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COMMUNICATION

Lisinopril–Lactose Incompatibility

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ABSTRACT

A chemical interaction between lisinopril and lactose was demonstrated and quantified in dilute mixtures in the solid state.

INTRODUCTION

Lactose (4-O-β-D-galactopyranosyl-α-D-glucopyranose) is perhaps the most common excipient in pharmaceutical oral dosage forms (tablets). It is generally considered to be unreactive and inert. However, lactose is a reducing disaccharide and reactions between it and drug entities containing amino groups have been reported (1). These interactions may be represented as condensation reactions (furnishing Schiff bases, i.e., imines) arising from anhydrosynthesis between the amino group of the drug moiety and the aldehyde group (anomeric C-1) of the open chain (linear) form of the glucose part in lactose:

$$R_1\text{–CHO} + H_2N\text{–}CH_2\text{–}R_2 \rightarrow R_1\text{–CH=N–}CH_2\text{–}R_2 + H_2O$$

Lisinopril ((S)-1-(N^2-(1-carboxy-3-phenylpropyl)-L-lysyl)-L-proline dihydrate) contains a free, primary amino group in the lysine part of the molecule and is therefore theoretically a potential candidate for interaction with lactose. The effect of a low lactose concentration in a lisinopril tablet formulation was investigated.

MATERIALS AND METHODS

All raw materials were of pharmacopeial (EP/USP) quality. Granulations were performed in an intensive mixer (Gral-25, Collette, Belgium) and tablet compression was accomplished in a rotary tableting machine (Manesty Betapress, Manesty, UK).

EXPERIMENTAL

Two 5-kg wet granulations were prepared and then dried, sized, and mixed with magnesium stearate, and compacted to a target tablet mass of 280 mg and nominal strength of 20 mg (anhydrous lisinopril). The composition of the two batches (A and B) was identical except that batch B contained 0.9% lactose. The main excipients were calcium hydrogen phosphate, mannitol, and starch in accordance with published data for commercial lisinopril tablets (2–4). The tablets were packaged into aluminium/PVC blisters and stored at 40°C and 75% relative humidity (RH). The two batches were analyzed for related compounds by HPLC using the method de-

scribed in USP (5) (slightly modified) following compression and after storage for 1 month.

RESULTS

The HPLC chromatograms for the two batches (A and B) were closely similar except for a conspicuous peak appearing only in batch B (containing lactose) at R_t 2.9 min. The concentration of this impurity (presumably a lisinopril–lactose interaction product) was only approximately 0.04% (calculated with reference to lisinopril) after tablet compression but increased to approximately 1.9% after storage for 1 month (at 40°C/75% RH).

DISCUSSION AND CONCLUSIONS

Examination of the pharmaceutical literature 1970–1997 (6) revealed relatively few reports (<30) on drug–lactose incompatibilities. Most of these were detected by differential scanning calorimetry using very high drug–lactose concentrations. The extent or type of interactions were generally not discussed in these papers. It is the opinion of this author that the present communication is the first published quantitative description of a drug–lactose interaction. It follows that lactose cannot be used with lisinopril, not even in the relatively low concentrations normally associated with tablet coloring or film-coating procedures.

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