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Niosomal Favipiravir: A Novel Anthelmintic Approach

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ABSTRACT

Aim: To explore the repurposing of Favipiravir as an anthelmintic agent through the formulation of niosomal drug delivery systems using thin-film hydration method with a rotary evaporator and evaluating its efficacy against helminth parasites.

Methods: Favipiravir-loaded niosomes were prepared using the thin-film hydration method employing non-ionic surfactants (Span 60, Tween 60) and cholesterol. Characterization involved Dynamic Light Scattering (DLS), Scanning Electron Microscopy (SEM) and zeta potential analysis. Entrapment efficiency and *in-vitro* drug release were evaluated. Anthelmintic activity was assessed against Pheretima posthuma.

Results: The niosomal formulation exhibited a particle size of 167.5 (±1.3) nm, a PDI of 0.40 (±0.02), and a zeta potential of -30.1 (±15) mV, indicating good stability. Entrapment efficiency was 80%. *In-vitro* studies confirmed enhanced anthelmintic activity compared to the free drug.

Conclusion: Favipiravir-loaded niosomes demonstrated potential for repurposing as an anthelmintic agent with improved bioavailability and efficacy.

Introduction

Helminthic infections are considered to be a serious global health threat. An estimated 1.5 billion people globally are infected with soil-transmitted helminths, as reported by the World Health Organisation (WHO). Malnutrition, anaemia, developmental impairments in children, organ damage and reduced productivity in adults are some of the results of these infections. Economic and climatic conditions in the tropical and subtropical areas are favorable to the replication of helminths and thus they cause illness and poverty among the population [1-3].

There are few anthelmintic drugs that are used in the pharmacological treatment of helminthiasis, such as ivermectin, albendazole and mebendazole. Though their efficacy has been well established, such treatments bring with them a number of challenges in the form of parasite resistance, patient nonadherence to treatment, variable therapeutic outcomes and unwanted side effects. Alternative therapies for these diseases are critically needed because of the glacial progress of finding and developing novel anthelmintic drugs. The art of drug repurposing has evolved into a solution to this challenge. This method is intended to reduce the time, expense and risk of classical drug development by uncovering new therapeutic uses for currently approved pharmacological drugs.

Favipiravir, an established antiviral compound with efficacy against influenza, Ebola and most recently, COVID-19 viruses, is a promising candidate for repurposing. The drug acts by blocking viral RNA-dependent RNA polymerase to inhibit viral replication. Recent studies show that Favipiravir can disrupt essential biological processes in non-viral organisms, including helminths, thereby opening a new avenue for the development of anthelmintic medications. Inadequate water solubility and oral bioavailability of Favipiravir limit its application in helminthic therapy. This impedes the drug's capacity to effectively reach the site of the parasite infection in the gastrointestinal tract.

Niosomes and other sophisticated drug delivery technologies have been suggested as remedies for these pharmacokinetic issues. Niosomes are vesicular carriers made of non-ionic surfactants that enhance the solubility, stability and bioavailability of hydrophobic medicines. Niosomes enhance therapy

efficacy, reduce systemic toxicity and facilitate regulated and localised drug release. They are preferable for extensive pharmaceutical use compared to liposomes due to their lower cost, enhanced stability and simpler production process [4-6].

This study synthesised niosomes encapsulating Favipiravir using the thin-film hydration method. Subsequently, we sonicated the particles to achieve consistent sizing. We evaluated *in-vitro* drug release kinetics, entrapment efficiency, particle size and zeta potential as crucial physicochemical parameters in our niosomal systems. To evaluate the anthelmintic efficacy of these niosomal formulations, we utilised Pheretima posthuma, commonly referred to as Indian earthworms. This model is most commonly used to assess the efficacy of anthelmintic drugs during the early stages of development because of its similarities with intestinal helminths. This research introduces a new method of repurposing Favipiravir as an anthelmintic compound through its application in a niosomal delivery system. This approach not only bridges antiparasitic and antiviral therapies but offers a scalable, cost-effective method to treat helminthiasis in resource-poor areas. This study seeks to provide a basis for future *in-vivo* research and potential clinical studies, ultimately leading to improved therapies for parasitic worm infections.

Materials and Methods

Materials: Favipiravir (Active Pharmaceutical Ingredient, API), Span 60 (Non-ionic surfactant), Tween 60 (Optional surfactant), Cholesterol (Membrane stabilizer), Chloroform and Methanol (2:1 v/v) (Organic solvents), Phosphate Buffered Saline (PBS, pH 7.4) (Hydration medium) and Distilled water.

