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American Journal of Biopharmacy and Pharmaceutical Sciences

Commentaries *Biomedical and Pharmaceutical Sciences*

Transdermal antimalarial drug delivery to improve poor adherence to antimalarials: A new light at the end of the tunnel

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Received: 22 August 2023
Accepted: 31 October 2023
Published: 02 December 2023

DOI
10.25259/AJBPS_14_2023

Quick Response Code:

ABSTRACT

Malaria, a perilous disease caused by *Plasmodium* parasites and characterized by a substantial mortality rate, has persistently posed as a global health challenge. Conventional antimalarial formulations, although effective, grapple with issues surrounding their bioavailability and palatability, and potentially hampering patient adherence and inadvertently fueling drug resistance and poor treatment outcomes. This paper meticulously delves into the predicaments associated with prevailing antimalarial delivery methods – oral, intravenous, and intramuscular. The paper navigates through the compelling merits of the transdermal pathway, drawing inspiration from its triumphant deployment in other medical realms. The investigation extends to encompass preclinical inquiries dedicated to exploring the transdermal administration of antimalarials. Transdermal antimalarials have shown complete suppression and elimination of *Plasmodium* parasites, as suggested by the preclinical studies. These preclinical studies emerge as a beacon of hope, exhibiting heightened bioavailability, enhanced safety margins, and notable cost-effectiveness when compared with oral antimalarials. Moreover, this innovative avenue for drug delivery not only offers convenience but also holds the potential to be a transformative solution to the adherence problems of traditional antimalarials, which currently afflicts standard therapeutic options.

Keywords: Transdermal, Antimalarial, Drug resistance, Adherence, Drug delivery

INTRODUCTION

Malaria is the deadliest parasitic disease, with 247 million cases and 619,000 deaths worldwide in 2021, including 274,030 children under the age of 5, yet available treatments are prone to drug resistance and lack palatability. The majority of malaria cases were recorded on the African continent.[1] Current antimalarials medications are administered either orally, intramuscularly, or intravenously. However, the drug efficacy and patient compliance of these conventional antimalarials therapies are hindered by emerging resistance by the parasite as well as lack of palatability, especially for the oral medications, negatively impacting efforts toward prevention, control, and utmost eradication of malaria. A study showed that more than 90% of the respondents following an antimalarial therapy felt that the medications had an unpleasant taste and that taking them was an uncomfortable experience. As a result, patients are more likely to stop taking their medication,[2] leading to poor adherence and development of drug resistance.[3]

Herein, our study intends to harness the potential benefits of the transdermal administered antimalarial solutions in addressing issues with palatability, adherence, and antimalarial drug resistance. We aim to explore the successful preclinical trials done so far on transdermal antimalarial therapies and suggest the possible commencement of clinical trials in humans.

Problems of Current Routes of Antimalarials

Despite the advancements in antimalarials therapies, malaria morbidity and mortality are still on the increase. This has mostly been attributed to the emergence and transmission resistance of the *Plasmodium* parasite to the drugs, which results from non-adherence to the traditional oral and parenteral antimalarials. Furthermore, non-adherence is associated with the bad or unpleasant taste of most oral antimalarials. In a study carried out by Afaya *et al*., over 90% of respondents agreed that antimalarials medications had bad taste, and thus, they had an unpleasant feeling while taking them.[2] One of the main barriers to uptake and adherence to prophylactic antimalarial medications among the African community in London is poor taste.[4] Lawford *et al*. observed that patients who dislike the taste or smell of Artemether (ART)-lumefantrine (LUM) were less likely to be completely adherent.[5] According to Matsui, non-adherence can compromise the efficacy of medication regimens, leading to failure to achieve the desired treatment goal.[6] Thus, non-adherence to antimalarials may lead to significant morbidity, wasted resources and/or resistance to these medications. In addition, poor adherence to oral antimalarials can be caused by medication overload or frequent dosing.[2,7] Individuals often have a preference for specific antimalarial drugs, particularly those that come with simple dosing instructions.[8,9] Furthermore, the therapeutic efficacy of artemisinins is constrained due to their inadequate bioavailability and restricted pharmacokinetics.[10] Oral antimalarials are faced with issues of poor bioavailability. Newton *et al*. found that the bioavailability of artesunate is only 61%.[11] Poor adherence to injectable antimalarials could be due to reaction at the site of injection and pain. In a research work carried out by Ampadu *et al*., there was low adherence to injectable antimalarials.[12] Since most antimalarials are administered through this route, there is a need to devise a better route that would promote adherence and curb resistance. This poor adherence to these traditional antimalarials plays a role in the future drug resistance by the *Plasmodium* parasites. As such, identifying ways to improve adherence and bioavailability with these antimalarials will help mitigate drug resistance.[2] Therefore, an alternative route of administration that could curb these challenges should be employed to drastically mitigate these problems.

