

# A Study of an Anthelmintic Drug- Albendazole Impurities and it's Chemical Synthesis, Portrayal, Mechanism of Action and Side Effects

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**Abstract:-** The control of drug contaminations is right now a basic intention to the drug business. The worldwide Conference on Harmonization has defined a functional rule with respect to the control of impurities. Albendazole is an expansive range of parasitocidal drug. Albendazole impurity A , Albendazole Impurity B (Albendazole Sulfoxide), Albendazole Impurity C and Albendazole impurity D are metabolic impurities or degradation while contamination E and pollutant F are measure related debasements. Albendazole meddles with the multiplication and endurance of helminths by hindering the arrangement of microtubules from tubulin. This prompts a debilitated take-up of glucose, a consumption of glycogen stores, and results in the worm's passing. Albendazole is utilized in the treatment of canine and pork tapeworm-causing sicknesses, including hydatid infection and neurocysticercosis. Albendazole may likewise be utilized to treat an assortment of other roundworm contaminations. (NCI05)

## Keywords:

1. Albendazole
2. Active /Dynamic pharmaceutical ingredients (API)
3. International/Worldwide Conference on Harmonization (ICH)
4. Impurities
5. Gastrointestinal tract (GI tract)

## I. INTRODUCTION

Human diseases brought about by parasitic worms, address quite possibly the main medical conditions on the planet and have a vital economic effect. In the course of the most recent twenty years, generous advancement has been made in the disclosure and improvement of medications for the treatment of the vast majority of human diseases. (1) As of late, the anticancer impacts of albendazole were moreover researched. The main mode of activity for albendazole is its prohibiting accomplished on tubulin polymerization prompting a diminishing of cytoplasmic microtubules.

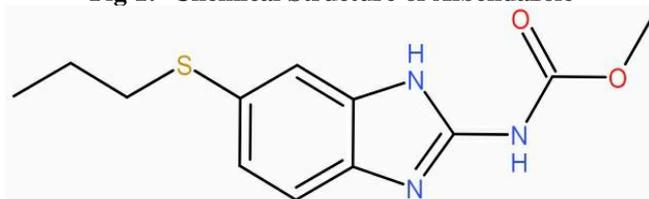
The impurities are undesirable synthetic substances that stay with the dynamic drug fixings (APIs) or create during plan or after maturing of the two API and detailing. The presence of these undesirable synthetic substances even in follow sum may impact the viability and wellbeing of wanted item. Accumulates created because of disintegration of substances of interest or (Active/Dynamic pharmaceutical

ingredients) is frequently called degradation products. (2) It is vital to be worried about these products just as those accomplished by corruption of different mixtures that may similarly be accessible as debasement in the prescription substance. Accordingly, it is prerequisite to consider the debasement profile of the (Active pharmaceutical ingredients) to be utilized in the assembling of medication substance. worldwide conference on harmonization rules suggested distinguishing and portraying all impurity that are available at a degree of 00.010% or more. (3)

Various latest articles have depicted a planned methodology and direction for secluding and distinguishing measure related debasements and degradation items utilizing various spectrometry method. (2)

Albendazole belongs to the class of Benzimidazole which is a Enormous gathering of such anthelmintic medications Broad range of movement against nematode parasitess of the enteric diseases. These anthelmintic drugs incorporate fenbendazoles, mebendazoles and albendazoles which are very much endured in creatures. (6)

**Fig 1:- Chemical Structure of Albendazole**



### 1. Albendazole and its impurity

Albendazole is an anthelmintic or hostile to worm prescription. It forestalls recently incubated unpleasant little animal hatchlings (worms) from creating or duplicating in your body. Albendazole is used to treat certain pollutions achieved by worms, for instance, pork tapeworm and canine tapeworm. Albendazole may hurt an unborn child.(4) Utilize compelling contraception while

Albendazole is oxidized into Albendazole sulfoxide by a liver enzyme. There is no technique is accessible in USP, EP, BP for separation of Albendazole and all the impurities in pharmaceuticals. Particularly in all the strategies including USP and BP impurity B and impurity C of Albendazole are not isolated and detailed by expansion of both the impurities.(1)

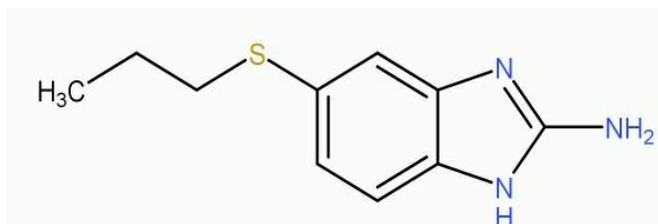
**1.1 Many types of Albendazole Impurities are**

- 1.1.1 Albendazole - Impurity A
- 1.1.2 Albendazole - Impurity B
- 1.1.3 Albendazole - Impurity C
- 1.1.4 Albendazole - Impurity D
- 1.1.5 Albendazole - Impurity E
- 1.1.6 Albendazole - Impurity F

Albendazole Impurity A, Impurity B, Impurity C and Impurity D are degradation or metabolic impurities and where as Impurity E and Impurity F are process related Impurities (5).

