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Formulation Development and Stability Studies of Aqueous Metronidazole Benzoate Suspensions Containing Various Suspending Agents

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ABSTRACT Metronidazole is a synthetic antibacterial and antiprotozoan agent. Crystallization occurs in aqueous metronidazole benzoate suspensions caused by an anhydrate to monohydrate conversion. This study aimed to develop an aqueous metronidazole benzoate suspension that does not exhibit this hydration and the accompanying crystal growth. Four suspending agent systems were evaluated. Xanthan gum and Avicel® RC-591 (a combination of microcrystalline cellulose and carboxymethylcellulose sodium) were found to be the suspending agents that resulted in optimal formulation properties. Monohydrate formation did not occur in product containing Avicel® RC-591, indicating that suspending agents may exert a positive effect on metronidazole benzoate suspension stability.

INTRODUCTION

Metronidazole is a synthetic, nitroimidazole derived antibacterial and antiprotozoan agent (McEvoy, 2001). Crystallization has been shown to occur in aqueous metronidazole benzoate suspensions because of the conversion from the anhydrous to the monohydrate form of the active pharmaceutical ingredient (API), thereby compromising product stability (Hoelgaard & Møller, 1983).

Previous formulation studies, aimed at producing a stable aqueous metronidazole benzoate suspension, which used a combination of magnesium aluminium silicate and carboxymethylcellulose sodium as suspending agents (Worthington, 2004, personal communication) were unsuccessful. Crystal growth was detected in products that were refrigerated at 2–8°C. According to differential scanning calorimetry (DSC) analysis, performed on these trial formulations, hydrate formation was detected in these products. It was decided that as insufficient information regarding the thermodynamics of the polymorphs and pseudopolymorphs of metronidazole benzoate was known at that time a decision was made to halt formulation development of the suspension.

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Currently, only the innovator product, Flagyl® 200 mg/5 mL suspension (Aventis), exists commercially on the South African market (Gibbon, 2003). A need thus exists for the development of a chemically and physically stable, cost-effective generic metronidazole benzoate suspension.

The aim of the study, therefore, was to investigate whether the inclusion of various natural and synthetic suspending agents into a suspension formulation would prevent the conversion of the anhydrous form of metronidazole benzoate to the hydrated form and inhibit the subsequent increase in particle size. The aim was to identify a formulation that would result in a stable product that does not exhibit crystal growth.

Polymers and surfactants are commonly included in suspension, emulsion and colloidal system dosage forms, generally with the aim of obtaining thickening or wetting effects. However, these components may have other effects, whether independently or because of interactions with other components; these effects being mostly attributed to the electrostatic, steric, electrosteric, or depletion mechanisms (Duro et al., 1999). For example, modifying the surface properties of colloidal particles by polymer adsorption may change their biopharmaceutical behavior. The tendency of polymers and surfactants to adsorb at interfaces is of great importance to these mechanisms and to the in vivo properties of colloidal pharmaceutical systems (Duro et al., 1999).

The choice of suspending agents in the present study was based on the suspending agent that was used in the formulation of the innovator product and suspending agents that showed good suspension properties in various studies sourced in the literature. In a study conducted by Burgalassi et al. (1997), it was found that the type of suspending agent, rather than the physical characteristics of the drug, appeared to exert the main influence on the physical stability of suspensions. The innovator product, Flagyl® suspension (Aventis), contains magnesium aluminium silicate (Veegum HV®) as the suspending agent (ABPI Compendium, 1999), while a generic metronidazole benzoate suspension available on the UK market, Norzol® suspension (Rosemont Pharmaceuticals Ltd, 2003), uses a combination of microcrystalline cellulose and carboxymethylcellulose sodium. A study performed by Burgalassi et al. (1997) proved that this combination produces a physically and chemically stable suspension with thixotropic flux. The incorporation of magnesium aluminium silicate into an aqueous piroxicam suspension was shown to increase the thixotropic characteristics by forming a tridimensional silicate network around the particles (Bregni & Iribarren, 1984). Zatz (1985) proved that xanthan gum could reduce or prevent sedimentation in preparations and Felmeister et al. (1973) showed that the polymer induced flocculation of pharmaceutical suspensions and led to an increase in sedimentation volume. Ziller & Rupprecht (1990) concluded that povidone inhibited crystal growth of a series of drugs in aqueous suspensions and were able to impede the dissolution of some crystals during temperature cycling. Methylcellulose and povidone were found to inhibit transformation of sulfamethoxazole to the semihydrate form in aqueous suspensions (Graf et al., 1982).