TRANSDERMAL ROUTE AS A SOLUTION

Transdermal drug delivery system (TDDS, patch) is a promising, alternative, and innovative route to the conventional drug delivery routes of oral ingestion and parenteral administration. Its unique advantages include noninvasiveness, prolonged duration of action, avoidance of the first pass effect, reduced dosing frequency, and improved patient compliance, the flexibility of terminating drug administration by removing the patch among others.[13] Regardless of its few disadvantages which include the skin's low permeability due to the barrier offered by the stratum corneum and local irritation at the site of application,[13] notable success has been recorded with the TDDS since the commercial use of Transderm-Scop® patch in the United States of America (US) – the first widely recognized TDDS indicated for motion sickness.[14]

Several other drugs have been formulated into a patch to mitigate against the limitations of their traditional forms [Table 1]; the Nitro-Dur I® (developed by Key Pharmaceuticals), Transderm-Nitro® (by Ciba Pharmaceuticals Company), and Nitrodisc® (Searle Laboratories) were all introduced in 1981 for the prevention and treatment of angina pectoris with an advantage of reduced dosing frequency;[14] transdermal clonidine for the treatment of hypertension with an advantage of reduced side effects and improved patient compliance;[14] and nicotine patches such as Habitrol®, Nicotrol®, Nicoderm®, and Prostep® developed for smoking cessation. This was popularly regarded as the first transdermal blockbuster due to its outstanding milestone where over 1 million smokers quit smoking.[14] In all these transdermal products, the advantages necessitate their delivery as patches. The different techniques for the enhancement of transdermal drug delivery also hold promise for these advantages.

These techniques gave rise to three generations of TDDS [Figure 1].[15]

First-generation delivery systems

They rely mostly on suitable drug characteristics that allow skin absorption without appreciably enhancing skin penetration and do not involve any patch system, drug is formulated into a typical liquid spray, gel, cream, or other topical formulations. Thus, this generation employs passive diffusion in achieving absorption of the drug and characteristic drugs must be of low molecular mass (<600 Da), high lipophilicity, and effective in low dose.[16]

Second-generation delivery systems

They aimed at enhancing skin permeability by adjusting the stratum corneum and applying a driving force (energy-driven methods) to the skin's surface while avoiding harm to the skin's deeper layers. This generation typically involves both skin hydration methods using various chemical enhancers and electrically assisted methods through iontophoresis in enhancing the absorption of the drugs into the skin.[17,18]

Third-generation delivery systems

They also employ energy-driven methods aimed at disrupting or removing the stratum corneum without causing damage to the deeper layers of the skin. Such techniques include microchannel creation as in electroporation and stratum corneum removal as in microscissioning.[15,16,18] Combinations of chemical enhancers, biochemical enhancers, cavitational ultrasound, and microneedles (vaccine delivery) also characterize this

Table 1: Marketed products of transdermal drug delivery.[16]

