International Journal of Pharmaceutics 403 (2011) 23–28

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Changed crystallinity of mebendazole solid dispersion: Improved anthelmintic activity

Juan J. García-Rodriguez[a], Paloma M. de la Torre-Iglesias[b], M. Carmen Vegas-Sánchez[a], Susana Torrado-Durán[b], Francisco Bolás-Fernández[a], Santiago Torrado-Santiago[c,*]

[a] Department of Parasitology, Faculty of Pharmacy, Complutense University, 28040 Madrid, Spain
[b] Department of Pharmaceutical Technology, Faculty of Pharmacy, Complutense University, 28040 Madrid, Spain
[c] Centro de Investigación Biomédica en Red de enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain

ARTICLE INFO

Article history:
Received 11 June 2010
Received in revised form 1 October 2010
Accepted 1 October 2010
Available online 8 October 2010

Keywords:
Mebendazole
Solid dispersions
Powder X-ray diffraction
Dissolution rate
Anthelmintic activity

ABSTRACT

To improve the efficacy of mebendazole (MBZ), a poorly water-soluble drug, MBZ solid dispersions containing different proportions of low-substituted hydroxypropylcellulose (L-HPC) were prepared by lyophilization process. The physical characteristics of recrystallized MBZ, and solid dispersions (SD) at different MBZ:L-HPC proportions were investigated in terms of morphology (scanning electron microscopy, SEM), powder X-ray diffraction (XRD), differential scanning calorimetry (DSC) and dissolution rate. The *in vivo* performance was assessed by anthelmintic activity studies against enteral (pre-adult) stage of *Trichinella spiralis* in mice. The XRD, DSC and SEM revealed a characteristic decrease in crystallinity when increasing the L-HPC proportions in the solid dispersions. The dissolution studies demonstrated a marked increase in the dissolution rate in comparison with recrystallized drug. The considerable improvement in the dissolution rate of MBZ from solid dispersions was attributed to decreased drug crystallinity and altered surface morphology (major) and to the wetting effect of L-HPC (minor). The *in vivo* studies revealed that the anthelmintic effects of solid dispersions in mice were significantly increased in comparison with recrystallized MBZ (1.74-fold for SD-1:1, 3.20-fold for SD-1:2.5 and 3.80-fold for SD-1:5). These results have shown the suitability of MBZ:L-HPC solid dispersions for the treatment of enteral helmintic diseases at low doses.

1. Introduction

Mebendazole (MBZ), methyl-5-benzoyl benzimidazole-2-carbamate, a broad-spectrum anthelmintic drug of the benzimidazole class, effective against a number of nematodal and cestodal species under oral administration as tablets or suspension, is recommended for the treatment of non-surgical cases and as a supplementary treatment prior to and post-surgery (Agatonovic-Kustrin et al., 2008). However, it has been observed that *in vivo* results are far from being as effective as those demonstrated *in vitro* due to its low absorption at the gastrointestinal level. The possible reason for variable low efficiency of benzimidazole derivatives may be attributed to the low water solubility of the drugs which limits their absorption resulting in low bioavailability (Daniel-Mwambete et al., 2004). Therefore a high dose of MBZ is required for helminthic infections causing many adverse effects. Furthermore the information available concerning the effectiveness of various benzimidazole derivatives (e.g., flubendazole, albendazole, mebendazole) is somewhat inconsistent (Maki and Yanagisawa, 1988; Chung et al., 2001; Siriyasatien et al., 2003). Thus the observation of different therapeutic outcomes have been to some extend attributed to the different polymorphs with different dissolution rates and anthelmintic activities (Rodriguez-Caabeiro et al., 1987; Swaneppoel et al., 2003a; De Villiers et al., 2005).

A possible way of overcoming the MBZ low aqueous solubility is to alter the physical properties of the drug by preparing a solid dispersion (SD). The solid state forms (i.e., crystalline polymorphs, solvates, amorphous solids) of a drug substance can have a significant impact on the drug's solubility, dissolution rate, activity and bioavailability. Low-substituted hydroxypropylcellulose (L-HPC), as an inert carrier, has been used by many authors for obtaining solid dispersions of poorly soluble drugs (Leuner and Dressman, 2000; Ambike et al., 2004; DiNunzio et al., 2010). It is well known that the solid dispersion system increases the solubility and the dissolution rate of the drug by simultaneously reducing drug particle size and altering the drug crystal form, usually to an amorphous state, therefore they have shown an increase in drug bioavailability

* Corresponding author at: Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad Complutense de Madrid, Avda, Complutense s/n, 28040 Madrid, Spain. Tel.: +34 91 394 1620; fax: +34 91 394 1736.
E-mail address: torrado2@farm.ucm.es (S. Torrado-Santiago).

