International Journal of Pharmaceutics 393 (2010) 161–166

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Role of the electrokinetic properties on the stability of mebendazole suspensions for veterinary applications

Mª José Cózar-Bernal[a], Visitación Gallardo[b], Eva Sáez-Fernández[b], Mª Ángeles Holgado[a], Josefa Álvarez-Fuentes[a], Mercedes Fernández-Arévalo[a], José L. Arias[b,*]

[a] Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Seville, Spain
[b] Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Granada, Spain

ARTICLE INFO

Article history:
Received 11 January 2010
Received in revised form 24 March 2010
Accepted 23 April 2010
Available online 7 May 2010

Keywords:
Colloidal stability
Electrokinetic properties
Mebendazole
Pharmaceutical suspension
Surface thermodynamics
Veterinary liquid dosage forms

ABSTRACT

This work is focused on the analysis of the effect of basic physicochemical aspects (surface thermodynamic and electrokinetic characteristics) on the stability and redispersibility properties of mebendazole aqueous suspensions. To our knowledge, previous investigations on the formulation of mebendazole suspensions have been not devoted to the elucidation of the colloidal behavior of this benzimidazole carbamate. A deep thermodynamic and electrokinetic characterization, considering the effect of both pH and ionic strength, was carried out with that purpose. It was found that the hydrophobicity and, the surface charge and electrical double layer thickness of the drug play a significant role in the stability of the colloid. Mebendazole aqueous suspensions display a controllable "delayed" or "hindered" sedimentation and a very easy redispersion which may contribute to the formulation of veterinary liquid dosage forms.

1. Introduction

The management of parasitic infestations in veterinary has become an important public health issue. The oral administration of liquid dosage forms is clearly the best way to provide the exact dose of any given drug to animals. In addition, it circumvents the discomfort associated to other traditional routes of administration (e.g., parenteral). However, the formulation of an adequate liquid dosage form is an important challenge that involves the study of different basic aspects. For instance, suspension formulation normally causes manufacturing, storage, and stability problems due to sedimentation and caking (Duro et al., 1998; Ruiz et al., 2003; Van Eerdenbrugh et al., 2008; Arias et al., 2009).

Mebendazole (methyl 5-benzoyl-1H-benzimidazol-2-yl-carbamate) (Fig. 1) is a broad spectrum benzimidazole carbamate classically used in human and veterinary medicine to treat a wide range of parasitic infestations. It is a white to slightly yellow powder that is insoluble in water, alcohol, ether, acid solutions, and chloroform, and freely soluble in formic acid. This drug acts by holding back essential intracellular microtubule-dependent transport processes in parasites. It inhibits glucose uptake, resulting in immobilization and death of the parasite. In humans, it has been satisfactorily used in the treatment of ancylostomiasis, uncinariasis, oxyuriasis, ascariasis, and trichuriasis (Krishnaiah et al., 2001; Dayan, 2003; de Villiers et al., 2005). In veterinary, mebendazole has been approved for use in several species, including pregnant animals. It is very active against: (i) gastro-intestinal nematodes in dogs, cats, horses, donkeys, and sheep; (ii) lungworm in sheep and donkeys, including *Dictyocaulus arnfieldi*; and, (iii) tapeworms in dogs and cats (*Echinococcus* and *Taenia* spp.), and sheep (*Moniezia* spp.). Mebendazole has been also combined with flukicidal drugs for the treatment of sheep with fluke and worm infections (Dayan, 2003; Velík et al., 2004; Cañete et al., 2009).

To our knowledge, the investigations previously completed to design mebendazole suspensions have been largely focused on the elucidation of thermal stability, and crystal purity aspects of the drug. For instance, de Villiers et al. (2005) analyzed the effect of the temperature on the transformation processes between mebendazole polymorphs. Agatonovic-Kustrin et al. (2008) developed an attenuated total reflectance-Fourier transform infrared (ATR-FTIR) spectroscopy technique for the quantitative assessment of the solid-state polymorphic composition of mebendazole drug substances in complex formulations. Finally, Van Eerdenbrugh et al. (2008) investigated the use of D-α-tocopherol polyethylene glycol 1000 succinate (TPGS) to overcome the problems of stability

* Corresponding author at: Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Granada, 18071 Granada, Spain.
Tel.: +34 958 24 39 00; fax: +34 958 24 89 58.
E-mail address: jlarias@ugr.es (J.L. Arias).

