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From lipid biophysics to first-in-human test: topical liposomal treatment for cutaneous leishmaniasis

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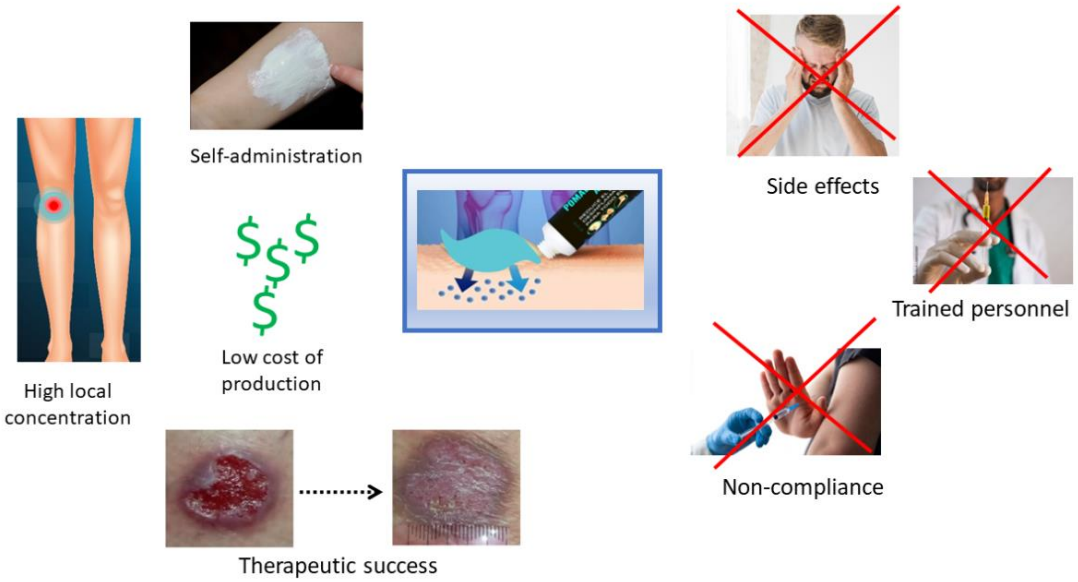
Graphical Abstract



Abstract

Cutaneous leishmaniasis (CL) remains a major neglected disease with limited therapeutic options and expanding geographic distribution. To develop a safe, accessible local treatment, we formulated topical Miltefosine gels incorporating different types of liposomes. Preclinical tests using low-dose Miltefosine (0.015% w/v) and ultrafluid liposomes were ineffective, leading us to increase the drug concentration and revise the liposomal design. At 0.5% w/v, Miltefosine—whether used alone or with fluid liposomes—produced complete lesion healing in a murine *L. amazonensis* model, with no relapse and sterile lesions at 30 days. Liposomes further accelerated the healing process. A first-in-human compassionate-use case with a patient refractory to standard therapies confirmed good local tolerance and eventual clinical cure using 0.5–1% Miltefosine gels + short Amphotericin B treatment. The experience also showed that ultrafluid liposomes are unsuitable for open ulcers, informing future optimization. Overall, topical Miltefosine at adequate concentration is a promising local treatment for CL, and liposomes can enhance therapeutic performance.

Keywords: Cutaneous leishmaniasis, topical treatment, Miltefosine, liposomes, nanoparticles, gel, clinical case

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Introduction

Cutaneous Leishmaniasis (CL) is an orphan parasitic disease endemic in 98 countries, including India and Argentina. It is estimated that between 600,000 and one million new cases occur each year. The currently available treatments are inadequate. Furthermore, the disease is expanding into regions that were previously disease-free, both northwards and southwards, for example, in central Argentina, the southern United States, and Europe.

Why use local treatments for CL? A locally applied treatment offers many advantages (see Fig. 1). For instance, the drug concentration is high at the target site and low in the rest of the organism. The method of application means that trained personnel are not required.

