4. Release of DS was negligible at low pH. At pH 5.7 and 7.4, however; zero-order release rate constants of 5.93 and 7.46 mg/h were obtained, respectively. Release of DT on the other hand, was almost insensitive to changes in pH in the studied range.

3.5. Comparison of release of dosage forms with marketed products

Release rates from gelatin capsules filled with treated beads of the two drugs were compared to those of the corresponding marketed products, namely, Cardizem SR 90 mg capsules, Dilzem SR 90 mg tablets and Voltaren-XR 100 mg tablets. Fig. 6 shows release rate–time profiles of the concerned products and suggests different release mechanisms for the different products. Release from the Cardizem product seemed to follow a non-Fickian diffusion mechanism, thus realizing a constant release from this dosage form. The Dilzem and the Voltaren XR products, on the other hand, showed no apparent constant release. It is probable that the release mechanism from these two products followed a first-order release kinetics. From this

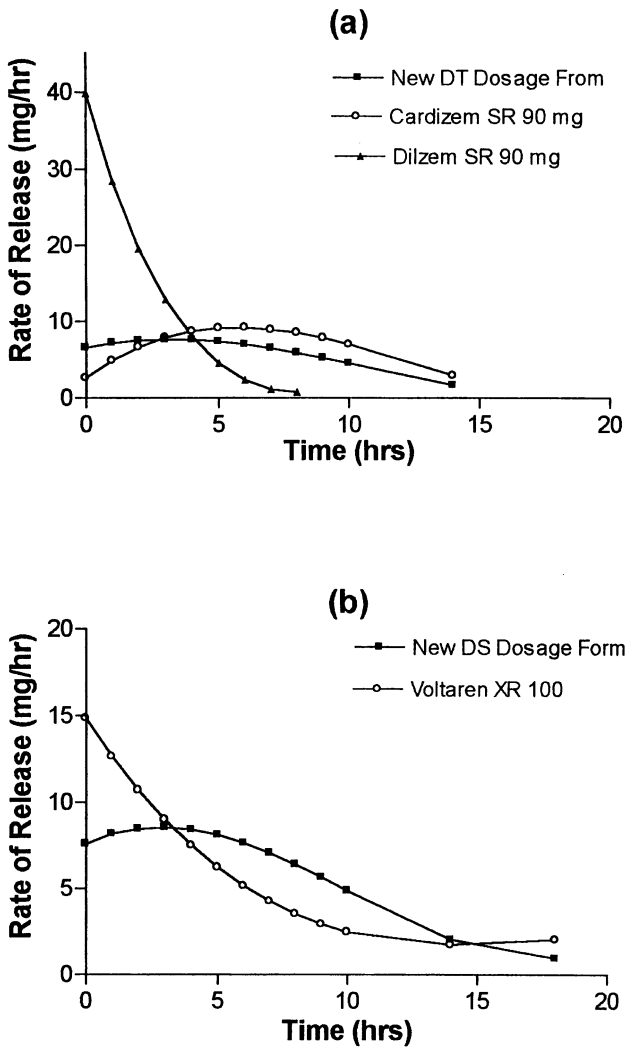

Fig. 6. Comparison of release rate-time profiles of new dosage forms vs. marketed products: (a) Diltiazem HCl, (b) Diclofenac sodium.

investigation, it is concluded that the non-Fickian zero-order release mechanism operating in the system of the newly developed dosage forms sustained a constant delivery of DT and DS for an appreciable length of time.

Acknowledgements

The authors wish to thank The Arab Company for Drug Industries and Medical Appliances for supporting the publication. The authors also wish to thank The Arab Pharmaceutical Manufacturing Company for the use of its facilities in part of this work.

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