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Pharmacokinetic Analysis and in Vivo Efficaciousness of Anti-Malarial Medications Co-Encapsulated in Tween 80 Niosomes

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ABSTRACT:

To enhance drug conveyance and healing outcomes, pharmacokinetic study and in vivo suitability of anti-malarial drugs co-encapsulated inside Tween 80 niosomes were investigated. The survey utilized an exhaustive approach to address the strength of the niosomal details, drug discharge profiles, and exemplification proficiency. The issue of further developed opposition much of the time plagues drugs utilized for malaria treatment and prevention. This renders them unfit for monotherapy and reduces their usefulness. Assuming they are repackaged and mixed properly, many of these neglected anti-malarial medications may eventually make it back into the therapeutic system. The effectiveness of niosome-encased curcumin (CC) and primaquine (PRI) as an anti-malarial combination is compared to that of the two drugs alone. Treatment with a mix of 35 mg/kg of CC plus either 5 mg/kg or 1 mg/kg of PRI resulted in complete anti-malarial action and 20 days of survival in Plasmodium berghei-infected mice. Expanded assurance and endurance rate were associated with counteraction in recrudescence with the hazardous based PRI-CC combo treatment. The review's findings suggest that a baneful-based PRI-CC combo treatment could be a promising malaria treatment approach.

Keywords: Pharmacokinetic analysis, efficaciousness, anti-malarial medications, co-encapsulated, Tween 80 niosomes

1. Introduction

Malaria continues to be a major global health concern, particularly in areas where access to powerful treatment is restricted. The enhancement of innovative drug delivery methods has sparked a great deal of interest in improving the pharmacokinetic characteristics and therapeutic results of anti-malarial drugs. Niosomes, or non-ionic surfactant vesicles, have emerged as one of these systems' most promising options because to their biocompatibility, security, and ability to successfully represent both hydrophilic and hydrophobic drugs.

The non-ionic surfactant Tween 80 is widely used because of its ability to balance out niosomal plans and biocompatibility. Tween 80 improves drug dissolvability and helps with the assisted delivery and delayed course of encapsulated medications in vivo when it is added to niosomes. This feature is particularly helpful when treating malaria, as it is important to maintain high drug concentrations for extended periods of time in order to eradicate the Plasmodium parasite and prevent the disease from returning.

Understanding the absorption, distribution, metabolism, and excretion (ADME) patterns of drugs encapsulated in niosomes is crucial, and pharmacokinetics focuses on this. Through exploring these limits, researchers can examine how niosomal schemes affect drug bioavailability and tissue distribution in comparison to traditional drug delivery methods. These kinds of details are essential for enhancing dosage schedules and predicting restorative sufficiency in medical environments.

Moreover, evaluating the in vivo survivability of anti-malarial drugs co-encapsulated in Tween 80 niosomes gives fundamental data regarding their ability to repress parasite development and mitigate adverse medication reactions. Preclinical investigations involving animal models enable researchers to observe drug behavior in an environment of natural selection by assessing factors such as parasite escape rates, survival rates, and histological alterations in vital organs. These findings are critical in determining the utility of niosomal information and guiding its progression towards clinical preliminary studies.

Combining pharmacokinetic analysis with assessments of in vivo viability provides a thorough approach to managing the advancement of anti-malarial drug delivery methods. Analysts hope to improve medicine solidity, extract useful adequacy, and ultimately contribute to more successfully managing malaria contaminations globally by outfitting the upsides of Tween 80 niosomes.

Anti-Malarial Medications

Plasmodium parasites, which cause malaria, are a potentially fatal disease that individuals contract through the nibbles of contaminated Anopheles mosquitoes. Effective treatment and prevention techniques are essential for managing and ultimately eliminating malaria. Anti-malarial drugs are essential to these tactics because they cure active infections, prevent sickness in high-risk groups, and reduce the spread of the disease.

Types of Anti-Malarial Medications

Anti-malarial drugs can be generally categorized into multiple groups according to the stage of the parasite life cycle they target and their mode of action. The primary classes include derivatives of artemisinin, antifolates, chemicals related to quinoline, and antibiotics.