0378-5173/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2010.10.002

(Daniel-Mwambete et al., 2004; Mutalik et al., 2008; Onoue et al., 2009; Kawabata et al., 2010). The objectives of present study were: (i) to evaluate the feasibility of L-HPC in altering the crystalline property of MBZ and enhancing its dissolution rate by preparing solid dispersions using a freeze-drying method and (ii) to determine the *in vivo* anthelmintic efficacy of formulations with high MBZ solubility at a low dose of 1 mg/kg.

2. Materials and methods

2.1. Materials

The materials used were as follows: MBZ (Sigma®, St. Louis, MO, USA) and L-HPC (LH-31, hydroxypropoxy content: 11%, Shin-Etsu®, Tokyo, Japan). All other chemicals reagents were of pharmaceutical grade or better.

2.2. Preparation of formulations

MBZ solid dispersions were prepared by conventional solvent method using L-HPC as a carrier. The solid dispersions of 1:1; 1:2.5; 1:5; and 1:10 (w/w) of drug to carrier were prepared. The required amounts of MBZ and L-HPC were co-dissolved in a minimal volume of a water:formic acid mixture (66/33, v/v) and frozen at −40 °C. The frozen mixtures were lyophilized using a Liolabar 7 (Telstat Inc., Madrid, Spain). After the freeze-drying process, each of the different formulations was ground and sieved to obtain a particle size fraction of 0.125–0.500 mm. After this procedure the vials were capped within 5 min and stored at room temperature (22–24 °C) in a desiccator containing silica gel.

The physical mixtures containing drug to carrier proportions of 1:1; 1:2.5; 1:5 and 1:10 (w/w) were prepared by mixing manually the appropriate amount of 0.125–0.500-mm particle size fractions of MBZ and carrier in a ceramic bowl using a polymeric spatula. Recrystallized MBZ was obtained by the same preparation method used for the solid dispersions but without any carrier.

2.3. Scanning electron microscopy (SEM) studies

Particle morphology, size and shape were analyzed by SEM. MBZ raw material; recrystallizated MBZ; physical mixture 1:10; SD-1:1; SD-1:5 and SD-1:10 were placed on an aluminium sample mount. After coating with a thin layer of gold–palladium, the samples were analysed with a Jeol® 6400 SEM. All micrographs were the product of secondary electron imaging used for surface morphology identification at magnifications of 500× or 2000× and an accelerating voltage of 20 kV.

2.4. Powder X-ray diffraction (XRD): structural and crystal size characterization

The structural characterization of the material included conventional θ–2θ powder X-ray diffraction with Cu-kα radiation (Philips X'Pert-MPD) (CAI Difraccion rayos X, Farmacia, UCM) of several samples (MBZ raw material; recrystallizated MBZ; PM-1:1; PM-1:2.5; SD-1:1; SD-1:2.5; SD-1:5; SD-1:10 and L-HPC) under study at room temperature. The 5–35° 2θ range was scanned at 0.04° step size and 1 s time per step in all cases. Approximately 200 mg of sample was dispersed onto a zero-background Si sample holder and care was taken to not to introduce a preferential orientation of the crystals.

2.5. Differential scanning calorimetry (DSC)

Differential scanning calorimetric (DSC) analysis was used to characterize the thermal behaviour of the: pure MBZ; recrystallized MBZ; L-HPC; PM-1:1; SD-1:1 and SD-1:2.5.

DSC thermograms were obtained using an automatic thermal analyzer system (Mettler Toledo TC 15, TA controller). Temperature calibration was performed using Indium Calibration Reference Standard (transition point: 156.60 °C). Samples were accurately weighed into aluminium pans, then hermetically sealed with aluminum lids and heated from 25 °C to 375 °C at a heating rate of 10 °C/min under constant purging of dry nitrogen 20 ml/min. An empty pan, sealed in the same way as the sample, was used as a reference.

2.6. In vitro drug release

These studies were carried out in a dissolution bath (Vankel® VK 700). A USP Apparatus 2 (paddle) was set up with a rotational speed of 75 rpm and 500 ml of dissolution medium (0.1 M hydrochloric acid). The temperature was maintained at 37.0 ± 0.1° throughout dissolution study. An amount of the solid dispersion equivalent to 10 mg of MBZ was introduced into the vessel. At predetermined time points, a sample of 5 ml was withdrawn and filtered through a 0.45 μm filter (Acrodisc®). The quantity of MBZ was determined at 286.8 nm using a UV-VIS Beckman DU®-7 Spectrophotometer. Carrier (L-HPC) does not absorb UV and therefore does not cause interfererence at this wavelength. The cumulative amount of MBZ released from the system was determined from the following calibration curve: $y = 0.05322x + 0.00603$ ($r^2 = 0.9995$). This assay method proved to be reproducible (RSD < 1.28%). Each determination at each time point was performed in triplicate and the error bars on the graphs represented the standard deviation.