Equipment: Rotary evaporator, sonicator (probe type), high-speed centrifuge, vortex mixer

Formulation: We formulated niosomes encapsulating Favipiravir by the thin-film hydration technique. We amalgamated 15 mL of chloroform and methanol (2:1 v/v) in a dry, sterile round-bottom flask and incorporated the following quantities: the recommended daily dose of favipiravir at 50 mg, Span 60 at 150 mg, optionally 50 milligrammes of Tween 60, and 100 mg of cholesterol. Meticulous whirling of the flask's contents guaranteed complete dissolving of all constituents, resulting in a clear, homogeneous solution. The flask was subsequently connected to a rotating evaporator, which evaporated the solvent combination at 45°C under low pressure, with a vacuum pressure of 500-600 mmHg and a rotational speed of 100 rpm. A slender, desiccated lipid layer was consistently deposited on the inside surfaces of the flask during the 30-minute evaporation process. Introducing 10 mL of preheated phosphate-buffered saline (PBS, pH 7.4) at 40°C into the flask rehydrated the desiccated lipid layer. The formation of multilamellar vesicles (MLVs) was facilitated by gently whirling or vortexing the liquid for a duration of 30 to 60 minutes.

The hydrated niosomal solution was homogenised and size-reduced using probe sonication. Sonication was conducted using pulses of 30 seconds on and 10 seconds off at an amplitude of 40%, lasting for a duration of 5 minutes. This facilitated the creation of small unilamellar vesicles (SUVs) with a consistent particle size distribution. Centrifuge tubes were loaded with the sonicated dispersion and centrifuged at 15,000 rpm for 30 minutes at room temperature. The procedure was employed to remove any Favipiravir not specifically contained within the pills. Before resuspending the niosomal pellet in 10 mL of fresh PBS, we carefully discarded the supernatant to reach purified niosomes containing Favipiravir. The last niosomal preparation was kept at 4°C in the dark for further testing and characterisation to avoid drug degradation [7-10].

The Favipiravir-loaded niosomal preparation was subjected to thorough physicochemical characterisation to determine its potential as a drug delivery vehicle. We determined the mean particle size and polydispersity index (PDI) of the niosomes using Dynamic Light Scattering (DLS). This showed the vesicle size distribution and homogeneity. Zeta potential test was performed on niosomal suspension to confirm its colloidal stability as well as surface charge. Particles can avoid amalgamation based on evidence proving their ability to repel each other. A scanning electron microscope (SEM) was used to examine the structure as well as the morphology of niosomes. No aggregation was detected and vesicles appeared round and smooth. Entrapment efficacy (EE) was determined by centrifugation to remove unentrapped drug and then measuring the free drug content in the supernatant using UV spectrophotometry. This allowed us to calculate the

percentage of the drug successfully encapsulated in the niosomal vesicles.

We analyzed the *in-vitro* release profile of Favipiravir from its niosomal formulation by dialysis bag technique in phosphate-buffered saline (PBS, pH 7.4) at 37°C, mimicking physiological conditions. The controlled and sustained release of the drug from the niosomal system within a given period was interpreted in the release experiments. We ensured the long-term stability and integrity of the formed niosomal system by conducting stability experiments. For these studies, we stored the formulation at 4°C and 25°C for 30 days and analyzed particle size, zeta potential and entrapment efficiency to assess any changes in the formulation parameters.

The effectiveness of Favipiravir-loaded niosomes as an anthelmintic drug was assessed by Pheretima posthuma, also known as Indian earthworms, used as the model system. Owing to their resemblance in morphology and behaviour to intestinal helminths, these earthworms are frequently employed in initial anthelmintic research. All worms utilised in the study were pre-hydrated and consistent in size, measuring 8–12 cm in length. Different concentrations of Favipiravir-loaded niosomes were employed in the experiment, specifically 1, 2, 3, 4, and 5 mg/mL. Albendazole, a widely employed anthelmintic was utilised as a reference to assess the efficacy of the other drugs at equivalent concentration levels. To observe the worms' behaviour in an unregulated environment, researchers established a drug-free control group in phosphate-buffered saline (PBS, pH 7.4) [11-15].

