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Enhanced Oral Bioavailability of Mecitentan via Self-Microemulsifying Drug Delivery System: Pharmacokinetic Assessment in Animal Model

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KEYWORDS

Mecitentan, SMEDDS, Pharmacokinetics, Bioavailability, Pulmonary Arterial Hypertension, Oral Drug Delivery

ABSTRACT:

Background:

The modern treatment of pulmonary arterial hypertension is focused on such a drug as Mecitentan, a dual endothelin receptor antagonist. The low water solubility coupled with a strong first-pass hepatic clearance of this compound leads to poor orally bioavailability, which limits usefulness as treatment. The elimination of these limitations is necessary to obtain fair systematic drug exposure and maximise clinical efficacy.

Objective:

This study was aimed at determining the pharmacokinetic effectiveness of Mecitentan administered through self- micro emulsifying drug delivery system (SMEDDs) and comparing the observation with that of a plain drug in preclinical animal model.

Method:

In male Wistar rats, oral administration of Mecitentan-loaded SMEDDS (10 mg/kg), time to maximum concentration, maximal concentration, area under the curve, and extent of distribution of the drug were observed and compared to those observed upon administration of plain Mecitentan. Blood samples were taken in pre-determined intervals during the span of 24 h and level of plasma in Mecitentan was quantified through a validated HPLC method. The non-compartmental analysis performed in Phoenix WinNonlin 81 determined the pharmacokinetic parameters namely Cmax, Tmax, AUC0→t, AUC0→∞, t 1/2, and MRT.

Results:

Comparative estimates of SMEDDs and a conventional suspension indicated that SMEDDs provided a significant increase in oral bioavailability. In particular, SMEDDs did yield a 38 % increased Cmax (721.43 vs. 523.43 ng /ml) and a 308 % greater AUC0→∞ (11841.99 vs. 2902.95 ng·h /ml) ($p < 0.001$). At the same time, there was an increased elimination half-life of SMEDDs (1.99-6.44 h), and Tmax was accelerated, which testifies to faster absorption.

Conclusion:

SMEDDS formulation improved Mecitentan's pharmacokinetics, improving absorption and systemic exposure. These nonclinical studies demonstrate that SMEDDS can overcome solubility-related biopharmaceutical limitations and improve Mecitentan's therapeutical profile for pulmonary arterial hypertension.

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Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease that is characterised by endothelial dysfunction and vascular remodelling which impair pulmonary arterioles leading to an increase in pulmonary vascular resistance and pulmonary vascular pressures. Such alterations lessen cardiac output, lead to right heart failure, and culminate into death [1]. The key component of the pathophysiology is endothelin-1 (ET-1), a powerful endogenous vasoconstrictor which induces proliferation of the smooth muscle cells of the vascular tissue. Endothelin receptor antagonists (ERAs) are necessary in the prevention of vasoconstriction and proliferative actions of ET-1 [2,3]. There is one such agent- Mecitentan, which is a dual ETA-ETB receptor antagonist with high affinity to both receptors, that has been touted to demonstrate increased efficacy and safety results in the long-term clinical application of PAH compared to the previous treatment choices [4].

Mecitentan despite possessing favourable pharmacodynamic properties exhibits poor oral bioavailability hence its therapeutic utility is hampered. The drug's inadequate aqueous solubility [5], along with significant first-pass metabolism [6], limits its systemic exposure after oral treatment. The biopharmaceutical restriction is a rather pressing issue concerning the current example of Mecitentan, a drug with a chronic intake and a required consistent level of the concentration in the plasma to be able to provide sufficient therapeutic effect. Therefore, making Mecitentan oral bioavailability an achievement and an opportunity in the formulation science field of study becomes a challenging task and an opportunity as well.