MATERIALS AND METHODS

Materials and Instruments

Metronidazole benzoate was obtained from Unique Chemicals (India). Magnesium aluminium silicate was obtained from Chemimpo (South Africa) povidone (Kollidon 90 F) was from Chempro Division (Germany), and xanthan gum was obtained from Danisco Cultor (France). Avicel® RC-591 (a combination of microcrystalline cellulose and carboxymethylcellulose sodium) was from Crest Chemicals (South Africa) and carboxymethylcellulose sodium was purchased from T&C Chemicals (France). Water was purified by the Nanopure® Infinity UV System, Model D8972-33 (Barnstead/Thermolyne Corporation, Dubuque, IA, USA) and all other excipients were obtained commercially. The South African innovator product, Flagyl suspension (Aventis®) was obtained locally.

A turbine laboratory mixer-homogenizer (Silverson® model L2R, Silverson Machines Ltd, Waterside, UK) was used for mixing of the bulk formulations. Particle size analysis of the suspensions was conducted using the small sample dispersion cell (Hydro 2000 SM) of the Malvern® Laser Diffraction Mastersizer 2000 (Malvern, Worcestershire, UK). DSC measurements were performed on DSC Q100 (TA Instruments, New Castle, Delaware). The HPLC system consisted of a Thermoseparation Products® isocratic solvent pump (Riviera Beach, Florida), a 20 μL fixed-loop injector (Rheodyne Inc., California), a Thermoseparation Products® UV detector (Riviera Beach, Florida) and a

25 μL Microliter™ #702 HPLC syringe (Hamilton Company, Reno). Dissolution studies were performed using a SRII 6-Flask Dissolution Test System (Hanson Research Corporation, California). UV spectra were recorded and assays performed using a UV-1601 UV-Visible spectrophotometer, equipped with a Sipper Cell sample unit (Shimadzu Corporation, South Africa). Rheological studies were performed using an air-bearing controlled stress/controlled rate rheostress 1 rheometer (ThermoHaake, Germany). A parallel-plate measuring system, (equipped with a PP60 Ti serrated sensor (60 mm diameter, 1 mm gap,) was used. Serrated upper and lower plates were used in order to counteract possible wall slipping effects.

TABLE 1 Formulation Composition of Metronidazole Benzoate Suspensions, Excluding Suspending Agents

Formulation composition	Quantity (% m/v or v/v)	Unit dose formula (per 5 mL)
API	6.43 % m/v	321.61 mg
Preservative	0.18 % m/v	9.00 mg
Preservative	0.02 % m/v	1.00 mg
Co-solvent	2.00 % v/v	0.10 mL
Wetting agent	0.05 % m/v	2.50 mg
Sweetener	0.07 % m/v	3.50 mg
Sweetener	15.00 % m/v	750.00 mg
Sweetener/vehicle	30.00 % v/v	1.50 mL
Flavorant	0.05 % v/v	0.0025 mL
Purified water to	100.00 % v/v	5.00 mL

Methods

Suspension Formulation

Four categories of metronidazole benzoate suspensions (320 mg/5 mL) were prepared on a laboratory scale (2500 mL) using a number of natural and synthetic suspending agents, including magnesium aluminium silicate, povidone (Kollidon 90F), xanthan gum and Avicel® RC-591, over a range of five concentrations.

