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A COMPARATIVE STUDY OF DIFFERENT MARKETED FORMULATIONS OF ALBENDAZOLE

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ABSTRACT

The objective of present study is to have comparative study of different marketed formulations of Albendazole. Albendazole is an anthelmintic (an-thel-MIN-tik) or anti-worm medication. It prevents newly hatched insect larvae (worms) from growing or multiplying in the body. There are different types of formulations**. Albendazole chewable tablets** were prepared by wet granulation method using two superdisintegrants such as croscarmellose sodium and sodium starch granules were evaluated for precompression parameters such as angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The formulated tablets were evaluated for diameter, thickness, hardness weight variation, friability, disintegration and drug content**. Fast dissolving tablet** of Albendazole was design with a view to and provide a quick onset of action. The main objective of the study fast dissolving tablets of Albendazole to achieve a better dissolution rate and further improving the bioavailability of the drug. It pre-compression parameters. The formulation of **Albendazole Suspension** is developed on the basis of three trials in which Xanthan gum, Sodium CMC, Sorbitol, Sugar are used in different concentration and also in combination. Evaluation done on the basis el **Albendazole Nanosuspension** was prepared by solvent diffusion technique followed by sonification. glycolate. A total of eight formulations were prepared and the 1 direct compression and using super disintegrants in different concentration and evaluated for the of the parameters ike Redispersability, Sedimentation, Odor Taste Surfactants plays an important role in the preparation of nanosuspensions. Tween 60 and Sodium Lauryl Sulphate are selected as surfactant which plays a vital role in the preparation of nanosuspensions. Different concations

are taken as a formulation variable in the preparation. The prepared nanosuspensions are evaluated for particle size, charge, morphology and solubility.

KEYWORDS: Albendazole, Chewable Tablets, Fast Dissolving Tablets, Suspensions and Nano-Suspensions.

INTRODUCTION

Albendazole is an anthelmintic (an-thel-MIN-tik) or anti-worm medication. It prevents newly hatched insect larvae (worms) from growing or multiplying in the body. Albendazole is used to treat certain infections caused by worms such as pork tapeworm and dog tapeworm. Albendazole, also known as albendazolum, is a medication used for the treatment of a variety of parasitic worm infestations.[1] It is useful for giardiasis, trichuriasis, filariasis, neurocysticercosis, hydatid disease, pinworm disease, and ascariasis, among others. It is taken orally.

Anthelmintics or antihelminthics are a group of antiparasitic drugs that expel parasitic worms (helminths) and other internal parasites from the body by either stunning or killing them and without causing significant damage to the host. They may also be called vermifuges (those that stun) or vermicides (those that kill). Anthelmintics are used to treat people who are infected by helminths, a condition called helminthiasis. These drugs are also used to treat infected animals. Pills containing anthelmintics are used in mass deworming campaigns of school-aged children in many developing countries.[2] The drugs of choice for soil-transmitted helminths are mebendazole and albendazole[3]; for schistosomiasis and tapeworms it is and praziquantel.[4]

TYPES

Antiparasitics that specifically target worms of the genus **Ascaris** are called **ascaricides.**

Benzimidazoles

Albendazole – effective against **threadworms, roundworms, whipworms, tapeworms, hookworms.**

Mebendazole – effective against various nematodes.

Thiabendazole – effective against various nematodes.

Fenbendazole – effective against various parasites.

Triclabendazole – effective against **liver flukes**.

Flubendazole – effective against most intestinal parasites.

Abamectin (and by extension **ivermectin**) - effective against most common intestinal worms, except tapeworms, for which **praziquantel** is commonly used in conjunction for mass dewormings.

Diethylcarbamazine – effective against **Wuchereria bancrofti, Brugia malayi, Brugia timori, and Loa loa.**

Pyrantel pamoate – effective against most nematode infections residing within the intestines

Levamisole

Salicylanilide – mitochondrial un-couplers (used only for flatworm infections):

Niclosamide

Oxyclozanide

Nitazoxanide – readily kills **Ascaris lumbricoides**,[5] and also possess antiprotozoal effects.

Praziquantel – effective against **flatworms** (e.g., tapeworms and **schistosoma**)

Octadepsipeptides (e.g. **Emodepside**) – effective against a variety of gastrointestinal helminths

Monepantel (aminoacetonitrile class) - effective against a variety of nematodes including those resistant to other anthelmintic classes

Spiroindoles (e.g. **derquantel**) - effective against a variety of nematodes including those resistant to other anthelmintic classes

Artemisinin – shows anthelmintic activity.

ANTHELMINTIC RESISTANCE

The ability of parasites to survive treatments that are generally effective at the recommended doses is a major threat to the future control of worm parasites in small ruminants and horses. This is especially true of nematodes, and has helped spur development of aminoacetonitrile derivatives for treatment against drug-resistant nematodes, as well as exploration of doxycycline to kill their endosymbiotic Wolbachia bacteria. The resistance is measured by the "fecal egg count reduction" value which varies for different types of helminths.[6] Treatment with an antihelminthic drug kills worms whose phenotype renders them susceptible to the drug, but resistant parasites survive and pass on their "resistance" genes. Resistant varieties accumulate, and treatment failure finally occurs.