**(2.1.1) Albendazole Impurity A**

- I. Chemical Name : Amino Albendazole
- II. Category : Aromatics, heterocycles, metabolites, Pharmaceuticals Standards, intermediates and fine chemicals
- III. Molecular Formula :  $C_{10}H_{13}N_3S$
- IV. Molecular weight : 207.30
- V. Storage : 2-8°C Refrigerator
- VI. Synonyms : 5-(Propylthio)-1H-benzimidazol-2-amine

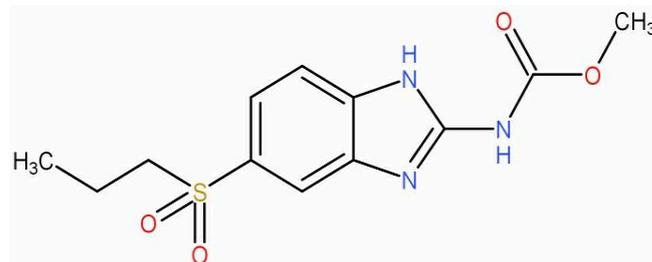
**(2.1.2) Albendazole Impurity B**

- I. Chemical Name : Albendazole Sulfoxide
- II. Category : Metabolites, pharmaceutical standards, intermediates and fine chemicals
- III. Molecular Formula :  $C_{12}H_{15}N_3O_3S$
- IV. Molecular Weight : 281.33
- V. Storage : 2-8°C Refrigerator
- VI. Appearance : White to Off-White Solid
- VII. Synonyms : methyl [5-(propylsulfinyl)-1H-benzimidazol-2-yl]carbamate

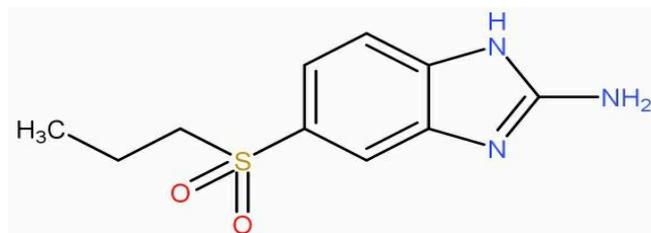
**(2.1.2) Albendazole Impurity C**

- I. Chemical Name : Albendazole Sulfone
- II. Category : Metabolites, Impurities, Pharmaceutical Standards, Intermediates and Fine chemicals
- III. Molecular Formula :  $C_{12}H_{15}N_3O_4S$

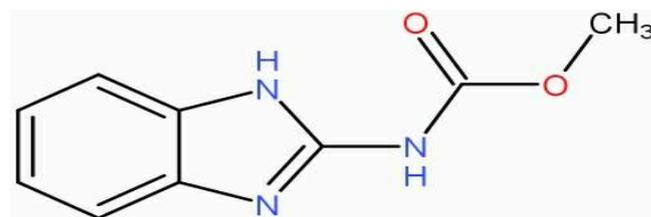
- IV. Molecular Weight : 297.33
- V. Storage : 2-8°C Refrigerator
- VI. Appearance : Yellow Solid
- VII. Synonyms : methyl [5-(propylsulfonyl)-1H-benzimidazol-2-yl]carbamate

**(2.1.4) Albendazole Impurity D**

- I. Chemical Name : Amino Albendazole Sulfone
- II. Molecular Formula :  $C_{10}H_{13}N_3O_2S$
- III. Molecular Mass : 239.29
- IV. Storage : 2-8°C Refrigerator
- V. Appearance : Off-White Solid
- VI. Synonyms : 5-(Propylsulfonyl)-1H-Benzimidazol-2-Amine

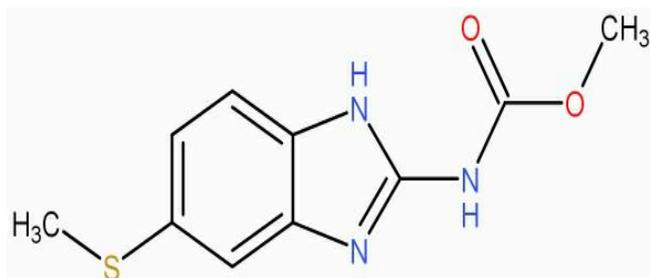
**(2.1.5) Albendazole Impurity E**

- I. Chemical Name : Methyl (1H-benzimidazol-2-yl)Carbamate
- II. Category : amines, heterocycles, pharmaceutical standards, intermediates, fine chemicals
- III. Molecular Formula :  $C_9H_9N_3O_2$
- IV. Molecular Mass : 191.19
- V. Storage : 2-8°C Refrigerator
- VI. Appearance : White Solid

