# Albendazole Generics—A Comparative In Vitro Study

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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 $SGF_{sp}$ and in a modified $SGF_{sp}$ which contained 0.1% of the nonionic surfactant Triton® X 100. Disintegration was tested according to the European Pharmacopoeia.

***Results.*** Dissolution experiments in $SGF_{sp}$ 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 $SGF_{sp}$, 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 $SGF_{sp}$ plus Triton® X 100 may be more meaningful than in $SGF_{sp}$, 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 $SGF_{sp}$ than in $SGF_{sp}$ 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 anthelmintic, which has weak basic properties ($pKa_1$ 2.68; $pKa_2$ 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 $SGF_{sp}$ (USPXXIII) 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 $SGF_{sp}$, 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.

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**Table I.** Albendazole Formulations Investigated

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

## 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, Groβ-Umstadt, Germany).

The following parameters were selected for sample analysis:

Mobile phase:MeOH:10mM $(NH_4)H_2PO_4$ 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

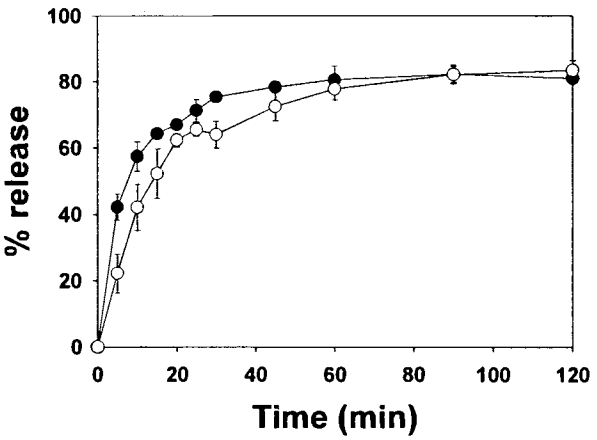


**Fig. 1.** Mean dissolution profiles of the innovator product in $SGF_{sp}$ at 50 (○) and 100 (●) rpm.

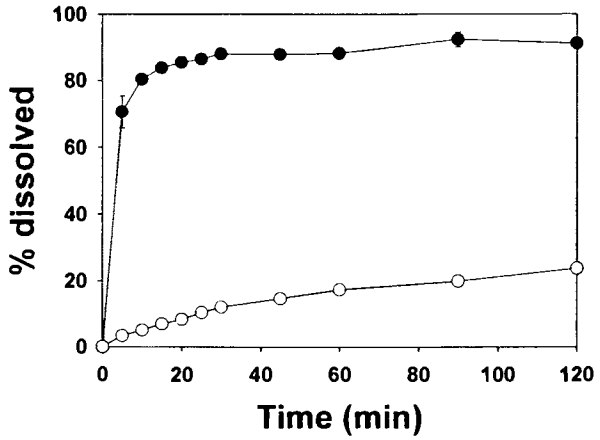


Fig. 2. Mean dissolution profiles of albendazole powder in $SGF_{sp}$ (○) and $SGF_{sp}$ containing 0.1 percent Triton® X 100 (●).

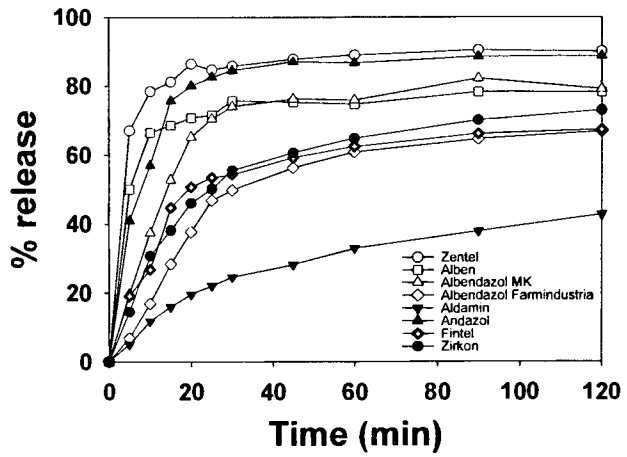


Fig. 4. Mean dissolution profiles of various albendazole formulations in $SGF_{sp}$ containing 0.1% Triton® X 100 at 100 rpm.

difference in release between stirring rates in the case of the innovator product is minimal; the same plateau value is reached in both cases after 60 minutes. We decided to run all experiments at 100 rpm to prevent the possibility of "coning", which sometimes occurs at lower rpm and the relevance of which *in vivo* is rather questionable (7).