2.7. Evaluation of the efficacy of MBZ dosage forms on a Trichinella spiralis mouse model

The GM-1 isolate of *T. spiralis* was used. The isolate was isoenzymatically identified as *T. spiralis* (Reference Centre for Trichinellosis, Istituto Superiore di Santá, Rome) and kept under the code MFEL/ES/S2 GM-1-ISS48 (García et al., 2003). In order to evaluate the anthelmintic activity of the formulations, groups of ten Swiss CD1 mice per treatment were orally infected with 300 ± 50 L1 muscle larvae isolated from infected mouse carcasses, following an artificial digestion. Average settlements established of *T. spiralis*, based on previous experience, was around 50% of adults in the intestine (García Rodriguez et al., 2001). Groups of ten mice were administered with the same doses of the different MBZ formulations (raw material, recrystallized and solid dispersions 1:1; 1:2.5 and 1:5) suspended in a 0.75% carboxymethylcellulose (CMC) solution by buccogastric tube. Ten mice were kept as control and were given the vehicle alone. Treatments were applied at the pre-adult stage of the parasite. For this stage, formulations were administered 24 h post infection (p.i.) at 1 mg/kg.

The effectiveness of the treatment against pre adult stage was assessed on day 7 p.i., after sacrificing the mice (previously anaesthetized with ether) by cervical dislocation. The numbers of adults remaining in the gut were collected and counted in accordance with the method described by García et al. (2003). The efficacy of each drug treatment was determined as the percentage of reduction from the average worm burden of untreated controls. The comparative statistical anthelmintic efficiency studies between the different group formulations were performed by paired Student's *t*-test. A *P* value of less than 0.05 was considered as significant.

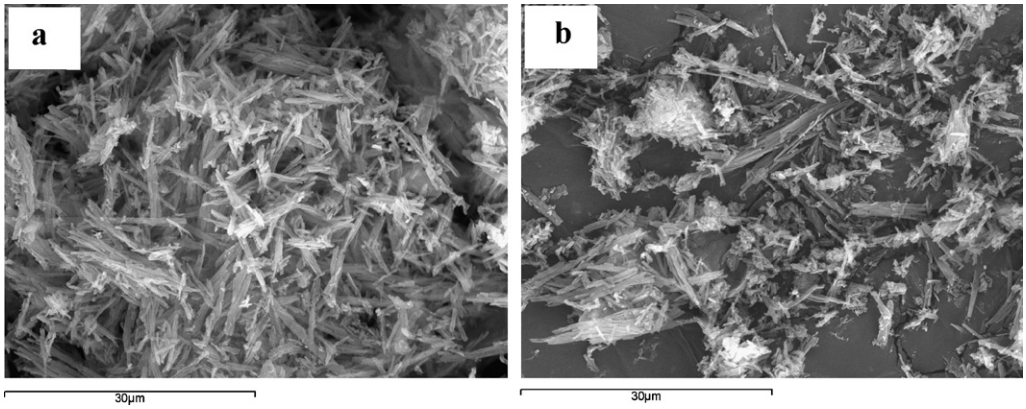

Fig. 1. Scanning electron micrographs of MBZ raw material (a) and recrystallizated MBZ (b). Photographs taken at a magnification of 2000×.

3. Results and discussion

3.1. SEM characterization

SEM was used to clarify the surface and shape characteristics of different samples (MBZ raw material; recrystallizated MBZ; PM-1:10; SD-1:1; SD-1:5 and SD-1:10). The MBZ raw material presented an acicular form (Fig. 1a). While the recrystallized MBZ observed at the same magnification (2000×) showed similar acicular forms to the pure drug (Fig. 1b). This recrystallized form sample presented fine crystals covering their surface, which may be generated due to the lyophilization process. Therefore, it is possible that the changes in the recrystallized MBZ could be confirmed in the XRD studies. On the other hand, the physical mixture (PM-1:10) and the solid dispersion (SD-1:10) presented a clearly different appearance (Fig. 2a and b at 500×, respectively). In the physical mixture we can distinguish between the smooth particles of L-HPC and the acicular crystallites of MBZ (Fig. 2a). However, in the solid dispersion 1:10 (Fig. 2b) only big smooth particles attributed to the L-HPC were seen (60–80 μm). But on the surface of SD-1:1 and SD-1:5 at a higher magnification (2000×, see Fig. 2c and d), there are some filament particles (1–3 μm) attributed to MBZ, due to their similar appearance with pure MBZ. When comparing both solid dispersions (SD-1:1 and SD-1:5) it was possible to observe that the amount of MBZ on the surface of the L-HPC particles decreased as the L-HPC ratio was increased. This reduction in the visible MBZ, observed in the solid dispersions with a MBZ:L-HPC 1:5, was attributed to the inclusion of MBZ in the L-HPC matrix (see Fig. 2d) (Yamashita et al., 2003).