0378-5173/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2010.04.031

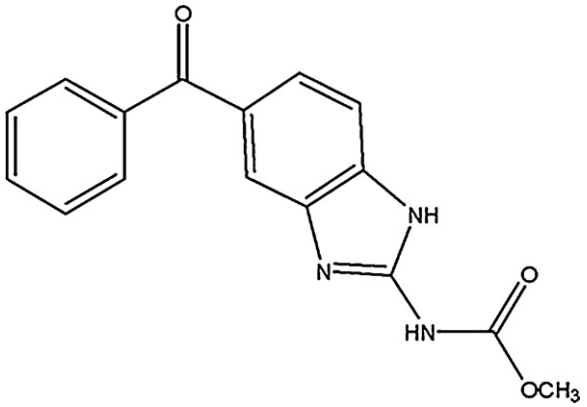

Fig. 1. Chemical structure of mebendazole.

of mebendazole aqueous formulations that are associated to the hydrophobicity of the drug.

The main drawback of the commercially available mebendazole suspensions [drug concentration: 2 to 20% (w/v)] is that the expiration date is conditioned by the stability of the suspension (Van Eerdenbrugh et al., 2008). Hence, the need for an extensive investigation of the basic physicochemical aspects related to the stability and redispersibility properties of this colloid. A preliminary clarification of basic aspects such as the surface properties and colloidal behavior is still missing. This is particularly important if we take into account that the surface electrical properties (i.e., electrokinetic potential and electrical double layer thickness), and the surface thermodynamics play a critical function in the stability of these systems (Arias et al., 2009). In this work we have investigated the thermodynamic properties (hydrophobicity/hydrophilicity) and the electrokinetic properties (electrical state) of mebendazole aqueous suspensions. The basic formulation conditions were clarified by investigating the effects of both ionic strength and pH on the stability of the suspensions.

2. Materials and methods

2.1. Materials

Mebendazole was purchased from Roig Farma-Fagron (Spain), and used as received. Regarding the geometry, hydrophobicity, and electrokinetic properties of the drug, no significant differences were observed when the supplier was Sigma–Aldrich (Germany), or Guinama (Spain) (data not shown for clarity). Water used in the experiments was deionized and filtered (Milli-Q Academic, Millipore, France). All other chemicals were of analytical quality from Panreac (Spain) except for formamide (Carlo Erba, Italy), and α-bromonaftalene (Merck, Alemania).

2.2. Methods

2.2.1. Characterization

Mean diameters of mebendazole particles were measured after suitable dilution of the drug suspensions at 25.0 ± 0.5 °C, by photon correlation spectroscopy (PCS) (Malvern 4700 analyzer, Malvern Instruments, U.K.) using a 75 mW, 488 nm wavelength argon ion laser (Cyonics). In order to confirm these results, the geometry (size and shape) of the particles were deduced from scanning electron microscope (SEM) photographs, which were obtained by using a Zeiss DSM 950 SEM (Germany) set at 80 kV accelerating voltage. Before inspection, a dilute mebendazole aqueous suspension (≈0.1%, w/v) was sonicated for 10 min, and drops were located on copper grids with formvar film, that were then dried at 40.0 ± 0.5 °C in a convection oven.

The electrokinetic properties of mebendazole suspensions (≈0.1%, w/v) were measured by electrophoretic determinations using a Zetasizer 2000 (Malvern Instruments, U.K.) electrophoresis device. The effect on these properties of both electrolyte concentration (NaCl, $CaCl_2{\cdot}4H_2O$, or $AlCl_3{\cdot}6H_2O$) and pH (adjusted with either NaOH or HCl) was investigated. The measurements were done at 25.0 ± 0.5 °C, after 24 h of contact at this temperature under mechanical stirring (50 rpm). The experimental uncertainty of the measurements was below 5%.

We selected NaCl, $CaCl_2$ or $AlCl_3$ as electrolytes in this investigation due to the fact that they have been reported to very efficiently stabilize medicines based on aqueous suspensions (Gallardo et al., 2003; Ruiz et al., 2004; Abrahamsson and Odman, 2008; Arias et al., 2009). NaCl and $CaCl_2$ are well-known pharmaceutical excipients that have been approved by the Food and Drug Administration (F.D.A.) for the formulation of medicines intended for the oral route. On the opposite, $AlCl_3$ has been not yet approved by the F.D.A. However, the use of the latter electrolyte comes from the need to accomplish the investigation of the effect of the type of electrolyte and its concentration on the stability of mebendazole aqueous suspensions.