1. **Quinoline-related Compounds**: Quinine, mefloquine, primaquine, and chloroquine are all included in this class. The main therapy for malaria used to be chloroquine, however due to widespread resistance, it is no longer as effective. Quinine, which is derived from the cinchona tree's bark, has been used for a very long time and is still effective against some resistant strains. Because of its exceptional capacity to selectively target the parasite's liver stage, primaquine is crucial for the drastic treatment of Plasmodium vivax and Plasmodium ovale infections.

2. **Antifolates**: These drugs, like sulfadoxine-pyrimethamine, prevent the parasite from combining folate, which is required for cell division and DNA synthesis. Although antifolates are viable, their use has been limited due to the quick advancement of resistance.

3. **Artemisinin Derivatives**: Artemisinin, which comes from the sweet wormwood plant, and its byproducts, artemether, dihydroartemisinin, and artesunate, are incredibly effective against the parasite at every stage. Because artemisinin-based combination treatments (ACTs) are so potent and quick to act, they continue to represent the gold standard for treating uncomplicated malaria. ACTs reduce the likelihood that resistance will improve by taking an artemisinin derivative along with a companion drug.

4. **Antibiotics**: Medications such as clindamycin and doxycycline are used in conjunction with other anti-malarial drugs to maximize effectiveness and prevent resistance. These antibiotics prevent the parasite from synthesizing proteins, which stops the parasite's growth and spread.

Mechanism of Action

Anti-malarial drugs remove the parasite from the host's body using a number of different methods. Quinoline-related substances interfere with the parasite's capacity to detoxify heme, which is produced during the digestion of hemoglobin, causing toxic buildup and eventual parasite death. The production of folic acid, which is essential for the replication of parasite DNA and cell division, is inhibited by antifolates. Reactive oxygen species produced by artemisinin derivatives harm the parasite's proteins and membranes, swiftly destroying it. Antibiotics suppress the growth and spread of parasites by interfering with the synthesis of proteins.

An essential component of treating and controlling malaria are anti-malarial drugs. Despite obstacles like drug resistance, ongoing research and innovation are working to expand the pool of treatments accessible, raising the prospect of a day when malaria is eradicated.

Role of Tween 80 In Niosome Formulation

Polysorbate 80, or tween 80, is an essential component in niosome formulation that improves stability, biocompatibility, and drug delivery efficiency. Niosomes are lipid-based vesicles that are designed to encapsulate both hydrophilic and hydrophobic medications. They are made of cholesterol and non-ionic surfactants. A popular non-ionic surfactant, Tween 80, has several benefits when it comes to niosome composition:

1. Stabilization and Size Control: Tween 80 reduces the interfacial pressure between the aqueous and lipid phases, which helps to stabilize niosomal vesicles. By enhancing the structural integrity of niosomes, this surfactant prevents drug encapsulation from aggregating and leaking. It also helps to regulate the niosome size distribution, ensuring consistency that is essential for drug delivery applications.

2. Enhanced Biocompatibility: Tween 80-formulated niosomes exhibit improved biocompatibility and decreased toxicity. This is especially helpful for biomedical applications where it's important to minimize negative effects on biological systems. Regulatory agencies have generally regarded tween 80 as safe (GRAS), which supports its use in pharmaceutical formulations.

3. Facilitates Drug Encapsulation: The encapsulation productivity of hydrophilic and hydrophobic pharmaceuticals within niosomes is improved by Tween 80. Because of its amphiphilic nature, it can solubilize a lot of medications throughout the formulation cycle, which increases the loading capacity and bioavailability of the pharmaceutical. Working on the therapeutic efficacy of anti-malarial drugs co-encapsulated in niosomes requires this characteristic.

4. Drug Release Modulation: The energy of drug release from niosomes can be affected by the presence of Tween 80. Tween 80 can support regulated drug release profiles, depending on its concentration and how it interacts with other elements of the niosomal formulation. Sustaining therapeutic levels and improving treatment outcomes depend on this control over medication release energy.

5. Compatibility with Biological Fluids: In biological liquids such as blood plasma, gastrointestinal liquids, and intracellular environments, Tween 80 improves niosome stability. This characteristic is essential to ensure that niosomes genuinely deliver encapsulated medications to intended locations throughout the body without pharmaceutical leakage or degradation occurring too soon.

