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A CRITICAL ANALYSIS ON THE BIOAVAILABILITY ENHANCEMENT APPROACHES FOR MEBENDAZOLE

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ABSTRACT

Mebendazole (MBZ), chemically methyl-5-benzoyl benzimidazole-2-carbamate is a broad-spectrum anthelmintic drug belongs to the benzimidazole class which is effectual against a number of nematodal and cestodal species. Clinical trials of mebendazole have shown that usage of mebendazole is not safe at high doses in humans. The pharmacokinetic studies related to absorption, distribution, metabolism, and excretion have exposed poor absorption, rapid metabolism and ultimately poor oral bioavailability. For best possible MBZ bioavailability, issues of solubility, metabolism, polymorphism and crystal habit must be addressed. An assortment of methods have been developed in recent years that can improve its bioavailability, such as solid dispersions, inclusion complexes, micronization, self-microemulsifying drug delivery systems (SMEDDS), self-emulsifying drug delivery systems (SEDDS), salt forms, prodrugs, crystal habit modification, polymorphic changes etc. This article significantly reviews the latest published literature on diverse techniques for enhancing the bioavailability of mebendazole

Key words: Anthelmintic, bioavailability, micronization, solid dispersion, solubility

INTRODUCTION:

Mebendazole (MBZ), chemically methyl-5-benzoyl benzimidazole-2-carbamate is a broad-spectrum anthelmintic drug belongs to the benzimidazole class which is effectual against a number of nematodal and cestodal species. It is widely recommended for the treatment of non-surgical cases and as a auxiliary cure prior to and post-surgery in hydatid disease patients by oral administration as tablets or suspension.[1] The major hurdle in the oral administration of MBZ is achievement of adequate oral bioavailability owing to its poor aqueous solubility. This consequences the administration of MBZ in higher dose for better therapeutic efficacy against helminthic infections. Intake of high doses leads to adverse effects like anemia and liver damage.[2]

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Physicochemical Properties of Mebendazole

Mebendazole is a synthetic benzimidazole derivative with a wide spectrum of anthelmintic activity. Three polymorphic forms of mebendazole, identified A, B and C can be formed through controlled crystallisation procedures. Polymorph C is apparently pharmaceutically favoured.

The structure of mebendazole is as follows:

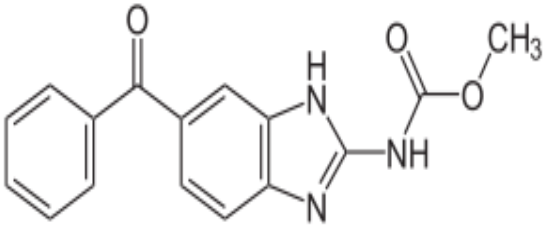


Fig 1 Chemical structure of Mebendazole

The chemical name of mebendazole is (5-Benzoyl-lH-benzimidazol-2-yl)- carbamic acid methyl ester. The molecular weight is 295.29 and the empirical formula is $C_{16}H_{13}N_30_3$ (USP, 2002:1054). The elemental composition of mebendazole is C, 65.08%; H, 4.44%; N, 14.23% and 0, 16.25%.[3] Mebendazole is a white or faintly yellowish powder, practically insoluble in water, alcohol, ether and methylene chloride and freely soluble in formic acid.

Pharmacokinetics of Mebendazole

Mechanism of action

MBZ causes selective and irreversible inhibition of the uptake of glucose and other nutrients in susceptible helminths. The inhibition of glucose uptake results in the endogenous depletion of glycogen stores in the helminths. Mebendazole does not inhibit glucose uptake in mammals. The principal anthelmintic effect of the drug appears to be degeneration of cytoplasmic microtubules within this intestinal and absorptive cells.[4]

Bioavailability

Mebendazole appears to be minimally absorbed from the GIT following oral administration. It possesses limited bioavailability of about 2-10% upon oral administration. Peak plasma concentrations of mebendazole take place around 0.5-7 hours after oral administration and show signs of wide interpatient variation. Absorption of mebendazole is increased if the drug is ingested with a fatty meal.[5]

Tissue Distribution

Mebendazole is highly bound to plasma proteins (95%). High tissue binding is one of the reasons for limited bioavailability.