The determination of the surface thermodynamics of the benzimidazole carbamate was done following the model of van Oss (2006; see also Arias et al., 2008, 2009), according to which the total surface free energy of any material i ($\gamma TOTi$) is the sum of two contributions: the non-polar Lifshitz–van der Waals component (γLWi) and the acid–base component (γABi). The latter is linked to the electron-acceptor (γ_i^+) and the electron-donor (γ_i^-) properties of the material. Likewise, the interfacial solid/liquid free energy ($\gamma TOTSL$), and its $\gamma LWSL$ and $\gamma ABSL$ components are related to the surface free energies of both the solid (subscripts S) and the liquid (subscripts L):

$$\gamma_{SL}^{TOT} = \gamma_{SL}^{LW} + \gamma_{SL}^{AB} = \gamma_{SL}^{LW} + 2\sqrt{\gamma_S^+\gamma_S^-} + 2\sqrt{\gamma_S^-\gamma_S^+} - 2\sqrt{\gamma_S^+\gamma_L^-} - 2\sqrt{\gamma_S^-\gamma_L^+} \quad (1)$$

The use of Young's equation (Adamson and Gast, 1997) allows establishing a relationship between these quantities and the contact angle (θ) between the liquid and the solid:

$$(1+\cos\theta)\gamma_L^{TOT} = 2\sqrt{\gamma LWS\gamma LWL} + 2\sqrt{\gamma_S^+\gamma_L^-} + 2\sqrt{\gamma_S^-\gamma_L^+} \quad (2)$$

The three unknowns (γ_S^{LW}, γ_S^+, and γ_S^-) can be obtained by solving the resulting system of 3 equations if we determined the θ of three liquids of known γLWL, γ_L^+, and γ_L^-: water (γLWL = 21.8, $\gamma_L^+ = \gamma_L^-$ = 25.5 mJ/m^2), formamide (γLWL = 39.0, γ_L^+ = 2.28, γ_L^- = 39.6 mJ/m^2), and α-bromonaftalene (γLWL = 43.6, $\gamma_L^+ = \gamma_L^-$ = 0 mJ/m^2) (van Oss, 2006). The θ of these liquids were measured using a Ramé-Hart 100-00 goniometer (USA) on drug pellets (diameter: 1.3 cm) at 25.0 ± 0.5 °C. These pellets were prepared by compressing the dry mebendazole powder in a Spepac hydraulic press (UK) set to 8 Ton during 5 min.

2.2.2. Stability of mebendazole suspensions

In addition to the electrokinetic study, another method was selected to investigate the stability of mebendazole aqueous suspensions. It consisted in the measurement of the sediment volume (V_s) after keeping the drug suspensions in 100 mL cylinders (inner radius: 1.2 cm) at 25.0 ± 0.5 °C. The concentration of mebendazole powder in each cylinder was 0.5% (w/v). For the characterization of the stability, the flocculation ratio (F) was the magnitude chosen. This quantity is defined as V_s/V_0 (%), where V_0 is the initial volume of the suspension (Matthews and Rhodes, 1970). We

also used a complementary method that is appropriate for dilute suspensions (Arias et al., 2009): the measurement at $\lambda = 300$ nm of the optical absorbance of mebendazole aqueous suspensions (0.5%, w/v) as a function of time, by using a PerkinElmer UV/Vis Lambda 40 (PerkinElmer, USA) spectrophotometer. Finally, the redispersibility of the mebendazole sediments was ascertained by visual inspection of the aqueous suspensions after placing them in an Branson 5200E4 ultrasonic bath (USA), set at 40 kHz and with a sonic power of 100 W (Arias et al., 2009). Moderate hand shaking for ≈3 min of the aqueous mebendazole suspensions did not show any significant difference compared to ultrasonication.

3. Results and discussion

3.1. Geometry of mebendazole particles

Mebendazole particles were of acicular (elongated) shape, in the colloidal size range and moderately polydisperse. The average diameter (± standard deviation) and polydispersity index were 1.9 ± 0.6 μm and 0.339, respectively. As an example, Fig. 2 shows a SEM microphotograph of the mebendazole dry powder and the size histogram (based on 100 particles counting).

3.2. Surface thermodynamics of mebendazole particles

The contact angles (θ) of water, formamide and α-bromonaftalene on the dry pellets of mebendazole were $69^\circ \pm 4^\circ$, $47^\circ \pm 6^\circ$ and $6^\circ \pm 2^\circ$, respectively. The γLWS, γ_S^+, and γ_S^- components represent a set of physical magnitudes that can be evaluated to determine the nature of the active agent, thanks to the true physical information on the surface thermodynamics given. It was determined that the γLWS component is 43.4 ± 0.1 mJ/m^2, the γ_S^+ component is 0.2 ± 0.3 mJ/m^2, and the γ_S^- component is 10.8 ± 0.8 mJ/m^2. Hence, mebendazole is basically a monopolar electron-donor material, in the sense given by van Oss (2006): this drug is capable of having acid–base interactions with phases of whatever polarity (γ^+, γ^-, or both, different from zero), although the acid–base forces do not contribute to its cohesion free energy.

