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From tablets to pharmaceutical nanotechnologies: Innovation in drug delivery strategies for the administration of antimalarial drugs

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ABSTRACT

Malaria pharmacotherapy has slowly progressed from empirical concoctions to present-age multidrug treatments. Malaria therapy complexity is due to the necessity of using multiple drugs to counter the insurgence of parasite resistance, while preventing recrudescence. The recent inclusion in malaria pharmacotherapy guidelines of drugs with suboptimal physicochemical characteristics, primarily artemisinin and its derivatives, urgently calls for the application of technological innovations in drug delivery systems for malaria treatment. New formulation approaches for the combination of two or more drugs in a single medicinal dosage form, could provide innovative medicinal products, improve therapeutic outcomes and enhance patient compliance. The present review focuses on recent technological innovations applied to the co-formulation of antimalarial drugs in drug delivery systems. Solid dosage forms, such as tablets capable of delivering combination of drugs with individual release rates (Dome Matrix® technology) and multiparticulate forms, such as dispersible soft agglomerates are discussed. Furthermore, the application of pharmaceutical nanotechnology to malaria pharmacotherapy is evoked and outlined.

1. Introduction

Malaria affected humanity for thousands of years. Records of occurrences of such disease are well established, emerging from different times and places in the ancient world. It was only in the 19th century that the French doctor Alphonse Laveran showed that malaria was not a direct consequence of breathing “bad air” (malaria in Italian), but a protozoan blood infection transmitted by female Anopheles mosquito bites [1]. Since then, a number of natural products (quinine) and synthetic therapeutic compounds (mepacrine, sontoquine, chloroquine and antifolates, such as pyrimethamine) were used for the treatment of malaria. However, by the 1970s *Plasmodium* strains resistant to many of the available drugs appeared, making the efficient treatment of the disease more challenging. The subsequent development of a new class of drugs obtained from Artemisia annua, i.e., artemisinin and its semi-synthetic and water-soluble derivatives artesunate, artemether and dihydroartemisinin, has provided new therapeutic approaches even against choloroquine-resistant strains of *Plasmodium falciparum* [2].

Malaria therapy involves complex dosage regimens that are known to reduce patient adherence to the therapy. Poor patient compliance contributes to the emergence of multidrug resistant strains of parasites [3]. Indeed, the complexity of the chemotherapy is due to the different stages of the parasite life cycle. The most difficult stage to address is the dormant form or hypnozoite, that causes relapse in *Plasmodium vivax* and *Plasmodium ovale* infected patients. Oral antimalarial preparations must rapidly clear the parasite burden during the acute phase of the infection and prevent malaria recrudescence by eliminating the residual parasites. This two-tier activity is achieved combining a fast-acting, short elimination half-life drug, such as an artemisinin-derivative, with a long-acting drug, such as lumefantrine or piperaquine. Therefore, the necessity of a multidrug treatment is stringent [4,5].

Hence, oral pharmacological treatment of malaria is based on the combination of at least two drugs differing in mode of action

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and pharmacokinetic characteristics. The aim of a combination therapy is to provide a rapid and positive therapeutic outcome and simultaneously reduce the risk of inducing parasite resistance. A desirable pharmaceutical preparation should be co-formulated and (ideally) administered once-a-day to ease therapeutic regimen and improve patient compliance. Unlike the concurrent intake of different drugs as individual dosage forms, fixed-dose combinations (FDCs) offer the advantage of assuring the correct dosing of the therapeutic agents in a single dosage form. This reduces the risk of under-dosing the drugs. Even if FDCs do not appear to have clinical superiority over their loose counterparts [6], the improvement of the administration scheme and facilitation of dosage form assumption still remain a critical step in malaria therapy. It should be also considered that most subjects affected by malaria live in countries where socioeconomic conditions might further complicate the therapy management and patient compliance.

The challenges that formulation scientists primarily face to develop such dosage forms are the suboptimal physicochemical properties of the antimalarial drugs, such as poor aqueous solubility and high lipophilicity. These largely affect the drug pharmacokinetic characteristics, in particular absorption and biodistribution, ultimately jeopardizing therapeutic efficacy. The preparation of a co-formulated product in a single dosage form may be also hindered by the high dose of the drugs along with the excipients required in a FDC product. The final pharmaceutical solid dosage form can become too large and difficult to swallow, especially for children, where a dispersible formulation is preferred. Recently, Coartem® Dispersible tablets (Novartis, Basel, Switzerland) have been marketed specifically for paediatric administration with this problem in mind.