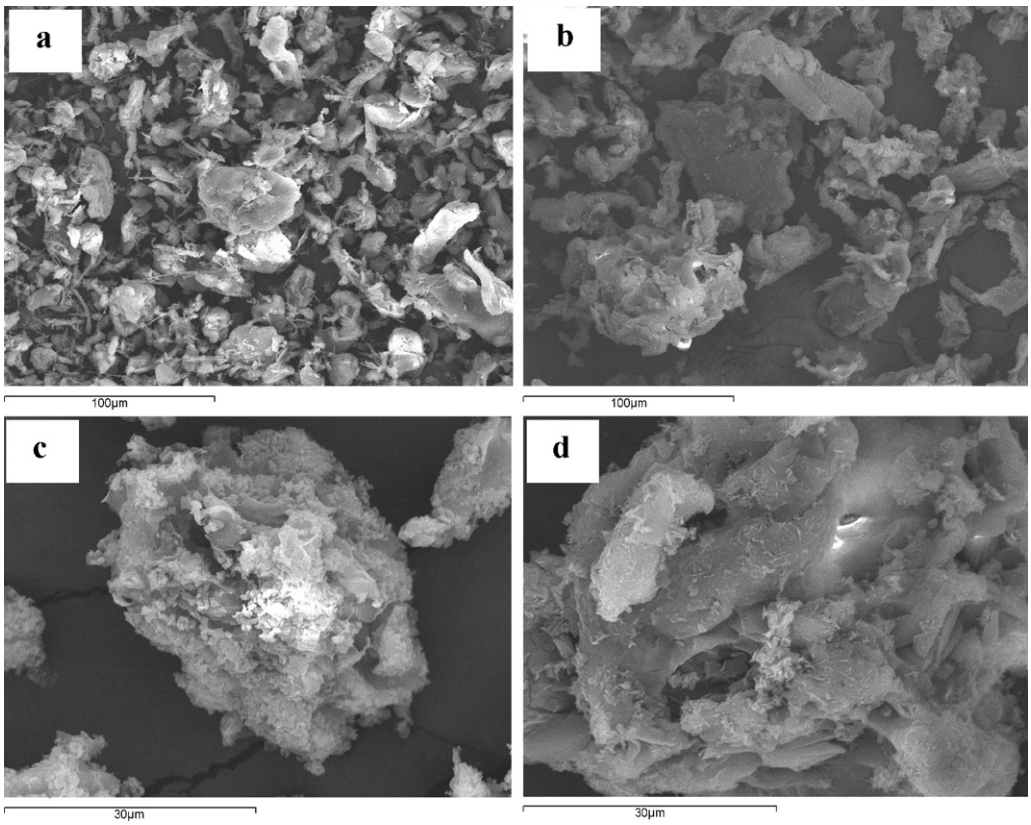

Fig. 2. Scanning electron micrographs of physical mixture 1:10 at 500× (a); SD-1:10 at 500× (b); SD-1:1 at 2000× (c) and SD-1:5 at 2000× (d).

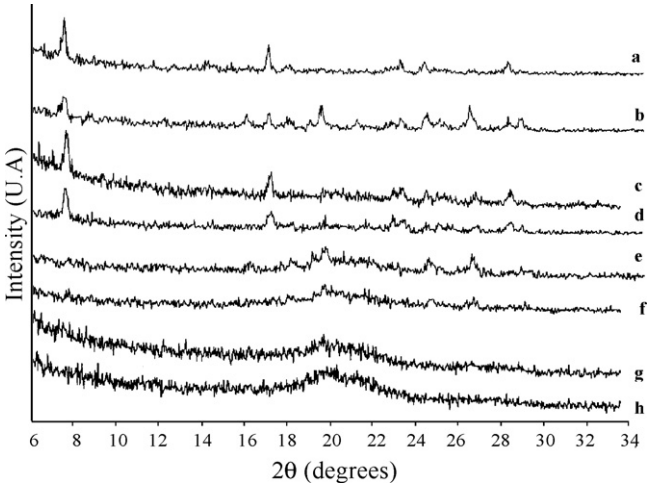

Fig. 3. Powder X-ray diffraction scans of different products: pure MBZ (a); recrystallized MBZ (b); physical mixture 1:1 (c); SD-1:1 (d); SD-1:2.5 (e); SD-1:5 (f) and SD-1:10 (g) and L-HPC (h).

