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COMMUNICATION

Fabrication of Multiunit Controlled-Release Phenylpropanolamine Hydrochloride Tablets

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ABSTRACT

Phenylpropanolamine hydrochloride (PPA) pellets were prepared in a fluidized-bed rotary granulator. Microcrystalline cellulose and distilled water were used as pelletization enhancer and binder, respectively. The pellets were coated with methacrylate ester copolymer (Eudragit® RS 100) solution containing a 1:1 ratio mixture of triethyl citrate and castor oil as plasticizers. The addition of approximately 30% microcrystalline cellulose and 2% croscarmellose sodium to the 50% coated pellets produced fast disintegrating tablets. Dissolution profiles of both pellets and their respective matrix tablets were comparable and conformed to the USP dissolution requirement for PPA extended-release capsules.

INTRODUCTION

Multiunit dosage forms are preparations that consist of several minireserviors, e.g., pellets or microencapsulated crystals contained in a capsule or a tablet. They offer several advantages as compared to single-unit dosage forms (1–4). Most multiunit dosage forms are controlled-release type, comprising pellets coated with gastrointestinal-fluid-insoluble polymers. The pellets can be produced and coated by using fluidized-bed processors (5–7). In most cases, the pellets are filled into hard gelatin capsules. This method appears to be the easiest means of dispensing pellets; however, there are some inherent disadvantages of capsules. Tableting of coated particles has been developed as an alternative method of delivering the multiunit dosage forms (2,8–11). A number of works deal with the effects of both processing and excipients on the tableting characteristics of pellets; however, little attention has been paid to the USP requirements for drug release (2,8). The objective of this study was to produce multiunit controlled-release tablets which conform to USP requirements.

MATERIALS AND METHODS

Phenylpropanolamine hydrochloride (PPA, Alps Pharmaceutical Industry Co., Ltd., Japan) was used as a

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model drug. Microcrystalline cellulose, MCC (Avicel® PH-101, Japan) was employed as spheronization enhancer and PH-102 was used as tablet filler. The coating material used was methacrylate ester copolymer (Eudragit® RS 100). Triethyl citrate (Eudraflex®) and castor oil were used as plasticizers. Croscarmellose sodium (Ac-Di-Sol®) was used as tablet disintegrant. The overcoat suspension contained hydroxypropylmethylcellulose 2905, HPMC (Methocel® E). All of the other materials were pharmacopeial grade.

Preparation and Evaluation of PPA Pellets

PPA and MCC were blended at a ratio of 1:3 and loaded into the rotary fluidized-bed granulator equipped with smooth rotating disk (Glatt GPCG1, Germany). Deionized water was sprayed into the product bed to enhance agglomeration of the drug–diluent mixture. The 20/30 mesh PPA pellets were selected and coated with 25% Eudragit RS 100 in acetone–ethanol solution in the GPCG1 granulator with Wurster chamber insert. Triethyl citrate and castor oil at the concentration of 2.5% each were employed as plasticizers. The PPA pellets were coated to the desired 30, 40, and 50% weight increases. The coated pellets were then further coated with an overcoat suspension consisting of 5% HPMC, 1.5% polyethylene glycol 6000, and 5% talcum in distilled water. The HPMC suspension was applied to obtain a 0.5% theoretical weight increase.

Both the uncoated and coated pellets were assayed for PPA contents in triplicate. The pellets were dispersed in distilled water and the absorbance of a filtered aliquot was determined in an ultraviolet/visible (UV/VIS) spectrophotometer (Beckman DU65) at 204 nm. The dissolution test was performed as described in USP 22, drug release for phenylpropanolamine hydrochloride extended-release capsules. The dissolution apparatus consisted of a dissolution station (Hanson QC 72 RB) and the DU65 spectrophotometer equipped with six 0.05-cm flow cells. Photomicrographs of the pellets were taken with a scanning electron microscope (model S-2500, Hitachi Science Systems).