**(2.1.6) Albendazole Impurity F**

- I. Category : Aromatics, Heterocycles, Metabolites, Impurities, Pharmaceutical standards, Intermediates and Fine Chemicals
- II. Molecular Formula :  $C_{10}H_{11}N_3O_2S$
- III. Molecular Mass : 237.28

IV.Storage : 2-8°C Refrigerator



## 2. Impurity Profile

Contamination profile portrays the distinguished and not recognizable debasements present in another medication stuff. Contamination profiling is the basic appellation of a gathering of insightful exercises, the pint from where is the location, distinguishing proof explanation and computable assurance of natural and inanimate pollutions just like leftover dissolvents in mass medications and drug plans. it makes a difference distinguishing the debasement present in drug detailing by logical strategy or techniques.

As indicated by USP Impurity have different segments which are debasements in ceremonial Articleless, standard debasements, and animate Volatiles Impurities. As per Worldwide conference on harmonization debasements happened or delivered by substance unions which are natural contaminations, Inanimate debasement, and leftover dissolvable.(7) There are different wellsprings of debasement like hard ore other stuff like corrupted finished results got during or subsequent to assembling of mass medication or items. The master working gathering of the Worldwide conference on harmonization of specialized necessities for enrollment of drugs for human being utilize usually realized Worldwide conference on harmonization has "characterized contamination is any compound of the therapeutic item which isn't the synthetic element characterized as the dynamic substance or as an excipient in the item".

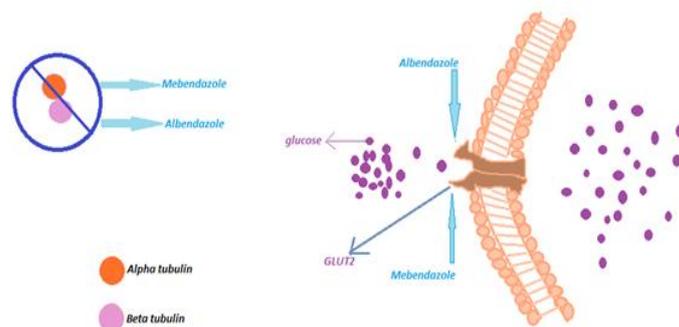
## 3. Mechanism of Action

The main mode of activity for albendazole is its inhibitory impact on tubulin polymerization prompting a diminishing of cytoplasmic microtubules..(8)

Actually microtubules are composed of dimmers made up of by alpha tubulin and beta tubulin. This fusion to form dimmer is inhibited by these drugs. So, on microtubules are formed. It also blocks GLUT-2 transporter. ATP production is decreased resulting in worm immobilization and death.(9)

Mebandazole and Albendazole are used to prevent the binding of alpha tubulin and beta tubulin. So, there is no possibilities formation of dimmer and no microtubules occur.(10)

GLUT-2 transport are blocked by the Mebandazole and Albendazole , there no glucose will be taken to the warm cells.(9)

