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Review Paper

A Brief Review on Quinine Sulphate Sustained Release Tablet

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ABSTRACT

Malaria continues to pose a significant global health burden, particularly in developing regions with limited healthcare access. Conventional antimalarial therapies, while effective, suffer from limitations such as short drug half-lives, poor patient compliance, and the rising threat of drug resistance. In response to these challenges, sustained release (SR) tablet formulations are emerging as a promising strategy to optimize antimalarial drug delivery. This review paper presents a comprehensive overview of the formulation approaches, materials used, pharmacokinetic benefits, and clinical implications of SR antimalarial systems. The paper discusses the use of both natural and synthetic polymers such as Hydroxypropyl Methylcellulose (HPMC), sodium alginate, and ethyl cellulose in designing matrix and reservoir-type SR tablets for drugs like artemisinin derivatives, chloroquine, and lumefantrine. The advantages of sustained release systems include prolonged therapeutic effect, reduced dosing frequency, and minimized plasma level fluctuations, thereby enhancing efficacy and reducing resistance potential. Additionally, we highlight the challenges in scaling up, stability considerations, and future directions in nano-based SR delivery systems.

INTRODUCTION

Malaria remains a major public health threat, particularly in tropical and subtropical regions. According to the World Health Organization (2023), an estimated 249 million cases of malaria occurred worldwide in 2022, resulting in over 600,000 deaths, with the majority reported in sub-Saharan Africa. The disease is primarily caused by protozoan parasites of the genus Plasmodium, transmitted to humans through the bites of infected Anopheles mosquitoes. The global burden of malaria continues to challenge health systems, especially in resource-limited settings where access to timely and effective treatment is often inadequate. [1]

Historically, quinine, an alkaloid derived from the bark of the Cinchona tree, was one of the first effective treatments for malaria and remained the cornerstone of therapy for centuries. Although

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quinine is still used today, especially in severe cases and in areas with multidrug-resistant Plasmodium falciparum, its utility is limited by several pharmacological drawbacks. These include a short elimination half-life, necessitating frequent dosing, and a narrow therapeutic index that can lead to adverse effects such as tinnitus, dizziness, and gastrointestinal disturbances.[1]

Conventional immediate-release quinine tablets often fail to maintain consistent plasma concentrations, which can reduce therapeutic efficacy and contribute to the development of drug resistance. Frequent dosing regimens can also compromise patient compliance, particularly in rural and underserved populations.[2]

To address these limitations, sustained release (SR) formulations have been proposed as a strategic alternative. SR systems are designed to release the active drug at a controlled rate, maintaining therapeutic levels over a prolonged period. This approach offers multiple advantages: improved patient adherence due to reduced dosing frequency, minimized peak-trough fluctuations in drug levels, and potentially lower incidence of side effects. Furthermore, SR tablets can enhance the overall bioavailability of the drug and contribute to better treatment outcomes, particularly in long-term malaria management and prophylaxis.

This review focuses on the development and therapeutic advantages of sustained release antimalarial formulations, with particular attention to quinine and other commonly used antimalarial agents.

ADVANTAGES OF SUSTAINED RELEASE DOSAGE FORM:

1. Decreased local and systemic side effects: - Reduced gastrointestinal irritation.
2. Better drug utilization: - Reduction in total amount of drug used. - Minimum drug accumulation on chronic dosing.[9]
3. Improved efficiency in treatment.
4. Optimized therapy.
5. Reduction in fluctuation of drug level and hence more uniform pharmacological response. 6. Special effects e.g. sustained release aspirin provides sufficient drug so that on awakening the arthritic patient gets symptomatic relief.[11]
6. Cure or control of condition more promptly.
7. Less reduction in drug activity with chronic use.[12]
8. Method by which sustained release is achieved can improve the bioavailability of some drugs e.g. drugs susceptible to enzymatic inactivation can be protected by encapsulation in polymer systems suitable for sustained release.[9],[10],[11]

DISADVANTAGES OF SUSTAINED RELEASE DOSAGE FORM:

1. Dose dumping: Dose dumping may occur with faulty formulation.
2. Reduced potential for dose adjustment.
3. Cost is more than conventional dosage form.
4. Increase potential for first pass metabolism.
5. For proper medication patient education is necessary.
6. Possible reduction in systemic availability.
7. Poor in vivo and in vitro correlations.[9],[10],[18]