3.2. Powder X-ray diffraction (XRD) and differential scanning calorimetry (DSC): structural and crystal size characterization

Fig. 3 shows the XRD patterns of the pure MBZ, recrystallized MBZ, PM-1:1, SD-1:1, SD-1:2.5, SD-1:5, SD-1:10 and L-HPC. MBZ raw material is crystalline, as demonstrated by sharp and intense diffraction peaks (Fig. 3a). XRD patterns were similar to those reported by Swaneppoel et al. (2003a). The crystal structure of pure MBZ drug with sharp peaks at 7.59° and 17.27° (2θ) (Fig. 3a) corresponds almost with polymorph A (De Villiers et al., 2005). Meanwhile, the recrystallized MBZ showed a different crystalline pattern as compared to the MBZ raw material (see Fig. 3b). This recrystallized MBZ is a mixture of mainly polymorph C (19.73°, 26.78° 2θ) and a minority of polymorph A (7.59° and 17.27° 2θ). The XRD pattern of L-HPC, a semi-crystalline powder, presented a broad halo between 15° and 25° 2θ and also small peaks although difficult to see due to the high background of this sample (Fig. 3h). As expected, the physical mixture PM-1:1 showed diffraction peaks consistent with the presence of crystalline MBZ raw material (Fig. 3c).

It was interesting to note that, SD 1:1 showed characteristic peaks of polymorphous A (7.59° and 17.27° 2θ) but as the L-HPC proportion was increased an amorphisation of polymorphous A was observed (see Fig. 3d–g). This suggested that a certain fraction of MBZ crystals were dissolved or dispersed in molecular or amorphous state in the L-HPC matrix (Cheng et al., 2009). On the other hand, only the solid dispersion 1:2.5 showed a limited evidence of crystalline peaks related to polymorph C slightly shifted and difficult to appreciate due to the high background (19.91° and 26.96° 2θ). These results revealed that MBZ existed primarily in amorphous state in SD-1:5 and SD-1:10. Similar data were obtained previously with other drugs (Fini et al., 2005; Overhoff et al., 2007; Yi et al., 2008). These findings were confirmed by DSC studies (data not shown), in which the absence of a clear MBZ melting peak in solid dispersion thermogram support the hypothesis that amorphous species of MBZ are being formed. Thus, solids dispersions could modify the crystallinity of the drug and represents a suitable modification for improving its dissolution profiles.

3.3. In vitro dissolution assay

According to the USP 33–NF 28 (2010) the dissolution medium for mebendazole, was 0.1 M hydrochloric acid solution containing 1% sodium lauryl sulfate (SLS), a surface active agent. This amount

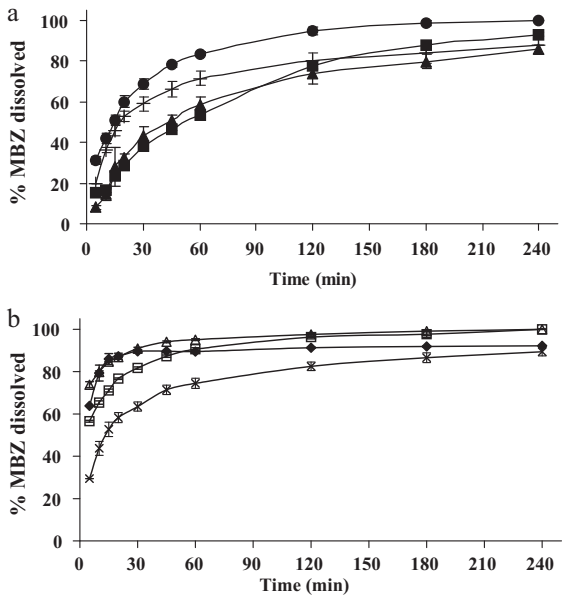

Fig. 4. Release profiles at 37 °C of several products in HCl 0.1 N: MBZ raw material (-▲-); recrystallized MBZ (-■-); PM-1:1 (-+-) and SD-1:1 (-●-) (a). PM-1:5 (-×-); SD-1:2.5 (-♦-); SD-1:5 (-□-) and SD-1:10 (-△-) (b). Each bar represents mean ± SE of 3 independent experiments.

of SLS produces such a rapid dissolution of the drug that it is impossible to observe differences in the dissolution profiles of MBZ raw material and solid dispersions. Swaneppoel et al. (2003a) reported that in the USP medium more than 90% of MBZ was dissolved in 120 min. Therefore, with the aim of obtaining slower dissolution profiles which allow the observance of differences in the dissolution rates among the different formulations, we attempted to carry out a dissolution study without any surfactant (Swanepoel et al., 2003b).

