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Release of diltiazem from Eudragit microparticles prepared by spray-drying

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Abstract

Microparticles containing diltiazem hydrochloride were prepared by the spray-drying technique using acrylate-methacrylate copolymers, Eudragit RS and Eudragit RL, as coating materials. The choice of solvent used during spray-drying determined the structure of the resultant microparticles. Spray-drying using dichloromethane as the solvent resulted in microspheres where the drug was distributed in the coating polymer matrix, whereas using toluene gave microcapsules with the drug coated by the polymer. The particle size distribution for both microspheres and microcapsules was narrow, with mean particle size below 10 μm. DTA-analysis showed that the drug was amorphous in the microspheres but crystalline in the microcapsules. The release pattern of diltiazem hydrochloride was affected by microparticle structure, whether the structure was matrix (microspheres) or reservoir (microcapsules). The results indicate that spray-drying is a method that can be used to prepare microparticles from the Eudragit acrylic resins RL and RS with a narrow particle size distribution. It is concluded that drug release rate can be controlled by choice of polymer type and production conditions during spray-drying.

Keywords: Microparticles; Spray-drying; Diltiazem; Drug release; Eudragit RL; Eudragit RS

1. Introduction

Eudragit RS and Eudragit RL are biocompatible copolymers synthesized from acrylic and methacrylic acid esters. The structure of Eudragit RS and RL differs only in the extent of the quaternary ammonium substitution, with RS being much lower than RL. Their permeability to water is unaffected by pH, but water can permeate more freely into Eudragit RL than RS, due to the relative hydrophilicity of the RL polymer (Lehmann, 1989). The acrylate-methacrylate polymers have been used in the formulation of dosage forms, most commonly in the preparation of matrix tablets for oral sustained release and in tablet coating, but they have also been used in other types of dosage forms, e.g. in the microencapsulation of drugs. Fouli et al. (1983) studied microen-

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capsulation of salicylic acid using Eudragit polymer coacervation by non-solvent addition. Barkai et al. (1991) incorporated nifedipine into polyacrylate-polymethacrylate microspheres using the solvent evaporation process and Kawata et al. (1986) used Eudragit RS polymer in the preparation of microparticles by the emulsion solvent evaporation technique.

Various techniques are available for the microencapsulation of drugs. The technique of spray-drying offers many advantages; it is an expeditious, single-step process, and the resultant microparticles have a narrow size distribution (Wan et al., 1991; Broadhead et al., 1992; Pavanetto et al., 1992). Spray-drying has been used successfully in the preparation of microparticles made from biodegradable polymers such as polylactic acid (Bodmeier and Chen, 1988; Pavanetto et al., 1993; Conte et al., 1994; Gander et al., 1995) or albumin (Pavanetto et al., 1994). The structure of microparticles obtained by spray-drying is dependent upon whether the drug is dissolved in or suspended in the coating solution prior to atomization in the drying chamber of the spray-drier. When the drug is dissolved in the solution the microparticle has a matrix structure, with the drug being distributed throughout the matrix, but if the drug has been suspended in the coating solution the drug crystal is coated with the coating polymer giving a microcapsule.

The purpose of the present study is to use spray-drying to prepare microparticles using two different forms of polymethacrylate polymers, Eudragit RS and Eudragit RL, and to investigate the effect of microparticle structure on drug release from them. The drug used was diltiazem hydrochloride which is a calcium channel blocker, widely used in the treatment of angina pectoris, arrhythmia and hypertension.

2. Materials and methods

2.1. Materials

Diltiazem hydrochloride was obtained from Profarmaco, Italy. The acrylate-methacrylate copolymers (Eudragit RS100 and RL100) were from Röhm Pharma, Darmstadt, Germany. All other chemicals were of reagent grade.

2.2. Preparation of microparticles

The microparticles were produced using a Büchi 190 mini spray-dryer. The experimental parameters of the process were set as follows: inlet temperature 70°C, outlet temperature 57–60°C, aspirator setting: 10, pump setting: 2–5 ml/min, spray-flow: 700 NL/h. A 0.5-mm nozzle was used throughout the experiments.