The choice of suspending agents used in the study was based on the suspending agents that were commercially available innovator products with good suspension properties mentioned in various studies available in the literature (Motawi et al., 1982; Bregni & Iribarren, 1984; Chowdary & Kumar, 1985; Zatz, 1985; Ziller & Rupprecht, 1990; Plazier-Vercammen, 1995,1996). It has been found that the type of suspending agent, rather than the physical characteristics of the API, appears to exert the main influence on the physical stability of suspensions (Burgalassi et al., 1997).

The remaining excipients included in the formulations consisted of preservatives, a wetting agent, co-solvent, sweetening agents and a flavorant. All excipients, apart from the suspending agents, were kept at constant levels in all formulations in order to study the effects of the suspending agents alone on API crystal growth (Table 1).

The manufacturing processes followed the same general method, with slight variations in the process based on the optimum method of hydrating and dispersing the individual suspending agents. Ingredients were added sequentially to the main portion of water (50% v/v) while mixing with the turbine mixer (Silverson® model L2R) with the mixing speed set to produce a vortex of approximately 2 cm. The preservatives were dissolved in the co-solvent with the aid of gentle heat (50–60°C) and manual agitation and added to the bulk product. The suspending agent(s) were then dispersed in the bulk liquid. The sweeteners were separately dissolved in water using manual agitation and the wetting agent and metronidazole benzoate were subsequently dispersed into the sweetener solution and added to the bulk product. The suspensions were completed with the inclusion of the flavorant and were made up to volume with water.

Initial Analysis of Suspensions

The suspensions were analysed qualitatively and quantitatively in terms of sedimentation, mean particle size, state of hydration (DSC) and dissolution studies. During particle size analysis, the small sample dispersion cell was filled with purified water (400 mL) and the stirring speed was set to 2000 rpm. Sufficient sample (2–4 mL) was added to the measuring cell with a 5 mL syringe and five measurements were performed once a stable obscurity of approximately 7.5% was reached. Dry nitrogen was used as the purge gas during DSC studies at a flow rate of 40–50 mL/min, and the temperature range covered was 25–110°C at a heating rate of 8°C/min.

The mobile phase employed during HPLC assay determinations consisted of acetonitrile 40% and acetic acid 0.1%, made up to volume with 0.01 M

potassium dihydrogen phosphate solution, adjusted to pH 4.5 with 10% m/v sodium hydroxide solution. A Phenomenex® Prodigy C-18 column (150 mm × 4.6 mm, 5 μm particle size) was used and the flow rate was set at 1.5 mL/min. The column temperature was ambient and column back-pressure varied between 2800–3000 psi. The wavelength of the detector was set at $\lambda = 271$ nm. The injection volume was 20 μL and the retention time for metronidazole benzoate under these chromatographic conditions was approximately 5.2 min.

The dissolution method was based on the USP (2004) monograph for metronidazole tablets, with modification of the method to include apparatus II (paddle method) in place of apparatus I (basket stirring method). The dissolution medium was 0.1 N hydrochloric acid (900 mL), the paddle rotation speed was 100 rpm and the sampling intervals were 10, 20, 30, 45, and 60 min. Dissolution samples were assayed by UV spectrophotometry at 242 nm. The UV method used was validated for linearity, accuracy and precision, and specificity. The wavelength of 242 nm chosen for the assay did not coincide with a maximum absorbance peak of metronidazole. Fit factors, described by Moore and Flanner (1996), were used to determine similarity in dissolution profile to the innovator product.

Yield point determinations (rotational rheological studies) were performed in controlled stress mode. Samples were placed onto the peltier plate of the rheometer and allowed to equilibrate at 25°C for 120 s, with zero rotation. Shear stress was increased from 0–50 Pa over 100 s (100 data points) at 25°C. The resultant deformation of the sample was plotted as a function of shear stress on a log-log axis, the point of greatest deformation corresponding to the stress at which the structure of the sample breaks, allowing flow to occur.

