

PRODUCT INFORMATION REPORT

ALBENDAZOLE
CHEWABLE TABLETS



AUGUST 2019



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The Promoting the Quality of Medicines (PQM) program is a cooperative agreement between the U.S. Agency for International Development (USAID) and the U.S. Pharmacopeial Convention (USP). The PQM program provides technical assistance to strengthen medicines regulatory authorities and quality assurance systems and supports manufacturing of quality-assured priority essential medicines for malaria, HIV/AIDS, tuberculosis, neglected tropical diseases, and maternal and child health.

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List of Acronyms

ALB	albendazole
API	active pharmaceutical ingredient
ASD	amorphous solid dispersion
AUC	area under the curve
BCS	Biopharmaceutics Classification System
FDA	Food and Drug Administration
FTIR	Fourier transform infrared
HPCD	hydroxypropyl- β -cyclodextrin
HPLC	high-performance liquid chromatography
IID	Inactive Ingredient Database
NMR	nuclear magnetic resonance
PIR	product information report
PQM	Promoting the Quality of Medicines (PQM)
PVP	Polyvinylpyrrolidone
SLS	sodium lauryl sulfate
TWA	total weight average
UV-Vis	ultraviolet visible
WHO	World Health Organization
XRD	x-ray diffractometry

Executive Summary

Albendazole chewable tablet is included in the World Health Organization (WHO) list of essential medicines as an intestinal anthelmintic and antifilarial medicine. Albendazole tablet was developed by SmithKline Animal Health Laboratories and approved by U.S. Food and Drug Administration (FDA) in 1996.

This product information report (PIR) provides a comprehensive literature review of the synthesis, physicochemical and biopharmaceutical properties, and analytical profile of albendazole. It is expected that this PIR will provide critical information and guidance to manufacturers and stakeholders concerned with access and supply of priority essential medicines.

The information presented in this PIR is based on extensive literature review of data available in the public domain and the opinion of several experts in the field. The authors have taken great care to appropriately cite all references and provide attribution as appropriate.

Information provided for albendazole includes chemical structure/formula, IUPAC name, physicochemical properties, and solubility related data. Albendazole has been characterized using various spectroscopic techniques, including Fourier transform infrared (FTIR), nuclear magnetic resonance (NMR), mass, and ultraviolet visible (UV-Vis) spectroscopy. These are summarized in the document. Different routes to synthesize albendazole are also discussed. This PIR highlights the stability of albendazole in aqueous solutions and in the solid state. Recently, a new tautomeric form of albendazole has been identified, and the relationship between the two forms is presented. As albendazole has poor solubility in water, numerous approaches have been attempted to improve its aqueous solubility. A summary of the representative approaches is also included. Analytical methods to analyze albendazole in formulation as well as in biological matrices have been summarized.

The definition of chewable tablets and the labeling requirements are pharmacopeia specific. A summary of the nomenclature and quality specifications for chewable tablets is compiled. FDA recently proposed revised guidelines for chewable tablets to include critical quality attributes such as hardness, disintegration, and dissolution, as well as all the factors that may influence drug bioavailability and bioequivalence. The relevance of these specifications with respect to albendazole chewable tablets is presented.

Key Challenges

Albendazole (ALB) is a benzimidazole carbamate having broad-spectrum anthelmintic activity. It is effective in the treatment of echinococcosis, hydatid cysts, and neurocysticercosis and has a potential role in lymphatic filariasis control. It is formulated as a tablet or for pediatric use as a chewable tablet. The formulation of ALB, specifically as a chewable tablet, can be quite challenging for a number of reasons:

- 1.** The high dose required for ALB (400 mg/tablet). This poses a challenge in developing tablets of a size appropriate for children to chew. In addition, a chewable tablet is expected to exhibit optimized hardness and chewability, which is generally achieved by incorporating an optimum quantity of suitable excipients such as mannitol.
- 2.** Extremely poor flow properties of ALB. The selection of suitable excipients with good flow behavior and wet granulation is the usual strategy to formulate such drugs. Chewable tablets can generally be prepared by roller compaction of a physical blend of the active pharmaceutical ingredient (API) and excipients. However, this approach cannot be used in the case of ALB, because of its poor flowability and compaction behavior. The high dose of ALB also limits the quantity of excipients that can be incorporated into the formulation. ALB chewable tablet is included in the WHO list of essential medicines as an intestinal anthelmintic and antifilarial drug.

Due to inconclusive data, ALB's categorization in the Biopharmaceutical Classification System as class II or IV is debatable. It exhibits extensive first-pass effect and variable bioavailability. ALB's poor solubility in aqueous media poses further formulation challenges with respect to evaluation and in vivo performance of the formulation.

Solid Dosage Forms

Due to its relatively low cost, good tolerance, and broad spectrum of activity, ALB is one of the most commercialized benzimidazole derivatives and is considered the drug of choice for helminthic intestinal infections in tropical and subtropical countries. In comparison to mebendazole, the other commonly used anthelmintic drug, ALB exhibits anticestodal and antiprotozoal action. It is included in the WHO list of essential medicines as an intestinal antihelminthic and antifilarial drug in the form of 400 mg chewable tablets [1]. More than 270 million preschool-age children and more than 600 million school-age children live in areas with high transmission rates of soil-transmitted helminth and need treatment and preventive interventions. WHO-recommended medicines—ALB or mebendazole chewable tablets—are effective and inexpensive. WHO also recommends using annual or biannual single-dose ALB to reduce childhood worm burden of solid-transmitted helminth infection [1]. Lymphatic filariasis or elephantiasis is spread in regions inhabited by ~1.28 billion people who are at risk of infection. The disease can be eliminated by stopping the spread of the infection through large-scale chemoprevention, consisting of a single dose of ALB chewable tablet (400 mg), administered with either ivermectin or diethylcarbamazine tablets given annually to an entire at-risk population [2].

ALB was developed by SmithKline Animal Health Laboratories in 1972 and was approved by FDA in 1996 (Albenza®).

ALB is predominantly formulated and marketed as tablets and suspensions (brand names include Albenza®, Eskazole®, and Zentel®). Eskazole® (400 mg) and Zentel® (200 mg, 400 mg) tablets are included in the list of Nationally Authorized Medicinal Products from the European Medicines Agency [4]. According to a WHO estimate, in 2006, nearly 50 million children of age ≤ 5 years were treated at least once with either ALB or mebendazole tablets. WHO recommends ALB chewable tablets as an effective treatment that can be administered by non-medical staff, including parents and teachers [2]. ALB chewable tablets, aimed for use by children and adults with swallowing difficulty, have better palatability than normal film-coated tablets. Although only Albenza® (200 mg) and Zentel® (200 mg) have been labeled by FDA as chewable tablets, Eskazole® (400 mg) and Zentel® (400 mg) can be chewed. A list of active Drug Master Files (DMF) for ALB API is presented in Table 1.

Table 1. Active DMF for ALB API as of March 31, 2019

DMF#	Type	Submit date	Holder	Subject (Title)
6104	II	11/20/1985	Smithkline Beecham Pharmaceuticals	ALB
12308	II	01/10/1997	Changzou Synthetic Material Plant	ALB
28558	II	08/13/2014	Solara A Pharma Sciences Ltd	ALB
25914	II	03/27/2012	Uquifa Mexico Sa De Cv	ALB
30967	II	10/28/2016	Cipla Ltd	ALB (B) USP
29493	II	06/30/2015	Cipla Ltd	ALB USP
31341	II	01/31/2017	MSN Life Sciences Private Ltd	ALB USP
32013	II	10/12/2017	Novugen Pharma (Malaysia) SDN BHD	ALB USP
17754	II	11/08/2004	Unimark Remedies Ltd	ALB USP

Excipients

A list of excipients used in the Albenza[®], Eskazole[®] and Zentel[®] “chewable” tablets is presented in Table 2 and Table 3. The list includes their proposed functions in the formulations and the maximum concentration approved as per FDA’s Inactive Ingredient Database (IID). The quantitative limits were checked under the column of uncoated chewable tablet [5]. Interestingly, Albenza[®] is formulated as a conventional chewable tablet. It contains mannitol, which is a popular diluent for chewable tablets because of its pleasant taste and texture. As mentioned above, Eskazole[®] and Zentel[®] are labelled as tablets that can be chewed. Both the formulations incorporate high amounts of flavor in order to improve palatability.

Table 2. Albenza® excipients

Ingredients	Function in tablet	IID limit (mg)	Usual recommended concentration (%)	Reference [6] (page # of reference)
Lactose monohydrate	Diluent	126.1*	-	364-369
Microcrystalline cellulose	Diluent, binder	639	5-15 (binder); 20-90 (diluent)	129-134
D-mannitol	Diluent	630	1.0-2.0	424-428
Sodium starch glycolate	Disintegrant	50	-	663-666
Povidone	Binder	2.5	0.5-5	581-585
Magnesium stearate	Lubricant	50	0.25-5	404-408
Crospovidone	Disintegrant	100	2-5	208-210
Polyvinyl acetate	Gum base ingredient	25.82*	-	-
Sucralose	Food products	1.88	0.03-0.24	701-703
Colloidal silicon dioxide	Glidant	30	0.1-1	185-189
Sodium lauryl sulfate	Lubricant	5	1.0-2.0	651-653
N-C Wild Berry Type Flavor	Flavor	-	-	-
D&C Red #30/ Helendon Pink Aluminum Lake	Coloring agent	-	-	-

* Limits with respect to chewable tablets.

Table 3. Eskazole® and Zentel® excipients

Ingredients	Function	IID limit (mg)	Usual recommended concentration (%)	Reference [6] (page #)
Microcrystalline cellulose	Diluent and binder	639	5-15 (binder), 20-90 (diluent)	129-134
Maize starch	Diluent, lubricant	-	-	695-696
Lactose	Diluent	108	-	359-361
Croscarmellose sodium	Disintegrant	25.5	0.5-5.0	206-208
Povidone	Binder	2.5	0.5-5	581-585
Magnesium stearate	Lubricant	50	0.25-5	404-408
Sodium lauryl sulfate	Lubricant	5	-	185-189
Orange flavor	Flavor	50	-	-
Vanilla flavor	Flavor	0.8 (tablet)	-	-
Passion fruit flavor	Flavor	-	-	-
Sodium saccharin	Sweetening agent	9	-	608-610
Sunset yellow lake E110	Coloring agent	-	-	[14]

Key Manufacturing Challenges

Table 4 summarizes key challenges associated with the manufacture and analysis of ALB chewable tablets containing 400 mg of the drug.