Tween 80 contributes in several ways to the formulation of niosomes, including stability, biocompatibility, drug encapsulation effectiveness, controlled release, and biological compatibility. These characteristics render it a highly adaptable and potent element in the enhancement of niosomal formulations intended to deliver anti-malarial drugs and additional therapeutic agents.

2. Materials and Methods

Reagents, chemicals, and instruments

Sigma-Aldirch gave the tween 80, cholesterol, and stearylamine (STA) (Mumbai, India). Ipca Laboratories Ltd. given a gift sample of primaquine diphosphate (Mumbai, India). A complimentary sample of curcumin was given by Konark Herbals and Health Care (Mumbai, India). Himedia Laboratories Pvt. Ltd. given field stains A (an azure color arrangement cushioned) and B (an eosin arrangement cradled) (Mumbai, India).

Making drug- and blank-co-loaded niosomes

A rotary evaporator was utilized in the thin film hydration methodology to prepare niosomes co-loaded with PRI and CC. The impacts of various molar ratios of cholesterol, Tween 80, and STA on size and medication encapsulation efficacy were assessed. After precisely gauging the excipients into a flask with a circular base, they were dissolved in chloroform. Utilizing a decreased strain and 100-150 rpm, the organic dissolvable was dynamically evaporated at 60°C to deliver a dainty, dry layer of the excipients on the flaskwall. PBS was used to hydrate the film (pH 7.4). When necessary, medications were introduced during the hydration interaction. To obtain consistent estimated Tween 80 medicine co-loaded niosomes, sonication and rapid centrifugation were used after this. Before cutting back using sonication, phase contrast microscopy was used to verify the production of niosomes.

Analysis of particle size and charge

Transmission electron microscopy (TEM) using a carbon-coated gold organization was used to analyze the size and shape of blank and medication coloaded niosomes. The niosome samples were made by putting a drop of co-loaded medication and blank formulations on various gold organizations, trailed by drying the dissolvable. A Philips CM200 electron microscope was used to see the size and shape of the sample at 80 kV following its absorption on the lattice. Photon correlation spectroscopy (PCS) (Malvern Zetasizer, USA) didn't completely settle the charge of the Tween-80 blank and pharmaceutical co-loaded.

Primaquine diphosphate and curcumin HPLC analyses

To measure PRI and CC simultaneously, an appropriate, express, exact, and thorough HPLC strategy was created and checked. The portable phase, which was acetonitrile and phosphate

solution (KH2PO4) (pH 4.5) poured at a rate of 1 milliliter each moment, was a stationary phase that was an inertsil ODS 3V exchanged phase C18 column. An array detector (DAD), ternary siphon, and ChromNav software comprised the chromatographic apparatus (Jasco 1200, Palo Alto, CA, USA) that was employed. A 250 nm measurement was made of the two medications' absorbance.

Efficiency of encapsulation

The medication-containing niosomal dispersions were centrifuged for five minutes at 4℃ at 200 g. Unentrapped CC remains in crystal structure after centrifugation, shaping a pellet, rather than solubilizing in the medium because of CC's restricted dissolvability in aqueous settings. Separating the pellet containing the unentrapped CC from the supernatant containing the niosomes loaded with CC was necessary. After dissolving the pellet in methanol, the medication content was calculated using the HPLC strategy, as of late mentioned. Using the accompanying equation, the encapsulation efficiency not totally settled:

$$EE\% = \frac{Intial\ drug\ added\ -\ Free\ drug}{Intial\ drug\ added} \times 100$$

Drug Release In Vitro

To tackle in vitro drug release in PBS (pH 7.4), the dialysis bag dispersion approach was employed. Brief hydration of the dialysis bags in PBS (pH 7.4) was performed before to the test. Two milliliters of the niosome formulation were loaded into a dialysis bag, which was subsequently placed in a vessel containing five hundred milliliters of 0.1% Tween 80 dissolving media. I set the paddle speed to 50 rpm while the temperature was 37 ± 2℃. It was standard procedure to remove 5 ml portions of medium from the container and replenish them at regular intervals. After being centrifuged for 10 minutes at 5000 rpm, portions were extracted using a 0.22 μm needle catheter. The HPLC method shown above was used to analyze the filtrates for drug concentration.