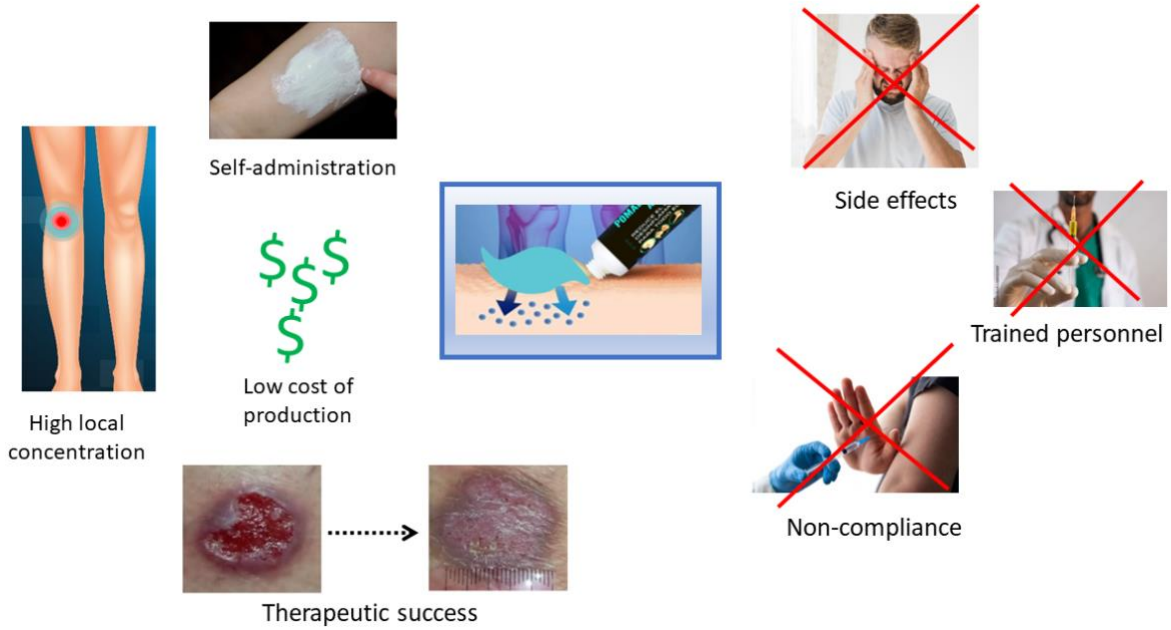

Figure 1: Advantages of local treatments

The medication can be self-administered, and its low systemic concentrations result in minimal side effects. Also, since it is a non-painful treatment, patient compliance is good. Moreover, a topical formulation is less expensive to produce than a parenteral formulation. Many drugs have been tried as topical treatments for CL, very few with good results [1].

Discussion

According to the literature and our own experience, the main physical property to consider when designing a liposome for use as a drug carrier across the skin is its fluidity at the skin's physiological temperature. This fluidity can be enhanced by creating so-called ultrafluid liposomes by mixing fluid lipids (low-fusion-temperature lipids) with detergents ("edge activators").

Based on this information, we initially decided to use ultrafluid liposomes when formulating a topical preparation containing Miltefosine and liposomes. We used a mixture of fluid lipids and added sodium cholate as an edge activator. The Miltefosine was incorporated into these liposomes. This was then dispersed into a hydrogel matrix to create a formulation with the appropriate viscosity for skin application.

In a first instance, we evaluated the *in vivo* topical efficacy in an animal model of cutaneous leishmaniasis caused by *Leishmania amazonensis*. The animals were infected with promastigotes via subcutaneous inoculation. Once an ulcer had formed, they were treated for three weeks with the gel containing pure Miltefosine or the gel containing Miltefosine (0.015% w/v) incorporated in liposomes.

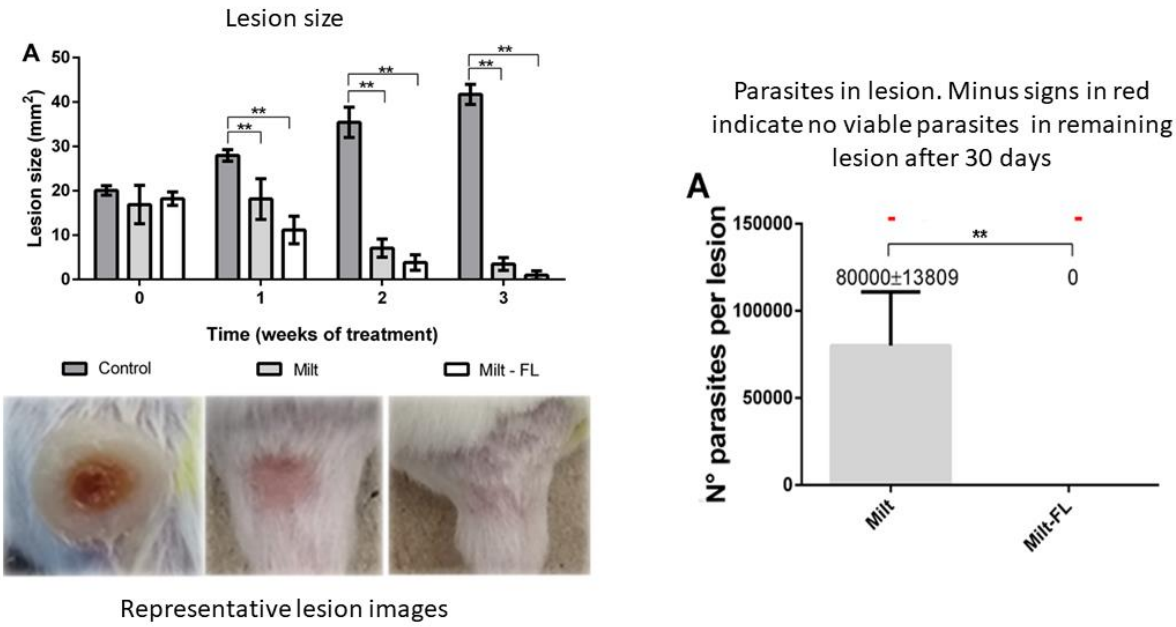

Figure 2: Topical in vivo efficacy of miltefosine formulations. Modified from [3].