### Dissolution of Albendazole Powder in $SGF_{sp}$ and Modified $SGF_{sp}$ Containing 0.1% Triton® X 100

The problems associated with the poor wettability of albendazole are reflected in Fig. 2. In $SGF_{sp}$ (surface tension measured to be 72 mN/m at room temperature) the albendazole powder floated on top of the dissolution medium surface in lumpy aggregates and only 24 percent dissolved within two hours, whereas in modified $SGF_{sp}$ the powder particles were easily wetted by the dissolution medium and rapidly dispersed, resulting in 91 percent dissolution within the same period.

### Dissolution in $SGF_{sp}$

Figure 3 shows the mean dissolution profiles of all albendazole products tested in $SGF_{sp}$. The rate and extent of dissolution varies greatly among the generic products. Only one product exhibited a dissolution profile similar to that of the innovator. All other formulations exhibited lower rates and extent of dissolution, releasing between 32 and 64 percent of the labeled amount of albendazole within two hours. Release profiles of three of the products formed a cluster, with only 32 to 35 percent label strength released within two hours.

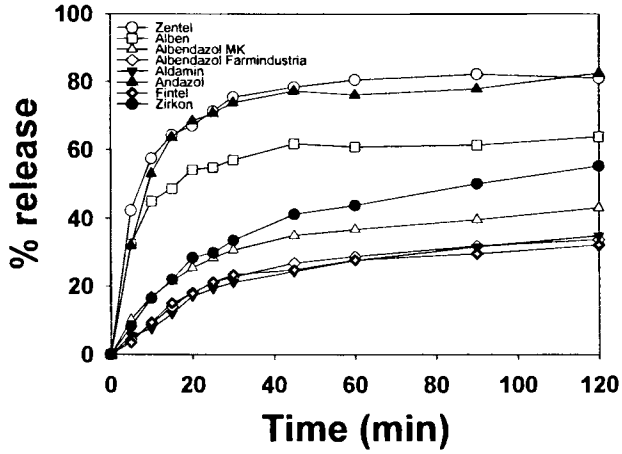


Fig. 3. Mean dissolution profiles of various albendazole formulations in $SGF_{sp}$ at 100 rpm.

### Dissolution in the Modified $SGF_{sp}$

Figure 4 shows the mean dissolution profiles of all albendazole products tested in the modified $SGF_{sp}$, containing 0.1 percent of the nonionic surfactant Triton® X 100. All products showed a higher rate and extent of dissolution compared to the compendial medium $SGF_{sp}$. Again only one generic product released about the same amount of albendazole as the innovator product. Whereas in $SGF_{sp}$ the profiles for other products tested varied from 32 to 64 percent release within two hours, they released between 67 and 79 percent in the modified medium. The only exception was Aldamin®, which released only 43 percent of label strength within the 120 minute test period.

### Disintegration of the Albendazole Formulations

As can be seen from Fig. 5 all formulations met the compendial requirements for uncoated tablets (i.e., disintegration

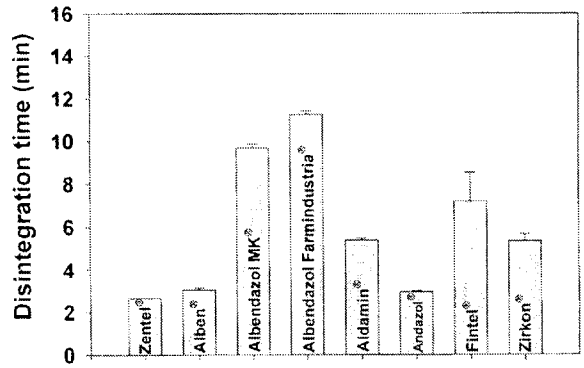


Fig. 5. Mean disintegration times of all tested albendazole products (n = 3; ± SD). The EP acceptance criterion is completion of disintegration within 15 minutes.

time < 15 minutes). Disintegration times ranged from approximately 2.5 minutes (Zentel®) to about 11 minutes (Albendazol Farmindustria®).

## DISCUSSION

Class II drugs like albendazole exhibit problematic dissolution characteristics. Reproducible and sufficient release of these compounds can only be guaranteed by careful formulation and high quality manufacturing procedures.