Haemocompatibility study

Any experimental work using human blood has to have Institutional Ethics Committee (IEC) approval before it could begin (NMIMS/IEC/007/2013).

One reasonable method of determining poisonousness is in vitro erythrocyte compatibility testing. It calculates the amount of in vivo membrane damage brought on by formulation. Five milliliters of heparinized blood from the blood donation center were centrifuged for twenty minutes at a weight of 1000 kg. The packed RBCs were removed from the buffy coat and three times cleaned with regular saline. A haematocrit of 50% was produced using ordinary saline. As it did not induce hemolysis, mixing 100 µl of cell suspension with 3 ml of normal saline served as a negative control. For the purpose of serving as a positive control that showed complete hemolysis, another test tube was filled with 100 µl of cell suspension and 3 ml of 18% Triton X-100 solution. Every test and control tube was also treated with Drabkin's solution. The absorbance of the partially fixed substance was measured at 504 nm using a spectrophotometer in comparison to a control sample. The testing sample's hemolysis initiation % (n = 3) was determined using the equation:

$$\%haemolysis = \frac{Absorbance\ of\ test\ sample}{Absorbance\ at\ 100\%\ lysis} \times 100$$

Animals used in experiments

We bought male Swiss albino mice from Bharat Serums and Vaccines in Mumbai, India. They weighed about 18 to 20 grams. The animals were kept in cages and subjected to standard living conditions, such as 12-hour light-dark cycles and temperatures ranging from 24 to 27 degrees

Celsius. Nutrivet Life Sciences of Pune supplied the dry pellets and water, which were accessible at all times. The animals were given 14 days to adjust to their laboratory environment before the studies began.

The Institutional Animal Ethics Committee's approval (CPCSEA/IAEC/SOS/P-01/2015) was acquired before any animal work began. All of the experiments were conducted in compliance with the Committee's guidelines with the approval of the Ministry of Social Equity and Strengthening, Administration of India's Control and Supervision of Experiments on Animals (CPCSEA).

Studies on Acute Toxicity

The acute harmfulness investigations were carried out in compliance with OECD Regulation 423. The mice were allowed a 12-hour fast before the review began. The niosome formulation was momentarily dissolved in saline, the channel was cleaned before use, and the mice were given a solitary portion of 2000 mg/kg b.w. intraperitoneally. Animals were noticed for any indications of injury, death, alterations in body weight, or behavioral changes all through the examination. At the finish of the 14-day center period, the animals were slaughtered for additional histological examination. Organs were eliminated, and the liver and kidney histological abnormalities were examined.

Assessment of in vivo pharmacodynamics: studies on antimalarial efficacy

- **Parasites**

The fatal rat malaria parasite P. berghei ANKA strain was utilized in vivo antimalarial investigations. The life pattern of this strain is nearly identical to that of human malaria parasites. It taints mice fatally and is resistant to all as of now utilized antimalarial medications, making it a suitable model for estimating the viability and survival. To maintain the parasite load in vivo, about 106 RBCs were intraperitoneally supplied to donor mice using the thawed frozen load provided by Dr. Shobhona Sharma of the Tata Organization of Fundamental Research, Mumbai.

- **Evaluation of parasitemia in infected mice**

Peripheral blood smears were partially recorded on glass slides utilizing blood drawn from the contaminated mice's tail veins. After five minutes of methanol fixation, the movies were stained with 5% Fields' stain. A light microscope with a 100× magnification was utilized to analyze blood smears. Not confirmed by counting a thousand erythrocytes in at least five fields of view.

