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RESEARCH PAPER

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Evaluation of Compatibility of Tablet Excipients with Albendazole and Closantel Using DSC and HPLC

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ABSTRACT

The compatibility between albendazole and closantel, with commonly used tablet excipients, was assessed by studying drug–excipient mixtures mixed in 1:1 ratio and 1:1 ratios granulated with water and dried at 50°C for 1 hr with a differential scanning calorimeter (DSC) and high-performance liquid chromatograph (HPLC). Results showed that there were interactions between closantel and/or albendazole and some tablet excipients. For example, magnesium stearate reacted with both drugs and the interaction was observed by DSC and HPLC. Exposure of mixtures, and even the drugs, to heat and moisture resulted in deteriorated compatibility as seen by both DSC and HPLC, but especially HPLC. Overall poor correlation between DSC and HPLC results was observed.

INTRODUCTION

Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the preformulation stage during the development of a solid dosage form. Successful compatibility studies require a good experimental design that furnishes the required information with the minimum of experimental effort (1). The most commonly used method is assessment of physical mixtures of the drug and excipients with differential scanning calorimetry (2,3) and quantitative assay after isothermal stress tests (4,5).

In this study the compatibility between albendazole and closantel, with commonly used tablet excipients, was assessed prior to the formulation of a bolus for veterinary use. Drug–excipient mixtures were prepared in 1:1 mixtures and 1:1 mixtures granulated with water and dried at 50°C for 1 hr. Both differential scanning calorimetry (DSC) and high-performance liquid chromatography (HPLC) analysis were used to evaluate mixtures for possible interactions. Results were compared

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statistically to determine the effect of analytical technique and sample composition and preparation on the outcome of compatibility assessment.

EXPERIMENTAL PROCEDURES

Albendazole and closantel were obtained from Sigma Chemical Corporation (St. Louis, USA; USP or BP grade; purity above 95%). Excipients tested were: Mannitol (Saarchem, South Africa); microcrystalline cellulose (Emcocel 50 M and 90 M, Mendell, England); dibasic calcium phosphate monohydrate (Mendell, England); sodium starch glycolate (Explotab, Mendell, England); croscarmellose sodium (Ac-di-sol, FMC, USA); gelatine (Saarchem); starch (Saarchem); magnesium stearate (Saarchem), and colloidal silicon dioxide (Aerosil 200, Degussa, USA).

The mixed samples consisted of albendazole and closantel in a 1:1 w/w ratio with each of the excipients. The same mixtures were made, but an equivalent amount of water was mixed with each of the samples. These samples were dried in an oven at 50°C for 1 hr. Samples containing single components, subjected to the same stress conditions, included albendazole, closantel, and each of the excipients. DSC thermograms were obtained with a Shimadzu DSC-50 differential scanning calorimeter, at a heating rate of 10°C min^{-1} under nitrogen purge with a flow rate of 35 ml min^{-1}. The instrument was calibrated using indium as a standard (melting point 156.4°C). Samples (1–8 mg) were weighed to the nearest 0.001 mg and sealed in aluminum pans. Mixtures were also studied under a hot-stage microscope at the same heating rate as for DSC (Leitz, Germany).

Analysis of albendazole and closantel used a Hewlett Packard HP1050 system with a HP3395 integrator (Hewlett Packard, Waldburg, Germany). A Nova Pak C_{18} cartridge (Waters, Massachusetts, USA, 250 × 3.9 mm ID, 4 μm particle size) was used and ultraviolet (UV) detection was at 254 nm for albendazole and 264 or 336 nm for closantel. The flow rate was between 1 and 1.5 ml min^{-1}. Standard solutions were dissolved in a solvent composed of methanol, tetrahydrofuran, and formic acid (75:15:10 v/v). These solutions were serially diluted and used to construct calibration curves. The optimum mobile phase for albendazole was a mixture of phosphate buffer (0.5 M dibasic ammonium phosphate) and methanol (75:25, v/v) with a pH of 3.6 (6). The mobile phase for closantel was a degassed mixture of acetonitrile and water (80:20 v/v) with a pH of 3.1 adjusted with phosphoric acid (7). Validation results for the assay methods are shown in Table 1.