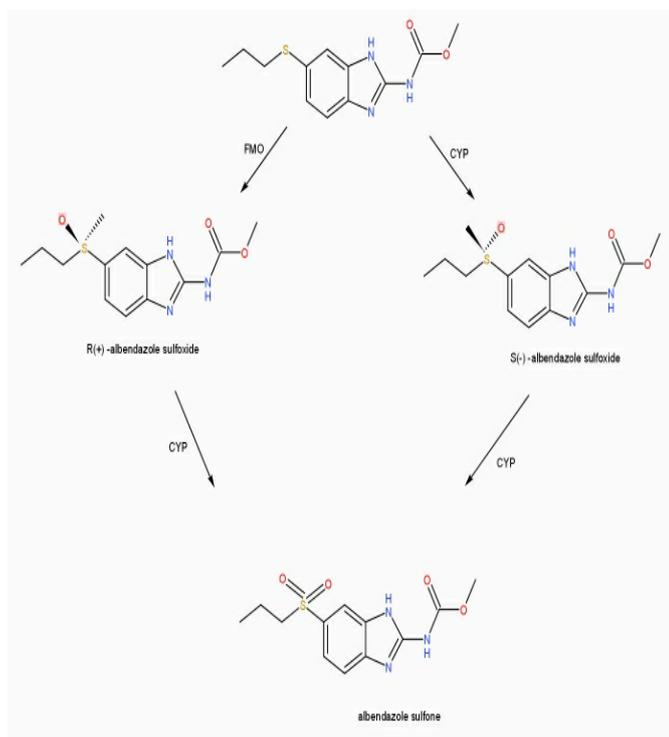


## 4. Pharmacokinetics

Albendazole applied through the mouth shifts among species, of 1-6% of the medication being effectively caught up in people, 25-35% in rodents(11), and half in steers. Retention likewise generally depends upon abdominal pH. Individuals have fluctuating abdominal pHs on void stomachs, and accordingly assimilation starting with one individual then onto the next can shift uncontrollably when taken without food (12). For the most part, the ingestion in the GI tract is not better because of less dissolvability of Albendazole in water (9). It's, not with standing, preferred consumed over other benzimidazole carbamates (13). Food animates gastric corrosive discharge, cutting down the pH and Making albendazole more soluble and in this way more advantageously held.

Pertaining to the mouth retention is peculiarly extended with an oily dinner, as albendazole separates better in fats, permitting it to cut across the fats limit made by the natural liquid superficial of the GI tract (14),(11). To pick out intestinal parasites, albendazole is extract on an unfilled stomach to remain inside the gut. Ingestion is likewise influenced by the measure of the albendazole is debased inside the little stomach related framework by metabolic proteins in the villi. (12),(16)

Albendazole goes through quick first pass digestion taking all things together species, to such an extent that the unaltered medication is imperceptible in plasma. (11) The vast majority of it is corroded into albendazole sulfoxide in the hepatic by cytochrome p4 50 .(17),(18)&(19) In people, the cytochrome p4 50 oxidases are thought to fuse CYP3A4(11).



**Fig:** - General metabolism of albendazole and its sulfoxides.

R(+) enantiomers is generated by the decomposition of Albendazole sulfoxide in presence of FMO, while decay the cytochromes and by specific impetuses and produce S(-), in the gut epithelium. R(+) and S(-) enantiomers is generated by different species in various amounts; people, canines, and highest different class(22) produce the R(+) enantiomer more analyze to the S(-) enantiomer, the R(+) has more noticeable pharmacological development, endures larger entire circulation system, Several albendazole is additionally changed over to Hydroxy albendazole, essentially by CYP 2J2. (23)

### 5. Side effects

The most well-known results of albendazole are:, sophisticated by more than 15% of individuals, migraine and unusual hepatolog capacity. (24) Rise of liver chemicals happen in 18% of patients getting healing explicitly for hydatid illness and disappears when healing closes. (8),(24) The liver chemicals ordinarily increment to two to multiple times the typical levels (a gentle to direct increment). An expected 1–15% of individuals involvement stomach agony, queasiness or heaving, discombobulation or dizziness, expanded within the skull pressing factor, meningeal signs, transitory balding, and fever. The cerebral torment, infection, and spewing are acknowledged to begin with accomplished by the abrupt annihilation, because of genuine aggravation.(26) Less than 5% of individuals get affectability responses (like Allergies), reduced the number of white blood cells (24).

Results can be unmistakable while mending for cyst sickness versus cysticercosis; for instance, Who are being treated in the past will undoubtedly experience raised liver synthetics and stomach torture; those being treated for the last will undoubtedly experience headache.(8) Treating

hydatid infection can likewise expose undiscovered cysticercosis.(8) Individuals accepting Albendazole for the treatment of cysticercosis may have neurological consequences such as seizures, expanded intracranial pressing factor, and central signs brought about by the incendiary response that happens (8)

### 6. Overdose

Due to its low dissolvability, albendazole frequently can't be caught up in adequately high adds up to begin with destructive.(26) Applied through the mouth (Lethal Dose, 50%) by albendazole in the rodents was discovered to be 2,50 mg/kg.(17) It lay hold up multiple times the ordinary portion to kill a sheep, and on various occasions the regular segment to slaughter cattle.(27) Overdose impacts the hepatic, balls. It could be show with laziness, waste of hunger, retching, loose bowels, intestinal issues, dazedness, seizures, and languor. There is no predetermined antitoxin.(28)

### 7. Animal treatment in use

Albendazole is principally utilized in cows and bovidae, yet has discovered not many utilization in cats and canines too Also it is used for beet drone in flightless birds. Also it is used off-name to treat endo drone (hookworms) in cattle.

## II. METHOD AND METHODOLOGY

Albendazole API was incorporated according to literature method. Reaction conditions referenced here are not enhanced and yields are of confined and purified items.

