Albendazole Generics—A Comparative In Vitro Study

E. Galia³, J. Horton² and J. B. Dressman¹,4

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Purpose. We sought to determine whether disintegration and dissolution behavior differs among various albendazole generic formulations obtained from third world countries and to compare them with the innovator’s product.

Methods. Dissolution behavior of various albendazole formulations was studied with USP Apparatus 2 in SGF₉₀ and in a modified SGF₉₀ which contained 0.1% of the nonionic surfactant Triton® X 100. Disintegration was tested according to the European Pharmacopoeia.

Results. Dissolution experiments in SGF₉₀ showed a wide range in rate and extent of albendazole dissolution. The innovator product released 81% percent within two hours, a profile matched by only one other formulation. For other formulations 32 to 64% was released within two hours. Use of a modified SGF₉₀ containing 0.1% Triton® X 100 to simulate the surface tension of gastric juice, resulted in less discrimination between products. The innovator product again showed the fastest and most complete dissolution, with ninety percent released within two hours. The generic formulations released between 67 and 82%, except for one formulation which achieved only 43% release. The results in SGF₉₀ plus Triton® X 100 may be more meaningful than in SGF₉₀, since the surface tension of the medium is closer to the physiological value. All formulations passed the disintegration test according to the European Pharmacopoeia, with disintegration times ranging from 2.5 to 11 minutes.

Conclusions. Generic albendazole products vary widely in their dissolution behavior. Differences among products were greater in SGF₉₀ than in SGF₉₀ plus Triton® X 100. These differences were not reflected in the disintegration behavior of the products.

KEY WORDS: dissolution; surface tension; compendial media; albendazole; generic products; disintegration.

INTRODUCTION

Quality assurance of drugs in third world countries is an oft neglected issue. To be commercially competitive with other products, quality assurance procedures may be compromised in some cases. Sometimes lack of quality assurance can lead to dire consequences, resulting in headlines such as “In Haiti 59 children die from contaminated acetaminophen syrup (1)” appearing in the news.

In addition to the content and purity of a drug formulation, its ability to release the required amount of drug within a certain time is an important factor in drug product quality. Especially for drugs with low solubility, the release characteristics of the dosage form play an important role in the availability of a drug, either in terms of its systemic availability or, where appropriate, for its local action in the gastrointestinal tract. The quality of excipients used (binders, lubricants, disintegrants, surfactants) in manufacturing and the quality of the process itself is consequently of great importance to the performance of formulations of poorly soluble drugs.

The drug under investigation in this study was albendazole, an anthelminthic, which has weak basic properties (pKa, 2.68; pKₐ, 11.83), an aqueous solubility of approximately 1 μg/ml (experimentally determined in buffer pH 6.0) and a log P of 3.5 (2). Albendazole is very frequently used in third world countries to treat intestinal nematodes and as such, must act locally within the intestinal tract. Ideal for this site of action would be a BCS class III drug (3), i.e., one that rapidly dissolves but is not readily absorbed across the gut wall, thus ensuring an adequate concentration over a prolonged time in the gut lumen. Albendazole’s physicochemical properties indicate that it is far from ideal for local action within the gut, since its solubility even at gastric pH is relatively low and its high partition coefficient is suggestive of good permeability via passive transcellular uptake mechanisms. As with other poorly soluble compounds, the dissolution rate is likely to be contingent on formulation and might lead to differences in performance among the many products available on the world market. Several commercially available albendazole generics from Guatemala, Thailand, Peru and Columbia were tested for their in vitro performance. The compendial medium SGF₉₀ (USPXXXIII) was chosen as one dissolution medium on the basis of its common use in dissolution testing and the fact that albendazole is sufficiently soluble in this medium to allow a discriminatory test. The modified SGF₉₀ containing 0.1 percent of the surfactant Triton® X 100 and having a surface tension of approximately 40 mN/m, was chosen as a medium to represent the surface tension in the stomach, which lies in the range of 35 to 50 mN/m (4). Since many poorly soluble drugs also display poor wetting characteristics, it may be important to simulate the wetting conditions extant in the gastric environment. Failure to do so could lead to in vitro dissolution rates substantially lower than those that would occur in vivo.

MATERIALS AND METHODS

Materials

Sodium chloride, sodium hydroxide, hydrochloric acid and ammonium dihydrogen phosphate, all analytical grade, were purchased from E. Merck (Darmstadt, Germany). Triton® X 100 was obtained from Serva GmbH (Heidelberg, Germany). Albendazole standard substance (Laboratory Reference No. 2) was supplied by SmithKline Beecham (Brentford, Middlesex, UK).