These γ_S components manifest themselves in the hydrophobicity/hydrophilicity of the drug: in order to determine whether a material can be considered hydrophobic or hydrophilic, it can be evaluated the free energy of interaction ΔG_{SLS} (not considering the electrostatic component) between the solid phases immersed in the liquid (van Oss, 2006). This quantity can be written as follows per unit area of interacting particles:

$$\Delta G_{SLS} = -2\gamma_{SL}^{TOT} \quad (3)$$

It was found that ΔG_{SLS} was negative for mebendazole (-39.8 ± 4.5 mJ/m^2) and, thus, this drug can be considered hydrophobic. This is due to the fact that the interfacial interactions favor the attraction of the microparticles to each other.

3.3. Effect of pH on the stability of mebendazole aqueous suspensions

The pH characteristically displays a considerable effect on the surface charge of numerous solids of pharmaceutical interest (drugs, polymers, etc.) (Gallardo et al., 2003; Ruiz et al., 2004; Arias et al., 2009). Thus, we investigated the influence of [H$^+$] on the colloidal stability of mebendazole. Fig. 3a shows the type of time evolution of the sedimentation curves of the drug aqueous suspensions: independently of pH, all suspensions developed a "hindered" or "delayed" sedimentation profile, in which the sediment front typically fall from the upper side of the suspension, leading to a patent boundary between the front and the clarified aqueous supernatant (Delgado et al., 1990). Almost the same time evolution of the sedimentation curves of the mebendazole aqueous suspensions was observed when the drug concentration was 2% (w/v) (the concentration usually used in veterinary) (data not shown for brevity). At the earliest stage of the sedimentation process, the aggregates extend to nearly the entire volume of the suspension. Thus, the sedimented volume was high and it decreased with time: only after ≈24 h the mebendazole microparticles settled giving a stable flocculation ratio. It could be also pointed out a slight tendency for minor flocculation values as the [H$^+$] decreased: 21%, 19%, and

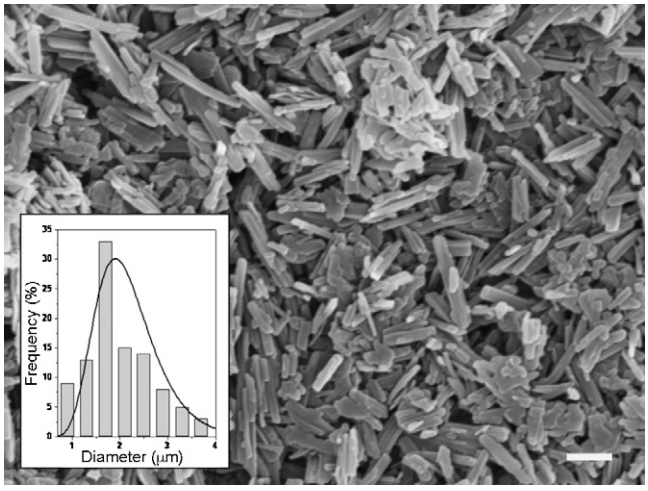

Fig. 2. Scanning electron microphotograph of mebendazole (inset: size histogram of the dry powder). Bar length: 2 μm.

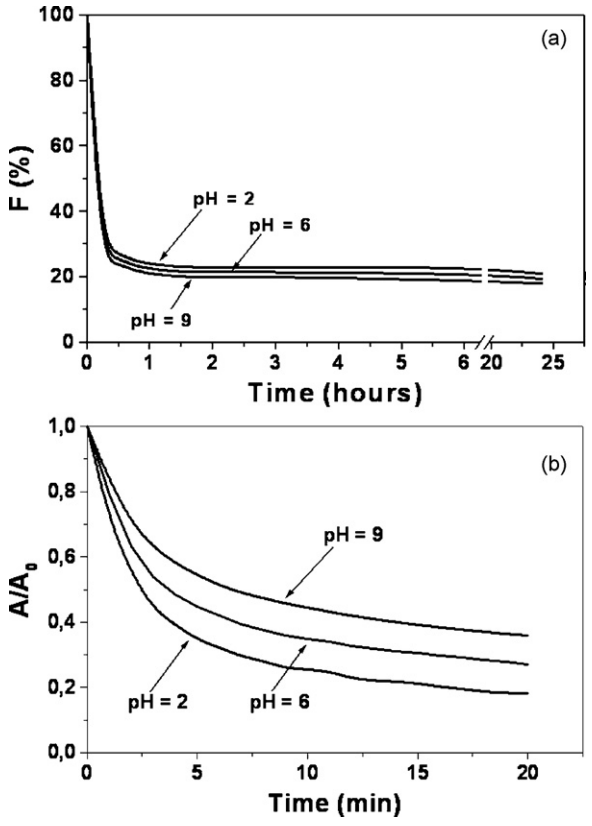

Fig. 3. Flocculation ratio F (V_s/V_0, %) (a) and optical absorbance A (relative to its initial value, A_0) (b) as a function of time for mebendazole aqueous suspensions at pH 2, 6, and 9.