**Albendazole Impurity A** (5-(Propylthio)-1H-benzimidazol-2-amine):-

Charged Albendazole (5g) to the round bottom flask at room temperature and added concentrated sulphuric acid: Water (50mL, 1:1; v/v) to it at R.T. Stirred the reaction mass (r/m) by placing a condenser on its head at 100°C for 10-12 hrs.

Response progress was observed by TLC (Mobile Phase: 100% in Ethyl acetate) and then cooled down the reaction mass (r/m) about to 25-30° C. Added drop wise reaction mass into the ice cold water (150 mL) at R.T in ~1-2h. Stirred the reaction mass at R.T for 30 min.

Reaction mass was basified utilizing Saturated sodium bicarbonate solution (25%, 200mL) and added ethyl acetate to extract the product. Separated the organic layer (Ethyl Acetate) and extracted the aqueous layer with ethyl acetate (5x50 mL),washed the combined organic layer with DM water. Distilled out the solvent below 50°C under vacuum pressure to get crude product residue. Crude product residue was purified by column chromatography and the mobile phase is 30% ethyl acetate in hexane and last 40% ethyl acetate in hexane to get buffed colored solid, yield 46%, 2.3g, HPLC purity 90.5.

**Albendazole Impurity B (Albendazole Sulfoxide):**

Charged Albendazole (5g) to the round bottom flask at room temperature and added methanol: water (50 mL, 1:1; v/v) to it, and then added potassium monopersulfate to it at 5-10°C. Raised the temperature of the reaction mass to 25-30°C in ~ 1h, stirred for 10-12h.

Filter the sample through the filter paper and washed with DM water (25mL), distilled out the filtrate under vacuum to crude product, added methanol and DCM (dichloromethane) (25ml, 1: 9). Solid observed was filtered and filtrate was distilled out under vacuum pressure to get off-white colored solid. Yield 66.34%, 3.317g, HPLC purity 92.45%.

**Albendazole Impurity C (Albendazole Sulfone):**

Charged Albendazole (10g) to the round bottom flask at room temperature and added dichloromethane (DCM) (150 ml) to it, and then added *m*-chloroperbenzoic acid(13g) to it at 5-10°C. Raised the temperature of the reaction mass to 25-30°C in ~ 1h, stirred for 6-8h. Response progress was observed by TLC (Mobile Phase: Hexane and Ethyl Acetate, 1:1).

Distilled out the solvent below 50°C under vacuum pressure to get crude product residue. Crude product residue was purified by column chromatography and the mobile phase is 30% ethyl acetate in hexane and last 50% ethyl acetate in hexane to get off-white solid, yield 78%, 7.8g, HPLC purity 95.7%.

**Albendazole Impurity D (Amino Albendazole Sulfone):**

Charged Albendazole impurity C (5g) to the round bottom flask at the room temperature and added concentrated sulphuric acid: Water (60 ml, 1:1; v/v) to it at R.T. Stirred the reaction mass (r/m) by placing a condenser on its head at 100°C for 10-12 hrs.

Response progress was observed by TLC (Mobile Phase: 100% in Ethyl acetate) and then cooled down the reaction mass (r/m) about to 25-30°C. Added drop wise reaction mass into the ice cold water (200 ml) at R.T in ~1-2h. Stirred the reaction mass at R.T for 30 min. Added ethyl acetate (80 ml) to it to remove the non-polar impurities. Reaction mass (r/m) was basified by utilizing aqueous sodium hydroxide solution (20% ,100 ml) and extracted with ethyl acetate and separated the organic layer (ethyl acetate) from the bottom layer (aqueous layer). Washed the aqueous layer with the small amount of ethyl acetate and separated it.

Combined the organic layer and washed them with DM water, Distilled out the solvent below 50°C under vacuum pressure to get orange colored solid (hygroscopic), yield 55.6%, 2.78g, HPLC purity 95.6%.

**Albendazole Impurity E (Methyl (1H-Benzimidazol-2-yl)carbamate )**

Charged 2-aminobenzimidazole (5g) to the Round Bottom flask at R.T and was added acetone (75 ml) and triethylamine (4.5) to it at the room temperature. Stirred the reaction mass for 20-30 min. at R.T.

Reaction mass was added drop wise in methyl chloroformate (4.25g) at the same temperature, stirred the reaction mass at room temperature for 7-8 h. Reaction progress was observed by TLC (Mobile Phase: 50% ethyl acetate in hexane) and then filtered the sample to get solid, and washed with small amount of acetone (70ml) then with water (30ml). Solid was dried under vacuum to get white colored solid, yield 70%, 3.5g, HPLC purity 99.59%.