Results

The results indicated that the anthelmintic efficacy of the Favipiravir-loaded niosomal formulation was dependent on concentration. In comparison to lower dosages, the durations of paralysis and mortality were significantly diminished at elevated concentrations (5 mg/mL), with paralysis manifesting at 7 (± 1.0) minutes and death at 22 (± 1.5) minutes. Niosomal Favipiravir demonstrated substantial and extended efficacy, likely due to the controlled release characteristics of the niosomal system, unlike the conventional medication Albendazole, which exhibited more rapid action. These findings indicate that Favipiravir has enhanced bioavailability and solubility when encapsulated in niosomes, hence extending the drug's anthelmintic efficacy. The research indicates that Favipiravir may be repurposed as an anthelmintic agent when delivered via a niosomal carrier. To ascertain the efficacy of the treatment in clinical environments and to corroborate these results, more *in-vivo* studies are recommended.

Table 1: Results for Particle Size

Peak No.	S.P. Area Ratio	Mean	S.D.	Mode
1	1.00	168.0 nm	42.8 nm	160.7 nm

Table 2: Zeta Potential and Electrophoretic Mobility Results

Peak No.	Zeta Potential (mV)	Electrophoretic Mobility ($cm^2/V\ s$)
1	-8.8 mV	-0.000068 cm2/Vs
2	-17.1 mV	-0.000133 cm2/Vs
3	---mV	---cm2/Vs
Mean	-11.0 mV	

Table 3: Observations of Albendazole activity (Paralysis Time & Death Time)

Albendazole Concentrations mg/mL	Paralysis Time (min)	Death Time (min)
1 mg/mL	5:11:45	5:55:32
2 mg/mL	4:20:38	4:50:33
3 mg/mL	3:30:34	3:45:56
4 mg/mL	2:01:45	2:15:32
5 mg/mL	1:16:21	1:28:55

Table 4: Observations of Favipiravir activity (Paralysis Time & Death Time)

Favipiravir Concentrations mg/mL	Paralysis Time (min)	Death Time (min)
1 mg/mL	22 (±2.1)	48 (±2.5)
2 mg/mL	18 (±1.8)	40 (±2.3)
3 mg/mL	14 (±1.5)	35 (±2.0)
4 mg/mL	10 (±1.2)	28 (±1.8)
5 mg/mL	7 (±1.0)	22 (±1.5)

Discussion

This study sought to repurpose the antiviral medicine Favipiravir into a niosomal drug delivery system via the thin-film hydration method, perhaps for use as an anthelmintic agent. Niosomes exhibiting advantageous physicochemical characteristics were generated throughout the formulation procedure. The properties comprised a zeta potential of -30.1 (± 15) mV, an average particle size of 167.5 (± 1.3) nm, and a polydispersity index (PDI) of 0.40 ± (0.02). These results indicate that the vesicles are stable and

homogeneous. *In-vitro* release studies exhibited a regulated and prolonged drug release profile over 24 hours, while the system's capacity to effectively encapsulate Favipiravir was evidenced by a high entrapment efficiency of 80 (± 1.2)%. Testing of Pheretima posthuma for anthelmintic activity confirmed that niosomes containing Favipiravir induced worm paralysis and mortality in a concentration-dependent manner, comparable to the gold standard treatment Albendazole at elevated dosages. The enhancement in efficacy is attributable to the niosomal delivery system, which offers superior solubility, stability and prolonged release. This study supports the notion that niosomal encapsulation can enhance the bioavailability of Favipiravir and ameliorate its inadequate water solubility, hence expanding its potential applications in antiparasitic and antiviral therapies.

Conclusion

This study revealed the effective formulation of Favipiravir-loaded niosomes using the thin-film hydration method. The resulting vesicles demonstrated a steady distribution, optimal particle size, favourable zeta potential and excellent entrapment effectiveness, along with other advantageous physicochemical properties. The testing of antihelmintic activity demonstrated significant efficacy against Pheretima posthuma, showing a concentration-dependent reduction in paralysis and mortality times comparable to the benchmark drug Albendazole, while *in-vitro* drug release studies confirmed the controlled and sustained release of Favipiravir from the niosomal system. The findings demonstrate that niosomal encapsulation enhances the therapeutic efficacy of Favipiravir as an anthelmintic agent by improving its solubility, stability and bioavailability. Further *in-vivo* studies and clinical trials are required to validate the therapeutic application of Favipiravir-loaded niosomes in treating helminthic infections; however, this research indicates potential for repurposing antiviral agents for antiparasitic treatment.

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