Brand Names

Albenza,[7] Alworm, Andazol, Eskazole, Noworm, Zentel, Alben-G, ABZ, Cidazole, Wormnil etc.

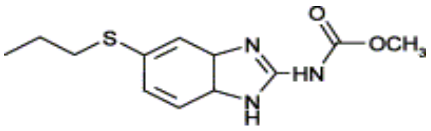
Cost

In many areas of the world it costs between US$0.01 and US$0.06 per dose. In the United States, however, it costs about US$50 per dose, as of 2014.[8]

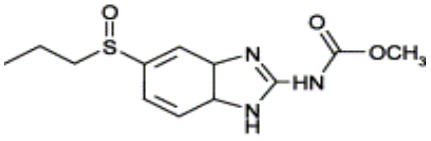
HISTORY

Smith Kline & French Animal Health were working on albendazole, which was first marketed as Valbazen, an animal anthelminth, in the UK in November of 1977. Albendazole was found to be considerably more active than other benzimidazoles. This was because it was metabolized to albendazole sulphoxide which was also an active anthelminthic, while almost all the other BZs were metabolized to inactive compounds. It was eventually approved for human use and marketing in 1987 (Horton, J). Albendazole, patented in 1975, was invented by Robert J. Gyurik and Vassilios J. Theodorides and assigned to Smith Kline Corporation. It was introduced in 1977 as an antihelminthic for sheep in Australia, and was registered for human use in 1982.

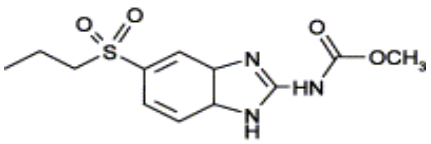
STRUCTURE



Albendazole (ABZ)



Albendazole sulphoxide (ASOX)



Albendazole sulphone (ASON)

DAYAN 2003

The structure of albendazole is (5-(propylthio)-1H-benzimidazol-2-yl)carbamic acid methyl ester (Dayan, 2003). Its molecular formula is C12H15N3O2S and its molecular weight is 265.34 (GlaxoSmithKline). It is relatively insoluble in water and most organic solvents, making it poorly absorbed in the GI tract. After absortion, albendazole is rapidly converted in the liver to the primary metabolite, albendazole sulfoxide, which is generally considered to be the form responsible for the therapeutic activity of albendazole. Albendazole sulfoxide is further metabolized to albendazole sulfone and other primary oxidative metabolites and is excreted from the body (Dayan, 2003).

PHARMACOLOGY

Albendazole is found to inhibit the polymerization of the parasite tubulin into microtubules. There is a higher affinity of albendazole to the parasite tubulin and so the activity is mediated mainly against the parasite rather than on the host. The loss of the cytoplasmic microtubules leads to impaired uptake of glucose by the larval and adult stages of the parasites. The worm is then unable to maintain energy production, which leads to immobilization and eventual death (Dayan, 2003). A secondary acton of albendazole may be the be the inhibition of the enzyme fumarate reductase, which is helminth-specific (PharmGKB).

As a vermicide, albendazole causes degenerative alterations in the intestinal cells of the worm by binding to the colchicine-sensitive site of β-tubulin, thus inhibiting its polymerization or assembly into microtubules (it binds much better to the β-tubulin of parasites than that of mammals). Albendazole leads to impaired uptake of glucose by the larval and adult stages of the susceptible parasites, and depletes their glycogen stores. Albendazole also prevents the formation of spindle fibers needed for cell division, which in turn blocks egg production and development; existing eggs are prevented from hatching. Cell motility, maintenance of cell shape, and intracellular transport are also disrupted. At higher concentrations, it disrupts the helminths' metabolic pathways by inhibiting metabolic enzymes such as malate dehydrogenase and fumarate reductase, with inhibition of the latter leading to less energy produced by the Krebs cycle. Due to diminished ATP production, the parasite is immobilized and eventually dies.

Some parasites have evolved to have some resistance to albendazole by having a different set of acids comprising β-tubulin, decreasing the binding affinity of albendazole. Drosophilia have many of the same mutations, meaning the drug does not affect fruit flies.

PHARMACOKINETICS

Oral absorption of albendazole varies among species, with 1–5% of the drug being successfully absorbed in humans, 20–30% in rats, and 50% in cattle. The absorption also largely depends on gastric pH. People have varying gastric pHs on empty stomachs, and thus absorption from one person to another can vary wildly when taken without food. Generally, the absorption in the GI tract is poor due to albendazole's low solubility in water. It is, however, better absorbed than other benzimidazole carbamates. Food stimulates gastric acid secretion, lowering the pH and making albendazole more soluble and thus more easily absorbed. Oral absorption is especially increased with a fatty meal, as albendazole dissolves better in lipids, allowing it to cross the lipid barrier created by the mucus surface of the GI tract. To target intestinal parasites, albendazole is taken on an empty stomach in order to stay within the gut. Absorption is also affected by how much of the albendazole is degraded within the small intestine by metabolic enzymes in the vili. The pharmacokinetics of albendazole differ slightly between men and women: women have a lower oral clearance and volume of distribution, while men have a lower serum peak concentration.