The dissolution profiles of MBZ raw material, the recrystallized product, the different solid dispersions and the physical mixtures 1:1 and 1:5 are illustrated in Fig. 4. MBZ raw material and the recrystallized product exhibited similar poor dissolution rates in 0.1 N HCl. The amounts of dissolved MBZ from the pure and recrystallized drug at 60 min were found to be 58.62 ± 3.79% and 53.61 ± 3.38%, respectively, besides 100% of both of them dissolves at 8 h. These data could be related to their crystalline patterns shown by XRD.

The physical mixtures 1:1 (Fig. 4a) and 1:5 (Fig. 4b) presented a slight improvement in the dissolution properties in comparison to the pure and recrystallized drug. The initial dissolution rate of the drug in the PM-1:5, with a higher L-HPC content, was larger than in the PM-1:1. These results suggested that L-HPC itself might act as a weak solubilizer in the present formulations, contributing to the limited increase in drug dissolution, as well as in preventing drug aggregation (Kawabata et al., 2010). SD-1:1 had a similar initial behaviour to the two physical mixtures (PM-1:1 and PM-1:5). In contrast, after 30 min an increase in the dissolution rate of MBZ could be achieved with solid dispersions containing L-HPC. All the MBZ:L-HPC solid dispersions presented a faster dissolution profile than the drug alone as evidenced by MBZ release over a range of 83.67–96.37% from SDs at 60 min. Similar results have been reported by other authors (Bley et al., 2010; Visser et al., 2010). The increase in dissolution of MBZ from the solid dispersions might be attributed to many factors such as a reduction in the drug crystallinity, specific form of drug and by a lowering of the surface tension of the medium by L-HPC resulting in a better wetting of the hydrophobic drug surface (Ambike et al., 2004). Nonetheless, the SD-1:1 (Fig. 4a) presented a slower dissolution rate than the other solid dispersions, probably due to its higher degree of crystallinity.

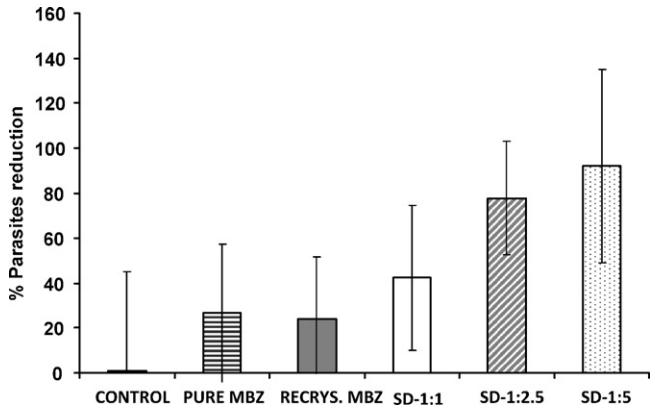

Fig. 5. Antiparasitic efficacy expressed as the percentages of reduction in parasite loads obtained for the following products: control (black bar); MBZ raw material (white/black striped bar); recrystallized MBZ (gray bar); SD-1:1 (white bar); SD-1:2.5 (white/gray striped bar) and SD-1:5 (white/black dotted bar) at the dose of 1 mg/kg on the pre-adult *T. spiralis* life stage. The values are expressed as the mean and standard deviation from ten infected animals.

The X-ray diffractogram of the SD-1:1 (Fig. 3d) clearly depicts two diffraction peaks at 7.59° and 17.27° 2θ corresponding to the crystalline MBZ. This was in line with our findings from SEM analysis. However, with a MBZ:L-HPC ratio of at least 1:2.5 (Fig. 4b), the fast dissolution profiles were in agreement with the inclusion of MBZ into the L-HPC matrix as observed by SEM and with its low crystalline content as shown by XRD. Generally, amorphous substances have higher solubility and dissolution rate than the corresponding thermodynamically stable crystalline forms, because their internal bonding forces are weak (Cheng et al., 2009).