At 0,015 % w/v, Miltefosine reduced, but did not eliminate, the lesions. Furthermore, Miltefosine included in ultrafluid liposomes was not as effective as the pure drug. When parasitic inhibition was measured at the endpoint of the experiment, it was observed to be very poor for Miltefosine included in ultrafluid liposomes, while it was about 70% for the gel containing pure Miltefosine. We then decided to use a higher Miltefosine concentration and to abandon ultrafluid liposomes in a subsequent experiment.

In our next experiment, we increased the Miltefosine concentration to 0.5% w/v and incorporated it into hydrogels that did or did not contain fluid liposomes. In this case, the size of the lesion decreased until it disappeared by the third week, both with pure Miltefosine and the same included in liposomes (see Fig. 2).

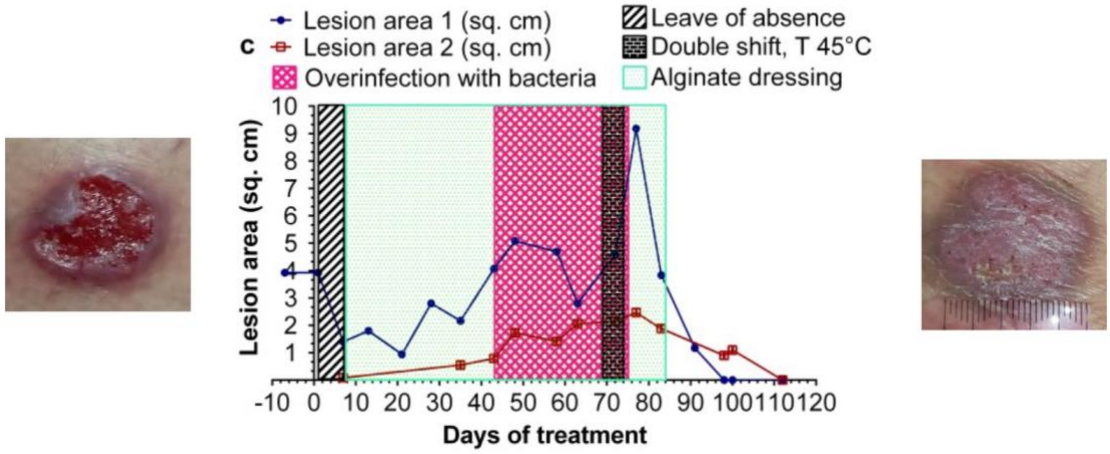

Figure 3: "Real-life" effects on CL treatment. Modified from [2]

To study possible recidivism, after 30 days, we evaluated whether viable parasites were present in the residual lesion. It was found that although amastigotes were still present in the tissue of the Miltefosine-treated animals, these parasites were not viable. In animals treated

with Miltefosine and phospholipids, no parasites were detected in the skin. In conclusion, treatment with 0.5% w/v Miltefosine resulted in clinical cure; no relapse was observed at 30 days, the lesion was sterile, and liposomes accelerated healing and improved efficacy (Fig. 2) [3].

In 2022, we conducted a first-in-human trial of our formulation in a real-world setting [2]. The patient was an adult male, a rural worker, who had CL refractory to Glucantime treatment and had experienced cardiotoxicity when treated with Amphotericin B deoxycholate. As a result, the physician faced a severe lack of therapeutic options. The patient had two active lesions on one leg. He was initially treated with the 0.5% gel with fluid liposomes for 15 days. The gel volume to be applied was too large, so we changed the formulation to 1% w/v miltefosine. We used an alginate patch to cover the lesion after applying the gel. The patient reported a moderate, tolerable stinging sensation during the first minute after gel application.

The patient's treatment initially yielded very good results, with a 60% reduction in lesion size after the first two weeks. However, the treatment was complicated by a bacterial overinfection and the physical stress the patient endured due to his working conditions. It was then decided to treat with Amphotericin B deoxycholate, which had to be suspended after three days due to renal and cardiac toxicity. Meanwhile, the gel continued to be applied until clinical cure of the wound was finally achieved on day 100 (see Fig. 3).

Conclusion and perspectives

It is noteworthy that the liposomes that best penetrate the skin, i.e., ultrafluid liposomes, are not the most suitable for treating an open ulcer produced by cutaneous leishmaniasis. Next steps underway are the evaluation of local safety (skin irritation) and drug penetration into systemic circulation. In our clinical case, good local tolerance and safety were observed; that is, the treatment did not cause local irritation and was very well accepted by the patient. The optimization of the formulation's physicochemical and microbiological stability is also underway.

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Conflicts of Interest: The authors declare no conflict of interest. For a written statement, please contact the journal office.

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