In the preparation of microspheres, diltiazem hydrochloride was dissolved in a solution containing 1 g of coating material in 200 ml of dichloromethane (ratio of drug to coating material 1:2, 1:4 and 1:8).

When preparing microcapsules, diltiazem hydrochloride (mean particle size, 2.1 μm) was suspended in a solution of 1 g of coating polymer in 100 ml toluene. This suspension was then treated in an ultrasound bath for 2 min and thereafter diluted to 200 ml. The ratio of drug to coating material was 1:2, 1:4 and 1:8.

2.3. Microparticle characterisation

Size and morphology were characterised by scanning electron microscopy. The microparticles were mounted on aluminium stubs, sputter-coated (Edwards S150B sputter-coating apparatus) with a thin layer of Au/Pd and examined using a Cambridge Instruments Stereoscan 240 scanning electron microscope.

2.4. Particle size measurements

The microparticles were dispersed in n-heptane (containing 1% Span 80), sonicated for 10 min and then measured by centrifugal sedimentation using a Horiba CABA 300 particle size analyser. The results are the average of three measurements.

2.5. Differential thermal analysis (DTA)

DTA analysis of polymers, drug, microcapsules and microspheres were recorded using a Stanton

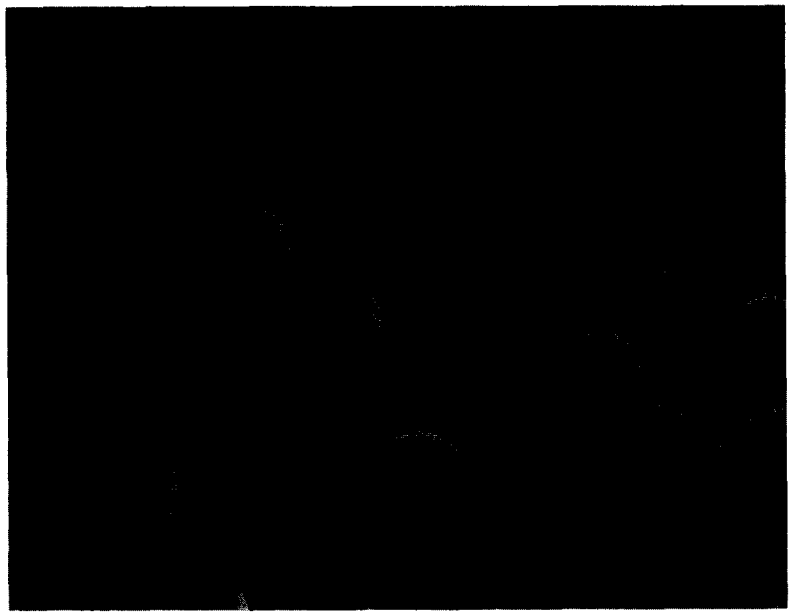

Fig. 1. SEM-photograph of Eudragit microspheres. Drug/polymer ratio 1:8.