Metabolism

Decarboxylation is the pathway followed by MBZ during metabolism. The metabolite is 2-amino-5 (6)-benzimidazolylphenylketone which is devoid of anthelmintic activity.[4]

Excretion

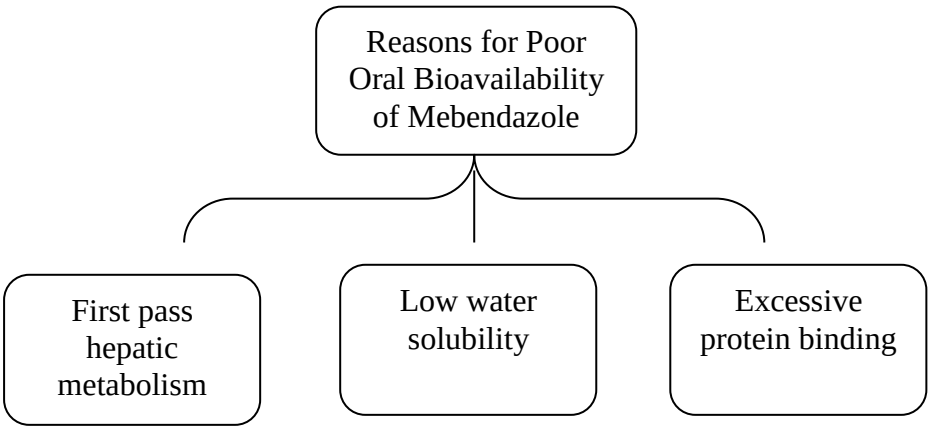
The elimination half-life has been reported to be about 2.8-9 hours. Mebendazole undergoes extensive first-pass elimination, being metabolised in the liver, eliminated in the bile as unchanged drug and metabolites, and excreted ~~infaeces.~~ Only 2% of a dose is excreted unchanged or as metabolites in the urine.[6]

Clinical uses:

Mebendazole is used for the treatment of trichuriasis (whipworm infection), enterobiasis (pinworm infection), ascariasis (roundworm infection), and hookworm infections caused by *Ancylostoma doudenaleor* and *Necator americanus.* The drug's broad spectrum of activity makes it useful in the treatment of mixed helminthic infections. Mebendazole has also activity against cestodiasis (tapeworm infection) caused by Hymenolepis nana (dwarf tapeworm), Taenia saginata (beef tapeworm), and Taeniasolium (pork tapeworm); strongyloidiasis (threadworm infection), cutaneous larva migrans (creeping eruption), toxocariasis (visceral larva migrans), capillariasis, trichostrongylosis, and draculiasis (guinea worm disease).

Causes for Limited Mebendazole Bioavailability

The major causes of limited Mebendazole bioavailability are solubility and polymorphism. The needle shaped crystal habit of MBZ causes poor flow and reduced compressibility which is the major problem during compression of mebendazole to tablets. Primary Reasons for Poor Oral Bioavailability of Mebendazole are hepatic first pass metabolism, low water solubility and excessive protein binding as depicted in fig 1.



Reasons for limited mebendazole bioavailability

Methods to Augment Mebendazole Bioavailability

Solid dispersions

Solid dispersions appear to be a viable technique for overcoming the bioavailability problem of poorly water-soluble substances.[7] This section addresses various solid dispersion formulations of Mebendazole that can lead to a highly bioavailable product. Kiran Kumar developed solid mixtures of Mebendazole using Hupu gum as carrier by physical mixing, co-grinding and kneading methods. Among the different methods used for the preparation, physical mixture showed maximum improvement in dissolution rate of Mebendazole.[8]