Albendazole undergoes very fast 1st-pass metabolism in all species, such that the unchanged drug is undetectable in plasma. Most of it is oxidized into albendazole sulfoxide (also known as ricobendazole and albendazole oxide in the liver by cytochrome P450 oxidases (CYPs) and a flavin-containing monooxygenase (FMO), which was discovered later. In humans, the cytochrome P450 oxidases are thought to include CYP3A4[9] and CYP1A1, while those in the rats are thought to be CYP2C6 and CYP2A1.[10]

USES

Albendazole is an effective treatment for.

Flatworms

Fasciolosis

Cestodes (tapeworms), as an alternative to praziquantel or niclosamide for adult beef tapeworms (Taenia saginata) and as an alternative to praziquantel for pork tapeworms (T. solium). It is also given for infections by T. crassiceps. Though praziquantel is often better at treating tapeworm infections, albendazole is used more often in endemic countries due to being cheaper and having a broader spectrum.

Cysticercosis (especially neurocysticercosis), which is caused by the larval form of the pork tapeworm (i.e. albendazole is the drug of choice for larval pork tapeworms, but not adult pork tapeworms). Old cysts are not affected.

Hydatic Disease (aka echinococcosis) of the liver, lung, and peritoneum (caused by the larval form of the dog tapeworm, Echinococcus granulosus) or of the alveoli (caused by E. multilocularis) when surgical excision is not possible. Some suggest that alveolar and cystic echinococcosis require lifelong treatment with albendazole, which only prevents the parasites from growing and reproducing rather than killing them outright.

Nematodes

Ascariasis, which can be cured with a single dose of albendazole.

Baylisascariasis, caused by the **raccoon roundworm**. **Corticosteroids** are sometimes added in cases of **eye** and **CNS infections**.

Enterobiasis (pinworm infection)

Filariasis; since albendazole's disintegration of the **microfilarie** ("pre-larva") can cause an allergic reaction, **antihistamines** or **corticosteroids** are sometimes added to treatment. In cases of **lymphatic filariasis (elephantiasis)** caused by **Wuchereria bancrofti** or **Brugia malayi**, albendazole is sometimes given as an adjunct to **ivermectin** or **diethylcarbamazine** in order to suppress microfilaremia.

Gnathostomiasis when caused by **Gnathostoma spinigerum**. Albendazole has a similar effectiveness to ivermectin in these cases, though it needs to be given for 21 days rather than the 2 days needed for ivermectin.

Hookworm Infections, including **cutaneous larva migrans** caused by hookworms in the genus **Ancylostoma**. A single dose of albendazole is sufficient to treat intestinal infestations by **A. duodenale** or **Necator americanus**

Intestinal capillariasis, as an alternative to mebendazole

Mansonelliasis when caused by Mansonella perstans. Albendazole works against the adult worms but not against the younger microfilariae.

Oesophagostomumiasis, when caused by **Oesophagostomum bifurcum**

Strongyloidiasis, as an alternative to ivermectin or thiabendazole. Albendazole can be givenwith diethylcarbamazine to lower microfilaremia levels.

Toxocariasis, also called "visceral larva migrans", when caused by the dog roundworm Toxocara canis or cat roundworm T. catis. Corticosteroids can be added in severe cases, and surgery might berequired to repair secondary damage.

Trichinosis, when caused by **Trichinella spiralis** or T.pseudospiralis. Albendazole has a similar efficacy to thiabendazole, but fewer side effects. It works best when given early, acting on the adult worms in the intestine before they generate larva that can penetrate the muscle and cause a more widespread infection. Corticosteroids are sometimes added on to prevent inflammation caused by dying larva.

Trichostrongyliasis, as an alternative to pyrantel pamoate. A single dose is sufficient for treatment.

Trichuriasis (whipworm infection), sometimes considered as an alternative to **mebendazole**. Only a single dose of albendazole is needed. It can also be given with ivermectin.

Giardiasis, as an alternative or adjunct to metronidazole, especially in children.

Microsporidiosis, including ocular microsporidiosis caused by Encephalitozoon hellem or E.cuniculi, when combined with topical **fumagillin Granulomatous amoebic encephalitis**, when caused by the ameba Balamuthia mandrillaris, in combination with miltefosine and fluconazole.

Arthropods

Crusted scabies, when combined with topical **crotamiton** and **salicylic acid Head lice** infestation, though ivermectin is much better.

Intestinal myiasis

Though albendazole is effective in treating many diseases, it is only FDA-approved for treating hydatid disease caused by dog tapeworm larvae and neurocysticercosis caused by pork tapeworm larvae.

SIDE EFFECTS

Along with its needed effects, albendazole may cause some unwanted effects. Although not all of these side effects may occur, if they do occur they may need medical attention. Check with your doctor immediately if any of the following side effects occur while taking albendazole.

