# Flubendazole as a Potential Macrofilaricide for Field Use

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## Introduction

A safe, field-usable chemotherapeutic agent that will rapidly kill adult filarial worms is urgently needed in tropical medicine. Ivermectin, distributed as Mectizan® by Merk & Co. Inc. has had an enormous impact on two major human filarial infections of developing countries, onchocerciasis and lymphatic filariasis. However, a macrofilaricide that safely kills adult filarial worms would be a major contributor to the current efforts to rid the world of filarial infections and the disease they cause. Given the challenges of discovery and development of agents for human use, a drug as described is most likely to come from the benzimidazole group of anthelmintics.

## Flubendazole

- Typical benzimidazole structure, containing an additional fluorine (Figure 1).
- Binds tubulin
- Binds nematode tubulin preferentially over mammalian tubulin
- Licensed in Europe for use in intestinal helminth treatment

## History as an Anthelmintic

- Parenterally administered flubendazole provides efficacy against adult filariae in multiple host species (Table 1).
- Effective against Dirofilaria in a a single parenteral dose
- An oral formulation has been effective against cysticercosis (*Ceballos et al. 2009 Para Int. 58: 354-358).*
- Has little to no microfilariacidal effect

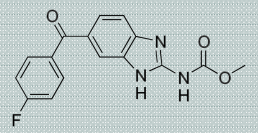


**Figure 1**. Flubendazole

**Table 1**. Minimum effective dose in various species

| Parasite | $LED_{90} \times 5$ (mg/kg) | $LED_{90} \times 1$ (mg/kg) |
|---|---|---|
| *Jird* | | |
| *Brugia pahangi*† | 1.5 | 25 |
| *B. pahangi*† | 1.56 | ND |
| *B. pahangi*† | 2.5 | ND |
| *B. pahangi*‡ | 12.5 | ND |
| *B. pahangi*† | 20¶ | ND |
| *B. pahangi*‡ | 10¶ | ND |
| *Dipetalonema viteae* | 100¶ | ND |
| *Acanthocheilonema viteae* | 1.56 | ND |
| *Rat* | | |
| *Brugia pahangi*‡ | 25 | ND |
| *B. malayi* | 12.5 | 50 |
| *A. viteae* | 3.1 | 1.6 |
| *Litomosoides carinii*‡ | 12.5 | 12.5 |
| *Mouse* | | |
| *Onchocerca lienalis*†† | 100 | ND |
| *Cat* | | |
| *B. pahangi*‡ | ND | 100 |

†Adult parasites in the peritoneal cavity.
‡Adult parasites in the lymphatics.
¶L3 larvae.
¶Not titrated, only dose reported.
‡Multimammate rat.
††Microfilariae transplanted into the skin.

## Development of a Macrofilaricide

### Target Product Profile

**Best**

An oral single dose preparation that has a long shelf life and is not subject to degeneration at tropical temperatures

**Acceptable**

A treatment that can be given over a short duration (e.g. daily for 3-5 days) via a safe route (oral or parenteral), and has a long shelf life and is not subject to degeneration at tropical temperatures

### Drug Reformulation

Various modern approaches to drug formulation are being tested including milling and the use of Hydropropyl-β-cyclodextrin

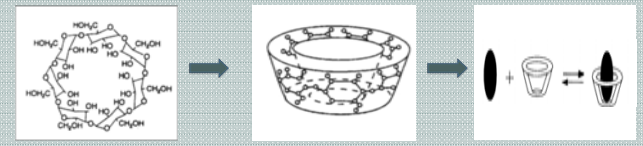


**Figure 2**. Hydropropyl-β-cyclodextrin.

## Reformulation: PK/PD Studies

**A Hydropropyl-β-cyclodextrin and carboxymethyl cellulose formulation of Flubendazole**

- Two species: Rats and Jirds
- Single 5mg/kg dose orally (n=44) and subcutaneously (n=44)
- Blood Plasma evaluated by HPLC for flubendazole and its metabolites (Figure 2 & 3).
  - Flubendazole
  - Hydrolyzed-Flubendazole

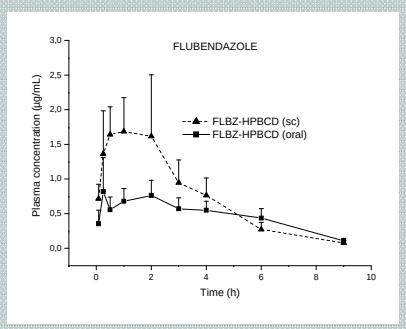
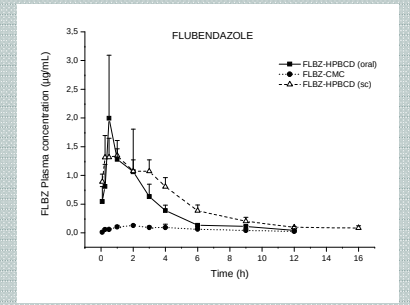



**Figure 3**. Comparative flubendazole (FLBZ) plasma concentrations profiles obtained after its oral administration as a hydroxypropil-β-cyclodextrin (FLBZ-HPBCD) by the oral or subcutaneous route to healthy jirds.



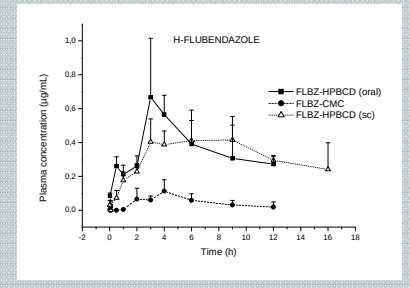




**Figure 4**. Comparative flubendazole (FLBZ)(a) and hydrolyzed FLBZ (H-FLBZ)(b) plasma concentration profiles obtained after administration of different formulations of FLBZ to uninfected rats.

## Conclusion

- Preliminary PK/PD studies of a hydropropyl-β-cyclodextrin formulation revealed that metabolic patterns and systemic exposure of parent flubendazole and its metabolites differ among species.
- Flubendazole pharmokinetic behavior can be markedly improved by changing the formulation
- The alterations in systemic exposure to flubendazole obtained with the cyclodextrin formulation (both oral and parenteral) is likely to have a great impact on clinical efficacy.

## Acknowledgements

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- REF: Mackenzie & Geary(2011). Expert Rev Anti Infect Ther. 9(5) 497-501.