Pharmacology of Quinine Sulphate

Chemical Structure and Properties: Quinine sulphate is a natural cinchona alkaloid, chemically classified as a stereoisomeric compound with the molecular formula C20H24N2O2·H2SO4·2H2O. It is a white crystalline powder, slightly soluble in water but freely soluble in alcohol. The compound contains a quinoline ring fused with a quinuclidine moiety, which is essential for its antimalarial activity. Its alkaloid nature allows it to readily cross biological membranes, contributing to both its therapeutic effects and potential toxicity.[3]

Mechanism of Antimalarial Action: Quinine primarily acts against the erythrocytic stage of Plasmodium parasites. Its mechanism of action involves inhibition of hemozoin biocrystallization. During hemoglobin digestion inside the parasite's food vacuole, toxic free heme is released. Quinine binds to this free heme, preventing its detoxification into non-toxic hemozoin. The accumulation of toxic heme leads to oxidative stress and parasite death.[4]

Pharmacokinetics and Pharmacodynamics: Quinine sulphate is rapidly absorbed following oral administration, with peak plasma concentrations occurring within 1 to 3 hours. It has a plasma half-life of approximately 10–12 hours, although this may vary depending on disease state and hepatic function. The drug is extensively distributed throughout body tissues, including the brain, which makes it effective in treating cerebral malaria. Quinine is metabolized hepatically, primarily by cytochrome P450 enzymes (especially CYP3A4), and excreted in urine both as metabolites and unchanged drug.[5]

Pharmacodynamically, quinine exhibits a concentration-dependent killing effect on malaria parasites. However, its narrow therapeutic index necessitates careful monitoring to avoid adverse effects like cinchonism, hypoglycemia, and cardiac arrhythmias, particularly in sustained or high doses.[5]

Need for Sustained Release Formulation:

1. **Challenges with Conventional Dosage:** Conventional quinine sulphate tablets are typically administered two to three times daily, which can lead to poor patient compliance, especially in regions with limited healthcare supervision. Moreover, the short plasma half-life and rapid elimination of quinine necessitate frequent dosing to maintain therapeutic concentrations. This frequent dosing increases the risk of missed doses, leading to subtherapeutic plasma levels and possible treatment failure or emergence of drug resistance.[1]
2. **Importance of Maintaining Therapeutic Levels:** The therapeutic window of quinine is narrow, meaning that plasma concentrations must be carefully controlled too low, and the drug becomes ineffective; too high, and toxicity ensues. Conventional formulations result in peaks and troughs in drug levels, which can compromise both efficacy and safety. Sustained release (SR) systems offer a solution by maintaining steady-state drug levels over a longer period, ensuring consistent therapeutic action and minimizing fluctuations that cause side effects or resistance development.[2]
3. **Improved Patient Compliance:** Sustained release formulations reduce the frequency of administration often to once daily there by enhancing patient adherence, particularly in remote or underserved regions where patients may have limited access to medical guidance or transportation. By simplifying dosing schedules and minimizing side effects, SR tablets support completion.[6]

Formulation Strategies:

Developing a sustained release (SR) antimalarial tablet, particularly for quinine sulphate, involves selecting appropriate excipients, delivery techniques, and modifiers that control the release rate of the drug, ensuring a prolonged therapeutic effect.

Common Excipients Used: Polymers play a central role in modulating drug release from sustained release formulations. Commonly used hydrophilic and hydrophobic polymers include:

Hydroxypropyl Methylcellulose (HPMC): A swellable, gel-forming polymer that slows drug release via matrix erosion or diffusion.

Ethyl Cellulose: A water-insoluble polymer used in matrix tablets and coatings to provide extended release by forming diffusion barriers.

Sodium alginate, Carbopol, and Eudragit RS/RL: Frequently used in combination for modifying release profiles and improving tablet integrity.[7]

Matrix Tablet Technique: In this approach, the drug is dispersed within a polymer matrix. Upon hydration, the outer layer of the tablet swells or erodes, allowing the drug to diffuse slowly. Matrix tablets are simple, cost-effective, and suitable for high-dose drugs like quinine.[2]

Coating Methods: Polymeric coatings—especially those made from ethyl cellulose or Eudragit—are applied to core tablets to regulate drug release. These film-coated systems act as semi-permeable membranes, controlling drug diffusion and providing site-specific delivery.[3]

Osmotic Pumps: Osmotic pump systems consist of a drug core and a semi-permeable membrane with a delivery orifice. Water enters the tablet, dissolves the drug, and pushes it out at a controlled rate through osmotic pressure. These systems offer zero-order kinetics, delivering a constant drug amount over time.[7]