In view of these results, there is evidence that all SD were superior in achieving 100% dissolution at an earlier time point than physical mixtures, i.e., the 1:5 and 1:10 solid dispersions achieved over 95% of MBZ dissolved at 120 min. These high improvements in dissolution times could have a major influence on the efficacies. So the *in vivo* tests, because of ethical reasons, have been performed comparing only best formulations (SD-1:1; SD-1:2.5 and SD-1:5).

3.4. Evaluation of the efficacy of MBZ dosage forms on T. spiralis model

Fig. 5 shows the anthelmintic efficacy for the following formulations at the same dose: control (0.75% CMC), raw material, recrystallized MBZ, MBZ:L-HPC solid dispersions (SD-1:1; SD-1:2.5 and SD-1:5), in the pre-adult stage of the *T. spiralis* life cycle. The therapeutic efficacy of MBZ raw material and recrystallized MBZ was low with similar percentages of worm reduction achieved at a low dose (1 mg/kg). These comparable effects of both products against the enteral parasite stages could be attributed to their similar dissolution profiles. In terms of efficacy, there is a significant improvement ($P < 0.05$), when SD-1:1 was used compared with both raw material and recrystallized MBZ. The reason behind this could be related with the lower crystallinity of the SD-1:1 and consequently its faster dissolution profile. Finally, as the L-HPC proportion in the solid dispersion was increased, formulations displayed higher levels of activity compared to recrystallized MBZ (3.20-fold for SD-1:2.5 and 3.80-fold for SD-1:5), with significant suppression of parasite burden ($P < 0.05$). These results were relatively consistent with the data from dissolution test, demonstrating the accelerated dissolution behavior of the MBZ:L-HPC systems. Interestingly, Fonseca-Salamanca et al. (2003) reported that in *T. spiralis* infected mice a similar worm burden reduction (83.2%) was achieved with MBZ raw material in comparison to our SD-1:2.5 (77.79%) but using a tenfold higher dose (10 mg/kg). This finding might be explained by the above mentioned better dissolution properties of the solid dispersions when compared to MBZ pure drug. Further studies shall indicate the relationship of the solubility of MBZ solid dispersions with their bioavailability properties.

4. Conclusions

MBZ:L-HPC solid dispersions are significantly ($P < 0.05$) more active than the conventional MBZ suspension at a low dose of 1 mg/kg against the enteral stages of a murine *T. spiralis* infection. The mixed use of SEM, XRD and DSC techniques let us know the reasons for an enhancement of the MBZ dissolution rate when formulated as L-HPC solid dispersions, attributed to reduced drug crystallinity and altered surface morphology (major) and to the wetting effect of L-HPC (minor). SEM was an especially useful tool as it allowed us to observe the raw material inclusion into the L-HPC matrix as the polymer proportion was increased. Therefore, for these systems, an increase in dissolution rate, leads to an increase in their anthelmintic effects at a low dose (i.e., 1 mg/kg). Further investigations dealing with the *in vivo* bioavailability and anthelmintic effectivity at different doses of these formulations, are now under way.

Acknowledgements

This work has been supported by a project from University Complutense of Madrid (project number: 910939). CIBEREHD is funded by the Instituto de Salud Carlos III.

