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# Pharmacopoeial standards

## Ensuring the efficacy of a deworming medicine: albendazole chewable tablets

Parasitic infections affect more than a billion people worldwide, many of them children. Albendazole chewable tablets are an effective treatment and can be administered by non-medical staff such as parents and teachers. However, chewable tablets are sometimes swallowed whole, either intentionally or unintentionally. *The International Pharmacopoeia* therefore requires that chewable tablets – like conventional tablets – comply with the tests for disintegration and dissolution. The monograph included in *The International Pharmacopoeia* for albendazole chewable tablets was revised recently. It provides publicly available quality standards, including a new test for the dissolution of these widely used tablets.

### Ensuring pharmaceutical quality of essential medicines

Pharmacopoeial standards help ensure the quality and safety of essential medicines by providing analytical methods and appropriate limits for testing and assessing the active pharmaceutical ingredients, excipients and finished products.

*The International Pharmacopoeia*<sup>1</sup> focuses on specifying the quality of essential medicines, i.e. those medicines that satisfy the health care needs of the majority of the population in WHO Member States. It underpins some of WHO's most important activities, including those

carried out by the WHO Prequalification Team: medicines and the Department of Control of Neglected Tropical Diseases, to assess and test the quality of medicines found in:

- the WHO Model List of Essential Medicines and the WHO Model List of Essential Medicines for Children;
- invitations to manufacturers to submit an expression of interest for product evaluation to the World Health Organization (WHO) Prequalification Team: medicines; and/or
- other United Nations/WHO documents recommending the use of specific medicines for treating specific diseases and/or for use by treatment programmes.

<sup>1</sup> Publicly available at: <http://apps.who.int/phint/en/p/about/>

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*WHO provides The International Pharmacopoeia free of charge for WHO Member States to enable quality control testing of active ingredients and finished pharmaceutical products. An example of how these global specifications provide added value for WHO Member States was published in a previous edition of this journal\*.*

*In 2015, publication of the Fifth Edition of The International Pharmacopoeia (Ph. Int.) and the 50<sup>th</sup> annual meeting of the WHO Expert Committee which is mandated to keep it relevant and updated, represented two major landmarks. The paper presented here describes another example of a monograph, newly included in the Fifth Edition of Ph. Int., that contributes to bringing affordable, safe and efficacious medicines of good quality to everyone, everywhere.*

\* *Global specifications: the example of capreomycin.* WHO Drug Information 2014; 28(4):431-3.

Priority is placed on monograph development for essential medicines that are not included or not sufficiently described in other pharmacopoeias. Many of these medicines are needed urgently, either because current production does not cover global treatment needs or because available products are not quality-assured. Albendazole chewable tablets is one such medicine.

### **Albendazole: a needed treatment**

Albendazole is an effective treatment for a range of parasitic diseases that represent a significant public health burden, as described below.

#### *Lymphatic filariasis*

Lymphatic filariasis, commonly known as elephantiasis, is a neglected tropical disease. It is caused by parasitic infection with nematodes (roundworms) of the family *Filariodidea* that are transmitted by mosquitoes. It is usually acquired in childhood and damages the lymphatic system. The painful and profoundly disfiguring visible manifestations of the disease occur later in life and lead to permanent disability. Patients are not only physically disabled, but suffer mental, social and financial losses contributing to stigma and poverty.

Currently, 1.23 billion people in 58 countries live in areas where lymphatic filariasis is transmitted and are at risk of being infected.

► Lymphatic filariasis can be eliminated by stopping the spread of the infection through use of large-scale chemoprevention, consisting of a single dose of two medicines — albendazole chewable tablets (400 mg) together with ivermectin tablets (150–200 µg/kg) or with diethylcarbamazine tablets (DEC)

(6 mg/kg) — given annually to an entire at-risk population. (1)

#### *Soil-transmitted helminth infections*

Soil-transmitted helminth infections are among the most common infections worldwide. They are transmitted by eggs present in human faeces which in turn contaminate soil especially in areas where sanitation is poor. The main species that infect people are the roundworm (*Ascaris lumbricoides*), the whipworm (*Trichuris trichiura*) and hookworms (*Necator americanus* and *Ancylostoma duodenale*).

More than 1.5 billion people, or 24% of the world's population, are infected with soil-transmitted helminth infections. Over 270 million preschool-age children and over 600 million school-age children live in areas with high transmission rates of these parasites and are in need of treatment and preventive interventions.

► The WHO recommended medicines — albendazole chewable tablets and mebendazole chewable tablets — are effective, inexpensive and easy to administer by non-medical personnel, for example teachers. (2)

### **Chewable tablets: a question of definition**

Pharmacopoeias define chewable tablets differently. The definitions deviate from each other in particular with regard to administration (*must* be chewed or *may* be chewed) and, consequently, not all pharmacopoeias require a disintegration test (*Box 1*). In *The International Pharmacopoeia*, a disintegration requirement has been included to address concerns about the efficacy of chewable tablets that are swallowed whole, either intentionally or unintentionally.

