# Controlled-release formulations for Parasitic disease

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## Abstract

Previous research has established a link between parasitosis, cancer, and co-morbid bacterial and viral infections. However, managing parasitic disease is more complex than commonly believed. While broad-spectrum anti-protozoan and anti-helminthic treatments are often used, they do not always fully resolve infections. This is because parasitic effectiveness is influenced not just by drug dosage but also by reproductive cycles, maturation processes, and overall population load. This preprint explores therapeutic alternatives aimed at addressing high parasitic burdens, with a focus on minimizing adverse effects and mitigating pancreatitis, hepatic, pulmonary, and gastrointestinal inflammation.

## Introduction

The link between parasitosis and cancer as well as co-morbid bacterial and viral infections has been proven in the previous work published on this preprint server,

however, a dose of reality makes us realize that parasitic disease isn't as manageable as we'd like to believe. Many veterinarians and oncologists have consequently thought that treating parasitic disease with a broad-spectrum anti-protozoan and anti-helminthic medicine fixes the problem, as it contrasts the infection, but realistically this isn't always the case.

Namely, this is because effectiveness in "parasitic invasions", that are not straightforward single cells, but pluricellular or unicellular microorganisms carrying a cell wall, doesn't depend on the dosage of the anti-parasitic preparation, it depends on its reproductive and life cycle, of deposing eggs and then maturity to worm or to resilient protozoan, and most importantly, of the population load.

It is known that moist seasons like early spring characterized by rainfalls followed by sunny days, give most wildlife, pet owners, and animals the impression that exposure to parasitic infections and viruses is minimized, yet moist seasons present the highest vulnerability to helminths that thrive in temperate and hot climates. Migratory birds, insects, as well as warmer temperatures favorable to viruses, provide an ideal hosting ground for helminths in the environment, and this can be viewed with a surge of pets visiting veterinarian practices. An uneven distribution of veterinary practice visits, is not casual but supports the source of exposure to these biological harmful organisms, and anti-parasitic drugs don't

always address large loads of parasites, due to the "dying-off" period which was discussed in the previous articles, inducing multi-organ failure.

Initially the organs affected are glandular full organs, i.e. the pancreas, or the kidneys, in which both protozoans and larvae of worms produce crystal stones leading to inflammation, but concomitantly, there is a release of hormonal toxins both in the live and post-death stage whereby the content of protozoans and worms is released in the pancreas, and the liver overloading metabolic cleansing, and ultimately the circulation, reaching the Chemereceptor Trigger Zone (CTZ) in the *medulla oblongata*, to provoke symptomatology that can be life-threatening in 3% of the cases (Acute pancreatitis). If that doesn't suffice, continuous irritation and inflammation of the pancreas can lead to excess immune activity to clear off the heavy load of remnants of dead worms and dead protozoan cells, resulting in a "fulminant" inflammation process, that can then affect other organs i.e. the bowels, in what we have learnt to call Inflammatory Bowels Disease (IBD).

Consequently, the whole picture needs to be considered in anti-parasitic drug management, as most patients or pet owners, me included, erroneously believe that symptomatic treatment is not as important as curing the "parasitic infestation". Moreover, infestation is often seasonal and recurrent throughout the year, posing the question on whether immune support should be considered as

well as vaccinations. Diagnostic procedures that absolutely detect protozoan and helminthic guests in a host are also scant, as well as the understanding of potential sources of exposure, e.g. house sheds, contaminated food and water, "expired meat", curious animal behavioral habits of going through the trash bins and so on, perhaps driven by *pica*; nonetheless, symptomatic treatment in the dying-off period remains important in conjunction with parasitic disease, as well as the necessity for novel anti-parasitic agents, or simply delayed release dosage forms.

**Histopathological investigations**

In support to the previous publication, it is now known that parasite guests recruit the host cells, and "drive them mad", in fact it turns out in a latest histology study that often protozoan staining is disregarded in acute pancreatitis, due to the focus on the secondary bacterial stains. More specifically, within the histopathological study that was carried out for this paper, it was noted that parasites actually attempt at converting the host cells into parasitic cells, introduced in the past paper with the concept of "*pluricellular cell segregation*" or we could call it "*unicellularization process*" is actually aimed at a "*walling-up process*" for the purpose of "parasitic cloning", yet resulting in tumoral or cancerous cells. As a matter of fact, cell-wall deposits are clear in many pancreatitic histological samples.

Currently, not many anti-parasitic chemotherapeutic drugs are broad-spectrum and are slow acting (delayed-release dosage forms), such as Fenbendazole® , thus the "*dying-off*" stage of parasites can trigger excess inflammation, particularly in immunosuppressed patients, e.g. patients on long-term high dose steroids or due to seasonal viruses, that struggle with cleansing their liver and pancreas from the remnants, and toxins.

Novel drug design, as such, might not suffice in resolving an overload during the "dying-off stage", because chemotherapeutic anti-parasitic agents, such as Mefloquine® already exist with a long half-life, but they are less broad spectrum and the reaction to the medicine still depends on the amount of protozoans in the host.