- **Commencement of the anti-malarial and recrudescence test**

Experiments were conducted in accordance with Osdene's strategy. The mice were split up into ten groups of eight individuals each for a brief period of time (Table 1). The effects of niosomes loaded with curcumin on the survival and development of parasitemia in P. berghei-contaminated mice during a 14-day period are displayed in the table; each group comprises six animals. On the third day, the mice treated with 35 mg/kg curcumin in Tween 80 solution (32.5 ± 9.23%) and those left untreated (27.9 ± 7.5%) had the highest levels of parasitemia, whereas the mice treated with 35 mg/kg curcumin niosomes (16.5 ± 5.3%) had the lowest levels. On day seven, mice treated with 10 mg/kg, 20 mg/kg, and 35 mg/kg curcumin niosomes demonstrated lower parasitemia and higher survival rates, while untreated mice and those given 35 mg/kg curcumin in Tween 80 showed high parasitemia (47.00% and 53.00%, respectively) and significant mortality (only 2 out of 7 made it). By day 14, survival was generally low in all groups; however, as compared to non-niosomal treatments, niosome treatments showed some improvement in survival and control of parasitemia. On days 1, 2, 3, 4, 5, 8, 12, 15, 18, 21, 24, 28, and 30, the parasite counts were performed using scant tail blood smears.

Table 1: Impact of niosomes loaded with curcumin on the survival and progression of parasitemia in mice infected with P. berghei. Each group has n = 6.

Treatment Groups	Day 3	Day 7	Day 14
No treatment	27.9 ± 7.5 (7/7)	47.00 ± 0.0 (2/7)	– (1/7)
35 mg/kg curcumin in Tween 80 solution	32.5 ± 9.23 (7/7)	53.00 ± 0.0 (2/7)	– (1/7)
10 mg/kg curcumin niosomes	27.4 ± 6.3 (7/7)	– (1/7)	– (1/7)
20 mg/kg curcumin niosomes	19.5 ± 5.10 (7/7)	– (1/7)	– (1/7)
35 mg/kg curcumin niosomes	16.5 ± 5.3 (7/7)	44.3 ± 14.5 (7/7)	– (1/7)

It is possible to infer from the findings in Table 1 that curcumin did not exhibit sufficient anti-malarial action on its own. As a result, we only used the most notable part of curcumin in combination with different dosages of primaquine diphosphate for the combination tests, and we collected the animals as shown in Table 2.

3. Results and Discussion

Analysis of particle size and charge

To manufacture niosomes with Tween 80, cholesterol, and STA, the delicate film hydration strategy was utilized. Five arrangements of niosomes were made, each with an alternate excipient molar ratio. Thermodynamic powers favor the production of niosomes, which are bilayered vesicles. Cholesterol assists with framing the bilayered structure, yet STA gives the niosomes a positive charge and keeps them from aggregating. After wetting the flimsy film and before down-measuring with a phase contrast microscope, unilamellar niosomes were easily visible. Indeed, even at this early stage, no aggregation was seen, proposing a reasonably stable formulation.

Since lyophilization improves the chemical and physical stability of the formulations, it was applied to both the blank and drug co-loaded niosomes after reduction. Both lyophilized formulations were easily dispersible in saline and/or PBS after thorough manual shaking. With a zeta potential that high, the particles were stable and wouldn't clump together. The niosomes' charge remained unchanged when the two drugs were added.

Development of HPLC methods

Efficiency of encapsulation

The ability of drug conveyance carriers to encapsulate pharmaceuticals is the primary concern during their formulation. It would be great if a good carrier could handle heavier doses of medication. It was observed that niosomes prepared with a ratio of 0.5:1:0.1 had a poorer entrapment efficiency compared to those prepared with a 1:1:0.1 ratio. Cholesterol forms a more stable and inflexible bilayer when dissolved to an acceptable degree at equal molar ratios, which may explain this. Cholesterol crystals, on the other hand, may form a mixture of micelles and vesicles at lower surfactant concentrations due to their poor solubility. The encapsulation efficiency for PRI was 91.25 ± 4.3% when loaded singly, but for CC it was 88.14 ± 5.4%.

For PRI, the encapsulation efficiency during co-loading was 87.25 ± 5.3%, whereas for CC, it was 84.14 ± 5.8%. Thus, when the two medications were co-loaded into the niosomes, their encapsulation efficiencies remained unchanged.