Less Common:- Fever.

Rare:- Black, tarry stools**,** bleeding gums**,** blood in the urine or stools**,** chest pain**,** chills**,** cough**,** painful or difficult urination**,** pinpoint red spots on the skin**,** sores, ulcers, or white spots on the lips or in the mouth**,** swollen glands**,** unusual bleeding or bruising**,** unusual tiredness or weakness.

Some side effects of albendazole may occur that usually do not need medical attention. These side effects may go away during treatment as your body adjusts to the medicine. Also, your health care professional may be able to tell you about ways to prevent or reduce some of these side effects. Check with your health care professional if any of the following side effects continue or are bothersome or if you have any questions about them.

More common:- Stomach Pain

Less common:- Nausea

Rare:- Dizziness, thinning or loss of the hair

Incidence not known:- Lack or loss of strength

General

Side effects differed between hydatid disease and neurocysticercosis. Symptoms were generally mild and resolved without treatment. Therapy was discontinued primarily due to leukopenia (0.7%) or hepatic abnormalities (3.8% in hydatid disease).

Hepatic

Very Common (10% or more): Elevated liver enzymes (up to 16%)

Uncommon (0.1% to 1%): Hepatitis

Frequency not reported: Hepatotoxicity, hepatic abnormalities, jaundice, hepatocellular damage

Postmarketing reports: Acute liver failure

Nervous System

Very common (10% or more): Headache (up to 11%)

Common (1% to 10%): Raised intracranial pressure, dizziness, neurological events.

Uncommon (0.1% to 1%): Vertigo, meningeal signs.

Gastrointestinal

Common (1% to 10%): Epigastric/abdominal pain, nausea, vomiting, upper gastrointestinal (GI)symptoms, GI disturbances.

Uncommon (0.1% to 1%): Diarrhea.

Rare (less than 0.1%): Pancreatitis. Upper GI symptoms (e.g., epigastric/abdominal pain, nausea, vomiting) and GI disturbances (abdominal pain, nausea, vomiting) were reported.

Diarrhea has also been reported during postmarketing experience.

Dermatologic

Common (1% to 10%): Reversible alopecia (thinning of hair, moderate hair loss).

Uncommon (0.1% to 1%): Itchiness, skin rashes.

Postmarketing reports: Erythema multiforme, Stevens-Johnson syndrome.

Reversible alopecia (thinning of hair and moderate hair loss) has also been reported during postmarketing experience.

Fever has also been reported during postmarketing experience.

Common (1% to 10%): Fever, hyperpyrexia

Postmarketing reports: Asthenia

Hematologic

Agranulocytosis and **pancytopenia** have also been reported during postmarketing experience.Patients with **liver disease** (including hepatic echinococcosis) appeared more susceptible to bone marrow suppression.

Common (1% to 10%): Leukopenia

Rare (less than 0.1%): Low red cell count, pancytopenia, thrombocytopenia

Frequency not reported: Granulocytopenia, agranulocytosis

Postmarketing reports: Aplastic anemia, bone marrow suppression, neutropenia.

Hypersensitivity

Uncommon (0.1% to 1%): Hypersensitivity reactions (including rash, pruritus, urticaria)

OVERDOSE

Because of its low solubility, albendazole often cannot be absorbed in high enough quantities to be toxic. The oral LD50 of albendazole in rats was found to be 2,500 mg/kg. It takes 20 times the normal dose to kill a sheep, and 30 times the normal dose to kill cattle. Overdose affects the liver, testicles, and GI tract the most. It can manifest with lethargy, loss of appetite, vomiting, diarrhea, intestinal cramps, dizziness, convulsions, and sleepiness. There is no specified antidote.

INTERACTION

The antiepileptics carbamazepine, phenytoin, and phenobarbital lower the plasma concentration and the half life of albendazole sulfoxide's R(+) enantiomer.[11]

The antacid cimetidine heightens serum albendazole concentrations, increases the half life of albendazole, and doubles albendazole sulfoxide levels in bile. It was originally thought to work by increasing albendazole bioavailability directly; however, it is now known that cimetidine inhibits the breakdown of albendazole sulfoxide by interfering with CYP3A4. The half-life of albendazole sulfoxide thus increases from 7.4 hours to 19 hours. This might be a helpful interaction on more severe cases, because it boosts the potency of albendazole. Paradoxically, cimetidine also inhibits the absorption of albendazole by reducing gastric acidity.

Several other interactions exist. Corticosteroids increase the steady-state plasma concentration of albendazole sulfoxide; **dexamethasone**, for example, can increase the concentration by 56% by inhibiting the elimination of albendazole sulfoxide. The anti-parasitic **praziquantel** increases the maximum plasma concentration of albendazole sulfoxide by 50%, and the anti-parasitic levamisole increases the AUC (total drug exposure) by 75%. Grapefruit inhibits the metabolism of albendazole within the intestinal mucosa. Finally, long-term administration of the anti-retroviral ritonavir, which works as a CYP3A4 inhibitor, decreases the maximum concentration of albendazole in the plasma as well as the AUC.