As such, an extended release formulation, i.e. a subcutaneous reservoir, can help distribute the load more effectively, or a selective drug that paralyses the parasitic guests, which is very similar to what algae do, by exquisitively filling the correct domain (View figure 1 below).

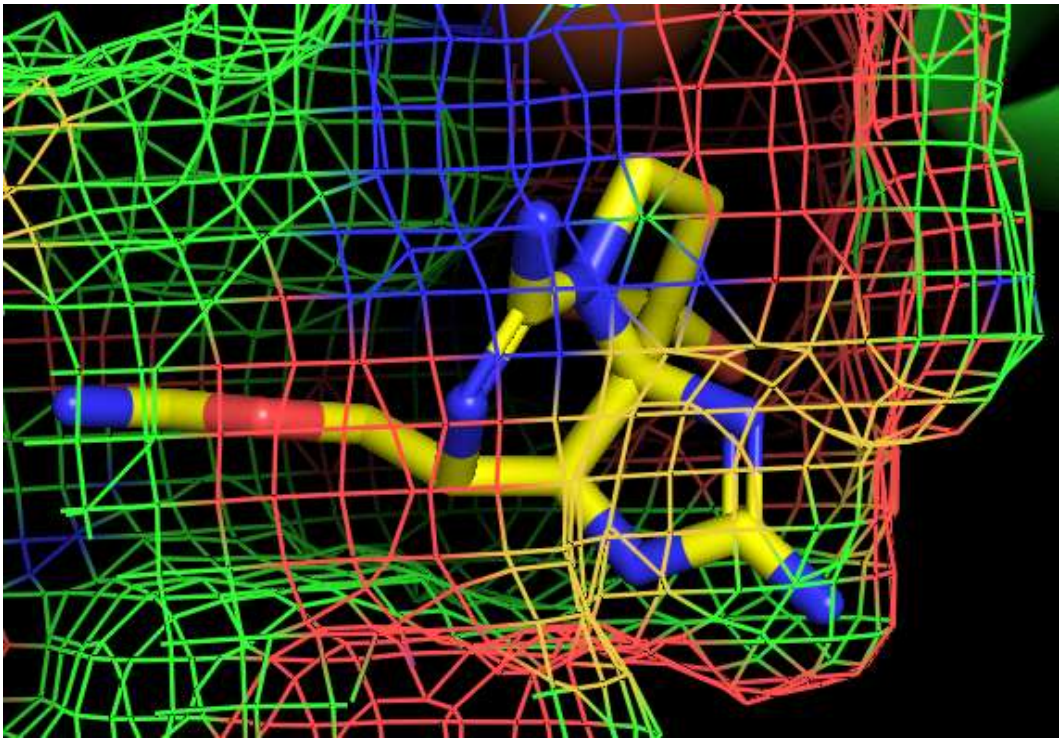

**Figure 1.** Crystal structure of a non-heme dioxygenase inhibited at sequence YTCEASE by a natural toxin produced by some algae (neurotoxic-paralysis inducing).

The above, leads us medicinal chemists to the design of the *moiety* depicted in figure 2 requiring safer isosters, such as "nitrogen-swapping" (between an 8 to 1 position) isoster, as well as other alternatives, such as a -CH replacing one of the N8 of the dipyrrolo-purin group (or di-indolo group).

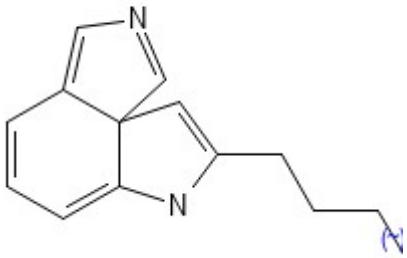


**Figure 2.** A simplified structural *moiety* that could fill the oxygenase domain pocket perfectly, without causing side effects, depending on the substituted side chain. Ideally this structure would impact dioxygenases in worms causing paralysis, before death; this could prevent the load on our organs and tissues, that can be taxing and exacerbate disease.

Alternatively, what is more of an intelligent solution is that of building controlled release system reservoirs that pharmaceutical technologists-engineers are familiar with, and that can lead to the constant quick or delayed release of the active ingredient; this can be achieved via the help of independent regulatory bodies.

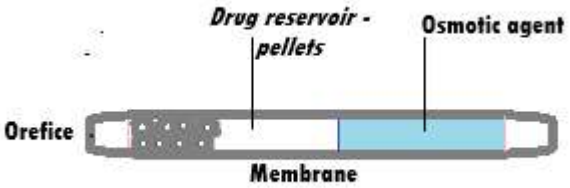


**Figure 3.** A subcutaneous implant (drug reservoir) delivering Fenbendazole or other anti-parasitic agents in a controlled-release way. A subcutaneous tablet containing pellets is also a great alternative.

Perhaps in the meantime, asking bioengineering companies to help and have other

regulatory bodies engage in the support of healthcare practitioners by elevating their standards of approval, can be a quicker solution and can help mitigate the losses caused by those that are currently denying basic healthcare to animals and humans globally, (for example employees at federal drug and other agencies) whilst engaging undisturbed in persecutory acts against practitioners, and whose expertise in such non-political matters remains dubious.

*No conflicts of interest to disclose.*