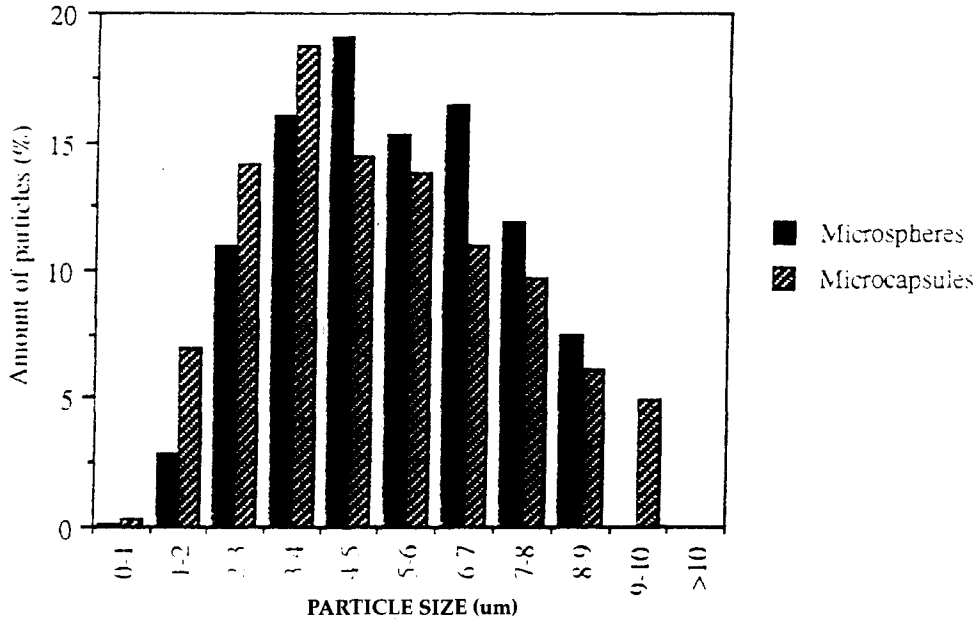

Fig. 2. Particle size distribution of diltiazem microcapsules and microspheres. Drug/polymer ratio 1:8.

Redcroft TG-DTA analyser. The instrument was calibrated with an indium standard. Samples (20 mg) were accurately weighed into aluminium pans and then sealed. The DTA runs were conducted over a temperature range of 130–250°C at a rate of 10°C/min.

2.6. Dissolution test

Dissolution tests were carried out in a USP XXII dissolution apparatus 2 (paddle method), using a phosphate buffer pH 7.4 as dissolution medium. Stirring rate was maintained at 100 rev./min and temperature at 37°C ± 0.5°C. The samples were assayed by UV-spectrophotometry (Perkin Elmer Lambda 3A) at the wavelength of maximum absorbance (240 nm). Each dissolution experiment was carried out in triplicate, all results being expressed as mean ± standard deviation.

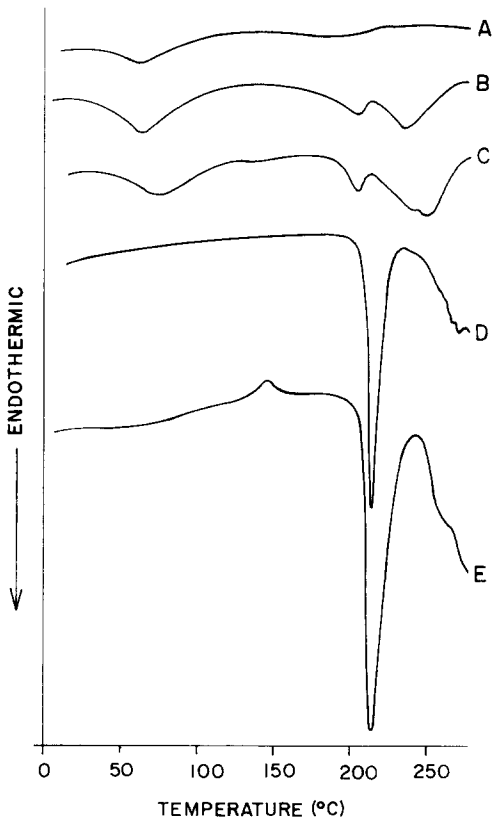

Fig. 3. DTA-graphs of diltiazem hydrochloride and Eudragit RS microparticles. (A) Eudragit RS microparticles without drug; (B) Eudragit RS microcapsules containing diltiazem; (C) Eudragit RS microspheres containing diltiazem; (D) diltiazem hydrochloride crystals; (E) spray-dried diltiazem hydrochloride.