FORMULATIONS

1. **ALBENDAZOLE CHEWABLE TABLETS**
2. **ALBENDAZOLE FAST DISSOLVING TABELETS**
3. **ALBENDAZOLE SUSPENSIONS**
4. **ALBENDAZOLE NANO-SUSPENSIONS**

1. ALBENDAZOLE CHEWABLE TABLETS

INTRODUCTION

Chewable tablets are designed for use by the children and such persons who may have difficulty in swallowing the tablets. These are intended to be chewed in the mouth prior to swallowing and are not intended to be swallowed intact. Additionally, chewable tablets facilitate more rapid release and hence more rapid absorption of active ingredients and

provide quick onset of action. Hence it was decided to formulate Albendazole chewable tablet to improve the compliance in children and to improve the solubility and dissolution. Albendazole (ABZ) is benzimidazole derivative that has been widely used in the treatment of worm infestations in both humans and animals. Albendazole is widely employed in the treatment of intestinal nematode infection. Albendazole has low water solubility, limiting its oral absorption and resulting in a lower bioavailability. The main objectives of the present study were to formulate and evaluate Albendazole chewable tablet dosage form at the dose of 400 mg using two superdisintegrants such as croscarmellose sodium and sodium starch glycolate and to study the various formulation variables that affect the drug release.

METHODS

Preparation of Albendazole Chewable Tablets

Chewable tablets containing 400 mg Albendazole were prepared with a total tablet weight of 1000 mg by wet granulation method. Quantity of Albendazole and excipients are given. Albendazole was sifted through #30 mesh and all other ingredients were sifted through #40 mesh. Albendazole, maize starch, lactose monohydrate, microcrystalline cellulose (MCC) and sodium lauryl sulfate (SLS) were loaded into Rapid Mixer to get a dry mix. Povidone K-30 and sunset yellow supra were dissolved in purified water to get a binder. Then the above dry mix was granulated with binder solution and dried in the rapid drier at 60o C. The dried granules were passed through #30 mesh. Then the granules were mixed with croscarmellose sodium (CCS), sodium starch glycolate (SSG), sodium saccharin, orange flavour and peppermint flavour in a granulator for 10 minutes. After that the granules are lubricated with magnesium stearate and aerosil and mixed for 2 minutes. The lubricated blend was compressed into tablets by using 19.2X8.9 mm punch oval shape and break line on one surface to get a tablet of the 1000 mg weight on a 8-station single rotary tablet machine.

EVALUATION OF TABLETS

General Appearance, Diameter And Thickness[12]

The general appearance of all tablets, its visual identity and overall elegance is essential for consumer acceptance. The formulated chewable tablets were evaluated for size, shape, organoleptic characters such as, colour, odor and taste. The diameter and thickness of the tablets were measured by using Vernier caliper.

Hardness

Hardness is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The hardness was measured using Monsanto Hardness tester. The values were expressed in Kg/cm2.

Weight Variation

Twenty tablets of each formulation were selected at random and weighed individually. The weight of individual tablets was noted. Average weight was calculated and the individual weights were compared with the average weight. The weight of not more than two tablets must not deviate from the average weight by more than 5%.

Friabilit[13]

The friability of tablets were determined by using Roche Friabilator. Ten tablets were weighed and placed in friabilator and rotated at 25 rpm for 4 minutes. Then the tablets were taken out, dusted and reweighed. The percentage friability of the tablets were calculated by the formula.

PERCENTAGE FRIABILITY = [(INITIAL WEIGHT – FINAL WEIGHT)/ INITIAL WEIGHT] × 100

Disintegration Time

Disintegration test was carried out by using Disintegration test apparatus. One tablet is placed in each tube, and the basket rack was positioned in a 1-litre beaker of water, at 37°C ±2°C. A standard motor-driven device is used to move the basket assembly containing the tablets up and down through a distance of 5 to 6cm at a frequency of 28 to 32 cycles per minutes. The time taken for the tablet to disintegrate completely was noted.

Drug Content Estimation

Albendazole content in all formulations was estimated by HPLC method .Twenty tablets were powdered. The powder equivalent to 100mg of Albendazole was weighed accurately and transferred to 50ml volumetric flask. To this 5 ml of methanolic sulfuric acid was added and shaken well. Finally the volume was made upto 50ml with methanol. It was filtered through whatman filter paper no: 41. First10ml was discarded. The clear filtrate was collected. 5ml of the clear filtrate was pipetted out to 50ml volumetric flask and make up to 50ml with methanol. 20µl of the standard preparation and the sample preparations were injected separately into the column. The flow rate was maintained at 2ml/min and

measurements were made at 254nm. The chromatograms were recorded separately for both standard preparation and sample.

In Vitro Dissolution Studies

The in vitro drug release studies were performed using USP dissolution apparatus Type II (paddle) using 900ml of 0.1N hydrochloric acid as the dissolution medium. The temperature of the dissolution medium was maintained at 37±0.5Oc and the paddle was rotated at 50 rpm. Aliquots were withdrawn at different time intervals of 10, 20 and 30 minutes and replaced by adding equal volume of fresh dissolution medium. The samples were suitably diluted and absorbance of the solutions was determined at the wavelengths of maximum and minimum absorbance at about 308nm and 350nm, in a UV- visible spectrophotometer.

