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THERMOANALYTICAL STUDY OF MICROSPHERES CONTAINING DILTIAZEM HYDROCHLORIDE

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The main purpose of our study was to produce microspheres containing diltiazem hydrochloride and to perform the thermoanalytical examination of the components and microspheres. Thermal analysis is a very frequently used method in the preformulation tests of solid dosage forms.

Diltiazem hydrochloride is a calcium-channel blocker with short biological half life, so it is a potential candidate for sustained or controlled release dosage forms.

Various techniques are available for the microencapsulation of drugs. The technique of spray-drying was used during our investigations.

It was found that the crystalline form of the active agents could not be observed in the drug-loaded chitosan microspheres, which indicates the molecular dispersion of the drug in the matrix. It was established that the preparation conditions influenced the morphology and size of the particles. Moreover, the sphericity of the microspheres was good. On the basis of our investigations, the 1:1 diltiazem hydrochloride–chitosan ratio is suggested as the best ratio.

Keywords: *chitosan, diltiazem hydrochloride, DSC, microspheres, TG*

Introduction

Diltiazem hydrochloride is a benzothiazepine calcium–channel blocker with peripheral and coronary vasodilating effect with limited negative inotropic activity. Its short biological half-life and thus frequent administration (usually three to four times a day) makes it a potential candidate for sustained or controlled release dosage forms.

Various techniques are available for the microencapsulation of drugs. The technique of spray-drying offers many advantages. It is a single-step process and the resultant microparticles have a narrow size distribution [1–3].

Spray-drying has been used successfully in the preparation of microparticles made from biodegradable polymers such as polylactic acid [4, 5] or albumin [6], etc.

In the present work chitosan was used as a biodegradable natural polymer. It is a result of partial alkaline deacetylation of chitin $(C_8H_{13}NO_5)_n$. Chitosan has one primary amino and two free hydroxyl groups for each C_6 building unit. Chitosan is a comprising copolymer of glucosamine and N-acetylglucosamine and this deacetylation and depolymerization of chitins happens in various stages, therefore it is not easily to be defined in terms of exact chemical composition.

Because of its easy availability as a second abundant polysaccharide next to cellulose, chitosan has a great potential for pharmaceutical applications due to its biocompatibility, high charge density and non-toxicity [7].

Chitosan carries a positive charge due to the easy availability of reactive hydroxyl and amino groups in its structure so it can react with many negatively charged surface and anionic systems. This results in the alteration of physicochemical characteristics of combinations such as salt formation [8].

Chitosan is a week base so it is sparingly soluble in water and practically insoluble in organic solvents and natural or alkali solutions at pH above approximately 6.5. Therefore it readily dissolves in dilute and concentrated solutions of most organic acids and to some extent in mineral inorganic acids [9, 10]. Microspheres with various active agent contents were produced with the use of chitosan [11–14].

The primary aim of the present study was to investigate the thermal behaviour of diltiazem hydrochloride and the microspheres containing this drug. Thermoanalysis is a very frequently used method in the preformulation tests of solid dosage forms [15–18].

Experimental

Materials

Diltiazem hydrochloride (Ph.Eur.) was provided by EGIS Pharmaceutical Ltd., Budapest, Hungary and Chitosan was provided by Sigma-Aldrich (St. Louis, USA).

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Methods

Morphological study

A scanning electron microscope (SEM) (Hitachi 2400S, Japan) was used to study the habits of the particles and pellets. A Bio-Rad (Sc502, VG Microtech, UK) sputter coating apparatus was applied to induce electric conductivity on the surface of the sample.

Thermoanalytical measurements

The thermoanalytical examinations of the materials were carried out with a Mettler-Toledo DSC 821^e instrument. The start temperature was 25°C, the end temperature was 400°C, the applied heating rate was 5°C min^{-1}. Argon atmosphere was used. 10±1 mg sample was measured into aluminium pans (40 mL). The peak areas were evaluated with STAR^e Software.