References

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.
Ambike, A.A., Mahadik, K.R., Paradkar, A., 2004. Stability study of amorphous valdecoxib. Int. J. Pharm. 282, 151–162.
Bley, H., Fussnegger, B., Bodmeier, R., 2010. Characterization and stability of solid dispersions based on PEG/polymer blends. Int. J. Pharm. 390, 165–173.
Cheng, L., Guo, S., Wu, W., 2009. Characterization and *in vitro* release of praziquantel from poly (-caprolactone) implants. Int. J. Pharm. 377, 112–119.
Chung, M.S., Joo, K.H., Quan, F.S., Kwon, H.S., Cho, S.W., 2001. Efficacy of flubendazole and albendazole against *Trichinella spiralis* in mice. Parasite 8 (Suppl. 2), S195–S198.
Daniel-Mwambete, K., Torrado Susana, Cuesta-Bandera, C., Ponce-Gordo, F., Torrado, J.J., 2004. The effect of solubilization on the oral bioavailability of three benzimidazole carbamate drugs. Int. J. Pharm. 272, 29–36.
De Villiers, M.M., Terblanche, R.J., Liebenberg, W., Swanepoel, E., Dekker, T.G., Songa, M., 2005. Variable-temperature X-ray powder diffraction analysis of the crystal transformation of the pharmaceutically preferred polymorph C of mebendazole. J. Pharm. Biomed. Anal. 38, 435–441.
DiNunzio, J.C., Brough, C., Hughey, J.R., Miller, D.A., Williams III, R.O., McGinity, J.W., 2010. Fusion production of solid dispersions containing a heat-sensitive active ingredient by hot melt extrusion and Kinetisol® dispersing. Eur. J. Pharm. Biopharm. 74, 340–351.
Fini, A., Moyano, J.R., Ginés, J.M., Perez-Martinez, J.I., Rabasco, A.M., 2005. Diclofenac salts, II. Solid dispersions in PEG6000 and Gelucire 50/13. Eur. J. Pharm. Biopharm. 60, 99–111.
Fonseca-Salamanca, F., Martínez-Grueiro, M.M., Martínez-Fernández, A.R., 2003. Nematocidal activity of nitazoxanide in laboratory models. Parasitol. Res. 91, 321–324.
García, J.J., Bolás, F., Torrado, J.J., 2003. Bioavailability and efficacy characteristics of two different oral liquid formulations of albendazole. Int. J. Pharm. 250, 351–358.
García Rodriguez, J.J., Torrado, J., Bolás, F., 2001. Improving bioavailability and anthelmintic activity of albendazole by preparing albendazole–cyclodextrin complexes. Parasite 8, S188–S190.
Kawabata, Y., Yamamoto, K., Debari, K., Onoue, S., Yamada, S., 2010. Novel crystalline solid dispersion of tranilast with high photostability and improved oral bioavailability. Eur. J. Pharm. Biopharm. 39, 256–262.
Leuner, C., Dressman, J., 2000. Improving drug solubility for oral delivery using solid dispersions. Eur. J. Pharm. Biopharm. 50, 47–60.
Maki, J., Yanagisawa, T., 1988. Comparative efficacy of flubendazole and mebendazole on encysted larvae of *Trichinella spiralis* (USA strain) in the diaphragm of mice and rats. J. Helminthol. 62, 35–39.
Mutalik, S., Anju, P., Manoj, K., Usha, A.N., 2008. Enhancement of dissolution rate and bioavailability of aceclofenac: a chitosan-based solvent change approach. Int. J. Pharm. 350, 279–290.

Onoue, S., Sato, H., Kawabata, Y., Mizumoto, T., Hashimoto, N., Yamada, S., 2009. *In vitro* and *in vivo* characterization on amorphous solid dispersion of cyclosporine A for inhalation therapy. J. Control. Release 138, 16–23.

Overhoff, K.A., Moreno, A., Miller, D.A., Johnston, K.P., Williams III, R.O., 2007. Solid dispersions of itraconazole and enteric polymers made by ultra-rapid freezing. Int. J. Pharm. 336, 122–132.

Rodriguez-Caabeiro, F., Criado-Fornelio, A., Jiménez-Gonzalez, A., Guzmán, L., Igual, A., Pérez, A., Pujol, M., 1987. Experimental chemotherapy and toxicity in mice of three mebendazole polymorphic forms. Chemotherapy 33, 266–271.

Siriyasatien, P., Yingyourd, P., Nuchprayoon, S., 2003. Efficacy of albendazole against early and late stage of *Trichinella spiralis* infection in mice. J. Med. Assoc. Thai. 86 (Suppl. 2), S257–S262.

Swaneppoel, E., Liebenberg, W., Villiers, M.M., 2003a. Quality evaluation of generic drugs by dissolution test: changing the USP dissolution medium to distinguish between active and non-active mebendazole polymorphs. Eur. J. Pharm. Biopharm. 55, 345–349.

Swanepoel, E., Liebenberg, W., de Villiers, M.M., 2003b. Differences between USP and BP dissolution results for oxytetracycline capsules after accelerated stability testing. Pharmazie 58, 601–602.

Visser, M.R., Baert, L., Van't Klooster, G., Schueller, L., Geldof, M., Vanwelkenhuysen, I., de Kock, H., De Meyer, S., Frijlink, H.W., Rosier, J., Hinrichs, W.L.J., 2010. Inulin solid dispersion technology to improve the absorption of the BCS Class IV drug TMC240. Eur. J. Pharm. Biopharm. 74, 233–238.

Yamashita, K., Nakate, T., Okimoto, K., Ohike, A., Tokunaga, Y., Ibuki, R., Higaki, K., Kimura, T., 2003. Establishment of new preparation method for solid dispersion formulation of tacrolimus. Int. J. Pharm. 267, 79–91.

Yi, T., Wan, J., Xu, H., Yang, X., 2008. A new solid self-microemulsifying formulation prepared by spray-drying to improve the oral bioavailability of poorly water soluble drugs. Eur. J. Pharm. Biopharm. 70, 439–444.