The suspending agents that yielded minimal sedimentation, API in the anhydrous pseudopolymorphic form, assay results within specification, and similar dissolution profiles to the commercially available innovator product were selected to be carried forward to stability studies.

Stability Studies

Real-time and accelerated stability studies were conducted on the suspensions containing xanthan gum (0.65% m/v and 0.85% m/v) and Avicel® RC-591 (0.8% m/v and 1.2% m/v) under environmental conditions that were in accordance with international conference on harmonization (ICH) guidelines, namely real-time conditions of 5 ± 3°C and 25 ± 2°C and 60 ± 5% RH. The accelerated conditions were 40 ± 2°C and 75 ± 5% RH. Samples were withdrawn from storage after one (T_1) and three months (T_3) and tested in order to detect significant change, as defined in the ICH Guidelines (ICH, 2003). The temperature cycle study consisted of three cycles of two days at refrigerated temperature (2–8°C) followed by two days under accelerated storage conditions (40°C and 75% RH). Samples were evaluated for significant change on completion of the cycle.

RESULTS AND DISCUSSION

Selection of Optimal Suspending Agent Systems

The suspension of particles in a liquid is a practical application of yield value, which is the initial resistance to flow under applied stress. Unless the force of gravity operating on a suspended particle of a given mass exceeds the liquid's yield value, it will not descend. Viscosity can slow down the rate of settling, but yield value in excess of the gravitational force acting on particles is needed to create permanent suspensions (Noveon™, 2002).

All of the povidone suspensions, all but the highest concentration of the magnesium aluminium silicate suspensions and the suspension with the lowest concentration of Avicel® RC-591 formed sediment when left to stand. Yield points (deformation of the sample versus shear stress) were determined for all of the metronidazole benzoate suspensions in an attempt to correlate yield point with the presence or absence of sedimentation. Sedimentation was observed in suspending agents systems with yield points below 6.8 Pa (Table 2). The yield point that prevented sedimentation was 7.4 Pa.

DSC studies showed that all of the suspensions contained metronidazole benzoate in the anhydrous pseudopolymorphic state, evidenced by asingle endothermic peak present on the thermograms with an onset temperature of 98–99°C, which indicated that the manufacturing process did not influence the state of hydration of the API. The metronidazole benzoate assay values fell within the accepted range of 95–105% m/v for all of the suspensions.

TABLE 2 Yield Points (Pa) and Similarity Factor f_2 for Dissolution Profiles of Metronidazole Benzoate Suspensions Compared to the Commercially Available Innovator Product

Formulation					
Suspending agent	Concentration (%m/v)	Yield point ± SD (Pa) $n = 3$	% RSD	Sedimentation occurred after 1 month	f_2
Magnesium aluminium silicate	0.50	3.13 ± 0.69	22.05	Yes	28.3
	1.00	6.68 ± 0.17	2.61	Yes	43.4
	1.50	4.22 ± 0.12	2.82	Yes	57.9
	2.00	6.88 ± 0.27	3.98	Yes	57.6
	2.50	9.65 ± 1.03	10.62	No	51.1
Povidone	2.00	*not observed	7.34	Yes	36.5
	3.00	*not observed	18.15	Yes	35.8
	4.00	*not observed	13.49	Yes	36.1
	5.00	*not observed	15.40	Yes	37.3
	6.00	*not observed	1.66	Yes	39.8
Xanthan gum	0.55	8.33 ± 0.03	0.35	No	59.2
	0.65	10.58 ± 0.10	0.93	No	56.3
	0.75	13.48 ± 0.18	1.34	No	55.2
	0.85	16.10 ± 0.28	1.76	No	56.2
	1.00	18.85 ± 0.04	0.19	No	57.5
Avicel® RC-591	0.40	*not observed	7.35	Yes	35.17
	0.80	7.41 ± 0.15	2.03	No	71.7
	1.00	8.29 ± 0.71	8.60	No	68.5
	1.20	11.03 ± 0.49	4.43	No	59.7
	1.40	17.08 ± 0.66	3.85	No	35.8

**No visible yield point was observed on the rheogram.*
$n = 3$ (samples tested in triplicate).
SD = Standard Deviation.
% RSD = Relative Standard Deviation, expressed as a percentage.