**Albendazole Impurity F (Methyl [5-(methylsulphonyl)-1H-benzimidazol-2-yl]carbamate)****Step A: - 2-Nitro-4-thiocyananiline:**

Charged 2-nitroaniline (5g) to the round bottom flask at room temperature and added ammonium thiocyanate (6g) to it and then added into methanol (50ml). Mixture was purged chlorine gas (Created in the research center Potassium permanganate and hydrochloric acid) for 4-5hrs at R.T, Stirred the reaction mass (r/m) for 2-3hrs at the same temperature. Response progress was observed by TLC (Mobile Phase : 20% ethyl acetate in hexane). Added water(50ml) to it and stirred it for 2h at 20-25°C. Filter the sample through filter cloth, washed with water(25ml) and distilled out the filtrate under vacuum to get yellow colored solid. Yield 38%, 3.9g. This was utilized as such for the subsequent Step.

**Step B: - 4-(Methylthio)-2-nitroaniline**

Make solution of 5g in methanol: water (33ml =1:1v) at room temperature and then added NaOH to it at the same temperature. Stirred the reaction mass at 40°C for 1h, now cooled down the reaction mass (r/m) to 10-15°C and added mesityl oxide at the same temperature and then heat the reaction mass up to 40°C and stirred it for 4hrs. Checked the TLC under 20% ethyl acetate in hexane medium (two spots will be observed). Reaction mass cooled to room temperature and then added water (70ml) and ethyl acetate (90ml) to extract the product. For the separation of two spots, reaction mass /product run in column under medium 5% ethyl acetate in hexane. The upper spot moves first and separated into initial fractions. After distillation dark orange (Reddish) solid observed. Yield 70%, 3.5mg. This was utilized as such for the subsequent Step.

**Step C: - 4-(Methylthio)benzene-1,2-diamine**

Charged the solution of 4-(Methylthio)-2-nitroaniline (3g) to the round bottom flask at R.T. and added ethanol (28ml) to it at same temperature. Reaction mass was added into conc. HCl at 10-15°C and stirred it for 10 min. Raised the temperature of reaction mass up to room temperature and added iron (4.5g) to it at same temperature and stirred it for 4-5h at the same temperature. Checked the TLC in 20% ethyl acetate in hexane. Added ethyl acetate: water (100ml, 1:1V), and basified by using NaOH pellets (5.1g).

Separated the organic layer from the aqueous layer and combined the organic layer and distilled out the organic layer under vacuum pressure to get brown colored solid, yield 86%, 2.6g. This was utilized as such for the subsequent Step.

**Step D: - Methyl-N-cyanocarbamate sodium salt:**

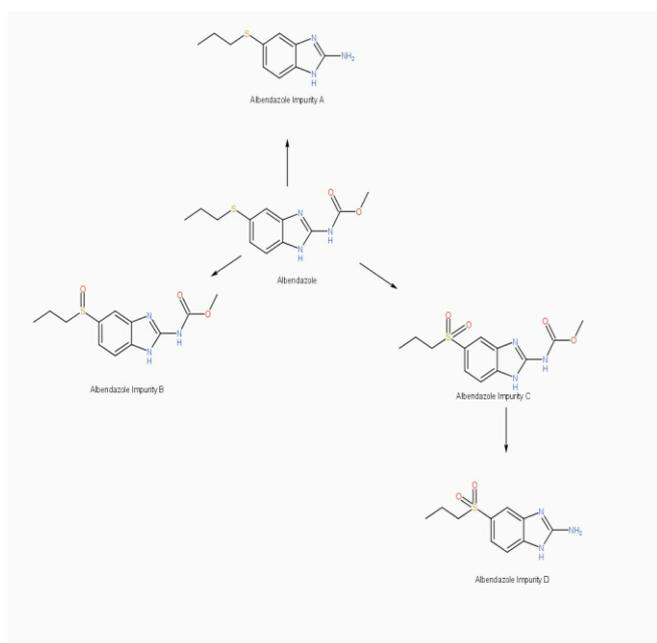
Charged Cyanamide (5g) to the round bottom flask at R.T. and added water (18ml) to it at the same temperature. It was added methyl chloroformate (7.5g) and sodium hydroxide (6.8 g) was added at the same time while keeping up temperature under 10°C and pH 7-7.5. After addition was finished pH was maintained to 8-8.5 utilizing aqueous sodium hydroxide solution. Stirred the reaction mass for 2-3hrs at 10-15°C. Distilled out the solvent under reduced pressure to get white solid, yield 90%, 11.2g. This was utilized as such for the subsequent Step.