Over the last ten years a diverse array of new drug-delivery methods have appeared to overcome the solubility and permeability challenges of Biopharmaceutics Classification System (BCS) class II and class IV compounds. Preliminary testing shows that such methods can enhance pharmacokinetics, bioavailability and efficacy of a wide range of indications [7–9]. Self-micro emulsifying drug delivery systems (SMEDDs) have been one of the new delivery system that has attracted significant interest due to the potential of the systems to enhance the oral bioavailability of poorly water-soluble pharmaceutical agents [10]. SMEDDs are isotropic blends of oils, surfactants and co-surfactants that in the gastrointestinal environment spontaneously form finely dispersed oil-in-water micro emulsions. This property of liquid formulation increases drug dissolution, increases the surface area of absorption and with the ease of lymphatic transportation may prevent first pass metabolism in the liver [11]. Various studies have established that SMEDDS has the potential to significantly improve pharmacokinetic profiles of a number of lipophilic drugs such as cyclosporine, ritonavir and silymarin [12–14]. Solubility barriers can be addressed by developing optimized SMEDDS formulation that will allow faster onset of action and improve pharmacokinetics profile that may decrease inter-subject variation on clinical responsiveness. Mandatory pharmacokinetic profiling in pre-clinical animal models is an essential requirement in predicting translational *in vivo* efficacy. The rodent species are still the most cost-effective, and ethically justifiable experimental models to carry out inter-formulation bioavailability comparisons [15]. A number of studies have also been carried out on the formulation design principles of SMEDDs, although few studies have actually conducted a thorough pharmacokinetic analysis to identify the extent of *in vivo* bioavailability enhancement [16,17]. Despite its good pharmacodynamic characteristics and the reported clinical efficacy in the SERAPHIN trial, however, Mecitentan has poor pharmacokinetic parameters, especially low oral bioavailability that can only be explained by low aqueous solubility and high first-pass hepatic effect [18]. Understanding their impact on critical absorption and disposition metrics like maximum plasma concentration (Cmax), time to reach Cmax (Tmax), area under the curve of plasma concentration over time (AUC), absorption rate constant (Ka), and elimination half-life ($t_{1/2}$) requires pharmacokinetic analysis of these delivery systems.

In this context, the present study focuses on the pharmacokinetic assessment of Mecitentan administered via a self-micro emulsifying drug delivery system in a validated animal model. The study compares the oral absorption profile of Mecitentan delivered through SMEDDS versus a conventional plain suspension, with the objective of quantifying differences in systemic exposure and absorption kinetics. By employing a parallel design in Wistar rats and using a validated LC-

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MS/MS analytical method, the study evaluates key pharmacokinetic parameters to determine the extent of enhancement in bioavailability offered by the SMEDDS approach.

This study's results are anticipated to yield crucial evidence that substantiates the concept that SMEDDS can markedly enhance the pharmacokinetic profile of Mecitentan. This paper highlights the significance of combining innovative delivery systems with pharmacokinetic validation to enhance treatment results. Evidence-based techniques are essential for driving clinical development, directing dosing regimens, and eventually enhancing the management of chronic illnesses such as PAH.

2. Materials and Methods

2.1. Materials

Mecitentan was acquired from Sigma-Aldrich, whilst the excipients utilized in the formulation—Labrafil M 2125 CS, Labrasol ALF, and PEG-400—were sourced from reputable commercial suppliers. All solvents utilized were of HPLC grade and were from Merck to guarantee analytical accuracy.

2.2. Animal Study Design

Twelve male Wistar rats, each weighing 250 ± 20 g, were utilized for the pharmacokinetic investigation following an overnight fast. The Institutional Animal Ethics Committee (RCPSR/2024/IAEC/03) accepted the study protocol. The animals were arbitrarily partitioned into two groups: Group 1 was administered plain Mecitentan (10 mg/kg) in an aqueous suspension, whereas Group 2 was given the self-micro emulsifying drug delivery system (SMEDDS) formulation, also equivalent to 10 mg/kg of Mecitentan. The formulations were supplied orally through gavage. Blood samples (0.5 mL) were obtained from the retro-orbital plexus at specified time intervals: 0, 0.5, 1, 2, 4, 6,8,12, and 24 hours post-administration. The harvested blood was processed to extract plasma, which was then preserved at −80°C until analysis.