Primaquine diphosphate with curcumin: an in vitro release study

The in vivo behavior of the drug delivery system was investigated by studying the physiological parameters of in vitro release. Figure 1 shows how the medication is released from the niosomes. In the instance of PRI, the initial burst discharge occurred during the first hour. Medication that is not encapsulated or medication that is already inside the micelles could

be the cause of this. PRI releases tend to occur at a faster rate than CC releases. This could be as a result of CC's hydrophobic properties. However, even though the PRI was contained inside, it displayed full release more quickly. This could be explained by the fact that PRI dissolves quite well in aqueous solutions. Whatever the situation, a sustained release of the medication was achieved in both circumstances. The bilayer of the Tween-80 niosomes may be functioning as a rate-restricting component during the sustained release phase.

Table 2: PRI and CC in vitro release profiles in PBS (pH 7.4) at 37℃.

	PRI	CC
0	0	0
5	60	20
10	90	25
15	93	27
20	95	29
25	95	31
30	95	33
35	95	37

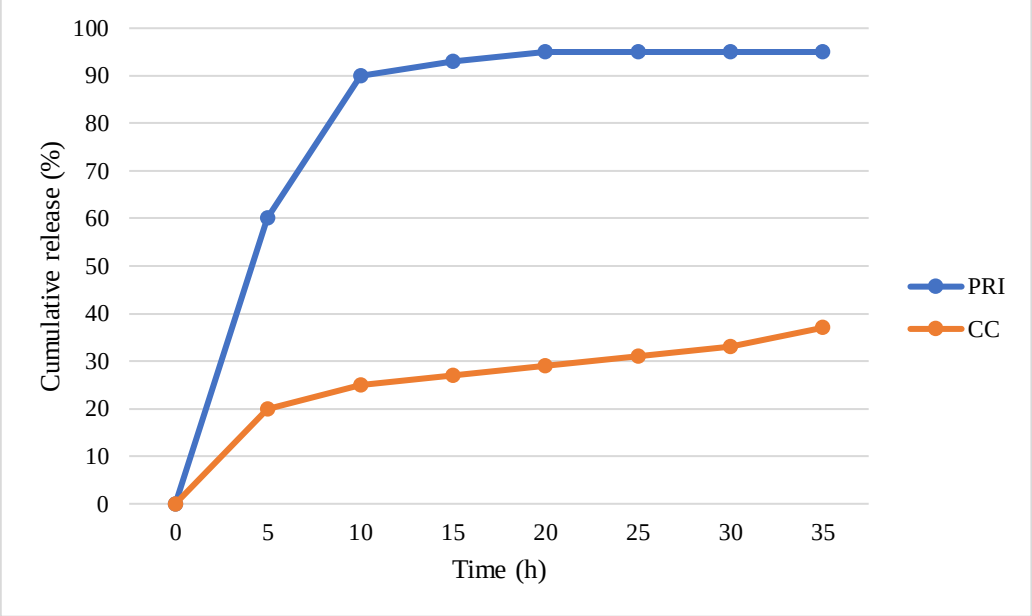

Figure. 1: PRI and CC in vitro release profiles in PBS (pH 7.4) at 37℃.

Haemocompatibility study

Isolated red blood cells (RBCs) were incubated with the samples as a hemolysis indicator in an in vitro method for evaluating the acceptability of niosome formulations for parenteral administration (Fig. 2). An 18% Triton X-100 solution served as the positive control, and it caused complete hemolysis. The final niosome formulation achieved a hemolysis percentage of 7.1%. This was within the acceptable range for intravenous administration.