Role of Release Modifiers and Binders: Release modifiers such as magnesium stearate, polyethylene glycol (PEG), or waxes are added to adjust the rate of water penetration or erosion of the matrix. Binders like polyvinylpyrrolidone (PVP) or starch help maintain tablet integrity and improve mechanical strength, which is crucial in SR systems where structural failure can cause dose dumping. choice and combination of excipients significantly influence the drug release kinetics, making preformulation studies essential for optimization.[6]

Biological factors influencing release from matrix tablet:

1.Biological half-life: Therapeutic compounds with short half-lives are excellent candidates for sustained-release preparations, since this can reduce dosing frequency.[10]

1.Absorption : The absorption rate constant is an apparent rate constant, and should, in actuality, be the release rate constant of the drug from the dosage form. If a drug is absorbed by active transport, or transport is limited to a specific region of the intestine, sustained-release preparations may be disadvantageous to absorptions.[11]

2.Metabolism: Drugs that are significantly metabolized before absorption, either in the lumen or tissue of the intestine, can show decreased bioavailability from slower-releasing dosage forms. Most intestinal wall enzyme systems are saturable. As the drug is released at a slower rate to these regions, less total drug is presented to the enzymatic process during a specific period, allowing more complete conversion of the drug to its metabolite

1. Physicochemical factors influencing oral sustained release dosage form design.[12]
2. Dose Size In general, single dose of 0.5 – 1.0 g is considered maximal for a conventional dosage form. This also holds true for sustained-release dosage forms. Another Consideration is the margin of safety involved in administration of large amounts of drug with a narrow therapeutic range.[12]
3. Ionization, pKa and aqueous solubility Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the pKa of the compound and the absorptive environment. Delivery systems that are dependent on diffusion or dissolution will likewise be dependent on the solubility of drug in the aqueous media. For dissolution or diffusion sustaining forms, much of the drug will arrive in the small intestine in solid form meaning that the solubility of the drug may

change several orders of magnitude during its release. The lower limit for the solubility of a drug to be formulated in a sustained release system has been reported to be 0.1 mg/ml.[13]

4. Partition coefficient Compounds with a relatively high partition coefficient are predominantly lipid-soluble and, consequently, have very low aqueous solubility. Furthermore these compounds can usually persist in the body for long periods, because they can localize in the lipid membranes of cells. Meaning that the solubility of the drug may changes several orders of magnitude during its release.[14]

Evaluation of Sustained release Matrix tablets:

Before marketing a sustained release product, it is must to assure the strength, safety, stability and reliability of a product by forming in-vitro and in vivo analysis and correlation between the two. Various authors have discussed the evaluating parameters and procedures for sustained release formulations.[16]

1. **Weight Variation:** Twenty tablets were weighed individually and then collectively, average weight of the tablets was calculated.
2. **Hardness:** Hardness test was conducted for tablets from each batch using Monsanto hardness tester and average values were calculated.[19]
3. **Friability:** The tablets were tested for friability testing using Roche friabilator, which revolves at 25rpm for 4min.
4. **Thickness:** The thicknesses of tablets were determined using micrometer screw gauge.
5. **Content Uniformity:** Using UV Visible spectrophotometer found the amount of the drug using the calibration curve method.[18]
6. **In vitro dissolution study:** Drug release study is generally determined in Rotating Paddles apparatus. Mainly buffer is used as a dissolution medium. The temperature of the bath maintained at 370C and required sample of the dissolution medium in which drug is release is taken at a regular interval and the same quantity of the medium is replace.[20] The amounts of the drug released is determined using an UV spectrophotometer a Drug dissolved at specified time period is plot as percent release versus time. [9],[10]
7. **Stability Studies:** Short Term Stability Study: To determine change in vitro release profile on storage, a short term stability study of the optimal batch.[8],[21]

CONCLUSION

Quinine sulphate remains a vital antimalarial agent, particularly effective against *Plasmodium falciparum* strains resistant to other treatments. The development of sustained release (SR) formulations of quinine sulphate has significantly enhanced therapeutic outcomes by maintaining consistent plasma drug levels, improving patient compliance, and reducing dosing frequency and side effects associated with peak-trough fluctuations. Various formulation strategies—including matrix systems, hydrophilic polymers, and novel drug delivery technologies—have demonstrated promising results in optimizing the release profile of quinine sulphate. Continued research and development in this area are crucial to addressing the challenges of drug resistance and to expanding the therapeutic utility of quinine through improved patient-centric delivery systems.

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