Table 4. Key challenges in manufacture and analysis of ALB chewable tablets

Challenge	Description of challenge and solution
Inherent API properties	ALB is quite hydrophobic and exhibits poor aqueous solubility. The powder exhibits poor flowability and compressibility. Considering the high drug dose, these API characteristics are relevant while formulating chewable tablets. ALB is tasteless or the taste is unknown, so a taste-masking strategy is not required.
Product development formulation	Given the poor flowability of ALB, the chewable tablet cannot be prepared by roller compaction, so wet granulation is the method of choice. To successfully formulate chewable tablets of desired attributes, a judicious selection of excipients is warranted.
Product development (quality specifications)	<p>There is no consensus among pharmacopeias with respect to specifications for chewable tablets. The monograph for ALB chewable tablets is not included in any pharmacopeia except the International Pharmacopeia.</p> <p>The clinical efficacy of ALB tablets has been shown to be broadly correlated with tablet dissolution performance. Given the poor solubility of ALB in aqueous media and demonstration of excipient influence on dissolution, the quality specifications for ALB tablets are proposed to include disintegration and dissolution tests. The monograph for ALB chewable tablets in the International Pharmacopoeia has been revised to include disintegration and dissolution tests.</p>
Bioequivalence	<p>The Biopharmaceutics Classification System classification of ALB is not well-defined. WHO does not recommend a biowaiver for the ALB chewable tablet because it is unknown whether poor bioequivalence is due only to poor solubility or due to both poor solubility and poor permeability?</p> <p>Although ALB is already included in the WHO Model List of Essential Medicines, there is no listing for ALB in WHO's list of prequalified APIs. The list contains sources of APIs that WHO has assessed and found to be acceptable for use in the manufacture of finished pharmaceutical products to be procured by UN agencies.</p>

ALB Overview

Mechanism of Action

ALB is a member of the benzimidazole group of parasitocidal agents that disrupts parasite energy metabolism. It specifically causes degenerative alterations in worm cells by binding to colchicine-sensitive sites of β -tubulin, a constituent cell protein, thus inhibiting its assembly into microtubulin. The specific action of ALB against parasitic cells rather than mammalian cells is attributed to its preferential binding to parasitic β -tubulin [7]. It leads to impaired glucose uptake by the adult and larval forms of the parasites, and eventually depletes glycogen storage. As a consequence, the production of adenosine triphosphate decreases because of insufficient glucose and leads to the death of the parasite [8]. At higher concentrations, ALB also disrupts parasitic metabolic pathways by inhibiting metabolic enzymes involved in Krebs cycle, such as malate dehydrogenase and fumarate reductase.

ALB also prevents the formation of the spindle-fiber needed for alignment of chromatin during cell division, which in turn inhibits cell division, egg production and development, and hatching of existing eggs. Lack of spindle formation also leads to reduced intracellular transport and cell motility [9]. Compared to other agents in the benzimidazole group, such as mebendazole, ALB has a higher activity in a single oral dose of 400 mg against ascariasis, hookworm infection, trichostrongylosis, and (to a slightly lesser extent) enterobiasis and trichuriasis [10].

Side Effects

Abnormal liver function and headache are the most common side effects of ALB treatment. In ~16 percent of patients receiving ALB, specifically for hydatid disease, the liver enzyme level increases to two to four times the normal level. This goes back to normal once treatment ends. Additional side effects reported include nausea, vomiting, dizziness, vertigo, fever, abdominal pain, temporary hair loss, and increased intracranial pressure. Some of these side effects are attributed to sudden destruction of parasitic larvae, which causes inflammation. Less common side effects include hypersensitivity in the form of rashes or hives, acute liver or renal failure, drop in the levels of white blood cells, reduced platelet counts, aplastic anemia, and (rarely) irreversible bone marrow suppression [11].

Interestingly, ALB side effects vary when treating for hydatid disease or neurocysticercosis [12]. Patients who use ALB to treat hydatid disease are more likely to experience elevated liver enzymes and abdominal pain, while patients using ALB for neurocysticercosis are more likely to experience headaches. In the case of neurocysticercosis patients, the death of parasites in the brain upon ALB treatment can lead to increased inflammation and thus increased intracranial pressure or occurrence of seizure. Table 5 describes incidence of side effects associated with ALB treatment in these two diseases.

Table 5. ALB adverse reactions (%) in patients with hydatid disease or neurocysticercosis

Side Effect	Hydatid Disease (%)	Neurocysticercosis (%)
Abnormal liver function	15.6	<1.0
Abdominal pain	6	0
Nausea/vomiting	3.7	6.2
Headache	1.3	11
Dizziness/vertigo	1.2	<1.0
Raised intracranial pressure	0	1.5
Meningeal signs	0	1
Reversible alopecia	1.6	<1.0
Fever	1	0

Absorption, Distribution, Metabolism, and Excretion

ALB is poorly absorbed from the gastrointestinal tract due to its low aqueous solubility (Biopharmaceutics Classification System (BCS) class II/IV compound; *vide infra*). Oral absorption of ALB in humans is <1-5%. As ALB undergoes rapid first-pass metabolism, its concentrations are negligible or undetectable in plasma [13]. The sulphoxide is generally considered to be the active metabolite responsible for ALB's therapeutic activity. Absorption and metabolism are rapid, as demonstrated by the peak level of radioactivity after oral administration of [14] C-ALB and of the intact drug (as sulphoxide) being reached within 2 to 3 hours [7].

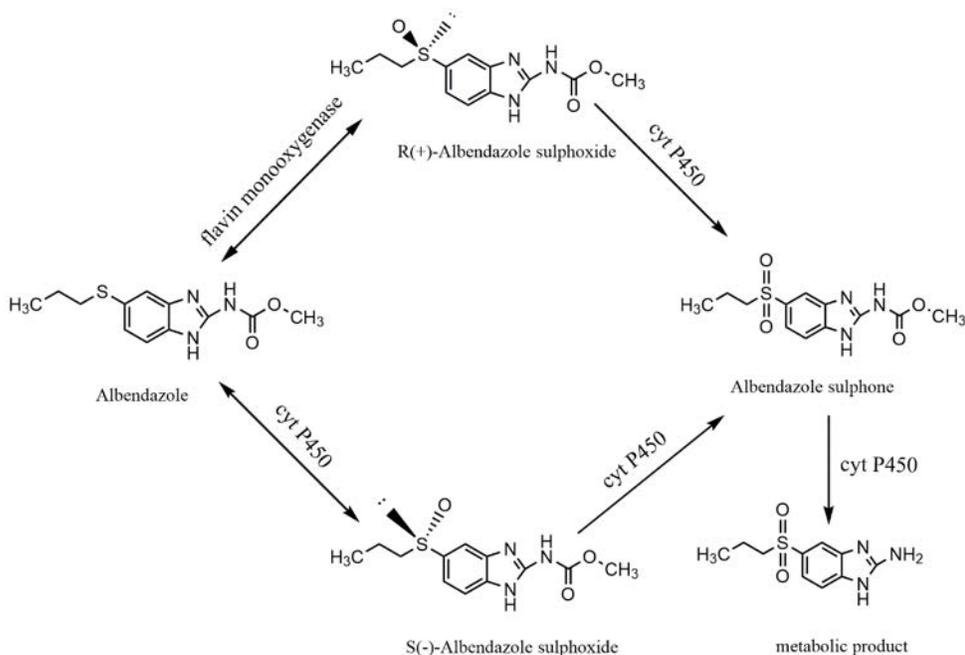
A fatty meal enhances absorption, and a five-fold increase in average plasma concentration of ALB sulphoxide was achieved when it was co-administered with a fatty meal

(estimated fat content 40 grams) in comparison to the fasted state [7]. The improved absorption was attributed to increased dissolution of the water-insoluble drug in the fatty matrix [14].

The relationship between the administered oral dose and the plasma area under the curve (AUC) of the parent drug or oxidized metabolites has not been directly reported. While one study showed C_{max} of ALB sulphoxide in plasma of 0.22-0.25 µg/mL, 2 to 3 hours after an oral dose of ALB 400 mg (about 6-8 mg/kg), another study reported a C_{max} of 0.46-1.58 µg/mL (average 1.31 µg/mL) after the same dose [15].

As mentioned above, ALB is rapidly converted to the primary metabolite, ALB sulphoxide, which is further metabolized to ALB sulphone and other primary oxidative metabolites (Figure 1). In humans, ALB sulphoxide is produced in the liver and probably in the intestinal wall. Independent oxidative pathways affect the alkyl side chain and the aromatic ring. The carbamate group is also rapidly removed by hydrolysis [7]. Metabolism depends both on cytochrome P450 oxidases and other flavin mono oxidases [15].

Figure 1. Scheme showing ALB metabolism



Source: Dollery CT

ALB sulphoxide has a chiral center, and formation of ALB (-) sulphoxide depends on cytochrome P450 enzymes, whereas that of ALB (+) sulphoxide depends on flavin monooxidase. Subsequent oxidation to ALB sulphone is mediated by cytochrome P450 isozymes. In humans, ALB (+) sulphoxide is the predominant form in plasma [15], with the relative AUCs being 8/9 times that for the (+)/(-) sulphoxide. Repeated administration of ALB alters its own kinetics, probably by affecting its metabolic clearance by inducing at least the P450s involved in its own metabolism.

ALB sulphoxide is 70 percent bound to plasma protein. It is widely distributed throughout the body, as is evident by its detection in urine, bile, liver, cyst wall, cyst fluid, and cerebrospinal fluid. Concentrations in plasma are 3 to 10 times and twice higher than in the cyst fluid and cerebrospinal fluid (simultaneously determined), respectively.