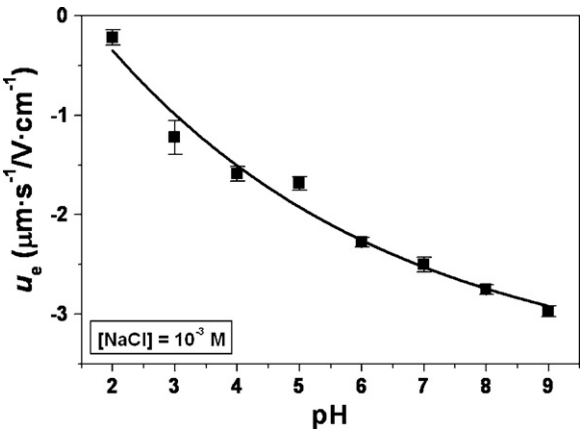

Fig. 4. Electrophoretic mobility (u_e) values of mebendazole microparticles as a function of pH in the presence of 10^{-3} M NaCl.

18% at pH 2, 6 and 9, respectively. Finally, redispersion was nearly finished after ≈3 min of ultrasonic shaking.

These results were confirmed by the optical absorbance data of mebendazole aqueous suspensions with different pH values. Fig. 3b shows the absorbance A (relative to its initial value A_0) as a function of time. It is clear that the ratio A/A_0 diminishes with time, indicating the disappearance of drug microparticles out of the light beam due to settling after coagulation. In this figure it can be also detected that the sedimentation rate was affected by the [H$^+$]: there is an inclination to greater rates as the pH becomes more acidic, probably a consequence of the bigger weight of these slightly more voluminous flocculi.

With the aim of qualitatively explaining the stability and redispersibility data in the frame of the DLVO classical theory of the stability of lyophobic colloids (Hunter, 2001), we studied the u_e values of mebendazole microparticles as a function of pH under equivalent conditions to those corresponding to the stability study. As can be observed in Fig. 4, u_e was negative for the whole pH interval, and it augmented in absolute value as the [H$^+$] decreased. This behavior could be explained on the basis of the charge generation mechanism at the mebendazole-solution interface: weak acid groups (presumably carboxylic) may be responsible for the generation of these negative values on the drug surface (pK_a of the drug: 6.82) (Ramanathan et al., 1993). As hydrogen in the carboxyl groups is acidic, loss of H$^+$ from the molecule can be considered an important factor that defines the net charge. Thus, the progressively more negative charge density could be understood by the effect of increasing pH (OH$^-$ concentration) in the solution, which tends to progressively enhance the loss of protons in the drug molecule. On the opposite, the decrease in absolute u_e values as pH becomes more acidic may be a consequence of the neutralization of the negative regions at the mebendazole surface by the chemical adsorption of increasing quantities of H$^+$ ions (Vera et al., 1996; Ruiz et al., 2004; Arias et al., 2008).

At acid pH, u_e will be low, and formation of open flocculi can occur rapidly because of van der Waals attraction, which is favored by the hydrophobic character of the drug (see Section 3.2). However, the open structure of the flocculi will include moderately big volumes of the supporting aqueous solution, and the average solid-solid distances will be rather large, despite the van der Waals attractions and the hydrophobicity of mebendazole. Therefore, the drug microparticles will be separated even after a mild shaking, and the drug suspensions will be easily redispersible. This behavior was also observed for basic pHs, even though the high u_e values of the mebendazole microparticles. We have to keep in mind the high hydrophobicity of the active agent to understand this similarity, which could determine that interfacial interactions favor the existence of attractions between the microparticles that support the formation of aggregates, which will be slightly smaller than at acid pHs due to the expected electrostatic repulsions. Finally, the previously commented small trend towards faster sedimentation rates for acid pHs could be a consequence of the slightly large volume (weight) of the aggregates obtained under these conditions.