Stability Analysis

The formulation F8 was subjected to stability studies, by storing at 40o±2Oc/75±5%RH for a period of 30 days. At the end of period, samples were 749nalysed for drug content, disintegration time and in vitro dissolution studies.

2. ALBENDAZOLE FAST DISSOLVING TABLETS

INTRODUCTION

Recent advance in novel drug delivery system aims to enhance the safety and efficacy of the drug molecule by formulating a dosage form being for the administration (Kuchekar et al., 2003). Difficulty in swallowing is experienced by patient such as pediatric, geriatric, bedridden, disabled and mental-ly ill (Seager et al., 1998). Fast dissolving tablets are solid dosage form containing medical substances which disintegrate rapidly, usually within few seconds when placed upon tongue requiring no additional water to facilate swallowing (Shu et al., 2002; Bradoo et al., 2001). Albendazole (ABZ), methyl [5-(propylthio)-1-H-benzimidazol-2yl] carba-mate, is a benzimidazol derivative with a broad spectrum of activity against human and animal helminth parasites (Cook et al., 1990). ABZ is effective in the treatment of echinococcosis, hydrated cysts and neurocysticercosis (Wen et al., 1993).

Direct compression is one of the techniques requires the incorporation of a superdisintegrants into the formulation the use or highly. The basic approach used in development of FDT was the use of superdi-sintegrants like cross linked Croscarmellose Sodium, Polyvinyl Pyrrolidone K30, Microcrystalline Cellulose, Crospovidone etc. which provide instan-taneous disintegration of tablet after placed on tongue, thereby releasing the drug in saliva.

METHODS

Preparation of Fast Dissolving Tablets

Fast dissolving tablets of Albendazole were pre-pared using direct compression method incorporating superdisintegrants Microcrystalline cellulose (MCC), Crospovidone (CP), Croscarmel-lose Sodium (CCS), Polyvinyl Pyrrolidone K30 (PVPK30). The Albendazole equivalent to 200mg, Mannitol and Microcrystalline Cellulose were mixed thoroughly in glass mortar using a pestle. Superdisintegrants were incorporated in the powder mixture according to each formulation in the tablets and finally Aspartame, and Magnesium stearate was added. The whole mixture was passed through Sieve No. 60 twice. Tablets were prepared using 12mm round flat-faced punch of the rotary tablet machine [Jaguar (JMD4-8)]. Compression force was constant for all formulations.

PRECOMPRESSION PARAMETERS

Angle of Repose

Angle of repose was determined using fixed funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose was calculated using formula (Rockville et al., 2007). $\theta = tan{-}1\ (hr)$ Where, θ is angle of repose, his height of pile and r is the radius of the base pile.

Bulk Density

Apparent bulk density (LBD) was determined by pouring blend into a graduated cylinder. The bulk volume (Vo) and weight of powder (M) was deter-mined. The bulk density was calculated using the formula (Rockville et al., 2007; Liberman et al., 1990).

LBD **=WEIGHT OF THE POWDER (M) VOLUME OF THE PACKING (Vo)**

Tapped Density

The measuring cylinder containing known mass of blend was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and weight of powder blend (M) as measured. The tapped density (TBD) was calculated using the formula (Rockville et al., 2007; Mukesh et al., 2009).

TBD **=WEIGHT OF THE POWDER (M)/TAPPED VOLUME OF THE PACKING (Vt)**

POST COMPRESSION PARAMETERS

Uniformity of Weight

This test is performed to maintain the uniformity of weight of each tablet which should be in the prescribed range, this is done by sampling and weighing 20 tablets at random and average weight is calculated. Not more than two of the individual weights deviate from the average weight by more than the percentage show in the Table 3 and none deviate by more than twice the percentage The mean and standard deviation were determined (Thahera et al., 2012).

Thickness

The thickness and diameter of the tablets was determined using a Micrometer screw gauge. Five tablets from each type of formulation were used and average values were calculated. It is expressed in mm (Liberman et al., 1990).

Hardness Test

The hardness of the tablet was determined using Monsanto Hardness Tester (Rockville et al., 2007).

Friability Test

Six tablets from each batch were examined for friability using Roche Fribilator (Tropical Equip-ment Pvt. Ltd. Mumbai, India) and the equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighted and % friability was calculated (Rockville et al., 2007).

PERFECT FRIABILITY = INITIAL WEIGHT-FINAL WEIGHT/INITIAL WEIGHT X 100

Water Absorption Ratio

A piece of tissue paper folded twice was kept in a Petri dish (internal diameter 5.5cm) containing 6ml of purified water. The tablet was placed on the tissue paper and allowed to wet completely. The wetted tablet was removed and reweighted. Water absorption ratio, R was determined according to the following equation (Bandari et al., 2008).

$$R = wa-wb/wawb \times 100$$

Where Wb and Wa are the weight before and after water absorption, respectively.