The $t_{1/2el}$ for the parent drug is not reported (low plasma level), while the $t_{1/2el}$ for ALB sulphoxide is 8 to 12 hours. Urinary excretion of ALB sulphoxide is a minor elimination pathway, with < 1% of the dose recovered in the urine. Excretion occurs largely in bile, as evident from the biliary concentration of ALB sulphoxide being similar to that achieved in plasma. Following 4 weeks of treatment with ALB (200 mg thrice daily), concentrations of ALB sulphoxide in plasma were approximately 20 percent lower than those observed during the first half of the treatment period. As mentioned above, the observation suggests that ALB may induce its own metabolism [15].

ALB is categorized as Pregnancy Category C, as it has been shown to be teratogenic (to cause embryotoxicity and skeletal malformations) in pregnant rats and rabbits [7]. There are no adequate and well-controlled studies of ALB administration in pregnant women, and it should only be used during pregnancy if the benefit justifies the potential risk to the fetus [15]. ALB is excreted in animal milk, but it is not known whether it is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ALB is administered to a nursing woman.

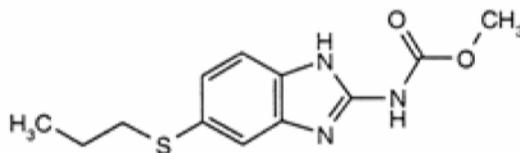
Active Pharmaceutical Ingredient

Chemical Structure and IUPAC name

IUPAC name:

Methyl-[6-(propylthio)-1Hbenzimidazol-2-yl] carbamate.

Figure 2. Molecular structure of ALB



Molecular Formula: C₁₂H₁₅N₃O₂S, molecular weight 265.34, C 54.32%, H 5.70%, N 15.84%, O 12.06%, S 12.09%

USP/BP/EP name:

USP 40/ Ph. Int: Carbamic acid, [5-(propylthio)-1H-benzimidazol-2-yl]-, methyl ester;
Methyl 5-(propylthio)-2-benzimidazolecarbamate

BP/EP: Methyl [5-(propylsulfanyl)-1H-benzimidazol-2-yl]carbamate

CAS: CAS-54965-21-8

pKa

4.27 and 9.51

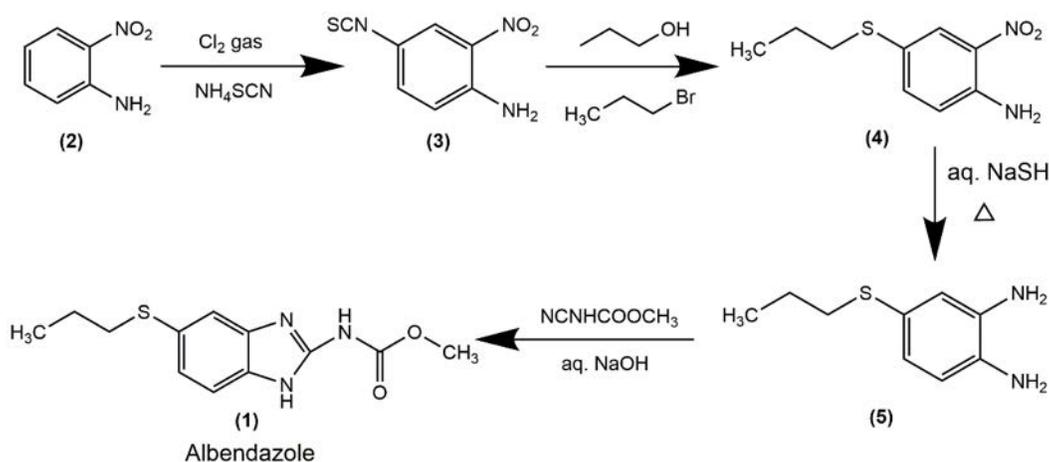
logP

2.7. Calculated logP (using BioLoom version 5.0) is 3.46.

ALB Synthesis

U.S. Pat. No. 4,152,522 describes the process by which 2-nitroaniline (2) is thiocyanated to obtain 2-nitro-4-thiocyanoaniline (3), then alkylated with *n*-propylbromide in the presence of *n*-propanol and methyl tributyl ammonium chloride or the tetrabutyl ammonium bromide as the phase-transfer catalyst and an alkali metal cyanide or alkaline metal cyanide to generate 4-propylthio-2-nitroaniline (4). 4-propylthio-2-nitroaniline (4) is reduced by sodium hydrogen sulphide in the presence of water to obtain 4-propylthio-*o*-phenylenediamine (5). This diamine is further reacted with sodium salt of methyl-*N*-cyanocarbamate to obtain the ALB (1). This method of synthesis (Figure 3) has a high yield, is a low-cost stable process, and is popularly used in industry [16].

Figure 3. Representative process for synthesis of ALB.



There are some limitations associated with the above process, and alternate synthetic routes have been proposed. One such method involves the reaction of chlorosulfonic acid and carbendazim to form a 4-chlorosulfonyl derivative of carbendazim. Methyl imidazole carbamate is reduced to obtain methyl 4-mercaptobenzimidazole carbamate, and then condensed with halogenated *n*-propane to obtain ALB. In another method, carbendazim is reacted with chlorine gas and potassium thiocyanate to form methyl 5-thiocyanobenzimidazole carbamate, which is hydrolyzed to obtain methyl 4-mercaptobenzimidazole carbamate. This is then condensed with a halogenated *n*-propane to give an ALB product. There are concerns with respect to the yield and cost of these alternative methods [17].

Physical Properties

ALB occurs as colorless crystals or as a white/almost white powder with a melting point of 208°C-210°C.

Solubility Profile

ALB has poor aqueous solubility. The solubility of ALB in sodium phosphate buffer (pH 6.0; 24°C) was found to be 0.016 mg/mL. The pH solubility profile (Figure 4) shows that, as the pH decreases, ALB solubility increases. ALB solubility increases in the presence of surfactants, and transcucol caused the maximum increase in solubility [18] (Figure 5).

Figure 4. Solubility of ALB (mg/mL) in various pH buffer solutions

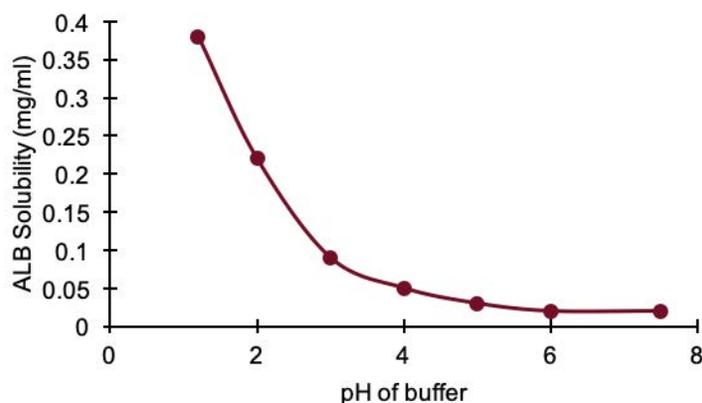
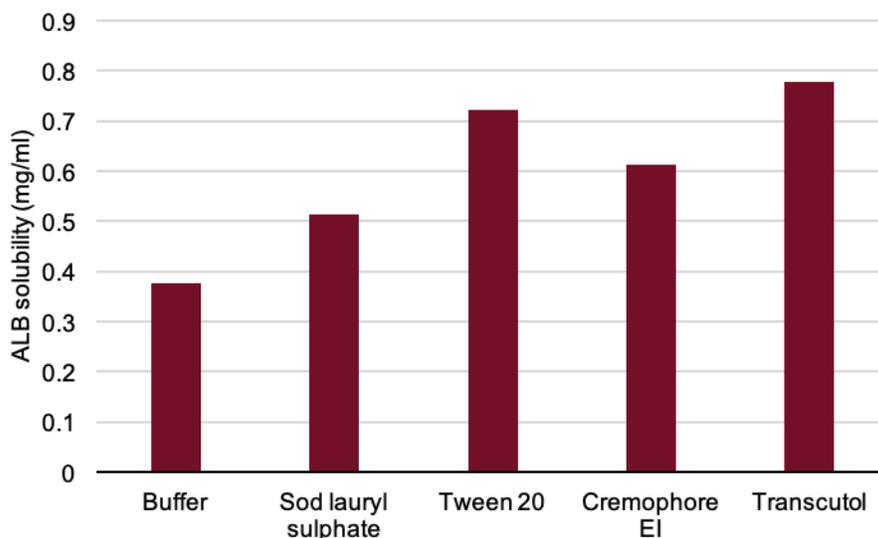


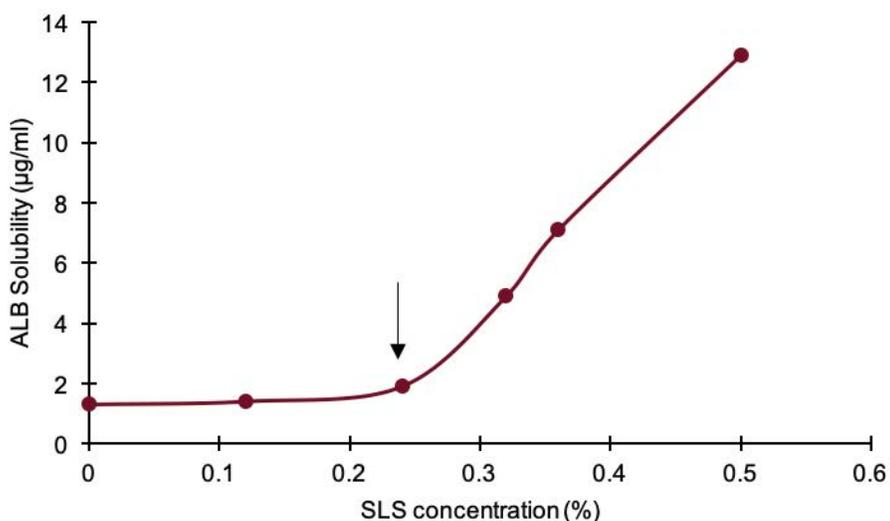
Figure 5. ALB solubility indifferent solubility enhancers



Solubility of ALB in water at 37°C is reported to be 1.3 µg/mL [19]. Solubility in a fasted state-simulated intestinal fluid is 2.1 µg/mL. ALB solubility increases linearly with sodium lauryl sulfate (SLS) concentration (Figure 6). It has been proposed that to avoid the time-consuming and rather expensive preparation of fasted state-simulated intestine fluid for dissolution studies, synthetic surfactants such as SLS may be acceptable to reflect the simulated intestinal fluid [19].