### The need for dissolution testing

Monographs for solid oral dosage forms in *The International Pharmacopoeia* usually contain a dissolution test and/or a disintegration test. The choice of testing disintegration or dissolution for a given product is based on international standards such as the International

Council for Harmonisation (ICH) guideline on Test Procedures and Acceptance Criteria for New Drug Products (3). This guideline advises that disintegration testing may be sufficient for rapidly dissolving medicines containing active ingredients that are highly soluble in the body. For alendazole chewable tablets,

#### Box 1. Definition of chewable tablets and disintegration requirements in different pharmacopoeias

- The **European Pharmacopoeia** (Ph. Eur. 8.7) states in the general monograph on tablets that *“Chewable tablets are intended to be chewed before being swallowed.”* As chewable tablets are not exempted from the test for disintegration of uncoated (or coated) tablets, they are required to comply with the test for disintegration.
- The **British Pharmacopoeia** (2016) includes the general monograph on tablets of the European Pharmacopoeia and would thus require that (uncoated or coated) chewable tablets comply with the test for disintegration. However, the requirement for disintegration usually does not apply either because the individual monographs on chewable tablets explicitly mention this or because a requirement for dissolution eliminates the need for a disintegration test (see also chapter entitled “Tablets” of the British Pharmacopoeia).
- The **United States Pharmacopoeia** (USP 38) states (in the section on tablets that is included in the general chapter on Pharmaceutical Dosage Forms <1151>) that *“tablets [...] that include ‘chewable’ in the title must be chewed or crushed prior to swallowing to ensure reliable release of the drug substance(s) or to facilitate swallowing. If tablets are designed so that they may be chewed (but chewing is not required for drug substance release or ease of swallowing), the title should not include a reference to ‘chewable’.”* Following this definition, chewable tablets are exempted from the disintegration test: *“Chewable tablets are not required to comply with the disintegration test”* (section on chewable tablets in the general chapter: <2> Oral Drug Products – Product Quality Tests).
- The general chapter on tablets in the **Indian Pharmacopoeia** (2014) determines that the disintegration requirement for uncoated and coated tablets does not apply to chewable tablets. In the section on “Tablets for Use in the Mouth” it is stated that *“where applicable the tablets should be chewed before swallowing”*.
- The **Chinese Pharmacopoeia** (2010) specifies that *“chewable tablets are tablets intended to be chewed and then swallowed”* and that *“chewable tablets may not be required to comply with the test for disintegration.”* (Appendix I, General Requirements for Preparations).
- According to ***The International Pharmacopoeia*** (Fifth Edition), chewable tablets are usually uncoated, and as such they have to disintegrate within 15 minutes (see general monograph on Tablets). This requirement was included to address concerns about the efficacy of chewable tablets that are swallowed whole. This may occur either intentionally or unintentionally. Accordingly, *The International Pharmacopoeia* defines chewable tablets as tablets that *“are intended to be chewed before being swallowed; however, where indicated on the label, they may be swallowed whole instead”*.

however, disintegration testing cannot replace dissolution testing as the solubility of albendazole at 37°C throughout the physiological pH range (pH value 1–7.5) is reported to be low (4, 5).

Compendial dissolution tests provide information about the drug-release characteristics of a particular formulation, or batch of a product, under standardized test conditions. Compliance with a dissolution test provides assurance that most of the active ingredient will dissolve in an aqueous medium within a reasonable amount of time when the preparation is subject to mild agitation. However, compliance with a dissolution test does not in itself guarantee bioavailability. Failure to comply with a dissolution test, on the other hand, may indicate that the bioavailability of the product is too low, since the active substance must be released from the dosage form for any local or systemic pharmacological activity to occur.

Surveys have shown that the dissolution properties of albendazole chewable tablets on the market are poor. In 2011 a survey of medicines for neglected tropical diseases showed that 57% of the products tested failed to comply with dissolution test requirements (6). A more recent study, performed in Ethiopia, produced similar results, with 8 of 19 tested albendazole tablets (42%) failing to comply with the dissolution test (7).

Investigations suggest that albendazole chewable tablets that pass disintegration and *in vitro* dissolution tests have better clinical effects, measured as cure rates and egg reduction rates for *Ascaris lumbricoides*, *Trichuris trichiura* and hook-worm infections, than those that fail these tests (8). Although the clinical implications of failure to comply with dissolution test requirements need to be evaluated in

detail, it is very likely that the efficacy of albendazole tablets is compromised if the ingredients are not released from the tablets. A publicly available test method to verify the dissolution properties of albendazole chewable tablets is therefore urgently needed.