Mean HPLC results were compared according to the Student–Newman–Keuls multiple range test (Statistica CSS 3.1, Statsoft, USA). A 95% confidence level ($p \leq 0.05$) was considered satisfactory for indicating significant differences.

RESULTS AND DISCUSSION

DSC analysis, Fig. 1, showed changes in the melting behavior of closantel and albendazole when mixed. This was more evident when the drugs were exposed to stress conditions, humidity, and heat, Tables 2 and 3. Quantitative HPLC assay showed that there was a significant decrease in closantel assay from 96 ± 0.62% to 91.59 ± 2.36% after being subjected to heat and moisture, $p = 0.0061$. For albendazole the concentration decreased from 101.02 ± 3.56% to 93.65 ± 4.65% ($p = 0.0049$). Analysis of mixtures of closantel and albendazole showed that there was no significant difference in the assay for closantel before, 96.15 ± 0.62%, and after mixing, 95.57 ± 0.53% ($p = 0.1600$). After exposure to stress conditions the closantel assay was again not significantly different, 91.59 ± 2.36% compared to 88.85 ± 1.49% ($p = 0.1000$). The albendazole assay was also not affected by the combination with closantel in a 1:1 mixture, $p = 0.092$ before and $p = 0.3700$ after exposure to stress.

Table 1

Calibration Data for HPLC Analysis of Albendazole and Closantel

Concentration Range (μm ml^{-1})	Regression Coefficient	Slope	Standard Error of Slope	*Y* Intercept	Standard Error of *Y* Intercept
Albendazole: 12–60	0.9995	494,117	2145	-40	11
Closantel: 20–100	0.9999	962,933	3581	-2284	226

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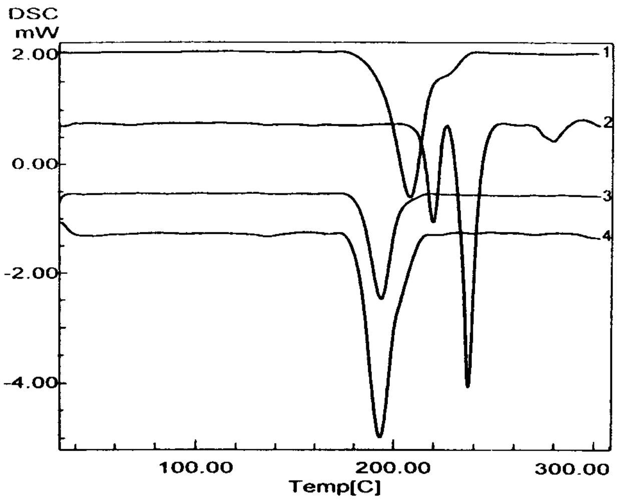

Figure 1. DSC analysis of albendazole–closantel combinations: 1, albendazole; 2, closantel; 3, 1:1 physical mixture, 4, 1:1 physical mixture subjected to stress conditions.

Changes in DSC thermograms observed for albendazole– or closantel–excipient combinations were large shifts in melting points, change in peak size, appearance of additional peaks, exothermal peaks, and disappearance of peaks. Large changes in melting behavior were confirmed by studying mixtures under a hot-stage microscope at the same heating rate used for DSC analysis. Magnesium stearate reacted with albendazole, causing shifting of melting points and changes in the size of the albendazole peak, Fig. 2 (3,4). Mixing colloidal silicon dioxide with albendazole caused shifting of melting points, Table 2, and changes in the size of the albendazole peak. These reactions were present when 1:1 mixtures and 1:1 mixtures subjected to stress conditions were studied.

Dibasic calcium phosphate monohydrate reacted with albendazole, causing changes in the positions of the melting point and appearance of an additional peak at 188°C. The additional peak was also present in the 1:1 mixture put under stress. When a sample of dibasic calcium phosphate monohydrate was granulated with water and dried at 50°C for 1 hr, this additional peak also appeared on the DSC thermogram.

