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COMMUNICATION

MOISTURE THE DOMINANT FACTOR IN THE STABILITY OF DOXYLAMINE SUCCINATE TABLETS

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ABSTRACT

During a stability trial at 55°C with doxylamine succinate combined with different excipients at different moisture contents, moisture was found to be the dominant factor affecting the stability of doxylamine succinate. Each excipient however also had a specific affect.

INTRODUCTION

During stability trials on doxylamine succinate tablets received from a pharmaceutical manufacturer the assay results decreased rapidly under all storage conditions. The tablets also turned brown. DSC scans on 1:1 physical mixtures of the drug and excipients was therefore performed to select compatible excipients. DSC is widely used during compatibility studies[1-4]. DSC revealed interactions with lactose, magnesium stearate and PVP, but no

interactions were seen with Avicel pH 101®, Ac-Di-Sol® and Syloid 244®.

Reformulation with compatible excipients revealed the same type of decrease in assay results during stability trials. There was however no browning attributed to lactose which was excluded from the reformulation. Moisture was then suspected to be the influencing factor since doxylamine succinate tends to be hygroscopic. Monkhouse[5] stated that moisture is perhaps the most important factor affecting the stability of dosage forms while Rupprecht et al.[6] found that stability of hydrolysable drugs like acetylsalicyclic acid is influenced more by water content and alkaline impurities than by interaction with silica (Aerosil® and Syloid®) itself.

Van Dooren[7] described a method where water was added to physical mixtures of drugs and excipients. DSC thermograms as well as assays were performed before and with certain time intervals during storage at 55°C. Samples for direct compression in the dry state was also tested.

In this study doxylamine succinate as received was wetted with water, used as such and dried under silicagel and subjected to stability at 55°C. The drug was also mixed with excipients which were also wetted, used as received or dried under silicagel. The 3 samples of mixture of the drug with each excipient were also subjected to stability at 55°C. Samples were assayed at zero time and at weekly intervals by DSC, HPLC and KF water determination.

EXPERIMENTAL

Materials

The following materials were used: doxylamine succinate (supplied by Twins Propan, Johannesburg, R.S.A.), Ac-Di-Sol®, Avicel pH 101®, Elcema G250®, Explotab®, Primojel®, Sta Rx 1500®, corn starch, dicalcium phosphate, Emcompress®, calcium sulfate

dihydrate, tricalcium phosphate, cross PVP, mannitol, Precirol Ato 5®, Sterotex® and Syloid®.

Differential Scanning Calorimetry (DSC)

Samples (4-10 mg) were measured (Sartorius micro-balance) and hermetically sealed in flat bottomed aluminum pans. These samples were heated in an atmosphere of nitrogen and thermograms were obtained on a Du Pont 910 DSC system equipped with a Du Pont 99 Thermal Analyzer programmer and a Hewlett-Packard X-Y recorder at a constant heating rate of 5°C per minute and a constant chart speed of 5 $mm.min^{-1}$. The individual substances and 1:1 physical mixtures of doxylamine succinate and excipients, prepared with mortar and pestle were heated over the temperature range of 35 - 240°C. The instrument was calibrated with an indium standard (melting point 156.5°C).

Karl Fischer water determinations

The moisture content of the samples where possible was determined by Karl Fischer titrations using a Mettler DL18 titrator. The Karl Fischer solution was standardized before each set of assays by using 30 µl of water weighed on a Sartorius balance.

High Performance Liquid Chromatography

A Knauer FR30 liquid chromatograph equipped with a variable wavelength detector set at 262 nm and connected to a linear recorder was used. The column was stainless steel (25 x 0.45 cm i.d.) packed with Nucleosil C_{18} (7 µm). The mobile phase was methanol-water (45:55) containing 1% acetic acid. The flow rate was 2 $mL.min^{-1}$. Samples were injected with a 20 µl Rheodyne loop injector. A calibration curve or a factor was derived before each set of assays by subjecting standard solution of 320, 400 and 480 µg per mL of the pure drug to the procedure.

Sample preparation and storage

To serve as reference doxylamine succinate without excipients was also subjected to the stability trial. Sample 1 was wetted with 1 µl of water, sample 2 was used as received and sample 3 was dried over silicagel for 2 months prior to this test. All excipients were also dried over silicagel for 2 months. For each excipient a 1:1 mixture with the dried doxylamine succinate was made except for Syloid®, Sterotex® and Precirol Ato 5® where 5:1 mixtures of drug to excipients was made. Sample 1 (50 mg mixture) was wetted with 10-30 µl water, sample 2 was used as is and for sample 3 the mixture was made with dried drug and excipients. One sample large enough for performing each assay was prepared for each of the three storage conditions before subjecting the samples to storage at 55°C. All assays were performed at zero time and at weakly intervals thereafter. Water determinations were not done with the wetted samples.