Brand name	Drug	Manufacturer	Indications
Nicotinell®	Nicotine	Novartis	Pharmacological smoking cessation
Matrifen®	Fentanyl	Nycomed AB	Pain relief patch
Ortho Evra®	Norelgestromin/ethinyl estradiol	ORTHO-McNEIL	Post-menopausal syndrome
NuPatch 100	Diclofenac diethylamine	Zydus Cadila	Anti-Inflammatory
Neupro®	Rotigotine	UCB and Schwarz Pharma	Early-stage idiopathic Parkinson's disease
Alora	Estradiol	TheraTech/Procter and Gamble	Post-menopausal syndrome
Nicoderm®	Nicotine	Alza/GlaxoSmithKline	Smoking cessation
Estraderm	Estradiol	Alza/Novartis	Post-menopausal syndrome
Climara	Estradiol	3M Pharmaceuticals/BerlexLabs	Post-menopausal syndrome
Androderm	Testosterone	TheraTech/GlaxoSmithKline	Hypogonadism in males
Nitrodisc	Nitroglycerin	Roberts Pharmaceuticals	Angina pectoris
Transderm-Scop®	Scopolamine	Alza/Novartis	Motion sickness
Nuvelle TS	Estrogen/Progesterone	Ethical Holdings/Schering	Hormone replacement therapy
Deponit	Nitroglycerin	Schwarz-Pharma	Angina pectoris
Nitro-dur	Nitroglycerin	Key Pharmaceuticals	Angina pectoris
Catapres TTS®	Clonidine	Alza/Boehringer Ingelheim	Hypertension
FemPatch	Estradiol	Parke-Davis	Post-menopausal syndrome
Minitran	Nitroglycerin	3M Pharmaceuticals	Angina pectoris
Duragesic®	Fentanyl	Alza/Janssen Pharmaceutical	Moderate/severe pain
Estraderm	Estradiol	Alza/Novartis	Post-menopausal syndrome
Fematrix	Estrogen	Ethical Holdings/Solvay Healthcare Ltd.	Post-menopausal syndrome
Transderm-Nitro®	Nitroglycerin	Alza/Novartis	Angina pectoris
Oxytrol®	Oxybutynin	Watson Pharma	Overactive bladder
Prostep	Nicotine	Elan Corp./Lederle Labs	Smoking cessation

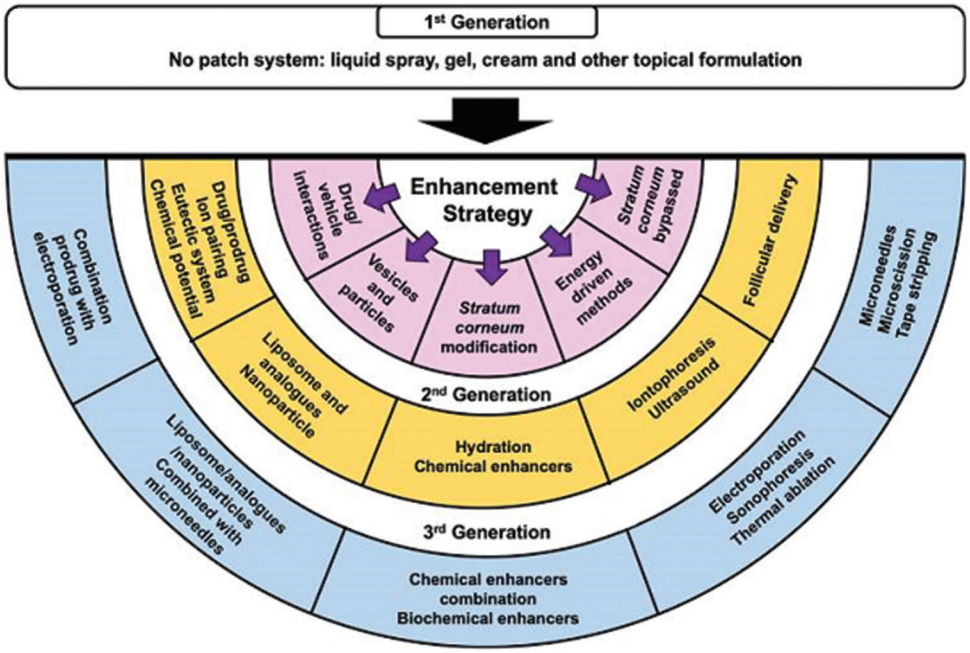

Figure 1: Techniques utilized for enhancing transdermal drug delivery.

generation[15] and they particularly enable transdermal delivery of macromolecules and vaccines.

Antimalarials are not left out in this possibility especially as numerous limitations are building up against the most widely used antimalarial agents – the artemisinin-combination therapies (ACTs); resistance, low bioavailability, and patient non-adherence being the most notable. On this note, several attempts have been made to develop new antimalarial drugs and novel delivery systems, of which transdermal patches are the most mooted option.