A common approach taken to improve the release rate of poorly soluble drugs is to increase the available surface area of drug for dissolution, either by increasing the surface area by means of micronization or by adding surfactants to the formulation (8).

In addition to formulation factors, the composition of the dissolution medium can also be expected to influence the dissolution of poorly soluble drugs (9). Surface tensions *in vivo* are lower than the surface tension of pure water, which is 72.8 mN/m at 20°C (10). Typical values found in the stomach lie between 35 and 50 mN/m (4). In the small intestine, due to excretion of bile and pancreatic enzymes, the surface tension is also reduced. For example, the surface tension of physiologically representative mixtures of bile salts and lecithin ranges from 45 to 50 mN/m (unpublished results, E. Stippler, 1998). The dissolution behavior of the albendazole powder reflects the wetting arguments described above. When the surface tension is lowered to a gastrically relevant value of about 40 mN/m by adding 0.1 percent of Triton® X 100 to $SGF_{sp}$, the extent of dissolution within two hours reaches the same plateau as the innovator tablet formulation (i.e., approx. 90 percent within two hours). These results can be overwhelmingly attributed to improvements in wetting: the solubility of albendazole increases less than 20 percent when 0.1% Triton® X 100 is added to $SGF_{sp}$, in accordance with the general finding that Triton® X 100 is a poor solubilizer (11).

In $SGF_{sp}$ there was strong discrimination of the dissolution behavior among the different formulations. Differences in profiles can probably be explained by a combination of variability in particle size of the active ingredient, the use of different excipients and differences in the manufacturing process. Solvang showed, for example, that the use of different binders influences the dissolution behavior of phenobarbital from tablet formulations to a large extent (12).

Upon changing the medium to $SGF_{sp}$ plus Triton® X 100, the overall percentage release was enhanced for each of the preparations studied. Whereas in $SGF_{sp}$ one cluster of generics released as little as 32–35 percent, the generic formulations showed a release of 67 to 79 percent in the Triton® X 100 containing medium, with the exception of Aldamin®, which released 43 percent of label strength. Comparison of results in the two media indicate that the compendial medium ($SGF_{sp}$) is more discriminatory than the medium which was modified to better reflect the physiological conditions ($SGF_{sp}$ plus Triton® X 100). In order to determine which of the two media is more appropriate for *in vitro/in vivo* correlation purposes, a biostudy (using nematode egg counts in the stool before and after treatment as the endpoint) with slow, medium and fast releasing formulations of albendazole should be conducted and the effectiveness of the products compared with their *in vitro* release profiles.

No correlation of disintegration time with *in vitro* dissolution was evident. The innovator product showed the shortest disintegration time at 2.5 minutes, which seemed to be reflected in its faster release *in vitro*. However, when the dissolution properties of Aldamin® and Albendazol MK® are compared with their disintegration properties, one finds faster dissolution of the latter product even though its disintegration time is almost double (9.7 min) that of Aldamin® (5.4 min). Disintegration of tablets containing albendazole does not guarantee the dissolution of this poorly soluble compound, as dissolution is likely the more time-consuming process in this case (see also the general USP XXIII comment on this problem in section ⟨701⟩ "disintegration"). A correlation of *in vitro* disintegration with *in vitro* dissolution is more likely for class I drugs, i.e., drugs that are readily dissolved as soon as the dosage form breaks up.

## CONCLUSIONS

In summary, the dissolution results indicate that the release characteristics of albendazole products vary widely among manufacturers, with likely ramifications for the bioavailability of the active ingredient. $SGF_{sp}$ is a simple dissolution medium that discriminates strongly among the albendazole formulations. As its surface tension does not reflect the physiological conditions and albendazole powder is poorly wettable, the medium should be modified in terms of surface tension if a prediction of *in vivo* performance from *in vitro* dissolution is desired. A suitable surfactant for these purposes is Triton® X 100 at a concentration of 0.1%, which lowers the surface tension of the dissolution medium to a physiological value without exhibiting pronounced solubilization effects. The suitability of this dissolution medium for IVIVCs will require further validation via a biostudy with slow, medium and fast releasing albendazole formulations.

For class II drugs such as albendazole, the disintegration test cannot be used as a surrogate for the more costly dissolution test, as the results show no correlation between the two methods.

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