Wetting Time

A piece of tissue paper (12cmX10.75cm) folded twice was placed in a small Petri dish (ID = 9 cm) containing 6ml pH 6.8 phosphate buffer, A tablet was placed on the paper and the time taken for complete wetting was noted. Three tablets from each formulation were randomly selected and the average wetting time was noted (Jain et al., 2012).

CONTENT UNIFORMITY TEST

Twenty tablets of each type of formulation were weighed and crushed in mortar and powder equivalent to 200mg of Albendazole was weighed and dissolved in 100ml of pH 6.8 phosphate buffer. From the stock solution 1ml sample was withdrawn and diluted to 10ml with pH 6.8 phosphate buffer, The absorbance was measured at wavelength 291nm using double beam UV-Visible spectrophotometer (IP, 2007). Content uniformity was calculated using formula % Purity = 10 C Absorbance of unknown (Au) Absorbance of Standard (As) Where, C – Concentration.

In Vitro Disintegration Time

Initially the disintegration time for fast dissolving tablets was measured using the conventional test for tablets as described in the Pharmacopoeia. Tablets were placed in the disintegration tubes and time required for complete disintegration without leaving any residues on the screen was recorded as disintegration time (EP, 1988).

In Vitro Dissolution Testing

Dissolution study was conducted for all the formu-lation using USP type-II apparatus (Electrolab, Mumbai, India.). The dissolution test was per-formed using 900ml of phosphate buffer (PH 6.8) was taken as the dissolution medium at 50 rpm and 37°C±0.5°C. Ten ml of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically at 291nm (Liberman et al., 1990).

3. ALBENDAZOLE SUSPENSIONS

INTRODUCTION

Oral suspensions are oral liquids containing one or more active ingredients suspended in a suitable vehicle. Suspended solids may slowly separate on standing but are easily redispersed. Albendazole is an anthelmintic. It prevents newly hatched insect larvae (worms) from growing or multiplying in your body. Albendazole is used to treat certain infections caused

by worms such as pork tapeworm and dog tapeworm. Its IUPAC name was **Methyl [5-(propylthio)-1H-benzoimidazol-2-yl]carbamate.**

Oral suspensions are highly used now days in children. Another benefit in case of development is that it will not require drug to be soluble or in other way we can say that practically insoluble drugs can be administered by this formulation type.

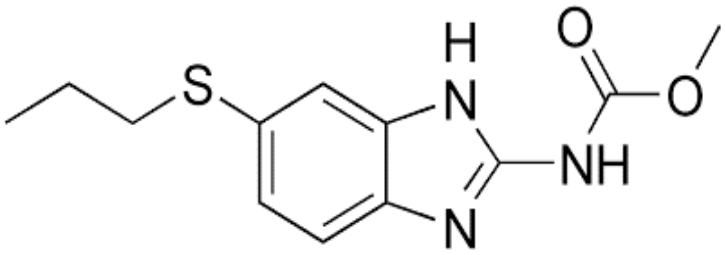


Figure no 1: - Structure of Albendazole.

METHODS

Formulation of Suspension

Three different trials were planned to develop the formulation. In this Base (Sorbitol and sugar) and Suspending Agent (Xanthan Gum, Sodium CMC) were used in different concentration to develop the formulation and it is shown in table no 1.

Table No 1: Three different trails of Formulation.

s.no	Ingredients	F1	F2	F3
1	Albendazole	40.00	40.00	40.00
2	Sodium CMC	5.00	-	3.00
3	Xanthan Gum	-	3.00	0.50
4	Sorbitol	300.00	-	300.00
5	Sugar	-	500.00	-
6	Glycerin	-	-	50.00
7	Sodium methyl paraben	1.00	1.00	1.00
8	Sodium propyl paraben	0.10	0.10	0.10
9	Bronopol	0.10	0.10	0.10
10	Sodium saccharin	1.00	1.00	1.00
11	Sodium citrate	2.00	2.00	2.00
12	Citric acid	3.00	3.00	3.00
13	Quinoline yellow	0.05	0.05	0.05
14	Flavour Mango	5.00	5.00	5.00

Use of Excipients

Different types of excipients are used for the development so their used explained down in Table no.2.

Table No 2: Use of excipients.

S.NO	INGREDIENTS	USE
1	Albendazole	Active
2	Sodium CMC	Suspending Agent
3	Xanthan Gum	Suspending Agent
4	Sorbitol	Base
5	Sugar	Base
6	Glycerin	Stabilizer
7	Sodium methyl paraben	Preservative
8	Sodium propyl paraben	Preservative
9	Bronopol	Preservative
10	Sodium saccharin	Sweetening Agent
11	Sodium citrate	Alkalizer
12	Citric acid	Acidifier
13	Quinoline yellow	Coloring Agent
14	Flavour Mango	Flavoring Agent

Table no 3: Data of stability studies for Final Formulation (F3)