Improvement of dissolution and bioavailability of Mebendazole by forming solid dispersion using polyethylene glycol (PEG) as was studied by Chiba. Greater bioavailability in rabbits was obtained after oral administration of the solid dispersion compared with the physical mixture.[9] Yellanki developed solid dispersions of Mebendazole using polymers such as PVP K30, PEG 8000 and pregelatinized starch by solvent evaporation and kneading method. The prepared solid dispersions were subjected to evaluation parameters like Dissolution studies, solubility studies and solid-state characterization studies and *in-vitro* antihelmintic studies. Dissolution studies revealed enhancement in drug release from formulated solid dispersion.[10] Garcia Rodriguez improved the efficacy of mebendazole (MBZ), by MBZ solid dispersions using different proportions of low-substituted hydroxypropylcellulose (L-HPC) prepared by lyophilization process. The dissolution studies demonstrated a marked increase in the dissolution rate in comparison with recrystallized drug. The pharmacodynamic activity has been tested by performing *in-vivo* studies in mice and results revealed that the anthelmintic effects of solid dispersions were significantly increased in comparison with recrystallized MBZ (1.74-fold for SD-1:1, 3.20-fold for SD-1:2.5 and 3.80-fold for SD-1:5). These results evidated the suitability of MBZ: L-HPC solid dispersions for the treatment of enteral helmintic diseases at low doses.[11] Polymer crystals (PCs) of MBZ have been developed by the combination of solid dispersion and nanocrystal techniques using polyethylene glycol (PEG) by Chaudhary. 32-fold increase in the solubility of the drug has been observed in the *in-vitro* solubility studies. Dissolution test of the PCs showed that the crystals exhibited an enhanced dissolution rate and results of the pharmacokinetic study showed a 2.12-fold increase in the bioavailability of the drug.[12]

Complexation

Complexation is also a choice of approach to increase the solubility of a compound. Cyclodextrin is known to enhance solubility of a variety of compounds by forming inclusion complexes. Alvarez enhances aqueous solubility of Mebendazole by using hydroxpropyl-beta-cyclodextrin (HP-beta-CD) in combination with water-soluble polymers (poly vinyl pyrrolidone or hydroxyl propyl methyl cellulose) and different organic acids (citric or tartaric acid). Increased solubility was observed on heating the mixture. The results clearly showed the increased solubility (680 mug/ml) and limiting degradation (2.5%) of MBZ complexes.[13]

Tablets

Dheeraj developed Mebendazole delayed release tablet using Eudragit L100, S100 by wet granulation method for colonic drug delivery development. The formulation showed a better sustained release of 99.89% over a period of 12 hours. The ~~result~~ showed that Mebendazole colon targeted matrix tablet remain stable in the stomach and shows better release into the colon with the help of pH dependent synthetic polymers.[14] Fiza Farheen developed Mebendazole chewable tablets by three methods viz. non aqueous granulation, aqueous granulation and direct compression. Prepared tablets were evaluated by different parameters such as average weight, hardness, carr's index, tapped density, friability, disintegration, content uniformity test, in-vitro dissolution etc. The dissolution study revealed that direct compression tablets of MBZ had faster dissolution rate when compared to the other batches and marketed product.[15] Krishnaiah developed Mebendazole ~~M~~matrix tablets using guar gum as a carrier by wet granulation technique using starch paste as a binder to achieve drug release at colon as a part of targeted drug delivery to enhance the therapeutic efficacy at low doses.[16]

SMEEDS

SMEDDS are isotropic mixtures of oils, surfactants, and/or co-solvents used in the oral delivery of poorly water-soluble drugs. They improve oral bioavailability via enhancement of gastrointestinal solubilization. Other advantages are potential reduction in dose, selective targeting of the substance toward specific absorption windows in the gastrointestinal tract, and protection of the substance from a hostile gut environment like acids and enzymatic degradation.[17] Solid and liquid self-microemulsifying drug delivery system of poorly water soluble drug mebendazole have been developed by Ahmed using Aerosil 200 as solid carrier. Oleic acid, tween 80 and polypropylene glycol were selected as oil, surfactant and co-surfactant respectively for the preparation of stable SMEDDS. The optimized microemulsion was converted into solid SMEDDS by spray drying technique using Aerosil 200 as solid carrier. Solid SMEDDS of mebendazole showed good drug content uniformity. *In-vitro* drug release and *in-vivo* plasma drug concentration of microemulsion and SMEDDS was much higher than that of marketed preparation which suggests the enhancement of dissolution rate and thus concomitantly bioavailability.[18]