Novel pharmaceutical technologies for oral drug delivery can provide optimized pharmacokinetic profiles, controlling the drug release rate and maintaining the drug concentration within its therapeutic window. Therefore, the risk of exposing parasites to sub-therapeutic drug levels, which may lead to the selection of resistant strains, is decreased. In addition, paediatric patients may further benefit from novel pharmaceutical preparations for they can provide individualized dosage forms that could account for the differences in patient body weight (biological development) and age (cognitive development). The roadmap to novel pharmaceutical technologies is easier, faster and cheaper than drug discovery. These technologies may improve the therapeutic efficacy of existing drugs and reduce the risk of resistance. Moreover, a formulation providing optimized drug release and absorption may also result in reduced adverse events and improved tolerability [7].

Indeed, this rediscovery of existing drugs could be an interesting approach not only in the treatment, but also in the prophylaxis of malaria. Although innovative drug delivery systems might have relatively higher manufacturing costs compared to conventional formulations, they still represent a cheaper alternative when considering the treatment overall long term costs due to recrudescence, therapeutic failure and parasite resistance incurred by the use of conventional formulations.

2. Combination products of antimalarial drugs

Combination therapy, i.e., the combined use in a single dosage unit of two or more drugs with independent mechanisms of action and/or different biochemical targets in the parasite, has become the official policy for malaria pharmacotherapy according to the WHO, particularly after the introduction of artemisinin. In fact, it has been understood that monotherapy increases (and has increased) the chances of developing resistance [8]. Moreover, in order to eradicate the parasite and prevent the development of resistance to each drug, compliance is especially relevant during malaria therapy [9]. Adherence to therapy could be achieved by interventions focusing on combined and personalized provision of doses, reducing the burden of multiple dosage forms [10]. This means that there is a real need for innovative dosage forms capable of simplifying the multidrug administration, maintaining the appropriate drug release conditions.

In this section, two proprietary technologies for drug delivery are described that represent a solution for combined drug administration to adults or children [11,12]. Such drug delivery technologies refer to a tablet dosage form for adults and a powder preparation apt for administration in patients unable to swallow tablets as such. As opposed to existing combination products in which the drugs are intimately mixed and delivered as immediate release dosage forms, these technologies enable the administration of two or more drugs in a single dosage unit, providing the optimal individual biopharmaceutical properties of each drug, i.e., dissolution and release.

The Dome Matrix® module assembly technology allows for the construction by assemblage of multidrug and multi-kinetics drug delivery systems [13]. Dome Matrix® modules or release units are disc tablets having one concave and one convex base, so that the assembly can be obtained by interlocking the convex base of one module in the concave base of another one. The modules can be formulated as matrices for prolonged release (e.g. swellable) or for immediate release, therefore offering different delivery programs. Each module contains one drug that can be released individually at a rate depending on module composition. Therefore, two or more antimalarial drugs could be formulated in the same preparation, each one in a separate module. If required by the different pharmacokinetics of the selected drugs, different release programs with respect to site and/or time of delivery of the single drugs can be obtained by module assemblage.

Strusi et al. proposed a novel drug delivery system for clindamycin and artesunate based on a modular dosage unit capable of releasing the drugs at different rates and sites (Fig. 1) [14]. In detail, four modules having different composition and/or shape were manufactured by tableting and assembled in the final dosage unit. The two central modules containing clindamycin, formulated as swellable matrices, were interlocked concave base to concave base forming a 'void' configuration system. Due to the presence of an internal cavity, the assembly exhibited floating properties providing gastroretention and prolonged release of clindamycin in the upper gastrointestinal tract. The enhanced gastroduodenal absorption of clindamycin would reduce the residual unabsorbed drug reaching the bowel, thus limiting one of the most common side effects, i.e., Clostridium difficile-associated diarrhoea. Drug release in gastroretentive conditions represents the optimal way to maintain the plasma concentration levels of clindamycin stable and within the therapeutic window, while minimizing intestinal adverse effects. In addition, a third module containing a fraction of the clindamycin dose for immediate release was added on one side of the previous assembly (module E of the assembly in Fig. 1). This module was conceived to provide the loading dose of the antibiotic. Finally, a fourth immediate release module containing artesunate (module B of the assembly in Fig. 1) was added by interlocking on the opposite side of the assembly. In summary, the resulting modular drug delivery system had the following properties: it contained and released two different drugs divided among four modules, collectively performing site-specific release of the drugs at two different kinetics (immediate and prolonged), optimizing the drug release characteristics of this antimalarial drug combination. The manufacturing of the final dosage form, particularly for the module assemblage step, can be performed industrially by fully automated equipment. However, it could be also envisaged that this technology will enable the pharmacist to provide a specific