3. Results and discussion

Diltiazem hydrochloride is soluble in dichloromethane but insoluble in toluene and by changing the solvent used during spray-drying, the structure of the resultant microparticle was determined. Spray-drying using dichloromethane as the solvent resulted in microspheres where the drug was distributed in the coating polymer matrix, whereas using toluene gave microcapsules with the drug coated by the polymer. SEM-photographs show that both Eudragit microspheres and microcapsules are spherical with a smooth surface. No drug crystals or irregularities can be observed on the surface (Fig. 1). Microparticles prepared at different polymer/drug ratios did not differ in terms of shape. Fig. 2 shows that the particle size distribution of the spray-dried product is narrow, with mean particle size below 10 μm. This applies to both microcapsules as well as microspheres.

The results from thermal analysis are shown in Fig. 3. From a DTA-graph of Eudragit RS it can be seen that the T_g is 65°C. The presence of diltiazem hydrochloride in the microspheres causes T_g to increase to 75°C. This increase is presumably caused by diltiazem hydrochloride being partly soluble in the polymer (Wendlandt, 1986). This should also result in the lowering and broadening of the melting point peak for diltiazem hydrochloride and this is indeed the case as the melting point peak of the drug is observed to be at approximately 200°C as compared with 213°C for the drug itself. Examination of the diltiazem hydrochloride graph shows a low and broad peak from 150–200°C which indicates the crystal change of diltiazem hydrochloride. This shows that the polymer and most likely the drug are (partly or completely) amorphous in the microspheres. Above 220°C the graph shows the decomposition and later the burning of the drug. From the DTA-graph for microcapsules containing diltiazem hydrochloride, T_g is observed to be at 75°C and the melting point for the drug at 200°C. No peak indicating crystal change of diltiazem hydrochloride is visible and it can be postulated that the drug is crystalline.

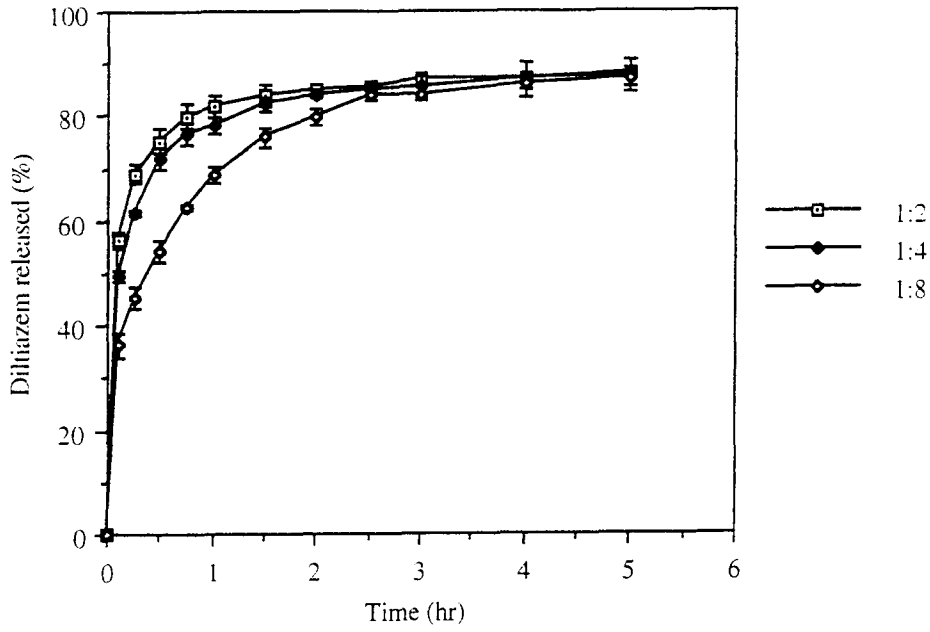

Fig. 4. Release of diltiazem from Eudragit RS microspheres. Drug/polymer ratio 1:2, 1:4 and 1:8.