Self emulsifying drug delivery system (SEDDS) of a lipophilic drug, Mebendazole was developed by Naveen to augment its solubility. Various oils, surfactants and co-surfactants were screened for their suitability in the development of SEDDS. The droplet size of the prepared SEDDS was determined by zeta sizer and it was found to be below 300 nm. The percentage drug release from the formulations was improved compared to that of pure drug. Thus, SEDDS can be an alternative technique to improve the solubility and dissolution of the drug, thereby increasing its therapeutic effectiveness.[19]

Polymorphs

Bai analysed various marketed and custom-formulated MBZ tablets for their polymorph content by IR spectroscopy and subsequently tested in orthotopic GL261 mouse glioma model for efficacy and tolerability. The pharmacokinetics and brain concentration of MBZ polymorphs and its two main metabolites were analyzed by LC-MS. Polymorph B and C showed increased survival in a GL261 glioma model, however polymorph B exhibited greater toxicity. Polymorph A exhibited no advantage. Both, polymorph B and C, reached concentrations in the brain that exceeded the 29-fold of IC50 in GL261 cells. In addition, polymorph C showed an AUC0-24h, brain-to-plasma (B/P) ratio of 0.82, whereas B demonstrated higher plasma AUC and lower B/P ratio. Among MBZ polymorphs, C is the better choice for brain cancer therapy as it reaches therapeutically effective concentrations in the brain tissue and tumor with less side effects.[20] Mebendazole mesylate monohydrate, a new stable salt of mebendazole (MBZ), has been synthesized from recrystallization of MBZ forms A, B, or C in diverse solvents with the addition of methyl sulfonic acid solution by De Paula. The crystal packing is first organized as a two-dimensional array consisting of alternating rows of MBZ molecules linked to columns of mesylate ions by hydrogen bonds. The three-dimensional structure is further developed by classical intermolecular interactions involving water molecules. Thermal analysis indicates that the compound is stable up to 50°C. Decomposition occurs in five steps. Solubility studies show, that the title compound presents a significant higher performance than polymorph C.[21]

Formation of Derivatives: Salt, Prodrug

Formation of water-soluble derivatives like salts and prodrugs is an alternative approach to increase the bioavailability of poorly soluble drugs like Mebendazole. Brusau synthesized Mebendazole hydrochloride (MBZ- HCl), a new stable salt of mebendazole (MBZ), from re-crystallization of MBZ forms A, B, or C in diverse solvents with the addition of hydrochloric acid solution. Crystallographic data depicted that the particular conformation assumed by the carbamic group contributes to the stability of the network. The thermal study on MBZ: HCl, indicates that the compound is stable up to 160° C approximately and solubility of drug was enhanced.[22] Prodrug concept has been investigated by developing various N-alkoxycarbonyl prodrugs of MBZ and administered to rabbits orally for bioavailability assessment by Lise. The compounds were administered in the form of aqueous suspensions at pH 5.0. Improvement in the absorption of Mebendazole has been monitored. All prodrugs were rapidly hydrolyzed to mebendazole after absorption. The bioavailability was improved for all prodrugs. The highest bioavailability was obtained with the N-methoxycarbonyl derivative which showed a 13-fold improvement in bioavailability compared to mebendazole. The improved bioavailability of the prodrugs was attributed to the increased water solubilities and appropriate lipophilicities. The N-alkoxycarbonylation of the benzimidazole moiety in mebendazole and other widely used benzimidazole carbamates may be a promising prodrug approach to enhance poor absorption of poorly soluble drug like MBZ.[23]

Crystal engineering

Crystal engineering is novel particle engineering technique adopted by the investigators for the solubility enhancement.