**Step E: - Methyl [5-(methylthio)-1H-benzimidazole-2-yl]carbamate:**

Charged the solution of 4-(Methylthio)benzene-1,2-diamine (2.6g) to the round bottom flask at R.T. an added acetone (25ml) and water (3ml) to it at same temperature. Reaction mass was added in conc. HCl (6.5 ml) at room temperature. Stirred the reaction mass (r/m) for 3-4hrs at 80-85°C. Response progress was observed by TLC (Mobile Phase: 80% ethyl acetate in hexane. Reaction mass was acidified by using conc. HCl to pH 4.0-6.7. Filter the sample through filter cloth and washed with water (20 ml) and ethyl acetate (15 ml). Blue colored solid observed, yield 69%, 1.8g and HPLC purity 91.68%.

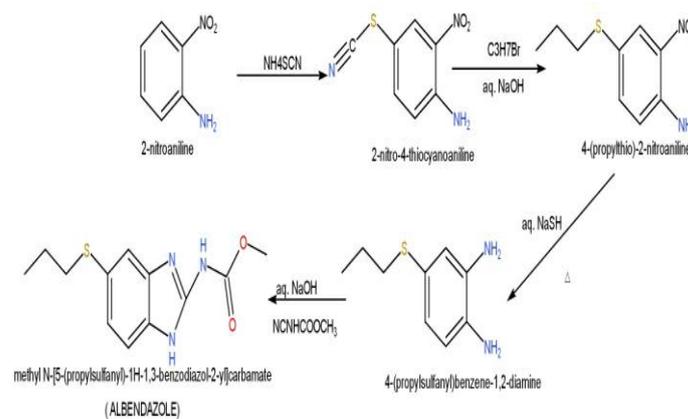
### III. RESULT AND DISCUSSION

Albendazole Impurities according to EP monograph are expected to combine separately in pure structure. The scope of the present work is to synthesize these impurities.

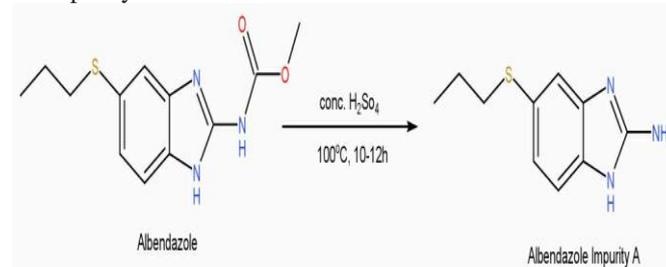


**Fig: Metabolic Impurities**

Albendazole was synthesized, when 2 nitroaniline reacted with ammonium thiocyanate followed by S-alkylation and then it form 2-nitro-4-thiocyno aniline, treat it with n-propyl bromide under basic condition and form 4-(propylthio)-2-nitroaniline and after that reduced it by using sodium hydrosulfide gives 4-(propylsulfanyl)benzene-1,2-diamine and then treat it with methyl-N-cyano carbamate yields Albendazole.

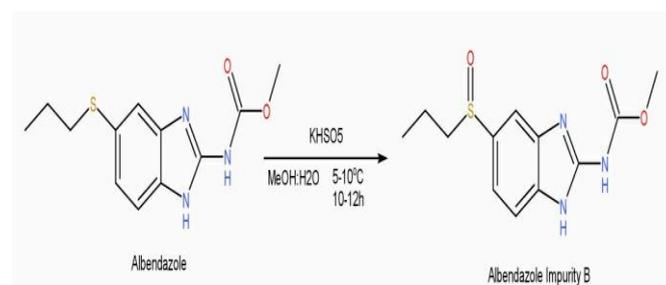


When Albendazole reacted with conc. Sulphuric acid and heated at its reflux temperature To get compatible amine as impurity A.

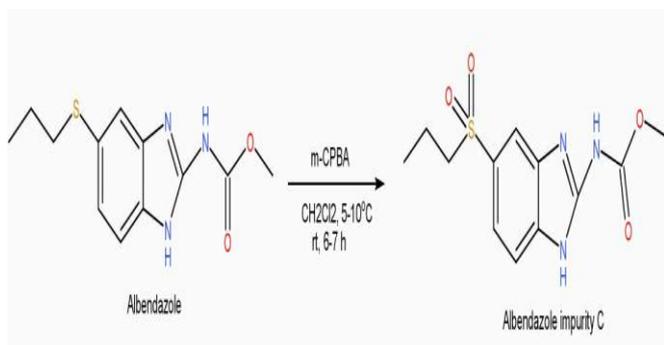


Albendazole quickly changed over in the liver to the essential metabolite, albendazole sulfoxide, (Albendazole impurity B) which is additionally used to albendazole sulfone ( Albendazole impurity C) and other essential oxidative metabolites that have been recognized in human urine.