### Setting up the dissolution requirements

Most guidance documents on dissolution testing require that chewable tablets – the whole tablets, not the crushed tablets – are subjected to *in vitro* dissolution testing (9). The FIP/AAPS guidelines (10) state: “*In principle, the test procedure employed for chewable tablets should be the same as that for regular tablets. This concept is based on the possibility that a patient might swallow the dosage form without proper chewing, in which case the drug will still need to be released to ensure the desired pharmacological action.*” However, “*because of the non-disintegrating nature of the dosage form, there may be a necessity to alter test conditions (e.g. increase the agitation rate) and specifications (e.g. increase the test duration).*”

To elaborate a dissolution test for albendazole chewable tablets for inclusion in *The International Pharmacopoeia* samples of albendazole chewable tablets were investigated for their *in vitro* release of the active ingredient. The product chosen for this investigation was the comparator product recommended for bioequivalence testing of medicines undergoing WHO prequalification (11), since that product’s quality, safety and efficacy have been fully assessed and documented in premarketing studies and post-marketing monitoring schemes. The comparator product can be swallowed whole, or crushed or chewed

and swallowed with water. Existing pharmacopoeial dissolution test conditions for albendazole tablets were taken as a starting point for the WHO investigations. The volume and composition of the dissolution medium were retained; but a higher rotation speed was selected to compensate for the non-disintegrating character of the dosage form.

The final test conditions (**Box 2**) were found to be discriminative, meaning that the modified test is suitable for comparing and evaluating the *in vitro* release properties of albendazole chewable tablets on the market.

### Adoption process

The procedure for developing monographs for *The International Pharmacopoeia* (12) is designed to ensure wide consultation and transparency, providing stakeholders and interested parties with the opportunity to submit comments on draft documents.

The draft revision of the monograph on albendazole chewable tablets, including the new dissolution test, was therefore

sent out for public consultation in June 2014 and posted on the WHO website (13) with an invitation to provide comments. Thereafter it was submitted, together with a compilation of all comments received, to the Expert Committee on Specifications for Pharmaceutical Products in October 2014. The Committee carefully reviewed the comments and adopted the revised monograph, including the new dissolution test (14). The revised monograph on albendazole chewable tablets is available in the Fifth Edition of *The International Pharmacopoeia* (15).

### References

- 1 WHO Media Centre. Lymphatic filariasis. Fact sheet N° 102. Updated May 2015 [web page].
- 2 WHO Media Centre. Soil-transmitted helminth infections. Fact sheet N° 366. Updated May 2015 [web page].
- 3 ICH Harmonised Tripartite Guideline. Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances. Q6A. Step 4 version. ICH: 1999.

#### **Box 2. The International Pharmacopoeia\*:**

##### **Dissolution test requirements for albendazole chewable tablets**

Carry out the test as described under Section 5.5 Dissolution test for solid oral dosage forms using 900 mL of hydrochloric acid (~3.65 g/L) TS as the dissolution medium and rotating the paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of about 15 mL of the dissolution medium through an in-line filter. Cool the filtered sample to room temperature. Transfer 1.0 mL of the clear filtrate to a 50 mL volumetric flask and dilute to volume with sodium hydroxide (0.1 mol/L) VS. Measure the absorbance (1.6) of a 1 cm layer of the resulting solution at the maximum at about 308 nm, using sodium hydroxide (0.1 mol/L) VS as the blank.

For each of the six tablets tested calculate the total amount of albendazole ( $C_{12}H_{15}N_3O_2S$ ) in the medium using the absorptivity value of 74.2 ( $A_{1\text{cm}}^{1\%} = 742$ ). The amount in solution for each tablet is not less than 80% (Q) of the amount declared on the label.

\* *The International Pharmacopoeia* is available on CD and online at <http://apps.who.int/phint/en/p/about/>

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- 11 WHO Prequalification of Medicines Programme. Recommended comparator products: Neglected Tropical Diseases. Guidance Document, 25 August 2015.
- 12 WHO. Procedure for the development of monographs and other texts for The International Pharmacopoeia. Annex 1. In: WHO Technical Report Series, No. 992. Geneva, Switzerland: 2015.
- 13 WHO. Essential medicines and health products. Current projects [web page]. [www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/projects/en/](http://www.who.int/medicines/areas/quality_safety/quality_assurance/projects/en/)
- 14 WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report. WHO Technical Report Series, No. 992. Geneva, Switzerland: 2015.
- 15 WHO. *The International Pharmacopoeia.* Fifth Edition. Geneva, Switzerland: 2015. Available free of charge at: <http://apps.who.int/phint/en/p/about/>