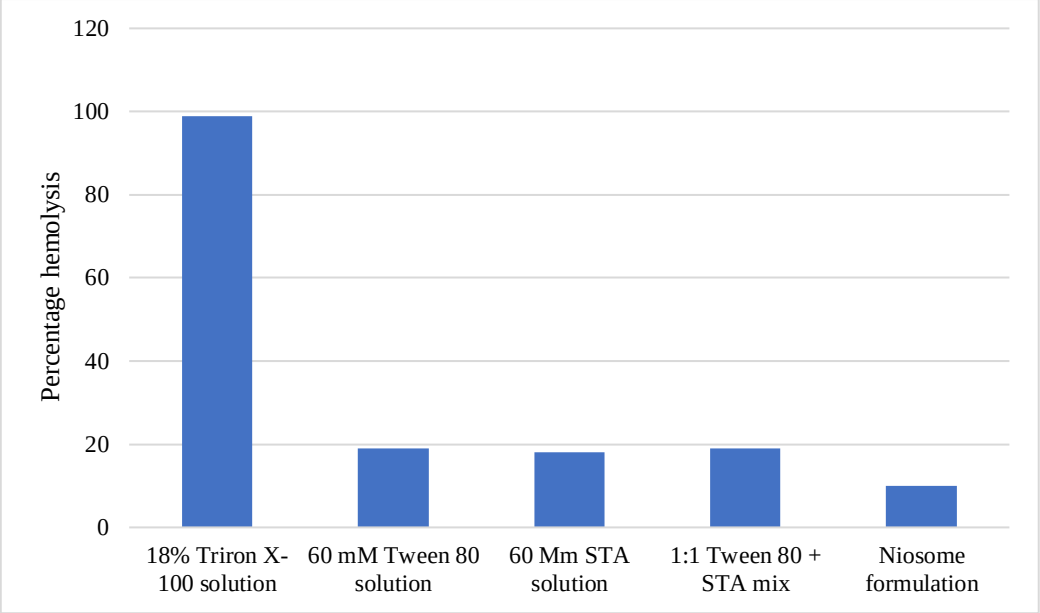

Figure 2: Percentage of haemolysis (n = 3)

Histopathological study and in vivo toxicity testing

Prior to the efficacy research, an acute harmfulness study was conducted to guarantee that the formulation was safe for intravenous usage. There was no mortality seen in any of the trial gatherings. No evidence of renal and hepatic poisoning was seen during the organs' histopathological testing (Fig. 3).

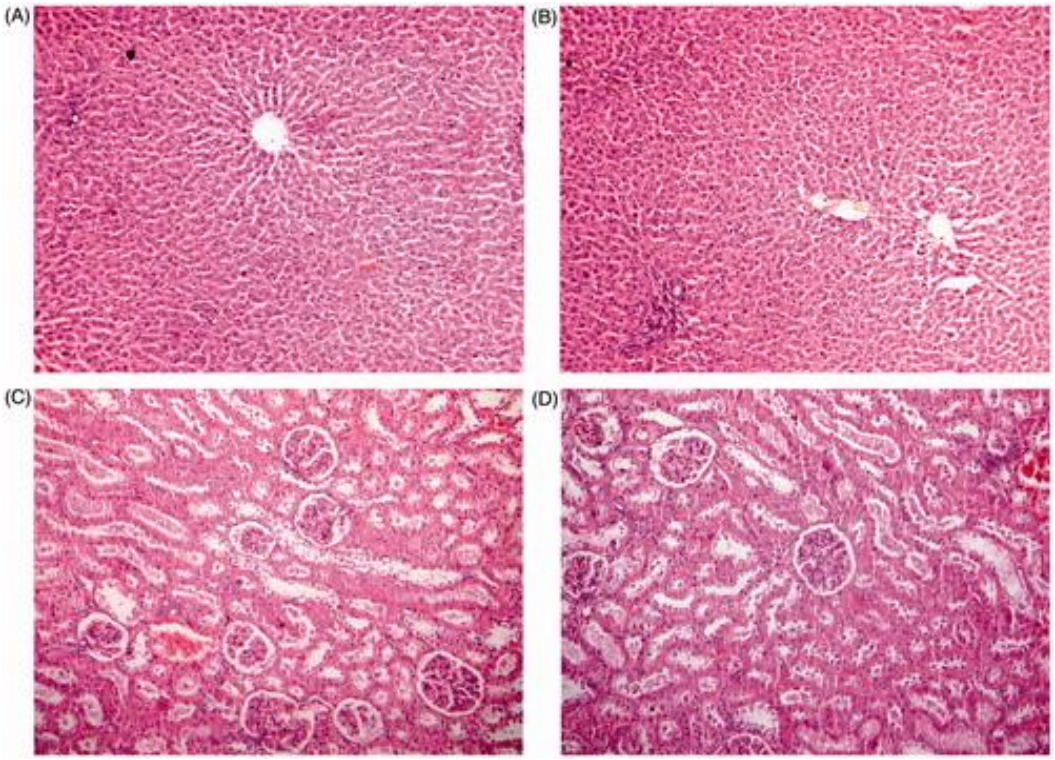

Figure.3: Analysis of the liver and kidney histopathologically after Tween 80 niosome formulation was administered. Normal liver (control) in (A), normal kidney (control) in (B), and normal liver histology following tests in (D). H&E staining (100× magnification).