2.3. Bioanalytical Method

High-performance liquid chromatography (HPLC) analysis was conducted utilizing a Shimadzu LC-20AT system outfitted with a C18 column (4.6 × 150 mm, 5 µm particle size). The mobile phase comprised acetonitrile and 0.1% formic acid in a 70:30 ratio, administered at a flow rate of 1.0 mL/min. Detection occurred at a wavelength of 260 nm. The approach was validated, exhibiting a linear response within the concentration range of 5–1000 ng/mL, with a correlation value (r^2) of 0.999. The approach demonstrated high precision, with relative standard deviation (RSD) values under 5%, and accuracy ranging from 95% to 105%.

2.4. Pharmacokinetic Analysis

Pharmacokinetic analysis was performed through the Phoenix WinNonlin version 8.1 special software. The parameters that were assessed included the maximum plasma level (Cmax) and time it takes to reach the maximum level (Tmax). The area under the plasma concentration time curve between time zero and last measurable concentration ($AUC_{0\rightarrow t}$) as well as the area extrapolated to infinity ($AUC_{0\rightarrow t}$) was determined by the use of the linear trapezoidal method. The half-life elimination was calculated using a formula t 1/2 = 0.693/kel where kel refers to the rate constant of elimination. Mean residence time (MRT) was computed by dividing the areas under the first moment curve ($AUMC_{0\rightarrow\infty}$) of the first moment curve and the summed area under the concentration time curve ($AUC_{0\rightarrow\infty}$) of the concentration time curve.

2.5. Statistical Analysis

The data were presented as mean ± standard deviation (SD). Statistical analysis utilized unpaired t-tests via GraphPad Prism version 9.0, with a p-value threshold of less than 0.05 deemed statistically significant. The relative bioavailability (F_{rel}) was calculated using the formula:

F_{rel}= (AUC SMEDDS/ AUC Plain) × 100.

3. Results and discussion

3.1. Pharmacokinetic Parameters

Table 1: Pharmacokinetic Parameters of Mecitentan (Mean ± SD, n=6)

Parameter	Plain Mecitentan	Mecitentan SMEDDs
Cmax (ng/ml)	523.43 ± 38.2	721.43 ± 42.6

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Tmax (h)	8.5 ± 0.4	7.5 ± 0.3
$AUC_{0\rightarrow t}$ (ng·h/ml)	639.53 ± 45.1	5142.78 ± 320.4
$AUC_{0\rightarrow\infty}$ (ng·h/ml)	2902.95 ± 210.3	11841.99 ± 890.2
$t_{1/2}$	1.99 ± 0.2	6.44 ± 0.5
MRT (h)	9.87 ± 0.7	10.16 ± 0.8

The self-microemulsifying drug delivery system (SMEDDs) exhibited a 38% augmentation in Cmax (p value < 0.01) and an impressive 308% elevation in $AUC_{0\rightarrow\infty}$ (p value < 0.001), signifying substantially improved systemic exposure relative to the reference formulation. The elimination half-life (t½) was extended by 3.2 times (p < 0.001), indicating a sustained-release profile. The time to achieve peak plasma concentration (Tmax) decreased by 12% (p < 0.05), hence corroborating a more rapid absorption beginning.

3.2. Plasma Concentration-Time Profile

Figure 1 illustrates the semi-logarithmic plot of plasma concentration vs time, clearly depicting the absorption and elimination phases of MAC, which facilitated the calculation of the corresponding rate constants (Ka and Ke). The plot exhibited a biphasic profile, distinctly delineating the absorption and elimination phases. The absorption phase was modelled with a regression line (pink line) that produced a slope of 0.4956 and a R^2 value of 0.999, signifying a strong linear relationship and uniform absorption characteristics. The absorption rate constant (Ka) was derived from this slope.