ALB is freely soluble in anhydrous formic acid; slightly soluble in methanol, chloroform, ethyl acetate, and acetonitrile; and very slightly soluble in methylene chloride and ethanol.

Figure 6. Solubility of ALB in SLS solution



Note: The SLS critical micelle concentration (8.2 mmol/l or 0.236% w/v) is marked with an arrow.

Hygroscopicity

The change in sample weight (a measure of the equilibrium water content) on exposing the ALB powder for a week at room temperature in chambers maintained at 11%, 43%, 75%, 83%, and 93% relative humidity (RH) were respectively -0.28%, 0.31%, 1.54%, 1.92%, and 3.54% w/w. Similar results were obtained using an automated moisture sorption balance. When stored at 80% RH (at 25°C) for a week, the increase in equilibrium moisture content of ALB was 0.1%; hence, the drug was classified as a non-hygroscopic compound [20].

Stereochemistry and Polymorphism

ALB demonstrates desmotropy, a rare phenomenon related to tautomerism, in which both tautomeric forms can be isolated in the solid state. ALB is available in form I. A tautomeric form of ALB, named Form II, was isolated from the methanol or dimethyl formamide solution by slow evaporation [21]. The new stable polymorph form (Figure 7) is enantiotropically related to the commercially available ALB (Form I), the latter being the metastable form at ambient temperature. Both forms proved to be physically quite stable, likely due to a high-energy barrier for the activation of the interconversion [22].

Solubility of ALB forms I and II in 0.1 N aqueous HCl solution, at a temperature range of 5°C-100°C, was experimentally determined. The differences in solubility are useful to understand the thermodynamic relationship between the two solid forms. The semi-quantitative phase diagram generated using the solubility data established at room temperature stability of Form II [22] is presented in Figure 8.

Figure 7. ALB tautomers corresponding to desmotropic forms I (a) and II (b)

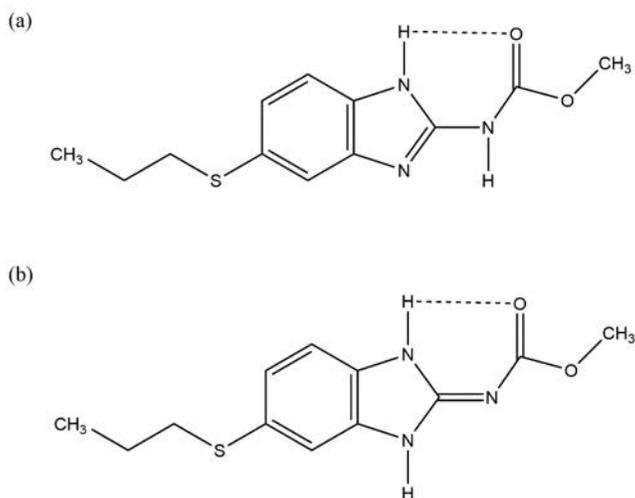
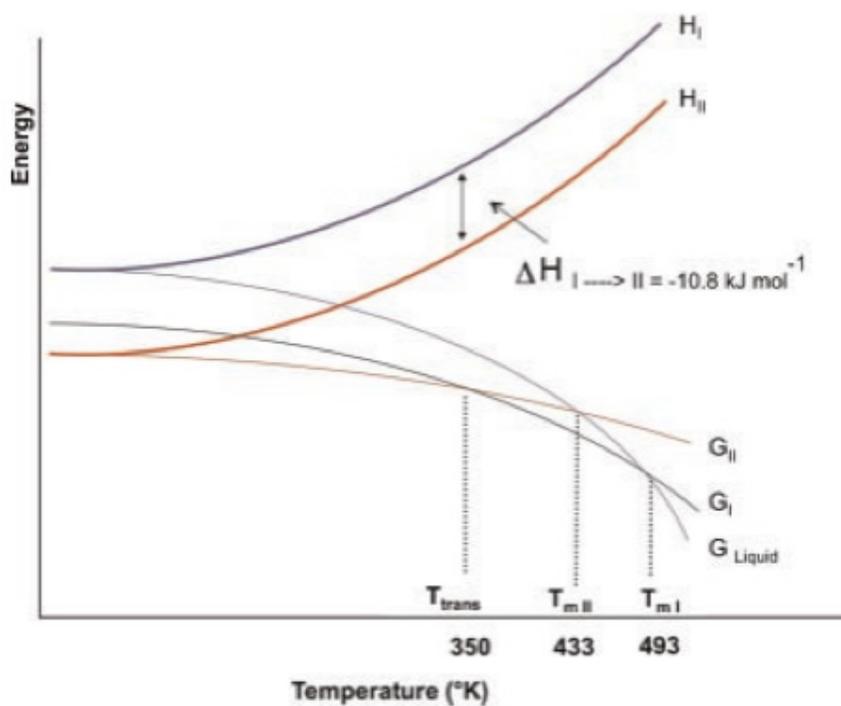


Figure 8. Semi-quantitative energy versus temperature diagram for the ALB Form I and Form II pair



Source: Chattah AK, Zhang R, Mroue KH, et al.

Powder Properties

The bulk and compressed densities of ALB were determined to be $0.259 \pm 0.005 \text{ g/mL}$ ($n=3$) and $0.409 \pm 0.010 \text{ g/mL}$ ($n=3$), respectively.

The Carr Index (CI) is a measure of the compressibility and flowability of a powder; for values between 5% and 15%, the powder is considered to have excellent flow; above 21%, it is considered to have poor flow and compression. Since the CI values for ALB were found to be $36.32 \pm 1.14\%$, the powder is considered to have poor flow.

The Hausner Index is another popular measure of flow. Values less than 1.25 indicate good flow, values above 1.5 indicate poor flow, and values between 1.25 and 1.5 indicate that lubricants are required to improve flow. The Hausner Index for ALB was 1.58 ± 0.04 , indicating that ALB is a poorly flowing powder [23].

The angle of repose technique and flow time confirmed the poor flow of ABZ powder, since there was no flow. Based on all these results from powder rheology, ABZ can be

classified as a poor-flow powder, and these findings are of great importance for the pre-formulation study required in drug development [24].

Permeability and BCS Classification

The apparent permeability (P_{app}) of ALB across Caco-2 cells is $3.14 \pm 0.03 \times 10^{-6}$ cm/sec [25]. Compounds with $P_{app} < 1 \times 10^{-6}$, 1×10^{-6} , and $>1 \times 10^{-6}$ cm/s are defined as poorly, moderately, and highly permeable, respectively. Therefore, ALB would be defined as moderately permeable [25].

For drug transport in Caco-2 monolayers, a cutoff point for highly permeable APIs of $P_{app} = 10^{-5}$ cm/s, was proposed, which should ensure a fraction dose absorbed $> 95\%$. Rinaki et al. [26] proposed quantitative BCS classification, wherein drugs can be grouped into the four categories according to their P_{app} and dose/solubility ratio q :

Class I - $P_{app} > 10^{-5}$ cm/s, $q \leq 0.5$

Class II - $P_{app} > 10^{-5}$ cm/s, $q > 1$

Class III - $P_{app} < 2 \times 10^{-6}$ cm/s, $q \leq 0.5$

Class IV - $P_{app} < 2 \times 10^{-6}$ cm/s, $q > 1$

A region for borderline drugs ($2 \times 10^{-6} < P_{app} < 10^{-5}$ cm/s, $0.5 < q < 1$) was also defined. For category I, complete absorption is anticipated, whereas categories II and III exhibit dose/solubility ratio-limited and permeability-limited absorption, respectively. For category IV, both permeability and dose/solubility ratio will control drug absorption.

It is well established that ALB is a poorly water soluble ($1.3 \mu\text{g/mL}$) drug. Considering that the highest strength is 400 mg, the dose solubility ratio (q) for ALB is >1000 . In accordance with the above classification from WHO prequalification team, ALB with $P_{app} \sim 3 \times 10^{-6}$ cm/s and $q > 1$, belongs to category IV of drugs and is expected to exhibit permeability. Dose/solubility ratio controls drug absorption. However, due to extensive first-pass effect and hence variable bioavailability, ALB is not specifically classified and is listed as a drug with inclusive data [27].

WHO does not recommend a biowaiver because it is not established whether the poor bioavailability of ALB is due to poor solubility or due to poor solubility coupled with poor permeability? [28]. WHO has issued guidelines for conducting bioequivalence study of ALB tablets. The data for albendazole should meet the following bioequivalence standards in a single-dose, crossover design study:

- The 90% confidence interval of the relative mean total AUC of the test to reference product should be within 80–125%.
- The 90% confidence interval of the relative mean C_{max} of the test to reference product should be within 80–125%.

The guidelines further recommend that the comparator product be a highly variable drug product for both total AUC and C_{max} in the fed state. Widening of the acceptance range for total AUC for ALB is acceptable. A replicate crossover study may be designed to estimate variability more accurately and to widen the acceptance range for C_{max} and total AUC [29].

Solubility Enhancement Approaches

In view of the extremely poor solubility of ALB, numerous solubility enhancement approaches have been attempted. A summary of some of the representative approaches is presented below.

The formation of the inclusion complex of a drug with a cyclodextrin derivative is a popular solubility enhancement strategy. The hydrophobic drug is enclosed within the interior cavity of the cyclodextrin molecules in aqueous solution. ALB inclusion complex with β -cyclodextrin, hydroxypropyl- β -cyclodextrin (HPCD), and methyl- β -cyclodextrin was prepared by freeze drying. Solubility enhancement was accomplished by this strategy. The bioavailability results show that the inclusion complex with HPCD complexes had faster absorption than a conventional ALB suspension formulation [30]. A colon-targeted matrix tablet formulation of ALB- β -cyclodextrin complex containing guar gum, microcrystalline cellulose, talc, and magnesium stearate was prepared by wet granulation. The formulations containing 30 percent and 40 percent guar gum were proposed to target ALB in improved concentrations to the colon without being released significantly in the stomach or small intestine.