Preparation and Evaluation of Multiunit Controlled-Release PPA Tablets

Each tablet contained 482.0-mg coated pellets equivalent to 75 mg PPA, 206.6 mg Avicel PH-102, 13.8 mg Ac-Di-Sol, and 2.1 mg magnesium stearate. The mixture was compressed into tablets on a single-punch tablet machine (Fette El, Germany) fitted with 13-mm standard concave punches. Tablet properties were determined after the tablets were aged for 24 hr at 25°C and 45% relative humidity (RH). The hardness was measured with an electronic hardness tester (Pharma Test model PTB 311, Germany). The disintegration time was determined using the USP 22 method. Drug release study and photomicrography were performed as previously described.

RESULTS AND DISCUSSION

The use of MCC as spheronization enhancer and filler reportedly produces satisfactory results for pellet formation in the rotary fluidized-bed granulator (12). In the present study, the PPA pellets containing PPA and MCC at the ratio of 1:3 were found to be satisfactory. The smooth plate was employed to minimize attrition during tumble drying. From the average of three batches, the size of 20/30 mesh represented 76% of the yield.

The content of core PPA pellets was 99.9%. The results indicated that loss of the drug during pellet preparation was negligible. The dissolution profile of the core pellets is depicted in Fig. 1. At 5 min, the drug release was more than 90%. Even though the PPA preparation is not official in the USP as the conventional dosage form, the release profile suggested that PPA pellets could be one of the very fast-release solid dosage forms.

In order to delay the release of the drug, PPA pellets were coated with Eudragit RS 100. The polymer exhibits low water permeability and has been employed in

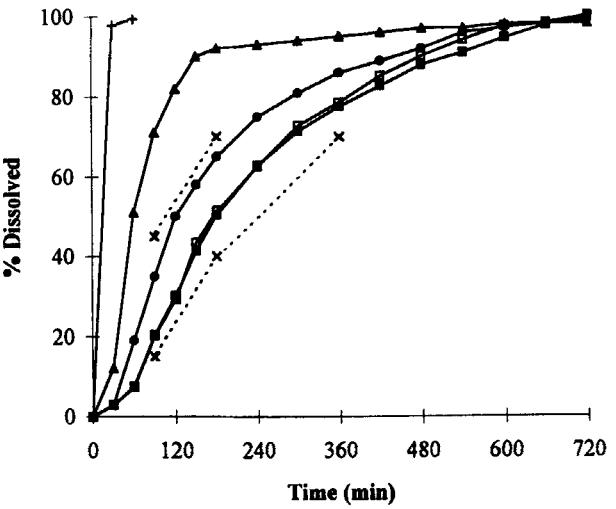

Figure 1. Dissolution profiles of PPA pellets and tablets. (+) Uncoated pellets; (▲) 30% coating; (●) 40% coating; (■) 50% coating; (□) tablets obtained from pellets with 50% coating. Dotted lines indicated USP limits.

controlled-release preparations (10,13,14). Two plasticizers, i.e., triethyl citrate and castor oil, were used at 1:1 ratio to obtain desired permeability. To reduce stickiness during drying, the Eudragit-coated pellets were subsequently coated with HPMC film.

Figure 2(a) depicts the scanning electron photomicrographs of the coated pellets. The content of PPA in the coated pellets was found to be 101.23%, which did not differ significantly from that of uncoated pellets. The dissolution profiles of the pellets coated at various thicknesses are presented in Fig. 1. The release profiles of pellets with 40 and 50% coatings were found to be within the USP requirements for PPA extended-release capsules. Nevertheless, the pellets with 50% coating exhibited a dissolution pattern which represented the average of the USP upper and lower limits. The pellets with 50% coating were, therefore, chosen for the preparation of tablets.