Spray drying

An aqueous solution of chitosan containing 1% acetic acid or 1% hydrochloric acid was prepared for spray drying. It was applied with a spray dryer apparatus (Mini Spray Dryer Büchi B-191) with a standard 0.5 mm nozzle. As a standard condition, the inlet temperature, the spray flow and the compressed spray air flow (represented as the volume of the air input) were set at 150°C, 3.5 mL min^{-1} and 10 L min^{-1}, respectively. The loaded chitosan microsphere was prepared by dissolving the model drug (drug-polymer ratios of 1:1, 1:1.5 and 1:2) in the chitosan solution prior to spray drying.

Results and discussion

Diltiazem hydrochloride (Fig. 1) is a crystalline powder, heterogeneous with a prismatic habit and some smaller particles can be seen on the surface of large crystals (Fig. 2).

Based on the thermoanalytical curves (Fig. 3) it can be seen that the spray dryer parameter 160°C had no effect on the melting point of diltiazem hydrochloride (207.5–212°C) and above the melting point – as the TG curve shows – the material was completely decomposed. The decomposition process consists of two steps (Fig. 4).

Chitosan powder consists of cotton-like flakes, macro-molecular particles with smooth surface, but it is used in solution.

The thermal behaviour of chitosan powder was divided into more steps. The early endothermic peak at about 75°C was mainly due to water evaporation, which may overlap the glass transition temperature. The transitions associated with loss of water

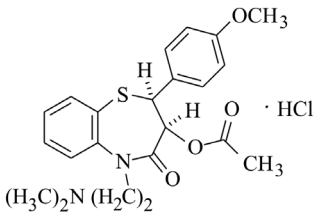

Fig. 1 Structural formula of diltiazem hydrochloride

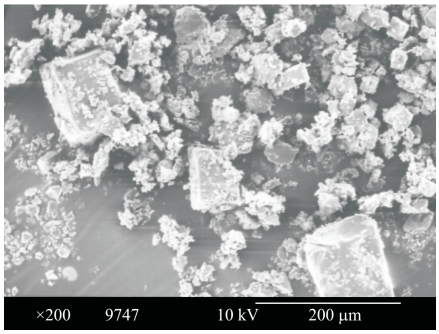

Fig. 2 Diltiazem hydrochloride powder (SEM)