ALB microparticles with methylcellulose, polyvinyl alcohol, and polyvinyl pyrrolidone (PVP) were prepared by spray drying. The dissolution rate of ALB was found to be substantially enhanced from the spray-dried microparticles when compared to the corresponding physical mixtures [31].

An amorphous solid dispersion (ASD) with a suitable polymer is a useful strategy for enhancing the aqueous solubility of poorly soluble drugs. A solid dispersion of ALB with PVP was prepared by solvent evaporation. Using a drug polymer ratio of 1:10 and 1:40, solubility increases of 3 and 13 times, respectively, were observed in ALB. A

similar enhancement in dissolution efficacy was reported [32]. Hot melt extrusion was also used to prepare ASD of ALB with PVP. A pronounced increase in the dissolution rate of ALB in gastrointestinal simulated media was achieved with values of 70 percent drug release for the extruded materials containing ALB-PVP K12 at the relative weight percentages of 1:99 and 10:90 [33].

ASD of ALB with Pluronic 188 were prepared by coprecipitation followed by quenching. The dissolution rate was significantly higher for ASD than the physical mixtures during the first 15 minutes of the test. Systems with lower Pluronic 188 content were comparatively more effective in increasing the ABZ dissolution rate. Importantly, ASD had better flow and compaction properties than the physical mixtures [34].

ASD of ALB with methanesulfonic acid and KollidonVR VA 64 were prepared by spray drying. The resulting dispersions substantially improved non-sink dissolution in acidic media as compared to bulk ALB (8-fold), physical mixture of ALB:KollidonVR VA 64 (5.6-fold), and ALB mesylate salt (1.6-fold) [35].

Stability

ALB shows high photosensitivity in solution but reliable stability in solid form and when exposed to temperatures up to 50°C [36]. Solutions of ALB in ethanol (20 mg/mL) were subjected to controlled irradiation for up to 10 hours and analyzed by high-performance liquid chromatography (HPLC). Exposure to light caused a marked degradation. In contrast, direct exposure to light of the drugs in solid form did not cause decomposition. The absence of degradation in the solid form could be attributed to necessity of water for the hydrolysis process [37].

The thermal degradation test, performed over the temperature range of 20°C to 50°C, demonstrated very high stability both in solid form and solution form. These temperature values were considered to represent drug storage under tropical conditions. The results confirmed that the degradation process was caused only by light and not by high temperature [37].

Handling and Storage Conditions

The ALB drug substance and products are required to be stored in closed containers protected from light. USP recommends storage of ALB tablets at a controlled room temperature.

Exposure Controls/Personal Protection Occupational Exposure Limits

Exposure to the drug substance in the workplace can lead to occupational diseases and illnesses that can manifest either immediately or after a long period of time after the exposure has stopped. It is important to identify and evaluate exposure following the techniques of anticipation, identification, evaluation, and control. The goal is to identify solutions for eliminating or reducing the hazard, and monitoring to ensure no further harm occurs. The permissible exposure limit is the limit for exposure of an employee to a chemical substance or physical agent such as high-level noise. It can be measured as the total weight average (TWA), which is the average exposure over a specified period (usually a nominal 8 hours). This means that, for limited periods, a worker may be exposed to concentration excursions higher than the permissible limit, so long as the TWA is not exceeded and any applicable excursion limit is not exceeded. For ALB [38], the TWA is 0.3 mg/m³ and 100 µg/m³. As seen in Table 6 [39], ALB is classified as a class 2 drug and should be handled accordingly.

Table 6. ALB hazards and controls

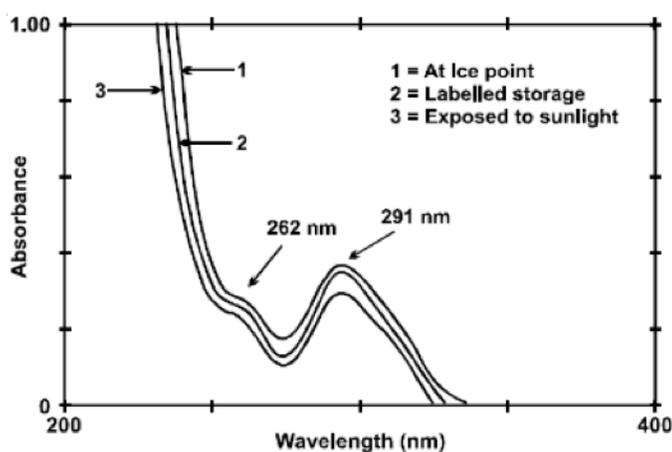
Band	TWA (dust and vapor respectively)	Hazard	Control
1	>1-10 mg/m ³ >50 to 500 ppm	Skin and eye irritants	Use good industrial hygiene practice and general ventilation
2	>0.1-1 mg/m ³ >5 to 50 ppm	Harmful on single exposure	Use local exhaust ventilation
3	>0.01-0.1 mg/m ³ >0.5 to 5 ppm	Severely irritating and corrosive	Enclose the process
4	<0.01 mg/m ³ <0.5 ppm	Very toxic on single exposure, reproductive hazard, sensitizer	Seek expert advice

Characterization by Various Techniques

UV Spectroscopy

Aqueous solution of ALB in 0.1N HCl show absorption maxima at 291 nm and 262 nm, and demonstrate a linear Beer-Lambert relationship over the concentration range of 2 µg/mL-20 µg/mL. The UV spectra demonstrate change in intensity ratio of these vibrational modes after the drug was stored in sunlight and at ice point (Figure 9). The authors concluded that spectroscopy can serve as an aid to check drug quality [36].

Figure 9. Comparative representation of UV-Visible spectra of ALB

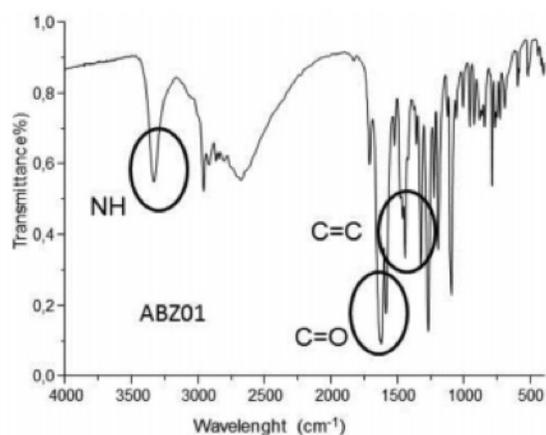


Note: The spectra is of ALB in 0.1 M HCl showing maximum absorption at 262 and 291 nm.

FTIR Spectroscopy

As per pharmacopeia requirements, FTIR spectroscopy is conventionally used for identification of API. The infrared spectra of ALB exhibits characteristic absorption bands at 3390 cm^{-1} and 1711 cm^{-1} attributed to the amide NH and ester C=O bond, respectively, corresponding to the carbamate part of the molecule [23]. The absorption band at 1622 cm^{-1} can be attributed to the aromatic C=C bond and amide NH bond of the benzimidazole portion of the ALB molecule. Additional vibrations are observed at 2959 cm^{-1} (aliphatic hydrocarbon group), 1096 cm^{-1} (ether bond), 1622 cm^{-1} (C-H) and 1096 cm^{-1} (S=C) (Figure 10).

Figure 10. Representative FTIR spectra for ALB



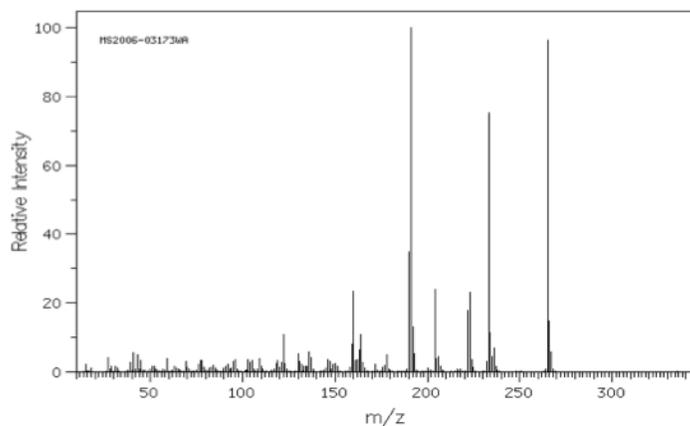
Note: Characteristic vibrations and bond attribution are highlighted for reference.

Mass Spectroscopy

The mass spectrum of ALB is presented in Figure 11. It was collected under the following conditions: source temperature of 250°C, sample temperature of 70°C, direct 70 eV. A list of major peaks and their intensities is compiled as follows.

m/z	Intensity
160	23.5
164	10.8
190	34.9
191	100
204	23.9
222	17.8
223	23
233	75.2
265	96.4

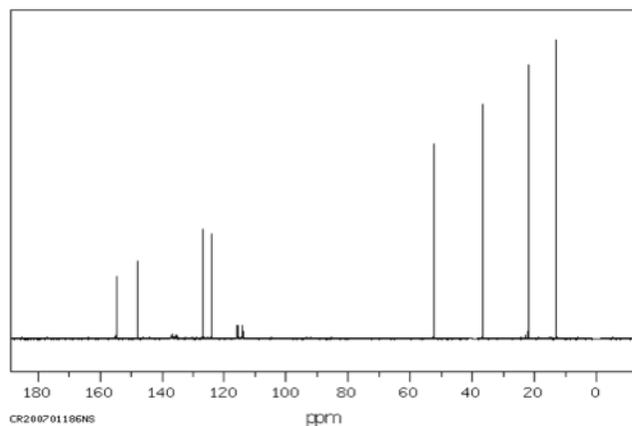
Figure 11. Representative mass spectrum of ALB



Solution-State NMR

The $[^{13}\text{C}]$ -NMR spectrum of ALB (0.038 g/mL) in DMSO- d_6 is presented in Figure 12. The chemical shifts along with their attribution is compiled in Figure 13.