Dissolution studies showed similarity to the innovator product's dissolution profile in the suspensions containing 1.5, 2.0, and 2.5% of magnesium aluminium silicate, 0.8, 1.0 and 1.2 % of Avicel® RC-591, and all of the suspensions containing xanthan *gu*m (Table 2). However, of the magnesium aluminium silicate suspensions shown to be similar, only 2.5% m/v concentration did not result in sedimentation.

Xanthan gum and Avicel® RC-591 were accordingly chosen as the suspending agents that resulted in optimal formulation properties, focusing on lack of sedimentation, similarity in dissolution profile to the innovator product and assay values within specification. The formulations containing xanthan gum 0.65% m/v and 0.85% m/v and Avicel® RC-591 0.8% m/v and 1.2% m/v, concentrations on the upper and lower ends of the initially chosen suspending agent concentration ranges, were selected for further stability studies.

Stability Evaluation of Xanthan Gum- and Avicel® RC-591-Containing Suspensions

Sedimentation did not occur in suspensions stored at 5°C and at 25°C/60% RH and after the temperature cycle. The Avicel® RC-591 0.8% m/v and 1.2% m/v formulations stored at 40°C and 75% RH displayed sedimentation at T_3. No sedimentation was observed in the xanthan gum formulations.

A Student's *t*-test (two-tailed distribution and two-sample unequal variance) was performed using Microsoft Excel® 2000 (Microsoft Corporation) in order to determine significance of change in mean particle size during the three month stability study and 12-day temperature cycle. The xanthan gum 0.85% m/v formulation showed significant mean particle growth under all environmental conditions at T_3 and after the temperature cycle study (Table 3). None

TABLE 3 Mean Particle Size (μm) and Student *t*-test *p*-Values Showing Significance of Change From T_0 Values of Metronidazole Benzoate Suspensions Stored at 5°C, 25°C/60% RH and 40°C/75% RH for 12 Weeks or for Three Cycles of 2 Days at Refrigerated Temperature (2–8°C) Followed by 2 Days Under Accelerated Storage Conditions (40°C/75% RH)

Formulation			Mean particle size (μm)			
			T_3			
Suspending agent	Concentration (% m/v)	T_0	5°C	25°C / 60% RH	40°C /75% RH	Temperature cycle
Xanthan gum	0.65	100.5	98.2 (p = 0.65)	100.6 (p = 0.98)	104.2 (p = 0.49)	96.1 (p = 0.42)
	0.85	95.1	102.6 (p = 0.02)	104.1 (p = 0.01)	102.0 (p = 0.03)	103.1 (p = 0.03)
Avicel® RC-591	0.80	83.7	84.2 (p = 0.77)	86.2 (p = 0.57)	91.0 (p = 0.14)	83.8 (p = 1.00)
	1.20	84.6	82.2 (p = 0.49)	87.2 (p = 0.69)	91.2 (p = 0.20)	84.6 (p = 0.99)

Significant difference is defined as $p < 0.05$.

of the Avicel® RC-591 suspensions showed any significant change in mean particle size ($p > 0.05$) throughout the studies (Table 3).

The monohydrate form of metronidazole benzoate was identified using thermal analysis (DSC) in T_3 samples of suspension containing xanthan gum 0.65% m/v stored at 25°C/60% RH. Two definite endothermic peaks were observed on the thermogram, namely the API melting point peak with an onset temperature of 99.03°C and the identifying monohydrate peak with an onset of 50.09°C (Fig. 1a). No second endothermic peak was observed for the xanthan gum 0.85% m/v suspension (Fig. 1b). This formulation showed the most significant increase in mean particle size, thus the presence of the monohydrate would be expected in these samples. The lack of the second broad endothermic peak may possibly be attributed to the fact that the monohydrate is present in the samples, but not yet in sufficient quantity to produce this second endothermic peak characteristic of hydrate formation. A single endothermic peak was present on the DSC curves for both of the Avicel® RC-591 formulations, indicating that the API present in these suspensions remained in the anhydrous state throughout the stability studies under all storage conditions.