The needle shaped crystal habit of MBZ and high electrostatic charge is the primary reason for poor flow and compressibility. This challenge has been overcome by spherical crystallization i.e., spherical agglomeration designed by Kumar. Spherical agglomeration of MBZ has been carried out using polymers (PEG, cross-povidone, starch, croscarmellose sodium, hydroxyl propyl methyl cellulose (HPMC), hydroxyl propyl cellulose (HPC), ethyl cellulose (EC), Eudragit S100, Eudragit RLPO, Eudragit RD100, Eudragit E) and bridging liquids (hexane, octanol, toluene, dichloromethane). The effect of different crystallization conditions such as variation of polymer type, polymer concentration and rate of stirring has been investigated. The presence of HPC and Eudragit-S100 indicated better compressibility of MBZ due to spherical crystal formation.[24]

Micronization

Particle size reduction is one of the techniques to enhance the solubility and bioavailability. Micronization of mebendazole has been studied by various researchers. Gemmell studied the effect of mebendazole in different dosage forms (powder, micronized powder and tablets of micronized powder). Dogs have been used as a model to evaluate the response of *Taeniahydatigena* and *Echinococcusgranulosus* parasites to different dosage forms of mebendazole. The study reveals that micronized powder proved to be the most active, the tablets less so and the normal powder least active suggesting the enhanced bioavailability of micronized Mebendazole.[25] The anthelmintic efficacy of Mebendazole by reducing the paticle, size was studied in rats undergoing a primary infection with *N. brasiliensis* by Kelly. A single oral treatment with fine ground mebendazole (particle size spectrum—54·95 per cent of particles less than 10·62 μ dia.; 86·06 per cent less than 21·27 μ) removed more than 98 per cent of adult worms from the intestine at a dose rate of 12·5 mg/kg body wt. The fine ground particles of MBZ showed increased anthelmintic activity by enhancement of solubility.[26]

Crystallization

The technique of crystallization has been followed by Shawky Tous to enhance the solubility and dissolution rate of mebendazole (MBZ). Crystallization was carried out using aqueous solutions of non-ionic surfactants (Tween 20, 40, 60 and 80) and ionic surfactants (sodium lauryl sulfate and cetrimide). The improvement of MBZ limited systemic availability has been observed.[27]

CONCLUSION

A number of approaches for increasing the oral bioavailability of Mebendazole have been extensively studied, including Solid dispersions, complexation with cyclodextrins, SMEDDS spherical crystallization, micronization, solubilization, polymorphism, crystallization, salts and Prodrugs. Another possible approach to improve bioavailability is to reduce the particle to nano size by methods like pearl milling, high pressure homogenization, emulsification, and precipitation, which can lead to superior ~~in vivo~~ drug performance. Apart from these novel targeted delivery systems such as Microspheres, Nanoparticles, Liposomes, Polymeric micelles are currently being explored for the successful delivery mebendazole with enhanced therapeutic efficacy. However extensive research work has to be carried out in this arena by the formulators.

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Conflict of interest: None

REFERENCES:

1. Hemphill A; Müller J. Alveolar and cystic echinococcosis: towards novel chemotherapeutical treatment options. *J Helminthol*. 2009, 83(2), 99–111.
2. Dayan AD. Albendazole, mebendazole and praziquantel. Review of non-clinical toxicity and pharmacokinetics. *Acta Trop*. 2003, 86(2–3), 141–159.
3. Badr AL; Tariq AM. Mebendazole. In Florey, K, ed. Analytical profiles of drug substances. NewYork: Academic Press. 1987, 6, 283-326.
4. Mc Evoy GK. ed. AHFS: drug information 88. Bethesda, Md.: American Society of Hospital Phamracidr. 1988. 2222 .
5. Goldsmith RS. Clinical pharmacology of the anthelmintic drugs: mebendazole. (In Katzung, BG ed. Basic & clinical pharmacology. 1998, 662-880.
6. Reynolds JEF. Martin the extra pharmacopoeia. 29th ed.London: The Pharmaceutical Press. 1989, 1896.
7. Sethia S, Squillante E. Solid dispersions: revival with greater possibilities and applications in oral drug delivery. *Crit. Rev. ther. Drug Carrier Syst*. 2003; 20:215-247.
8. Kiran Kumar S, Prasanna Kumari J, Ganesh Kumar G, RajeshamVV and Yanadhaiah JP. Dissolution Enhancement of Mebendazole using by Hupugum. *J. Pharm. Sci.Technol.* 2010, 2 (4), 213-216.
9. Chiba Y, Kohri N, Iseki K, Miyazaki K. Improvement of dissolution and bioavailability for mebendazole, an agent for human echinococcosis, by preparing solid dispersion with polyethylene glycol. *Chem Pharm Bull (Tokyo)*. 1991, 39(8), 2158-60.
10. Yellanki, Shiva Kumar. Formulation, Dissolution Characterisation and in-Vitro Anthelmintic Activity of Several Fast-Release Solid Dispersions of Mebendazole. Journal of Pharmacy Research. 2010; 3(6), 1288.
11. Garcia Rodriguez JJ, de la Torre-Iglesias PM, Vegas-Sanchez MC, Torrado-Duran S. Changed crystallinity of mebendazole solid dispersion: improved anthelmintic activity. *Int J Pharm.* 2011, 403(1-2), 23.
12. Chaudhary S, Garg T, Rath G, Murthy RR, Goyal AK. Enhancing the bioavailability of mebendazole by integrating the principles solid dispersion and nanocrystal techniques, for safe and effective management of human echinococcosis. *Artif Cells NanomedBiotechnol.* 2015, 17, 1-6.
13. Alvarez covadonga, vanhees Thierry . Preparation of mebendazole HP-beta-cyclodextrin complexes using water-soluble polymers and organic acids. *STP Pharma Sciences*. 2001; 11(6), 439-442.
14. Dheeraj Baviskar, Amarjit Rajput, Kapil Bare. Development and *in vitro* characterization of mebendazole delayed release tablet for colonic drug delivery. *Pak. J. Pharm. Sci*. 2014:27(2), 249-253.
15. Farheen F, Bharadwaj S. Formulation and Evaluation of Chewable Tablets of Mebendazole by Different Techniques. *PharmaTutor*. 2014:2(6), 183-189.
16. Krishnaiah Y S, Veer Raju P, Dinesh Kumar B, Bhaskar P; Development of colon targeted drug delivery systems for Mebendazole. *J Con. Rel*. 2001, 77(2), 87-95.
17. Porter CJ, Pouton CW, Cuine JF, Charman WN. Enhancing intestinal drug solubilisation using lipid-based delivery systems. *Adv Drug Deliv Rev.* 2008, 60, 673-691.
18. ~~AH Ahmed~~. Preparation and Evaluation of Liquid and Solid Self-Microemulsifying Drug Delivery System of Mebendazole. *Iraqi J Pharm Sci*. 2014, 23(1), 89-100.
19. Naveen P, Aparna L. Enhancement of solubility of Mebendazole by SEDDS. LAP Lambert Academic Publishing. 2012

20. Bai RY, Staedtke V, Wanjiku T, Rudek MA, Joshi AD. Brain Penetration and Efficacy of Different Mebendazole Polymorphs in a Mouse Brain Tumor Model.*Clin Cancer Res*. 2015.
21. Paula K, Camí GE, Brusau EV, Narda GE, Ellena J. Mebendazole mesylate monohydrate: a new route to improve the solubility of mebendazole polymorphs. *J Pharm Sci*. 2013, 102(10), 3528-38.
22. Brusau EV, Cami GE, Narda GE, Cuffini S, Ayala AP, Ellena J. Synthesis and characterization of a new mebendazole salt: mebendazole hydrochloride. *J Pharm Biomed Anal*. 2005, 38(3), 435-41.
23. Nielsen LS. Improved peroral bioavailability of mebendazole in rabbits by administration of various N-alkoxycarbonyl derivatives of mebendazole. *Int J Pharm*. 1994, 104(2), 175–179.
24. Kumar S, Chawla G, Bansal AK. Spherical crystallization of mebendazole to improve processability.*Pharm Dev Technol*. 2008, 13(6), 559-68.
25. Gemmell MA, Johnstone PD, Oudemans G. Significance of particle size of mebendazole in the treatment of tapeworm infections.*J Pharm Pharmacol*. 1985, 37(9), 659–660.
26. Kelly JD, Chevisa RA, Goodman HT. Effect of particle size on the anthelmintic efficacy of mebendazole against *Nippostrongylusbrasiliensis* in the rat. *Int J Parasitology*. 1975, 5(3), 275–280.
27. Shawky TS, Mohammed FA, Farrag AY. Improvement of the in vitro dissolution rate of mebendazole via crystallization in aqueous surfactant solutions.*J Drug Del Sci Tech*. 2008, 18(5), 359–366.

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