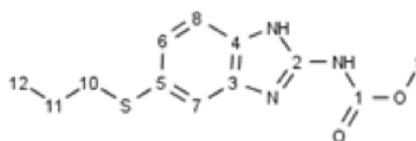
Figure 12. ^{13}C -NMR spectrum (100 MHz) of ALB



Note: Chemical shift is with respect to tetramethylsilane in DMSO.

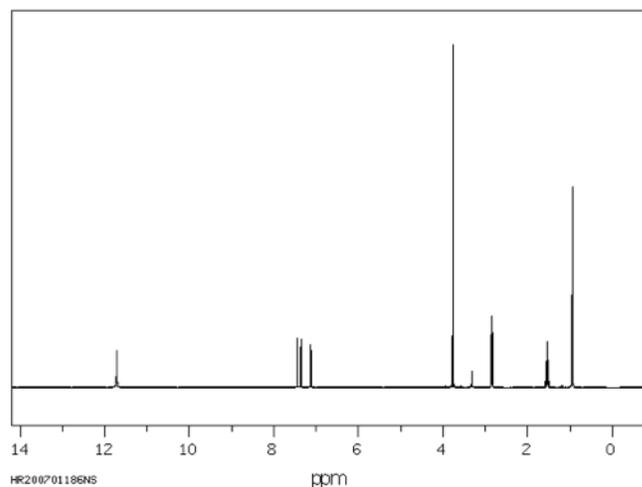
Figure 13. Chemical shifts and their attributions for ALB C13 NMR

ppm	Intensity	Assignment
154.7	204	1
144.77	258	2
136.72	11	3
135.39	10	4
126.82	362	5
123.99	347	6
115.78	41	7
114.09	42	8
52.4	651	9
36.62	784	10
22.02	914	11
12.98	1000	12



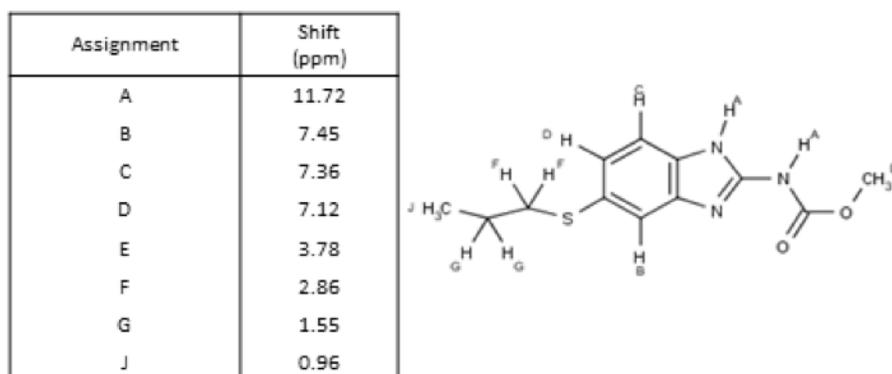
The ¹H-NMR spectrum of ALB (0.038 g/mL) in DMSO-d₆ is presented in Figure 14. The chemical shifts and their attributions are compiled in Figure 15. These spectra were obtained from the Spectral Database for Organic Compounds (SDBS).

Figure 14. 400 MHz proton NMR spectrum of ALB in DMSO



Note: ¹H NMR chemical shifts referred to tetramethylsilane in DMSO.

Figure 15. Chemical shifts and their attribution for ALB H-NMR



X-ray Diffractometry

The calculated x-ray diffractometry (XRD) pattern of ALB form I (ref code in Cambridge Structure Database: BOGFUC) is presented in Figure 16. Both forms I and II belong to the monoclinic crystal system. The experimental powder XRD patterns for the two forms are presented in Figure 17. Using Cu K α X-rays (λ 1.548Å), the XRD pattern of form I exhibited peaks at 6.9°, 11.3°, 11.6°, 13.8°, 17.9°, 18.8°, 19.9°, 22.1°, 24.4°, 24.7°, 27.2°, and 30° (2 θ). On the other hand, form II showed distinct peaks at 7.3°, 10.7°, 12.4°, 14.6°, 18.1°, 24.7°, 25.6°, 29.5°, and 30.7° (2 θ). The distinct XRD patterns of the two forms suggest different solid-state forms of the drug [22].

Figure 16. Calculated XRD pattern of ALB (ALB CCDC # 668711)

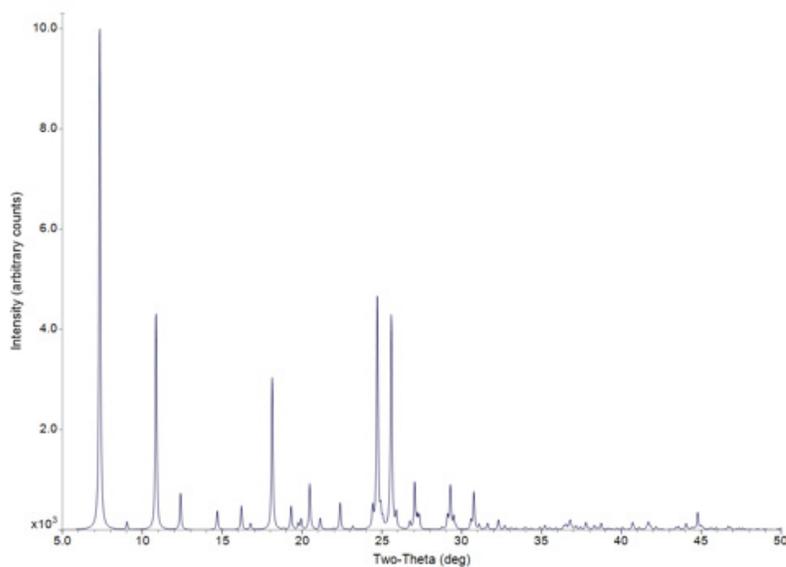
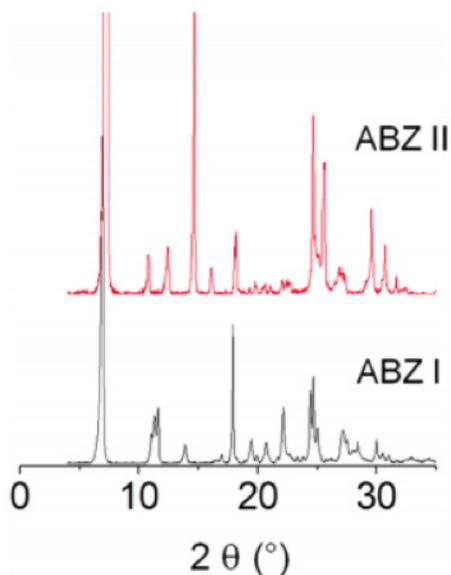


Figure 17. Overlay of powder XRD patterns of ALB forms I and II



Analysis of ALB Drug Substance

For the assay method for the ALB drug substance, all the pharmacopoeias suggest non-aqueous titration using a potentiometric endpoint. The drug is freely soluble in formic acid and acetic acid; hence, these solvents are used to prepare the drug solution, which is then titrated with perchloric acid. The method is detailed as follows: (1) dissolve 0.250 g in 3 mL of anhydrous formic acid and add 40 mL of anhydrous acetic acid, and (2) titrate with 0.1 M perchloric acid, determining the endpoint potentiometrically. The ALB content was calculated as 1 mL of 0.1 M perchloric acid, which is equivalent to 26.53 mg of $C_{12}H_{15}N_3O_2S$. To avoid overheating during the titration, the contents should be mixed thoroughly throughout, and the titration should be stopped immediately after the endpoint is reached.

Test for related substances:

The European and British pharmacopoeias elaborate the HPLC method for the limit of related substances. The method recommends preparation of test and reference solutions of ALB with concentrations of 0.5 and 0.0025 mg/mL, respectively. Oxybendazole is added to a second reference solution for system suitability test, optimizing the process parameters for chromatographic analysis. Using a mixture of ammonium dihydrogen phosphate solution and methanol as the mobile phase and spectrophotometric determination at 254 nm, the approximate retention times for impurities A to E are 0.8, 0.43, 0.43, 0.40, 0.47, and 0.57 times, respectively, with respect to ALB. The

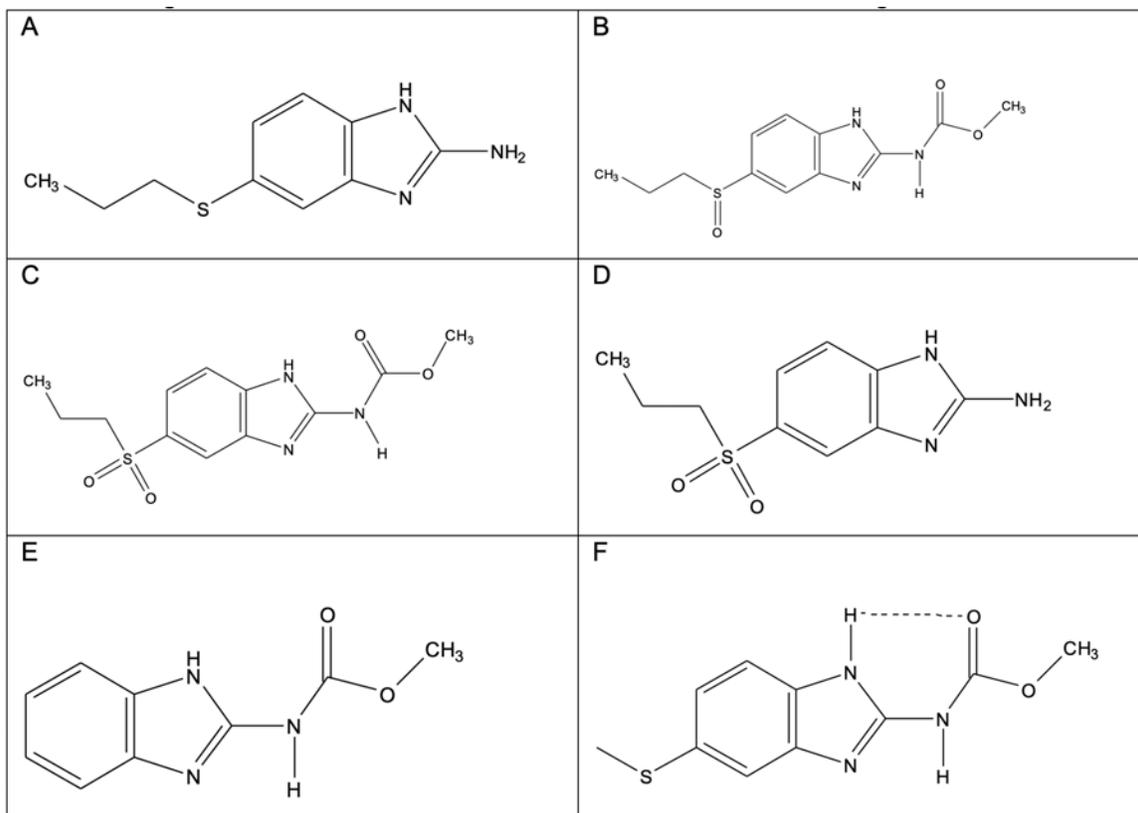
following impurities are listed. Their chemical structures are presented in Figure 18.