Anti-malarial effectiveness in vivo in mice infected with P. berghei

A fatal efficacy testing model was utilized for this survey. This trial showed a 72-hour treatment delay, while Peter's four-day suppression test showed a 2-hour delay. Considering that therapy for malaria in humans is typically started after the infection has already become established, the 72-hour treatment delay model is more similar to a model for treating malaria in humans. Fig. 4 shows the survival analysis and percent suppression as for anti-malarial activity.

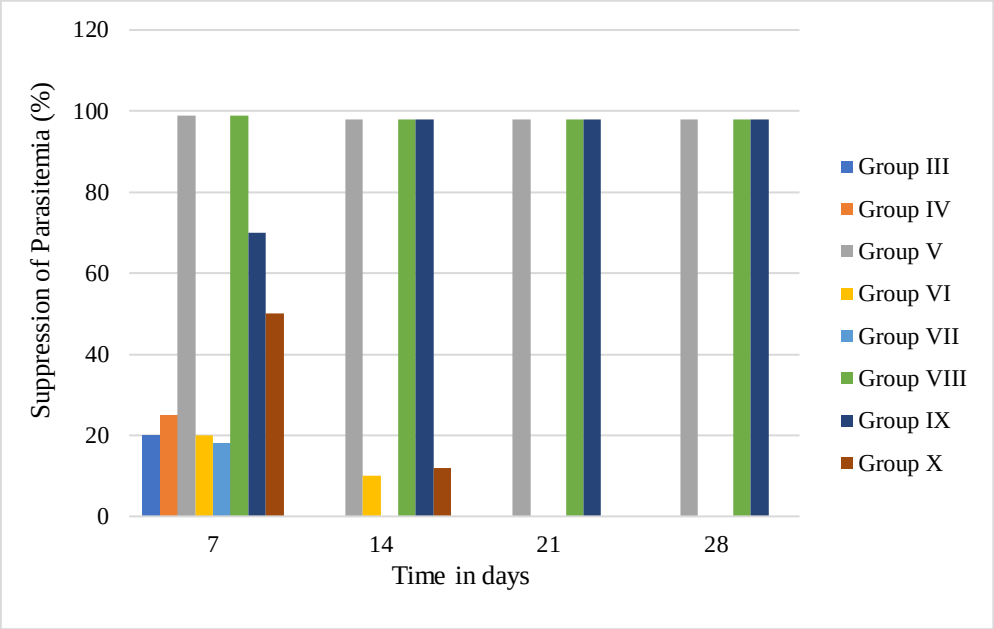

Figure 4: The in vivo anti-malarial assessment of niosomes loaded with drugs.

4. Conclusion

Studies on the pharmacokinetics and in vivo effectiveness of anti-malarial drugs co-encapsulated in Tween 80 niosomes have shown notable improvements in drug delivery and therapeutic results. In contrast to traditional formulations, the use of Tween 80 niosomes improved bioavailability, extended drug circulation, and improved the therapeutic efficacy of the encapsulated medications. A niosome that was co-loaded with curcumin and primaquine diphosphate was effectively designed and described. Additionally, their suitability for use as an injectable formulation was assessed. When PRI and CC co-loaded niosomes were used instead of single medication-loaded niosomes, the anti-malarial action was more effective in terms of parasitemia advancement and survivorship. Higher drug levels at the liver, the site of action, may be the cause of the combination's improved therapeutic efficacy. Even though this work has provided some preliminary data regarding the suitability of co-loaded niosomes for treating malaria, more research is still necessary to fully understand their pharmacokinetic behavior.

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