3.4. Effects of electrolyte type and concentration on the stability of mebendazole aqueous suspensions

We investigated the time evolution of the sedimentation curves of the mebendazole aqueous suspensions at pH 6, the natural pH of the drug suspensions, when three common electrolytes (NaCl, $CaCl_2$, and $AlCl_3$) were added in concentrations ranging from 10^{-5} to 10^{-1} M. It was observed that independently of the electrolyte type and concentration, all suspensions developed a "delayed" or "hindered" sedimentation (see Fig. 5a as an example), and only after ≈24 h a stable flocculation ratio was achieved. It was also possible to detect a slight tendency to greater flocculation values as the electrolyte concentration was increased. For instance, in the case of $AlCl_3$: 21%, 19%, and 18% at 10^{-1}, 10^{-3} and 10^{-5} M, respectively. When the drug concentration was 2% (w/v), no significant differences were observed in the time evolution of the sedimentation curves (data not shown for brevity). Redispersion was almost complete after ≈3 min of ultrasonic shaking, without significant differences between the electrolytes and their concentrations. These results were confirmed by the relative absorbance versus time data (e.g., Fig. 5b), where it was also observed that the sedimentation rate was affected by the electrolyte concentration: there was a slight trend to higher rates as the electrolyte concentration becomes greater, probably a consequence of the bigger weight of these slightly more voluminous sediments. Finally, as previously

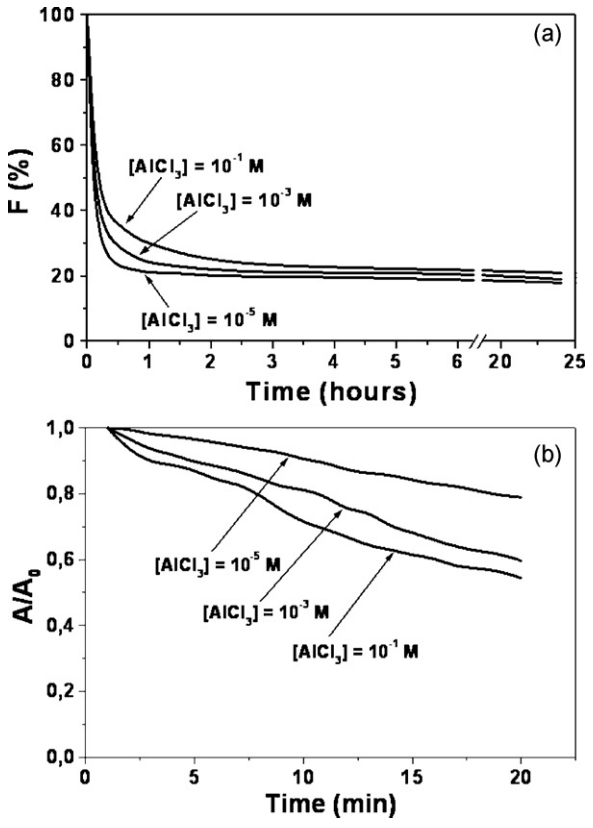

Fig. 5. Flocculation ratio F (V_s/V_0, %) (a) and optical absorbance A (relative to its initial value, A_0) (b) as a function of time for mebendazole suspensions (pH 6) at the $AlCl_3$ molar concentrations: 10^{-1}, 10^{-3}, and 10^{-5}.

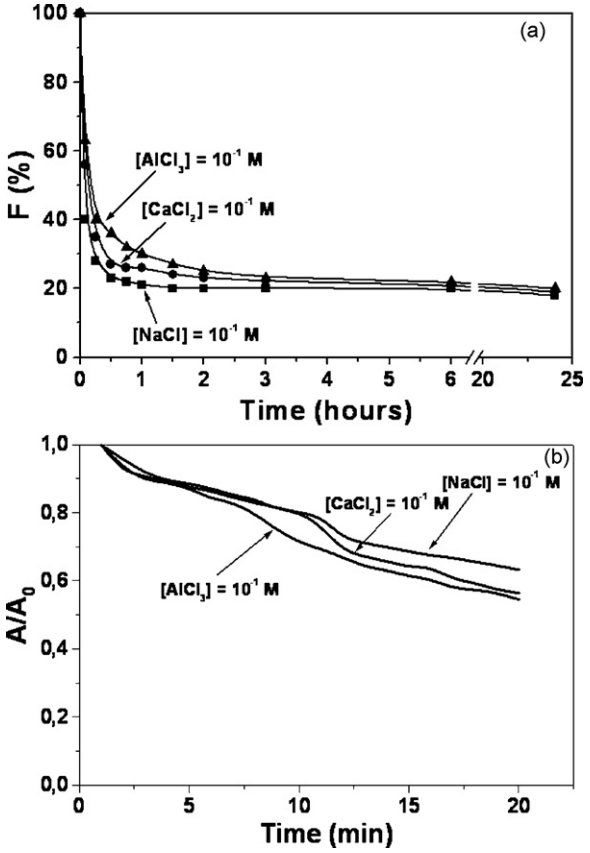

Fig. 6. Flocculation ratio F (V_s/V_0, %) (a) and optical absorbance A (relative to its initial value, A_0) (b) as a function of time for mebendazole suspensions (pH 6) at 10^{-1} M NaCl, $CaCl_2$, and $AlCl_3$.

commented, the absence of significant differences between the electrolytes (see Fig. 6 as an example) and their concentrations can be partially explained by considering the hydrophobicity of mebendazole which induces the formation of aggregates despite the tendency of the drug to settle as individual particles at low electrolyte concentrations (high u_e values, as discussed below).