The melting thermogram of closantel showed two endotherms, a small one at 220° and a larger one at 237°C, Fig. 1. Magnesium stearate reacted with closantel, causing the disappearance of the closantel peaks, Fig. 3. This reaction was present both when the 1:1 mixture and when the 1:1 mixture granulated with water and dried at 50°C was studied. Mixing of microcrystalline cellulose with closantel caused the appearance of an exothermal peak. The closantel melting point, Table 3, also varied. DSC showed that dibasic calcium phosphate monohydrate reacted with closantel and these reactions were mainly changes in the melting point of closantel. Although the smaller endotherm at 220°C was not observed in mixtures of closantel and mannitol, no

Table 2

DSC and HPLC Results for Albendazole in Albendazole–Excipient Mixtures Compared to Albendazole Treated Similarly[a]

Excipient	Sample Preparation[b]	m.p. (°C)	Assay (% ± *SD*)	*p*
Colloidal silicon dioxide	1	199	99.92 ± 2.31	0.0680
	2	187	76.39 ± 0.03	0.0000
Microcrystalline cellulose	1	204	92.71 ± 2.11	0.7100
	2	203	96.38 ± 1.77	0.0660
Dibasic calcium phosphate monohydrate	1	209	101.47 ± 1.68	0.0220
	2	209	102.13 ± 0.69	0.6600
Starch	1	208	100.03 ± 1.99	0.0064
	2	202	94.21 ± 0.96	0.0069
Sodium starch glycolate	1	208	96.42 ± 2.04	0.4500
	2	200	91.95 ± 0.16	0.0003
Magnesium stearate	1	191	101.61 ± 3.95	0.0200
	2	191	79.81 ± 0.69	0.0000

[a] $p < 0.05$ for significant differences.
[b] Melting point (m.p.) of albendazole before stress 208°C and after stress 205°C. 1, 1:1 physical mixture; 2, 1:1 physical mixture exposed to stress.

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Table 3

DSC and HPLC Results for Closantel in Closantel-Excipient Mixtures Compared to Closantel Treated Similarly[a]

Excipient	Sample Preparation[b]	m.p. °C	m.p. °C	Assay (% ± *SD*)	*p*
Colloidal silicon dioxide	1	220	238	93.14 ± 2.75	0.3500
	2	220	237	90.81 ± 3.29	0.0000
Magnesium stearate	1	210	222	86.62 ± 0.28	0.0030
	2	208	—	77.18 ± 3.26	0.0000
Microcrystalline cellulose	1	218	242[c]	95.60 ± 7.64	0.1600
	2	219	242[c]	95.85 ± 1.06	0.4500
Dibasic calcium phosphate H_2O	1	212	230	98.47 ± 4.63	0.0000
	2	217	233	90.83 ± 2.41	0.0000
Gelatin	1	220	234	102.35 ± 2.21	0.0000
	2	220	234	77.57 ± 3.08	0.0000
Mannitol	1	—	232	93.75 ± 4.45	0.2000
	2	—	233	102.74 ± 1.67	0.0000
Sodium starch glycolate	1	220	237	94.96 ± 0.91	0.0044
	2	220	237	92.46 ± 0.93	0.0000

[a]$p \leq 0.05$ for significant differences.
[b]Melting point (m.p.) of closantel before stress 220°C and 237°C, and after stress 219° and 234°C. 1, 1:1 physical mixture; 2, 1:1 physical mixture exposed to stress.
[c]Exotherm.

interaction was indicated because when the mixtures were studied under a hot-stage microscope it was found that closantel dissolved in the mannitol melt, causing the closantel endotherms to broaden and merge.