RESULTS AND DISCUSSION

The percentage decrease in doxylamine succinate content after 12 weeks with the initial moisture content in brackets for the samples not wetted with water are given in Table I. It is clear from the results that moisture had a great influence on the stability of doxylamine succinate. In all the wetted samples the percentage decrease after 12 weeks was much greater than for the undried and dried samples. It is also clear that the excipients in question also had some influence (doxylamine succinate alone only 11.6% down). All wetted mixtures gave breakdown of nearly twice as much or more than doxylamine succinate alone. When the non-dried and dried samples are inspected it is clear that the dried samples with a lower initial moisture content gave a much lower breakdown than the non-dried samples. This may indicate that moisture at the

TABLE 1
Percentage decrease in Doxylamine succinate content with initial moisture content in brackets.

Drug mixed with	1 Samples wetted with water	2 Samples without manipulation of excipient	3 Samples where excipients were dried
Doxylamine succinate (alone)	11.6	3.5 (0.35)	2.0 (0.32)
Ac-Di-Sol®	25.3	9.3 (2.76)	7.9 (2.04)
Avicel pH 101®	44.9	8.8 (2.33)	7.9 (2.09)
Elcema G 250®	31.4	3.9 (4.27)	2.3 (2.88)
Explotab®	25.2	9.1 (4.46)	0.2 (2.78)
Primojel®	30.1	12.5 (5.37)	8.5 (3.83)
StaRx 1500®	19.9	2.9 (4.60)	2.2 (3.40)
Corn starch	30.0	3.7 (5.89)	3.4 (4.68)
Dicalciumphosphate	29.5	3.3 (0.62)	2.0 (0.58)
Calciumsulphate.$2H_2O$	30.1	3.0 (2.06)	2.4 (2.03)
Tricalciumphosphate	29.5	2.3 (1.95)	2.2 (1.45)
Cross PVP	48.4	11.6 (5.02)	7.7 (4.89)
Mannitol	44.8	3.3 (0.57)	2.5 (0.48)
Precirol Ato 5®	28.7	2.8 (0.78)	1.6 (0.77)
Sterotex®	13.4	4.0 (0.75)	3.2 (0.44)
Syloid®	20.4	4.6 (3.00)	4.5 (2.13)

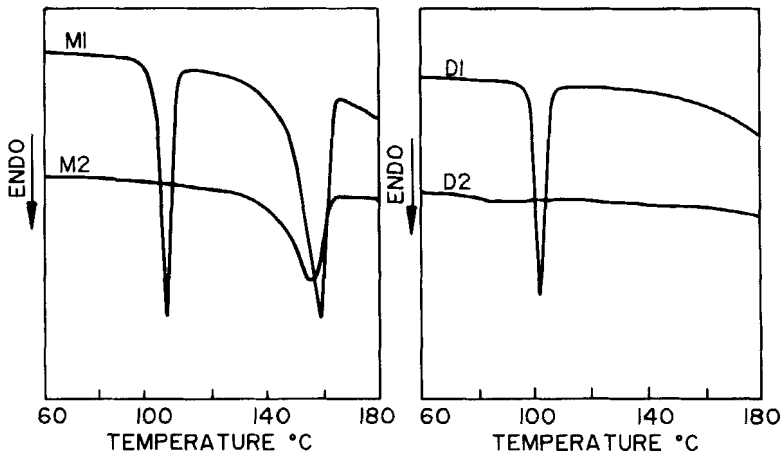

FIGURE 1

DSC thermograms of wetted mixtures of doxylamine succinate with mannitol (M) and dicalcium phosphate (D) at zerotime (1) and after 12 weeks (2).

specific temperature triggers the breakdown reaction which is then enhanced by the specific excipient.

The DSC thermograms taken initially and with time only showed disappearance or diminishing of the drugs thermograms with the wetted samples and not with the dried and non-dried samples. In figure 1 the original thermogram is compared with the thermogram of the wetted sample after 12 weeks for mannitol and dicalcium phosphate.

It is clear that the thermogram for the drug disappears in both cases. This is also true for most of the other excipients. In some instances (not so much breakdown) the thermograms got smaller. DSC therefore shows that the drug is disappearing from the sample. In most instances no other peaks appeared which may indicate that breakdown is taking place and not complex formation.

CONCLUSION

The stability of doxylamine succinate stored at 55°C is influenced by the specific excipient but to a larger extend by the moisture content. In order to formulate stable doxylamine succinate tablets it is recommended that excipients with the lowest breakdown be chosen from the table and that the granules be dried prior to compression to a moisture content of less than 5%. The tablets should then be stored with a desiccant in order to keep the moisture content at a low level.

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