We now investigate to what extent the flocculation data can be explained by the electric double layer properties. Fig. 7 shows that u_e values were negative throughout the range of concentrations tested for NaCl and $CaCl_2$, and that the absolute value tended to decrease as concentration of either electrolyte increased. This trend was more evident for $CaCl_2$ due to a stronger specific adsorption

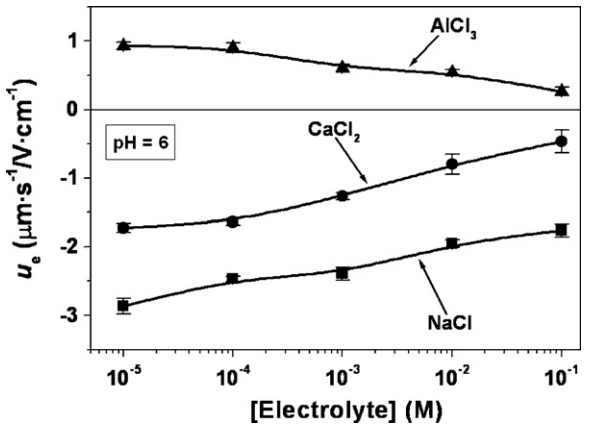

Fig. 7. Electrophoretic mobility (u_e) values of mebendazole microparticles as a function of the concentration of NaCl (■), $CaCl_2$ (●), and $AlCl_3$ (▲) at pH 6.

in the Stern layer (Ruiz et al., 2004; Arias et al., 2009). Decreased u_e resulted from the effect of double-layer compression (Fig. 7): the counterions accumulate closer to the particle surface, such that the double layer shrinks as concentration increases. This leads to a lower electrical potential in the shear plane (or slip surface) that limits the value of u_e and, therefore, favors the formation of voluminous aggregates that settle down slightly faster (tendency also observed in $CaCl_2$ solutions as compared to NaCl, see Fig. 6).

On the opposite, the very significant effect of highly charged counterions on the magnitude and sign of the surface charge of drug microparticles was clear when the medium contained $AlCl_3$. Fig. 7 shows that u_e was positive within the range of concentrations of this electrolyte studied. These results are a consequence of surface adsorption of Al^{3+} ions onto mebendazole with a consequent increase in cationic charge and decrease in u_e. This suggests that trivalent cations are more effective than divalent cations (which in turn are more efficient than monovalent cations) in reducing u_e. This behavior is a consequence of the Schulze-Hardy rule, according to which higher counterion valence is associated with greater decrease in u_e. The specific or chemical adsorption of Cl^- ions onto the mebendazole surface could justify the essential aspects of this phenomenon. At low NaCl or $CaCl_2$ concentrations, counterions are unable to cover completely the drug surface, and Cl^- ions might thus be capable to reach the particle surface. This in turn could lead to an additional increase in net negative charge and hence u_e. When the concentration is increased, the greater number of cations may be more effective in impeding contact between microparticles and Cl^- ions and, hence, it can prevent (or at least reduce) the adsorption of co-ions. This effect is compensated by double-layer compression caused by the increasing counterion concentration. Thanks to the greater charge of Ca^{2+}, this cation is more efficient in this coating effect than Na^+. It would explain why the very low u_e detected in $CaCl_2$ solutions (indicating a decrease in the number of Cl^- ions adsorbed) is not found in the presence of Na^+. On the contrary, trivalent cation salts have a much greater effect on u_e that determines a move to positive values, a clear indication that Al^{3+} interacts strongly with the drug surface (Ruiz et al., 2004). In addition, the very low u_e values generated even at the weak ionic strengths of $AlCl_3$ could explain the generation of much voluminous macroaggregates that, due to their higher weight, will sediment slightly faster.

4. Conclusions

In this work we have determined that the stability of mebendazole aqueous suspensions is principally controlled by its hydrophobic character and, by the electrokinetic properties of the microparticles and the thickness of their ionic double layers. Even though hydrophobicity strongly defines the flocculation curves, the modification of pH and the addition of electrolytes could also help in the enhancement of the stability of mebendazole aqueous suspensions. The combined use of high concentrations of $AlCl_3$ and acidic pHs is expected to allow the formulation of mebendazole suspensions with very suitable stability and redispersability for veterinary applications.

Acknowledgements

Financial support from Junta de Andalucía, Spain, under Project PE-2008-FQM-3993 is gratefully acknowledged.