Many preclinical studies have revealed promising benefits with transdermal antimalarials. A skin spray of artemisone – a relatively new artemisinin derivative[19] formulated as microemulsions (ART-ME) revealed a high transcutaneous bioavailability and, most significantly, showed complete elimination of *Plasmodium Berghei,* and prevented cerebral malaria (dose: 13.3 mg/kg) when compared to artesunate-ME (dose: 40 mg/kg), untreated, and placebo-treated mice.[20] A similar study also revealed significant suppression of *P. berghei* for transdermal asiatic acid-pectin patch (5 mg/kg) than chloroquine.[21] Increased bioavailability was noticed in a study that identified transdermal surfactant-based ART-LUM (S3AL) as a potential new candidate for the treatment of malaria,[22] thus solving the problems of the low solubility of oral-based therapy ART and LUM. In addition to the aforementioned advantages of TDDS, a cost-effective transdermal bio-adhesive containing ART showed higher absorption and permeation rates,[23] highlighting transdermal antimalarials as a cheap and safe option for patients from low-resource areas. It is imperative to note that following the potentials offered by the various strategies for the enhancement of TDDS as discussed earlier, the properties of the third-generation delivery systems – enabling the transdermal delivery of macromolecules – could be applied to these potential transdermal antimalarial drugs as they are stepped up to human clinical trials.

TOXICOLOGICAL STUDIES OF THE TRANSDERMAL ROUTE

The transdermal route is considered generally safe but not devoid of possible toxicities. Volpe-Zanutto *et al*. showed that the S3AL formulation, out of other formulations used in the study, was found to be the most promising option for a transdermal system based on surfactants in the toxicological investigations.[23] In this formulation, LUM and ART are combined in a liquid crystal system. At concentrations of 1.95 μg/mL of the formulation, almost 80% of human keratinocyte cells were still alive, demonstrating its low toxicity and promise as a drug candidate.[22] In Ananda *et al*.'s preclinical study involving a combination of transdermal patch and solid microneedles for the transdermal delivery of Primaquine, histopathological analyses confirmed the results of *in vitro* hemolytic and *in vivo* irritation tests, which were used to assess the safety of the transdermal patch. Results show hemolysis of less than 5% and no significant damage, which highlights the safety of this approach.[24] In addition, a skin tolerance test was conducted for the nanogel transdermal formulation of ART, and following a 5-day treatment period, no signs of skin reaction, including redness/erythema, wrinkles, papules, and/or dermatitis, were noted.[25] The transdermal antimalarial route has shown to be safe and less toxic. However, it could have common complications faced by the general transdermal route, namely, skin irritation and hypersensitivity and drug accumulation on the skin and patch residue; thus, human clinical trials could offer further perspective on the toxicity profile of these potential transdermal antimalarials.

CONCLUSION

Transdermal delivery offers a viable alternative to oral administration of drugs. Unlike oral delivery, it does not pose adherence issues and can be self-administered. This method enables the sustained release of medications over extended periods, leading to improved patient adherence. In addition, transdermal systems are cost-effective. Numerous drugs have been successfully formulated into patches, overcoming the limitations associated with their traditional forms. However, antimalarials face various challenges when administered orally, even the most widely used antimalarial agents. To address these limitations, formulating antimalarial drugs as transdermal patches, especially while integrating the characteristics of third-generation delivery systems, presents a potential solution as suggested in successful preclinical studies. By doing so, some of the side effects associated with certain antimalarial agents can be mitigated. Transdermal patches offer several advantages, including enhanced safety, improved bioavailability, affordability, and easy accessibility for individuals. This approach has the potential to provide a safe and convenient option for delivering antimalarial medications; thus, clinical trials could be the route to seeing the light at the end of the malaria tunnel.

Authors' contributions

Dr. Chinonyelum Emmanuel Agbo and Dr. Uzochukwu Emmanuel Chima conceptualized and designed this work. All the authors were involved in drafting the full manuscript.

Ethical approval

Not applicable.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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How to cite this article: Agbo CE, Chima UE, Ogbobe SC, Omotayo FO, David SC. Transdermal antimalarial drug delivery to improve poor adherence to antimalarials: A new light at the end of the tunnel. Am J Biopharm Pharm Sci 2023;3:4. doi: 10.25259/AJBPS_14_2023