All albendazole tablet formulations were supplied by SmithKline Beecham (Brentford, Middlesex, UK). Generic formulations were purchased by SmithKline Beecham from pharmacies in their local markets. Table I summarizes the products investigated.
Table I. Albendazole Formulations Investigated

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Dose (mg)</th>
<th>Batch #</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zentel®</td>
<td>200</td>
<td>BN822</td>
<td>SmithKline Beecham, UK</td>
</tr>
<tr>
<td>Alfen®</td>
<td>200</td>
<td>T51034</td>
<td>Biolab CO., Ltd, Thailand</td>
</tr>
<tr>
<td>Albendazol MK®</td>
<td>200</td>
<td>5548R1</td>
<td>Tecnquimicas S.A., Columbia</td>
</tr>
<tr>
<td>Albendazol Farmindustria®</td>
<td>200</td>
<td>90706426</td>
<td>Farmindustria S.A., Columbia</td>
</tr>
<tr>
<td>Aldamin®</td>
<td>200</td>
<td>N M</td>
<td>Pharmanova, Guatemala</td>
</tr>
<tr>
<td>Andazol®</td>
<td>200</td>
<td>961111</td>
<td>Bi, as we received only a blister from this product, the origin of this product is unknown</td>
</tr>
<tr>
<td>Fintel®</td>
<td>200</td>
<td>90100977</td>
<td>Laboratorios Cofana, Peru</td>
</tr>
<tr>
<td>Zirkon®</td>
<td>200</td>
<td>HC364</td>
<td>Donovan Werke, Guatemala</td>
</tr>
</tbody>
</table>

Methods

For all dissolution tests an Erweka DT 6 dissolution tester (Erweka, Heusenstamm, Germany) was utilized. Experimental conditions consisted of the USP Apparatus 2 (paddle method), employing 500 ml of dissolution medium at a temperature of 37 ± 0.5°C and a rotational speed of 100 rpm.

Samples of approximately 5 ml were withdrawn at appropriate times, using a 5 ml Fortuna Optima® syringe (Fischer Labortechnik, Frankfurt/Main, Germany) fitted with appropriate stainless steel tubing to facilitate representative sampling with sample replacement. Aqueous samples were filtered through 0.45 μm (Schleicher & Schüll Rezist® 30/0.45 PTFE) filters. Samples were kept in 100 × 16 mm screw cap glass test tubes prior to dilution. Checks for adsorption to the filters revealed no significant loss of drug. All experiments were run in triplicate.

Composition of the Media Used

$SGF_{sp}$ $SGF_{sp}$ was composed as described in USP XXIII (5) without pepsin. This medium has a pH of 1.2 and its surface tension was determined to be 72 mN/m.

Modified $SGF_{sp}$. The modified SGFsp was composed as the compendial medium but contained an additional 0.1% w/ v Triton® X 100. This medium also has a pH of 1.2 and its surface tension was determined to be approximately 40 mN/m.

HPLC-Analysis

The HPLC system used consisted of a Bischoff Degaser Unit SDU 2003 (Bischoff, Leonberg, Germany), a LaChrom L7200 autosampler, a LaChrom L7100 HPLC pump, a Lichrocart® 4-4 RP 18 guard column, a Hibar® 125 × 4.0 mm Lichrospher® RP-18 (5 μm), a Merck L4250 UV-detector (all from Merck, Darmstadt, Germany) and a Jasco Borwin® integration system (Jasco, Groß-Umstadt, Germany).

The following parameters were selected for sample analysis:

Mobile phase: MeOH:10mM (NH₄)₂H₂PO₄ buffer 60:40
Injection volume: 50 μl

Flow rate: 1.2 ml/min
Detection wavelength: 254 nm

Data Presentation

Data at early sampling times (5 to 15 minutes) occasionally showed large coefficients of variation (CV up to 79%), which were attributable to variable disintegration of the dosage forms. Thereafter, the CVs remained in the range 0.1 to 15%. Representative standard deviations are shown in Fig. 1. Concentrations were corrected for the sampled amount of drug dissolved at the corresponding time point.

Disintegration

All tablet formulations were subjected to a disintegration test according to the European Pharmacopoeia (EP) (6). An Erweka ZT 32 (Erweka, Heusenstamm, Germany) disintegration tester was used. All tests were conducted at 37 ± 1°C. Due to the limited number of samples only three tablets (the EP calls for 6) per formulation were tested.

RESULTS

Influence of the Rotational Speed on Dissolution Characteristics

Figure 1 shows the mean dissolution profiles of the innovator product in $SGF_{sp}$ obtained at 50 rpm and 100 rpm. The

Fig. 1. Mean dissolution profiles of the innovator product in $SGF_{sp}$ at 50 (○) and 100 (●) rpm.