References

Abrahamsson, B., Odman, J., 2008. Pharmaceutical compositions. US Patent 0 058 399 A1, 6 March.

Adamson, A.W., Gast, A.P., 1997. Physical Chemistry of Surfaces, sixth ed. John Wiley & Sons, Inc., New York.
Agatonovic-Kustrin, S., Glass, B.D., Mangan, M., Smithson, J., 2008. Analysing the crystal purity of mebendazole raw material and its stability in a suspension formulation. Int. J. Pharm. 361, 245–250.
Arias, J.L., Reddy, L.H., Couvreur, P., 2008. Magnetoresponsive squalenoyl gemcitabine composite nanoparticles for cancer active targeting. Langmuir 24, 7512–7519.
Arias, J.L., Gómez-Gallo, A., Delgado, A.V., Gallardo, V., 2009. Study of the stability of Kollidon® SR suspensions for pharmaceutical applications. Colloids Surf. A: Physicochem. Eng. Aspects 338, 107–113.
Cañete, R., Escobedo, A.A., Almirall, P., González, M.E., Brito, K., Cimerman, S., 2009. Mebendazole in parasitic infections other than those caused by soil-transmitted helminths. Trans. R. Soc. Trop. Med. Hyg. 103, 437–442.
Dayan, A.D., 2003. Albendazole, mebendazole and praziquantel: review of non-clinical toxicity and pharmacokinetics. Acta Trop. 86, 141–159.
de Villiers, M.M., Terblanche, R.J., Liebenberg, W., Swanepoel, E., Dekker, T.G., Song, M., 2005. J. Pharm. Biomed. Anal. 38, 435–441.
Delgado, A.V., Gallardo, V., Parera, A., González-Caballero, F., 1990. A study of the electrokinetic and stability properties of nitrofurantoin suspensions. II. Flocculation and redispersion properties as compared with theoretical interaction energy curves. J. Pharm. Sci. 79, 709–715.
Duro, R., Gómez-Amoza, J.L., Martínez-Pacheco, R., Souto, C., Concheiro, A., 1998. Adsorption of polysorbate 80 on pyrantel pamoate: effects on suspension stability. Int. J. Pharm. 165, 211–216.
Gallardo, V., Ruiz, M.A., López-Viota, J., Salcedo, J., Delgado, A.V., 2003. Electrokinetic study of omeprazole drug in aqueous suspensions. Colloids Surf. A: Physicochem. Eng. Aspects 218, 21–26.
Hunter, R.J., 2001. Foundations of Colloid Science, second ed. Clarendon Press, Oxford.
Krishnaiah, Y.S.R., Raju, P.V., Kumar, B.D., Bhaskar, P., Satyanarayana, V., 2001. Development of colon targeted drug delivery systems for mebendazole. J. Control. Release 77, 87–95.
Matthews, B.A., Rhodes, C.T., 1970. Use of the Derjaguin, Landau Verwey and Overbeek theory to interpret pharmaceutical suspension stability. J. Pharm. Sci. 59, 521–526.
Ramanathan, S., Nair, N.K., Mansor, S.M., Navaratnam, V., 1993. Determination of a new antifilarial drug, UMF-058, and mebendazole in whole blood by high-performance liquid chromatography. J. Chromatogr. 615, 303–307.
Ruiz, M.A., Gallardo, V., Arias, J.L., Delgado, A., 2003. Effect of latex and plasticizer concentration on glucocorticoid release from ointments. Pharm. Ind. 65, 454–457.
Ruiz, M.A., Gallardo, V., Ouazzani, N., López-Viota, J., López-Durán, J.D.G., 2004. Electrophoretic properties of acrylic latex suspensions (Kollicoat® MAE 30 D) and ibuprofen. Il Farmaco 59, 657–662.
Van Eerdenbrugh, B., Froyen, L., Van Humbeeck, J., Martens, J.A., Augustijns, P., Van den Mooter, G., 2008. Drying of crystalline drug nanosuspensions—the importance of surface hydrophobicity on dissolution behavior upon redispersion. Eur. J. Pharm. Sci. 35, 127–135.
van Oss, C.J., 2006. Interfacial Forces in Aqueous Media, second ed. CRC Press, Boca Raton.
Velík, J., Baliharová, V., Fink-Gremmels, J., Bull, S., Lamka, J., Skálová, L., 2004. Benzimidazole drugs and modulation of biotransformation enzymes. Res. Vet. Sci. 76, 95–108.
Vera, P., Gallardo, V., Salcedo, J., Delgado, A.V., 1996. Colloidal stability of a pharmaceutical latex: experimental determinations and theoretical predictions. J. Colloids Interf. Sci. 177, 553–560.