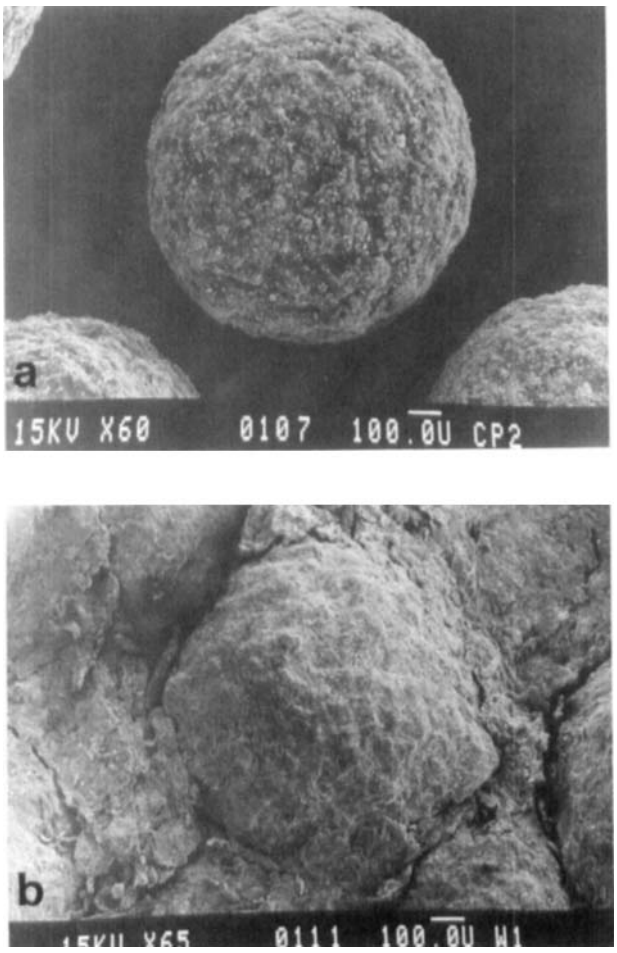

Figure 2. Scanning electron photomicrograph. (a) Pellets coated with 50% film; (b) cross-section of tablet.

Multiunit Controlled-Release PPA Tablets

The tablets containing approximately 68.4% of coated PPA pellets and 29.3% MCC were compressed at 103 MPa. The drug content was found to be 102.40%. The tablets exhibited the average crushing strength and disintegration time of 80 N and 15 sec, respectively. It was observed that the tablets broke apart rapidly and produced the original pellets. These results confirmed the properties of multiunit dosage forms which disintegrated into individual sustained-release subunits after administration. The dissolution pattern of the tablets was comparable to that of their coated pellets, even though Torrado and Augsburger (8) found that, under their experimental conditions, the coating membranes were always damaged. In the present study, because the dissolution pattern of the tablet matrix did not differ from that of the coated pellets, it is believed that the damage of the coating membranes was negligible. Figure 2(b) reveals that the coated pellets remained intact after compaction. The photomicrograph clearly showed that the coated pellets were well preserved. It is believed that the coating layer was thick enough to plasticly deform during compaction. Moreover, the excipients incorporated as the intergranular phase could protect the pellets against crushing. Therefore, the damage of the coating layer under compaction was eliminated.

CONCLUSIONS

PPA pellets could be easily produced in the rotary granulator equipped with a smooth plate rotating disk. The release of drug from the pellets was relatively rapid. The application of Eudragit RS 100 coating solution containing a mixture of triethyl citrate and castor oil as plasticizers decreased the release of the drug from the pellets. The drug release characteristics of the pellets coated with 40 or 50% coating appeared to conform to USP requirements for PPA extended-release capsules. The addition of approximately 30% of MCC and 2% of croscarmellose sodium to the pellets with 50% coating was found to facilitate the tableting process. Scanning electron photomicrography revealed that the coated pellets were still intact after compaction. Both coated pellets and the resulting tablets gave comparable dissolution profiles. Although the capsules filled with the coated pellets were not prepared, it is reasonable to believe that the dissolution pattern would be similar. We concluded that the multiunit controlled-release PPA dosage forms could be produced in both capsule and tablet matrix forms.

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