The dissolution rate profiles of all the metronidazole benzoate suspensions remained similar to the innovator product throughout the stability studies ($f_2 > 50$).

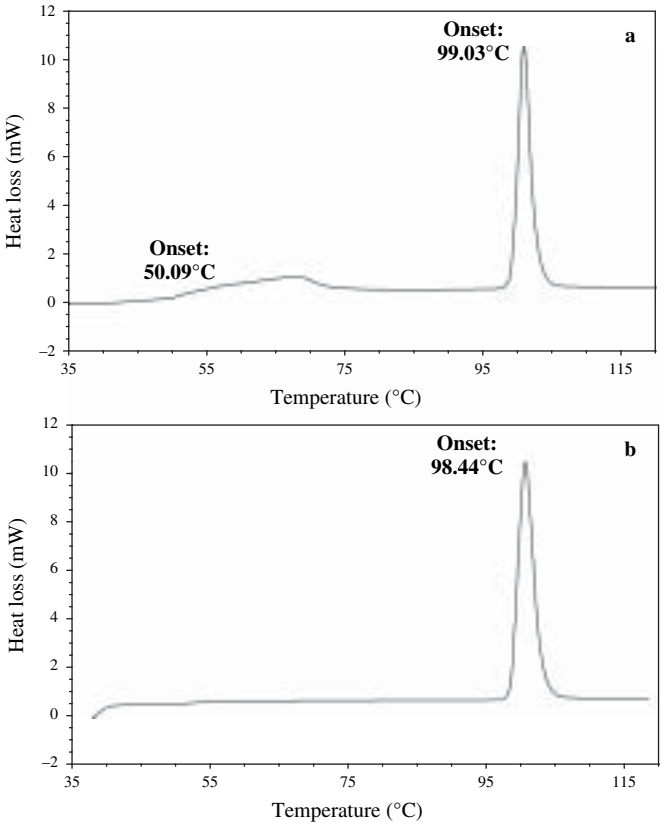

FIGURE 1 DSC Thermograms of Metronidazole Benzoate Suspensions Containing Xanthan Gum After Storage at 25 ± 2°C/ 60 ± 5% RH for 3 Months (a) 0.65% m/v Xanthan Gum Formulation and (b) 0.85% m/v Xanthan Gum Formulation.

CONCLUSIONS AND RECOMMENDATIONS

Metronidazole benzoate suspensions containing xanthan gum displayed no sedimentation, but crystal growth related to monohydrate formation was observed. Suspensions containing Avicel® RC-591 were physically and chemically stable at 25°C/ 60% RH and 5°C for three months but sedimentation occurred at 40°C/75% RH, possibly associated with a temperature-dependent decrease in yield point. Rheological studies should be performed to investigate the effect of temperature on yield points

and the possible need to increase the Avicel® RC-591 concentration to achieve sufficient yield point at 40°C/75% RH.

Sedimentation occurred at T_3 in the Avicel® RC-591 suspensions stored under accelerated conditions, which is classified as a significant change in terms of the ICH guidelines. It is, therefore, recommended that long-term stability studies be performed on the Avicel® RC-591 suspensions, with the ICH intermediate condition of 30 ± 2°C/65 ± 5% RH included (ICH, 2003).

The suspending agent system consisting of Avicel® RC-591 thus shows promise in preventing the conversion of metronidazole benzoate from the anhydrate to the monohydrate form, thereby inhibiting the subsequent increase in particle size caused by the crystal growth.

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