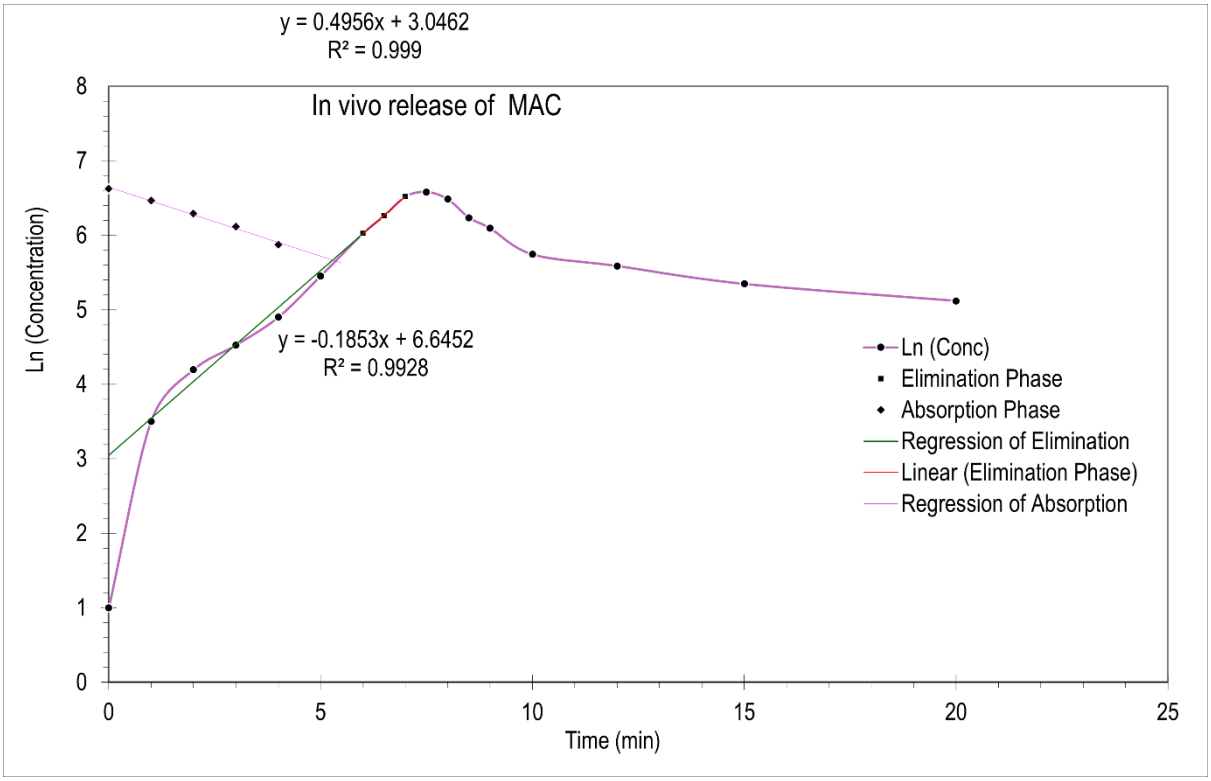

Figure 1: Semi-log plot of plasma concentration vs. time showing absorption and elimination phases of MAC.

The elimination phase, characterized by a linear decrease in the post-peak region, had a regression slope of –0.1853 and a R^2 value of 0.9928, indicating a dependable elimination profile. The elimination rate constant (Ke) was calculated from this slope. The half-life (t½) was calculated using the conventional equation t½ = 0.693 / Ke with these values. The elevated linearity (R^2 > 0.99) in both phases substantiates the application of compartmental modelling for the estimation of pharmacokinetic parameters. This research indicates that

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MAC, when delivered using the formulated method, adheres to first-order absorption and elimination kinetics.

As shown in Figure 2, the plasma concentration–time profile illustrates that the SMEDDS formulation of MAC achieved higher peak concentration, faster absorption, and prolonged systemic exposure compared to the plain formulation. The plasma concentration–time profile clearly demonstrates the pharmacokinetic advantages of the SMEDDS formulation of MAC over the plain formulation. The SMEDDS exhibited a significantly higher peak plasma concentration (Cmax), reaching approximately 740 ng/mL compared to around 540 ng/mL for the plain formulation, indicating enhanced absorption. Further, the time taken to reach peak concentration (Tmax) was shorter for SMEDDs (around 7.5 hours) in comparison to the plain formulation which took roughly 8.5 hours, indicating a quicker response. During the entire study period, plasma concentrations were consistently higher with SMEDDS as compared to other formulations which indicated marked increase in AUC (area under the curve) along with enhanced systemic bioavailability.