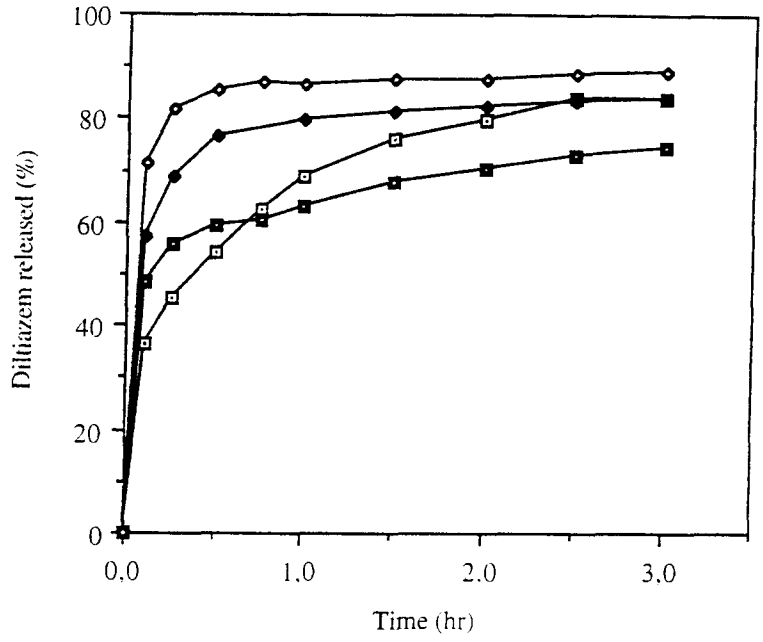

Fig. 5. Comparison of drug release from Eudragit microparticles. – □ –Eudragit RS microspheres; – ◆ –Eudragit RL microspheres; – ■ –Eudragit RS microcapsules; – ◇ –Eudragit RL microcapsules. Drug/polymer ratio 1:8. Results shown are mean of three experiments; error bars omitted for clarity.

Fig. 4 illustrates that the release of diltiazem hydrochloride from Eudragit RS microspheres increases with increasing proportion of the drug. This can be explained by an increased amount of drug being close to the surface and also by the fact that the likelihood of a part of the drug being uncoated increases with higher drug loading (Alex and Bodmeier, 1990). A plot of drug release from the microspheres is linear with respect to the square root of time which indicates that the drug release obeys the Higuchi diffusion controlled model (Higuchi, 1963). Two release phases appear, as there is a clear break in the line. The earlier more rapid phase is due to the polymer taking up water and swelling concurrent with the diffusion of the drug taking place. In the second phase, only the diffusion of drug applies. Drug release during the second phase was slow, with the drug still being released when dissolution testing was discontinued after 5 h. The difference in release between Eudragit RS and RL is because the first release phase is shorter for Eudragit RL, as the RL polymer is more permeable to water. In general, the retardation of drug release after microencapsulation with both the acrylic resins was smaller than expected, as even after using a ratio of drug to coating material of 1:8, more than 60% of the drug was released in the first hour.

As was found for drug release from microspheres, diltiazem hydrochloride release from microcapsules made from Eudragit RL polymer is faster than from the RS polymer (Fig. 5). Drug release from microcapsules shows a large burst effect, thereafter the release is dissolution controlled. In comparing drug release from microcapsules and microspheres made from Eudragit RS polymer it is seen that the initial release from microcapsules is faster, presumably due to some uncoated drug crystals. This can be explained by the initial diffusion pathlength for the drug being shorter in the matrix-type microspheres than in the microcapsules, where the coating around the drug controls the release. When comparing the drug release from microparticles made from Eudragit RL polymer, the opposite was found: drug release was faster from the microcapsules in spite of the drug being in the amorphous state in the microspheres. From these results, it is apparent that due to greater permeability of the Eudragit RL polymer it is a less effective barrier to drug diffusion in the microcapsules than in the microspheres.

It can be concluded from this work that spray-drying can be used to prepare microparticles from the acrylic resins, Eudragit RL and RS, with a narrow particle size distribution. The release pattern of diltiazem hydrochloride was affected by microparticle structure, whether the structure was matrix (microspheres) or reservoir (microcapsules). The results indicate that release rate can be controlled by the choice of polymer type and the production conditions during spray-drying.

Acknowledgements

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