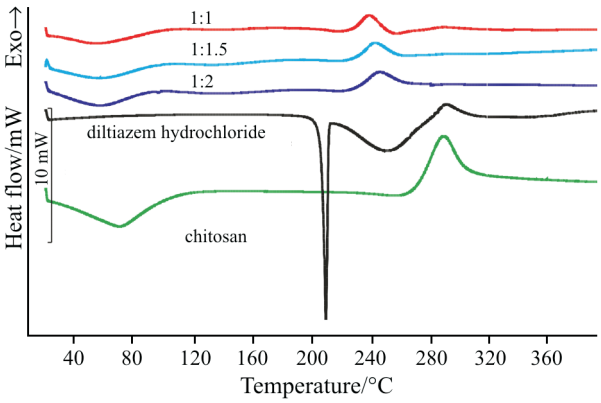

Fig. 3 DSC curves of diltiazem hydrochloride, chitosan and microspheres

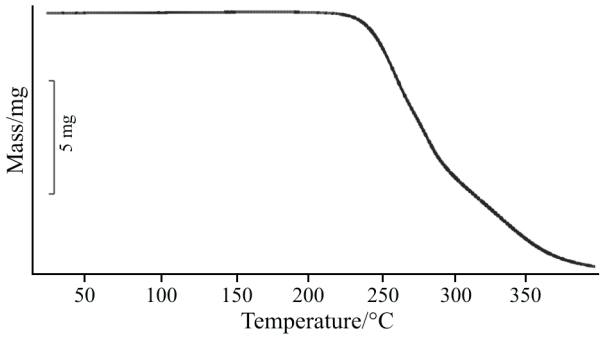

Fig. 4 TG curve of diltiazem hydrochloride

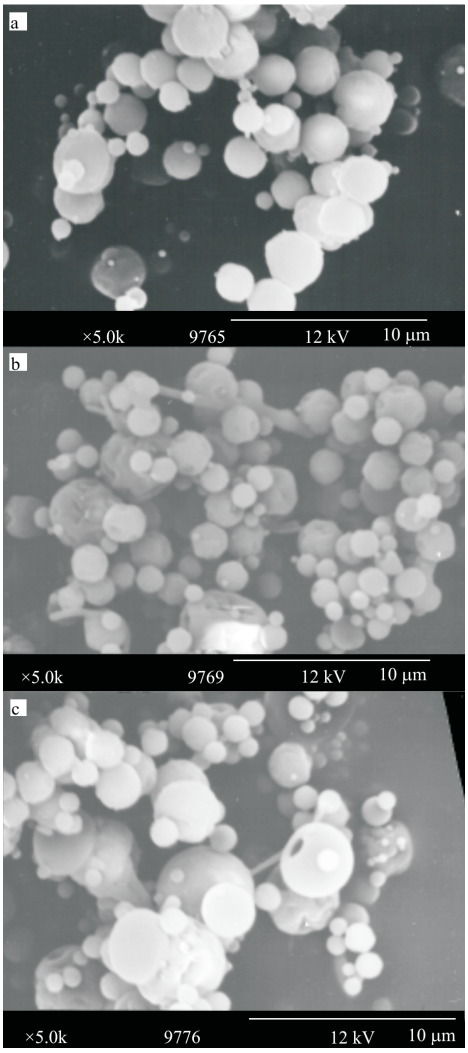

Fig. 5 Microspheres: diltiazem hydrochloride–chitosan ratio a – 1:1, b – 1:1.5 and c – 1:2 (SEM)

correspond to the hydrophilic nature of the functional groups of the polymer (Fig. 3). T_g may also lie at temperatures lower than the starting temperature of the DSC analysis, 25–27°C. At about 160°C (spray dryer parameter) no change was observed.

The second main thermal event registered was a wide exothermic peak occurring in the range of 295–300°C. This area can express the overall exothermic effect connected with decomposition.

The microsphere of 1:1 diltiazem hydrochloride–chitosan ratio: shows nice spheres (Fig. 5a). More aggregated microparticles can be seen rather than separate individual ones.

The 1:1.5 diltiazem hydrochloride–chitosan ratio: macromolecular fibres among other microspheres can be seen. The surface is not smooth as in the case of the 1:1 ratio (Fig. 5b).

The 1:2 diltiazem hydrochloride–chitosan ratio: macromolecular fibres can be seen again and there is a hole inside the microspheres (Fig. 5c).

The endothermic peak characteristic of chitosan shifted to 60–63°C and between the different ratios some differences can be seen (Fig. 3), but it is the same for the 3 products (62°C), the ΔH value slightly increased with the increase of chitosan quantity, it became more characteristic. Raw chitosan and diltiazem hydrochloride as pure agent each presents an exothermic peak in the range of 230–280°C. The exothermic peak for the microsphere shifted to a lower temperature range with smaller height and wider range. The data reveal that the greatest shift of the exothermic peak can be observed in the case of the lowest chitosan concentration (1:1=245°C, 1:1.5=249°C, 1:2=252°C). No melting point typical of diltiazem was detected in the DSC curves of the microspheres, so there are no free diltiazem crystals in the system. The products exhibit thermic behaviour characteristic of amorphous substances.

Conclusions

The broadened and shifted peaks suggest that the presence of the crystalline form of the active agents was not observed in the drug-loaded chitosan microspheres, as an indication of the molecular dispersion of the drug in the matrix. It was established that the preparation conditions influenced the morphology and size of the particles. Furthermore, the sphericity of the microspheres was found to be good. Based on our investigations, the 1:1 diltiazem hydrochloride–chitosan ratio is suggested as the best ratio.

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