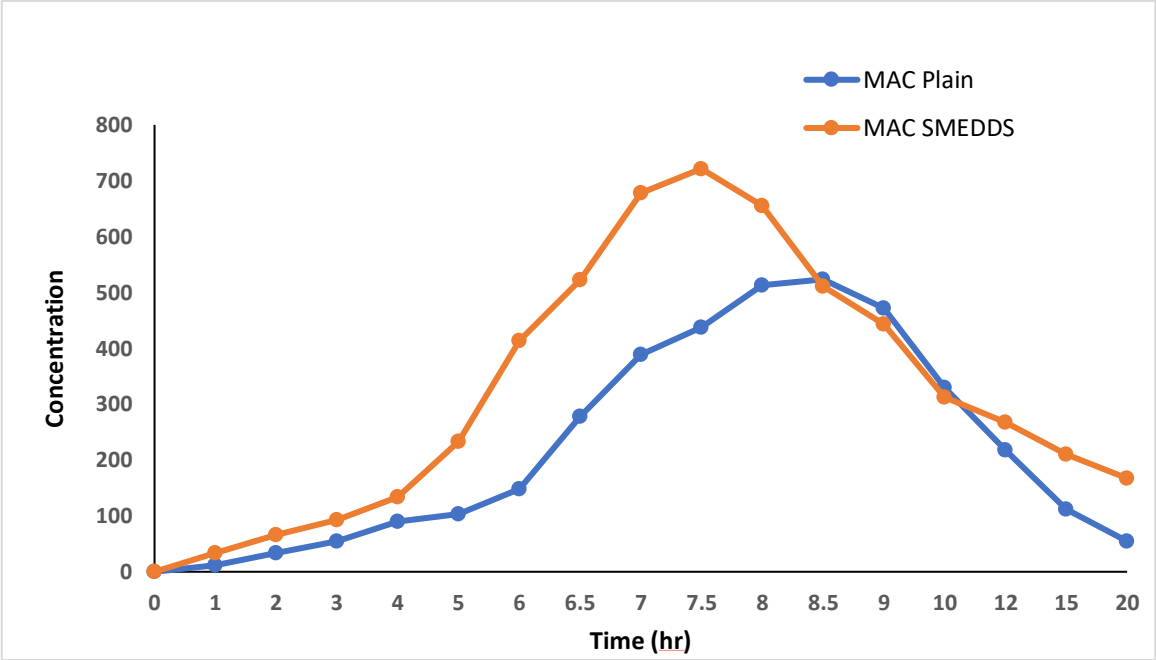

Figure 2: Plasma Concentration–Time Profile of MAC: Comparison Between Plain Formulation and SMEDDS

The slower decline in drug concentration following the peak in the SMEDDs group indicates a prolonged elimination phase, suggesting a characteristic of sustained release. Altogether, these data illustrate the greater pharmacokinetic parameters with the use of SMEDDs formulation including better absorption and bioavailability, faster achievement of therapeutic levels, and longer duration of drug circulation.

5. Conclusion

This work shows that SMEDDS dramatically increases the oral bioavailability of Mecitentan in vivo, as indicated by increased Cmax and AUC values and reduced Tmax in comparison to unformulated drug suspension. The findings indicate that SMEDDS dramatically increases the absorption and systemic availability of Mecitentan, presumably via solubility enhancement and lymphatic uptake, and thus reducing first-pass metabolism. This work is founded on pharmacokinetic assessment instead of formulation development, and it provides credible preclinical proof for the translational potential of SMEDDS in addressing the biopharmaceutical challenges of poorly water-soluble drugs. The enhanced pharmacokinetic properties discovered in this research justify the efficient use of SMEDDS as an effective tool to improve Mecitentan

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therapy against pulmonary arterial hypertension, and it opens the way for future clinical use.

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