- A.** 5-(propylsulfanyl)-1H-benzimidazol-2-amine,
- B.** methyl [5-(propylsulfinyl)-1H-benzimidazol-2-yl]carbamate,
- C.** methyl [5-(propylsulfonyl)-1H-benzimidazol-2-yl]carbamate,
- D.** 5-(propylsulfonyl)-1H-benzimidazol-2-amine,
- E.** methyl (1H-benzimidazol-2-yl)carbamate,
- F.** methyl [5-(methylsulfanyl)-1H-benzimidazol-2-yl]carbamate.

In the chromatogram of test solution, AUC of peaks attributed to any of the impurities A-E should not be more than 1.5 times. The integrated area should not be more than three times the area of the principal peak in the chromatogram obtained with reference solution.

To determine organic impurities, USP and International Pharmacopoeia recommend a thin-layer chromatography method using the albendazole RS as the reference material.

Figure 18. Chemical structure of related substances in ALB drug substance



A number of chromatographic methods have been proposed to determine ALB content in the presence of excipients in dosage form (e.g., oral suspensions and tablets). Representative methods included the following:

1. One method uses a LiChrospher 60 RP select B 125-3 (5 μ m) column and a mobile phase consisting of a mixture of ammonium dihydrogen phosphate solution and methanol (40:60) at a flow rate of 1.3 mL/min, with detection wavelength set at 254 nm and ALB elution time about 5 minutes. It was possible to quantify ALB content in the presence of various excipients (e.g., lactose, and polymers polyvinyl pyrrolidone, hydroxyl propylmethyl cellulose) [19].
2. ALB content was quantified in oral suspensions using HPLC and spectrophotometric methods, and the results were compared. Using the UV method, the absorbance at 230 nm was linearly related to concentration over the range of 2.5 to 7.5 μ g/mL of ALB, with a coefficient of correlation of 0.9995. In the HPLC method, a C18 column (Nucleosil; Phenomenex) was used, and the flow rate was 1.0 mL/min, and the mobile phase was a mixture of methanol and phosphate buffer 0.05 M (pH 5.8) (70:30; v/v). The injection volume was 20.0 μ l, and the absorbance was measured at 254 nm. In this case, a linear correlation was observed between the peak area and the ALB concentration over the range of 0.1 to 15.0 μ g/mL. The study concluded that it is possible to use either of the two methods for the analysis of ALB in oral suspensions [40].
3. ALB content was determined in the presence of cosolvents and surfactants using Lichrosorb RP 18; 200 \times 4.6 mm reverse-phase column. The column was eluted with methanol-water (60:40 v/v), with a flow rate of 1 mL/min and the detector set at 291 nm. The calibration curve was found to be linear in the range of 0-150 μ g/mL. The HPLC method was stability indicating [18].
4. A gradient dilution method for quantifying various benzimidazoles in the presence of excipients was studied. To simultaneously quantify ALB and mebendazole, the influence of pH on separation was observed (the lower the pH, the worse the separation). The following specific chromatographic conditions were identified: Nucleosil C8 5 mm, 250 \times 4.6 mm column; mobile phase A: 85% orthophosphoric acid, water, and acetonitrile (0.05: 75: 25, v/v/v) adjusted to pH 4.5 (with 15% NaOH solution), phase B: a mixture of 8 % orthophosphoric acid, water, and acetonitrile (0.05: 50: 50, v/v/v) adjusted to pH 4.5 (with 15% NaOH solution). The gradient system, used in terms of phase B composition, was 0-7 minutes \rightarrow 0%; 8-9 minutes \rightarrow 0-100%; 10-20

minutes → 100%; 21-22 minutes → 100-0%; 23-25 minutes → 0%. ALB eluted at ~15 minutes. The method can be used for identification and determination of several excipients in suspensions (saccharin, benzenecarboxylic acid, sorbic acid, methyl p-hydroxybenzoate, and propyl p hydroxybenzoate). The method was found to be specific, linear, and accurate for the ALB, fenbendazole, and mebendazole tablets by means of recovery analysis [41].

Assay from Biological Samples

A number of HPLC-based methods have been proposed to determine ALB and its metabolite content in plasma, blood, urine, and milk. A summary of representative methods is presented below:

1. An HPLC assay of ALB for plasma and gastrointestinal (GI) fluid was proposed by Bogan and Marriner (1980). The method involved liquid-liquid extraction and had a recovery of 83 to 100 percent. It had a sensitivity of 20 ng/mL with a 4 mL sample of plasma or GI fluid. The assay was specific for ALB, although it did not quantify ALB metabolites such as ALB sulfoxide or sulfone [42]. The methods were gradually evolved to reduce the sample volume requirement.
2. Another HPLC assay method for quantification of ALB and its principal metabolites in sheep plasma was reported by Alvinerie and Galtier (1984). The method is sensitive, specific, and reproducible using normal phase chromatography with mebendazole as the internal standard and UV detection at 225 nm. Only 100 µl of the sample was used and extracted using ethyl acetate as the extraction solvent. The standard curves in plasma were linear for ALB and its metabolites over the concentration range of 0.1-10 µg/mL. The extraction recovery of ALB, sulphoxide, and sulphone were 78.2%, 84.2%, and 81.2%, respectively [42].
3. Hoaksey et al. reported a sensitive and selective reversed-phase HPLC method for the determination of ALB and its active metabolite, ALB sulphoxide, in human plasma. The method involved single-step extraction of plasma with dichloromethane and separation on a Bondapak phenyl column. The limit of detection was 50 ng/mL for ALB and 20 ng/mL for ALB sulphoxide.
4. A sensitive assay for ALB and sulphoxide determination in plasma and cerebrospinal fluid was proposed. Mebendazole was the internal standard, and an ODS C18 column was used for chromatographic separation (Hurtado et al. 1989). The calibration curve was validated over a concentration range of 30-1000 ng/mL at a wavelength of 295 nm. Extractions were made using

SepPak C18 cartridges. Recovery of ALB and ALB sulphoxide from plasma extracts ranged from 95 to 100 percent.

5. Given the importance of ALB metabolites in its activity, Valois et al. reported a method to determine ALB sulphoxide and sulphone, using a liquid extraction with chloroform-isopropanol, separation on an RP-18 column, and detection at 290 nm.
6. Garcia and coworkers have reported chromatographic conditions for selective quantitative determination of ALB and for sulphoxide and sulphone by using a reversed phase HPLC method with an ODS2 column and two different mobile phases [43].
7. Lanchote et al. developed an HPLC method for the simultaneous determination of ALB sulphoxide enantiomers and sulphone in human plasma. The compounds were extracted from plasma with ethyl acetate, separated on a Chiralpak AD column, and detected by fluorescence. The limits of quantification were 5 ng/mL for both the sulphoxide enantiomers and 1 ng/mL for sulphone.
8. Chiap et al. reported a method for ALB and its metabolites in bovine plasma by liquid chromatography. The method uses dialysis as a purification step, followed by enrichment of the dialysate on a pre-column and liquid chromatography. A gradient elution method was used for separation of the analytes. UV detection was at 295 nm, and the limits of quantification for albendazole and metabolites were 10 and 7.5 ng/mL, respectively.
9. A nonaqueous capillary electrophoresis method for the determination of plasma albendazole and its metabolites was described. The assay uses liquid-liquid extraction with dichloromethane with recovery between 63 and 98 percent. The limit of detection for the three compounds was $8E-7$ M, which is less sensitive than most HPLC methods. ALB was undetectable in all patient samples, and sulphone was below or close to the limit of detection [44].
10. An HPLC method using UV detection (295 nm) was developed for the determination of ALB and its metabolites in human plasma. Analytes were extracted from human plasma by loading onto a conditioned C18 SPE cartridge, rinsing with 15% methanol, and eluting with 90% methanol. Samples were evaporated under a stream of nitrogen, reconstituted with mobile phase [1.25% triethylamine in water-methanol-acetonitrile (72:15:13, v/v/v) (pH 3.1)], and injected

into an HPLC column. The retention times of ALB and its metabolites were approximately 24.4, 7.9, and 13.4 minutes, respectively. The assay was linear for concentration ranges in human plasma of 20-600 ng/mL for ALB, 20-1000 ng/mL for sulphoxide, and 20-300 ng/mL for sulphone [45].