Comparison of HPLC results for the drugs, Tables 2 and 3, in combination with excipients showed that sample treatment had a significant influence on results. The assay results for 1:1 mixtures subjected to stress conditions were significantly lower than results for the equivalent 1:1 physical mixtures. The assay results for magnesium stearate and colloidal silicon dioxide in 1:1 mixtures and in 1:1 mixtures subjected to stress, with

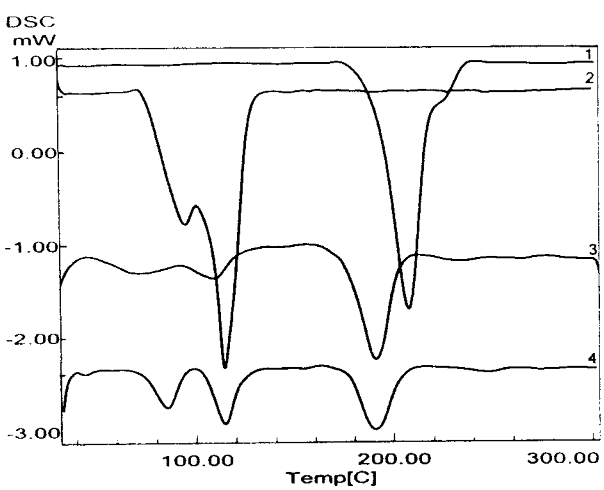

Figure 2. DSC analysis of albendazole–magnesium stearate combinations: 1, albendazole; 2, magnesium stearate; 3, 1:1 physical mixture; 4, 1:1 physical mixture subjected to stress conditions.

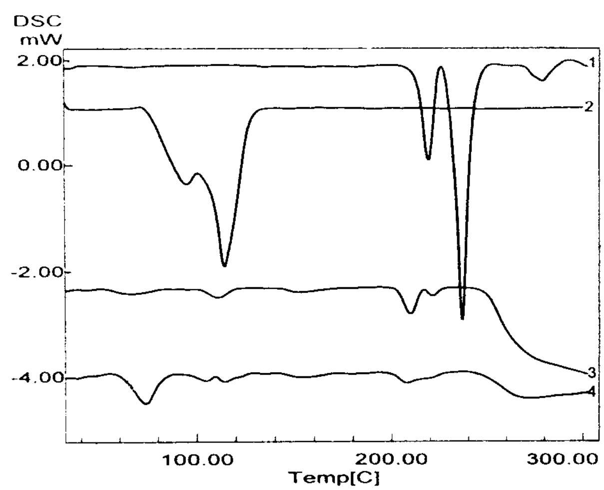

Figure 3. DSC analysis of closantel–magnesium stearate combinations: 1, closantel; 2, magnesium stearate; 3, 1:1 physical mixture; 4, 1:1 physical mixture subjected to stress conditions.

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Table 4

Comparision Between DSC and HPLC Results: A Represents 1:1 Mixtures and B 1:1 Mixtures Exposed to Stress, + for Incompatibilities and – for No Incompatibilities

	Albendazole				Closantel			
	DSC		HPLC		DSC		HPLC	
Drug or Excipient	A	B	A	B	A	B	A	B
Closantel	+	+	–	–				
Albendazole					+	+	–	–
Mannitol	–	–	–	–	–	–	–	+
Microcrystalline cellulose	–	–	–	–	–	–	+	+
Dibasic calcium phosphate	+	+	+	–	+	+	+	+
Starch	–	–	–	–	–	–	–	–
Sodium starch glycolate	–	–	–	+	–	–	+	+
Gelatin	–	–	–	–	–	–	+	+
Magnesium stearate	+	+	+	+	+	+	+	+
Colloidal silicon dioxide	+	+	–	+	+	+	–	–

albendazole, were significantly lower than all the other albendazole assay results. For closantel the assay results of 1:1 mixtures with magnesium stearate, with and without stress, and gelatin subjected to stress were significantly lower than all the other closantel assay results.

In Table 4 DSC and HPLC results are compared. Except for the interaction with magnesium stearate, no correlation was observed between the interactions predicted by DSC and HPLC. Only for albendazole–excipient mixtures, not exposed to stress, did the DSC and HPLC results coincide.

CONCLUSIONS

Results showed that there were interactions between closantel and/or albendazole and some tablet excipients. Magnesium stearate reacted with both drugs and the interaction was observed by DSC and HPLC. Other than this, no correlations between DSC and HPLC results were seen. This means that when assessing compatibility between drugs and excipients, these evaluation methods should not be used in isolation. Furthermore, exposure of mixtures, and even the drugs, to heat and moisture resulted in deteriorated compatibility as seen by both DSC and HPLC, but especially HPLC.

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