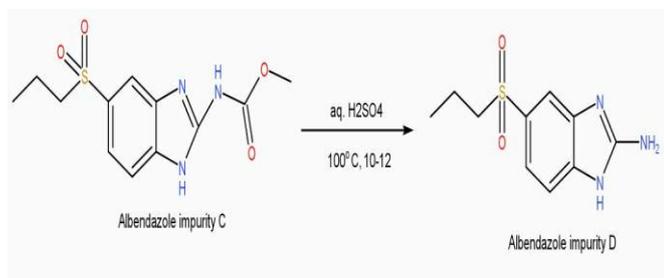
Oxidation of Albendazole when it reacted with potassium monopersulfate in the aqueous methanol at 5-10 degree Celsius and R.T to get Albendazole Impurity B (Albendazole sulfoxide).



Oxidation of Albendazole when it reacted with meta-chloroperbenzoic acid (m-CPBA) in DCM (dichloromethane) at 5-10 degree Celsius and R.T for 6-7 h to get Albendazole impurity C (Albendazole Sulfone).

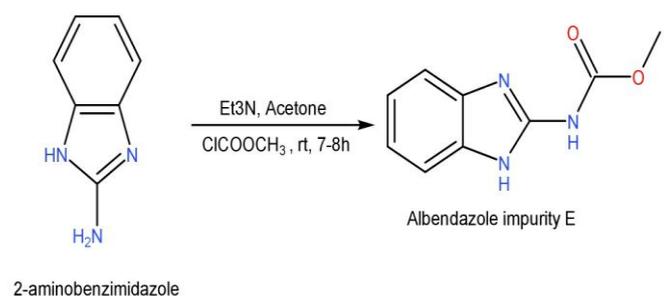


When Albendazole Impurity C (Albendazole Sulfone) reacted with conc. Sulphuric acid and heated at its reflux temperature for 6-7 h To get compatible amine as impurity D, 5-(propylsulfonyl)- 1H-benzimidazol-2-amine.

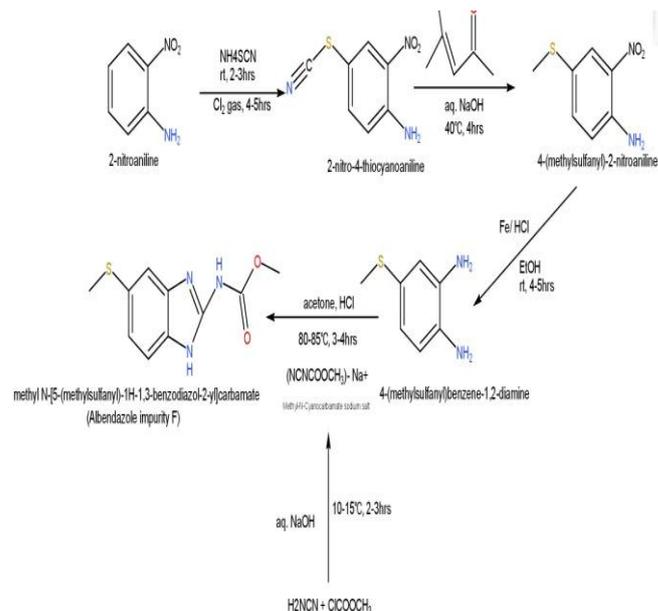


Albendazole Impurity E and Albendazole Impurity F are process related Impurities.

Albendazole Impurity E (Methyl (1H-Benzimidazol-2-yl)carbamate ) was synthesized, when 2-aminobenzimidazole reacted with methyl chloroformate under basic condition.



Methylthio simple of albendazole is impurity F (Methyl [5-(methylsulphonyl)-1H-benzimidazol-2-yl]carbamate) was synthesized, when 2 nitroaniline reacted with ammonium thiocyanate followed by S-alkylation and then it form 2-nitro-4-thiocyano aniline, treat it with mesityl oxide in basic condition gives 4-(methylsulfonyl)-2-nitroaniline and then reduced it by using Fe/HCl to give 4-(methylthio)benzene-1,2-diamine and treat it with methyl-n-cyanocarbamate sodium salt to form methyl [5-(methylthio)-1H-benzimidazol-2-yl]carbamate (Albendazole impurity F).



#### IV. CONCLUSION

Albendazole Impurities according to EP monograph are expected to combine separately in pure structure . Albendazole is a benzimidazole created more than 20 years prior. It is thought to act by restricting to parasite - tubulin, hindering its polymerization and disabling glucose take-up. Albendazole is at first oxidized to albendazole sulphoxide, a functioning medication, and afterward further oxidized to albendazole sulphone, which is latent. Albendazole has in significant job in the treatment of cestode (for example tapeworm) diseases. In a multicentre preliminary including 112 patients with hydatid sickness caused by Echinococcus granulosus, albendazole demonstrated more viable than mebendazole.

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