- 11.** A fast (4-minute chromatogram) method of liquid chromatography in tandem with mass spectrometry (LC/MS-MS) was developed to determine simultaneously the plasma levels of ABZ and its metabolite sulphoxide for pharmacokinetic and clinical analysis. Plasma samples were extracted by solid phase extraction using phenacetin as an internal standard. The extracted samples were eluted with a Zorbax XDB-CN column using an isocratic method. The mobile phase, consisting of water with 1% acetic acid (40%, A) and MeOH (60%, B), was used at a flow rate of 1 mL/min. Both the analytes were detected and identified by mass spectrometry with electrospray ionization in the positive ion mode. The method was linear in the range of 5-1000 ng/mL for ABZ and 10-1500 ng/mL for sulphoxide, with a 5 and 10 ng/mL lower limit of quantification for ALB and sulphoxide, respectively [46].
- 12.** An HPLC-tandem mass spectrometry (LC-MS/MS) method was proposed for the analysis of ALB sulfoxide, ALB sulfone, praziquantel, and trans-4-hydroxy-praziquantel in plasma. The plasma samples were prepared by liquid-liquid extraction using dichloromethane as the extracting solvent. The partial HPLC resolution of drug and metabolites was obtained using a cyanopropyl column and a mobile phase consisting of methanol: water (3:7, v/v) plus 0.5% of acetic acid, at a flow rate of 1.0 mL/min. Multi-reaction monitoring detection was performed by electrospray ionization in the positive ion mode, conferring additional selectivity to the method. The quantification limit was 5 ng/mL, and the linear range was 5-2500 ng/mL for all analytes. The method was used for the determination of drug and metabolites in swine plasma samples and proved to be suitable for pharmacokinetic studies [47].

ALB Chewable Tablets

The rationale for development of ALB chewable tablets include improved patient acceptance, especially for pediatric patients, through pleasant taste and patient convenience by eliminating the need of water for swallowing.

USP recognizes and differentiates between two types of chewable tablets:

1. Tablets that may be chewed for ease of administration or may be swallowed in their entirety. The labels include a statement indicating that the tablets *may* be chewed.
2. Chewable tablets that must be chewed and/or crushed before swallowing to avoid choking and to ensure the release of the active ingredient. The label must include a statement indicating that the tablets must be chewed. The label must indicate "Chew or crush tablets completely before swallowing" and, if possible, "Do not swallow tablets whole."

In general, as the required amount of API per tablet gets smaller, the task of arriving at acceptable formulation becomes easier, as a greater number of formulation options is available. Conversely, extremely bad tasting and/or high-dose drugs are difficult to formulate into chewable tablets. With the comparatively high dose of ALB (400 mg), in order to limit pill burden, the selection of the type and amount of diluent becomes critical. Since ALB demonstrated poor flow characteristics, wet granulation followed by compression is the usual strategy for the preparation of its chewable tablets. The other usual challenges associated with chewable tablets must be considered including proper incorporation of the coloring agent, assurance of necessary particle size distribution, maintenance of correct moisture content, and achievement of proper tablet hardness [48].

Quality Specifications for Chewable Tablets

As per the recent FDA quality guidelines [49], a chewable tablet should be (1) easy to chew, (2) palatable (taste masked or of acceptable taste), (3) of appropriate size and shape, and (4) able to disintegrate readily to facilitate dissolution. Critical quality attributes for chewable tablets should include hardness, disintegration, and dissolution, as well as all factors that may influence drug bioavailability and bioequivalence.

In addition to the conventional tablet evaluation, the following additional tests need to be considered with respect to chewable tablets.

Physical appearance: Since the tablets are colored, examination for mottling and other evidence of non-uniform color distribution is necessary. A suitable magnifying glass may be used to appropriately view the sample if needed. For tablets that may be chewed or swallowed whole, the guidance for industry, for size, shape, and other physical attributes of generic tablets and capsules recommends that largest dimension of a tablet intended to be swallowed whole, should not exceed 22 mm.

Hardness: Chewable tablets should be hard enough to withstand packaging and shipping but not so hard as to create undue difficulty upon chewing. FDA recommends that hardness for chewable tablets be kept low (e.g., <12 kp). A higher hardness value (e.g., >12 kp) may be considered if justified. An example of such justification could be demonstrating significant disintegration and/or reduction in hardness of such tablets following brief (approximately 30 seconds) exposure to saliva before chewing. A chewing difficulty index has been proposed to evaluate tablets on a similar scale. The index is the product of tablet thickness and load required to break the tablet using the diametral compression test and a measure of the difficulty of breaking/chewing the chewable tablets.

Disintegration tests: Disintegration tests initially may not appear appropriate for chewable tablets, since these are designed to be chewed before they are swallowed. However, patients (especially pediatric and geriatric) have been known to swallow these chewable dosage forms. This test would thus indicate the ability of tablet to disintegrate and still provide the benefit of the drug if it is accidentally swallowed.

Dissolution tests: Dissolution tests are conventionally used as a quality control tool for checking batch-to-batch uniformity. Chewable tablets should preferably be tested in two forms: intact (in case the dosage form is accidentally swallowed) and partially crushed (to simulate chewing). WHO has recently revised the ALB chewable tablet monograph to include a single point dissolution test at 30 minutes. There is a discrepancy in official requirements with respect to disintegration and dissolution test requirements. Table 7 provides a summary of observations.

Table 7. Summary of observations

Pharmacopoeia	Definition	Requirements
European Pharmacopoeia (Ph. Eur. 8.7)	Chewable tablets are intended to be chewed before being swallowed.	Disintegration test
British Pharmacopoeia (2016)	Chewable tablets are intended to be chewed before being swallowed.	Disintegration test not required
USP 38	“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.’”	Chewable tablets are not required to comply with the disintegration test
Indian Pharmacopoeia (2014)	“Tablets for Use in the Mouth” stated that “where applicable the tablets should be chewed before swallowing.”	No requirement for DT
Chinese Pharmacopoeia (2010)	Chewable tablets are intended to be chewed and then swallowed.	Chewable tablets may not be required to comply with the test for disintegration
The International Pharmacopoeia (Fifth Edition),	Chewable tablets are intended to be chewed before being swallowed; however, where indicated on the label, they may be swallowed whole instead.	Disintegration test (15 min); Dissolution test (single time point at 30 min)

The British Pharmacopoeia (2016) includes the general monograph on ALB tablets 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.

ALB chewable tablets are not included in any pharmacopoeia other than International Pharmacopoeia, which recommends conduction of disintegration and dissolution tests. Investigations suggest that ALB 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 hookworm infections) than those that fail these tests [50]. It is very likely that the efficacy of ALB tablets is compromised if the ingredients are not released from the tablets, so the dissolution test is justifiable.

A recent study by Vogt et al. highlights the importance of commonly used excipients in the formulation in influencing the dissolution behavior of ALB. The dissolution rate of ALB is known to limit its absorption from the gastrointestinal tract. FaSSIF (Fasted State Simulated Intestinal Fluid) increases the solubility of ALB by 60 percent, indicating modest solubilization by bile salt micelles. In this report, the dissolution of physical and coground mixtures of micronized ALB with different excipients in 0.25% SLS solution (in which ALB solubility matches that in simulated intestinal fluid) was studied. Co-grinding with lactose or PVP led to maximum dissolution within 10 minutes, while the physical mixture with lactose dissolved slowly and failed to approach the solubility limit within the experimental period [19]. The result further supported the importance of the formulation excipient and processing in modulating dissolution behavior of API, specifically for a poorly water soluble drug such as ALB. The result also highlights the importance and relevance of conducting a discriminating dissolution test for ALB chewable tablets.

Analytical Method for ALB Chewable Tablets

ALB chewable tablets are not official in USP (USP 29), although for ALB tablets, the RP-HPLC method using ammonium phosphate and methanol as mobile phase is recommended.

As per the International Pharmacopoeia, assay of ALB in chewable tablets may be either by chromatographic or spectrophotometric methods. While the HPLC method uses a mixture of methanol and ammonium phosphate as mobile phase, the second method involves measuring absorbance of solution, prepared from tablet powder and processed, at 308 nm. A summary of the methods is presented below:

- **Spectrophotometric method.** To an accurately weighed quantity of the powdered tablets containing about 20 mg of ALB, 30 mL of hydrochloric acid/methanol (0.1 M) is added, mixed for 15 minutes, and diluted to 50 mL. The

solution is mixed and filtered, and the first 10 mL of the filtrate is discarded. The subsequent filtrate is diluted 50 times its volume with sodium hydroxide (0.1 M). The absorbance of the resulting solution is measured at 308 nm, using sodium hydroxide (0.1 M) as the blank. The standard absorptivity value of 74.2 (A 1%, 1cm) for ALB is recommended to be used for estimation of ALB content.

- **Chromatographic method.** The method uses an HPLC column packed with octadecylsilyl base-deactivated silica gel for chromatography R (5 μ m). The mobile phase is a mixture of aqueous solution of monobasic ammonium phosphate and methanol (3:7).
- A solvent mixture (SM) containing sulfuric acid and methanol (1:99) is prepared. The reference solution is prepared with albendazole RS (1mg/mL) in a mixture of methanol and SM. The test solution is prepared by dissolving the powdered tablets in solvent mixture and filtering. The filtrate is diluted suitably with methanol to achieve a concentration of ALB ~1 mg/mL. Oxybendazole is added to a diluted reference solution for optimizing the resolution. The test is considered valid only when the resolution factor between the peaks due to albendazole and due to oxibendazole is at least 3.0 in a solution containing both. The recommended flow rate is 0.7 mL/min and detector in the ultraviolet spectrophotometer is set at a wavelength of 254 nm. Separately, 20 μ l of solutions are injected, and peak responses from reference and test solutions are used to determine the content of ALB in tablets.

Conclusion

Parasitic infections affect more than a billion people worldwide, many of them children. Albendazole chewable tablets are an effective treatment for the prevention and treatment of soil-transmitted helminthic infections and, in conjunction with ivermectin, for lymphatic filariasis. The present PIR provides background information on albendazole as an API and in formulation as a chewable tablet. No significant stability issues are linked to formulation factors associated with the solid form of the drug. Albendazole is generally available in single stable solid form. Due to its poor solubility and variable bioavailability, there is no clear BCS classification of albendazole. Development of a chewable formulation would need to circumvent ALB's poor flow characteristics, most likely by selection of appropriate excipients. In light of the high drug dose, a suitable formulation needs to be designed, while keeping the "pill burden" to a minimum. A number of chromatographic methods are available for assay of drug content in formulations in the presence of excipients.

There is growing concern in regulatory bodies regarding quality specifications for chewable tablets. As these tablets are, in general, meant to be chewed before swallowing, the applicability of disintegration and dissolution tests is debatable. However, to ensure that the drug is available to perform its desired action, albendazole chewable tablets should be subjected to disintegration and dissolution tests as quality specifications.

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