S.NO	PARAMETERS	INITIALS	TIME PERIODS		
			1 MONTH	2 MONTH	3 MONTH
1.	Colour	Light yellow	Light yellow	Light yellow	Light yellow
2.	Odour	Mango	Mango	Mango	Mango
3.	Taste	Sweet	Sweet	Sweet	Sweet
4.	pH	4.9	4.95	5.00	5.10
5.	Viscosity	8278	8234	8180	8100
6.	Sedimentation Volume	0.70	0.75	0.80	0.85
7.	Redispersibility	+++	+++	+++	+++

4. ALBENDAZOLE NANO-SUSPENSIONS

INTRODUCTION

Nanosuspensions are colloidal dispersions and biphasic system consisting of drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1μm in size. Reduction of drug particles to nanometre range leads to an enhanced dissolution rate due to increased surface area and saturation solubility. Albendazole is selected as a model drug for formulation of nanosuspension. It is a BCS class II drug having low solubility and high permeability. Thus it is challenging to enhance the solubility. Hence, the aim of the work is to improve the bioavailability of Albendazole by increasing solubility through nanosuspension as a novel drug delivery. Nanosuspension will increase in saturation solubility and consequently an increase in the dissolution rate of the drug.

METHODS

Fourier transforms infrared studies

The stability of a formulation depends upon the compatibility of the drug with the excipients. It was significance to detect any possible physical or chemical interaction. FT-IR was a fast and reliable method to screen drug-excipients compatibility and provide maximum information regarding functional groups.

The FT-IR spectrum was recorded for albendazole, SLS, Tween 60 and physical mixture. The FT-IR spectrum was recorded in the region of 4000-400cm-1.

Preparation of Albendazole Nano-Suspensions

Nanosuspensions are prepared by emulsion solvent diffusion technique followed by sonification method. An accurately weighed quantity of Albendazole was dissolved in acetic acid then the solution was dispersed in the aqueous phase containing different quantity of stabilizer with stirring to form nanosuspensions. The size reduction was carried out by sonification method. The stabilizer and concentration of stabilizer are changed to desire formulation.

EVALUATION OF ALBENDAZOLE NANO-SUSPENSION

Solubility Study

The solubility of Albendazole was studied in various mediums like 1.2 pH Hcl buffer and Phosphate buffer pH 7.4. Albendazole was suspended separately in 5ml of different mediums at room temperature in tightly closed test tube and shaken with wrist action.

Particle Size and Zeta Potential Measurement

Measurements of the mean particles diameter of the nanosuspensions are conducted with the use of a dynamic light scattering particles size analyser (Zetasizer Ver.6.2 Malvern instruments Ltd., UK). The final particle diameter was calculated from the average of at least three measurements. The zeta potential values of the nanodispersion were measured, which measured the distribution of the electrophoretic mobility of particles.[14]

Scanning Electron Microscopy Observation

Scanning Electron Microscopy (SEM) was performed to evaluate the surface morphology of nanosuspension (JOEL JSM 5610, Japan). Nanosupensions were dried on glass slide before analysis. A small amount of nanosupensions was stuck on a double sided tap attached on a metallic sample stand then coat under argon atmosphere with a thin layer of gold. A scanning electron microscopy photograph was taken at the acceleration voltage of 20KV.[15]

Drug Content

Nanosuspension preparation was taken and diluted appropriately with dissolution medium. Aliquot was withdrawn and the absorbance was measured at 247 nm and the drug content was calculated from the calibration curve.

In-Vitro Drug Release Studies

Drug release studies were carried out by using a diffusion cell, whereby a dialysis membrane with a molecular weight cut off of 12,000 – 14,000 Da separated the acceptor from the donor compartment. The acceptor compartment was filled with 1.2 pH HCL buffer with stirring rate of 100 rpm and temperature was kept constant at 37±5°C. The sample were withdrawn at predetermined time intervals 5ml of samples from the centre of medium vessels for a period of drug concentration was determined by UV spectrophotometricaly at 247 nm.

CONCLUSION

From all the above observations, it was concluded that the formulation F8 was found to be better in terms of maximum percentage drug release when compared with all other formulations. F8 showed a better drug release of 81.03% at the end of 30 minutes. The stability study of formulation F8 revealed that the drug was stable under accelerated stability conditions. Hence the formulation F8 containing Albendazole 400mg may be formulated as chewable tablet by wet granulation method which satisfied all the criteria for chewable tablets.

Fast dissolving tablets of Albendazole can be successfully prepared by direct compression techniques using selected superdisintegrants for the better patient compliance and effective therapy. The relative efficiency of these superdisintegrants to improve the disintegration and dissolution rate of tablets was found in order i.e. Crospovidone > Croscarmellose sodium.

The final Batch (F3) prepared with two different combination in which one is combination of Xanthan Gum and Sodium CMC and another is use of Sorbitol showed satisfactory result in every aspect of evaluation parameters and stability criteria in comparison with other formulation. So on the basis of above F3 formulation was selected.

Solvent diffusion method has been employed to produce nanosuspensions of Albendazole. Based on the data mention in results, it is concluded that the nanosuspensions of Albendazole increase the bioavailability through enhancing the solubility by size reduction and also effective treatment for the helminthiasis.

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