

Lee M. Tatham¹, Alison C. Savage², Steve P. Rannard² & Andrew Owen¹

¹Department of Molecular and Clinical Pharmacology, University of Liverpool, UK

²Department of Chemistry, University of Liverpool, UK



Introduction

It is estimated that over 36 million people are living with HIV globally and over 1 million people died from HIV in 2015¹. Maraviroc is an orally dosed selective CCR5 antagonist used against CCR5-trophic HIV type-1². Maraviroc prevents the binding of HIV-1 gp160 to CCR5, which subsequently prevents the virus from fusing with the human cell membrane, required for effective viral entry³. Maraviroc is a P-glycoprotein (P-gp) substrate, limiting effective absorption, and it is estimated that over 60% of the absorbed drug is metabolised at first pass, primarily by CYP3A4, resulting in a bioavailability of ~33%⁴. Additionally, Cmax-driven postural hypotension has been described⁵. The aims of this study were to apply an emulsion-templated freeze-drying technique⁶ to develop and optimise maraviroc-loaded Solid Drug Nanoparticles (SDNs) for improved oral pharmacokinetics.

Results

1. SDN production and characterisation

An emulsion-templated freeze-drying screen was used to produce and optimise solid drug nanodispersions of MVC, achieving up to 70 wt.% drug-loading. Materials used in this study are outlined in Table 1.

Table 1. MVC SDNs prepared using emulsion-templated freeze-drying and characterised using dynamic light scattering (Malvern Instruments, UK).

MVC Nanodispersion	Composition	Z-average size (nm)	PDI
1	70% MVC; 20% PVA; 10% Tween	801.9	0.443
2	70% MVC; 20% PVA; 10% NDC	578.5	0.342
3	70% MVC; 20% PVA; 10% AOT	682.8	0.345

MVC was initially dissolved within an internal phase of dichloromethane-in-water emulsion, with stabilised polymers and surfactants in the aqueous continuous phase. Following rapid freezing and drying, the samples were reconstituted in water to produce MVC nanodispersions and subsequently used for pharmacological assessment.

3. In vivo oral pharmacokinetics

Enhanced pharmacokinetic exposure was highlighted following the oral dosing of the lead drug-loaded SDN preparation compared to an equivalent unformulated MVC dose in male Wistar rats (Figure 2.A). Specifically, Cmax, Cmin and AUC values were shown to be 1.6-, 3.9- and 2.4-fold greater than those observed for unformulated MVC, respectively. A 2.8-fold reduction in the Cmax:Cmin ratio was also noted in the SDN dosed animals (Figure 2.B).

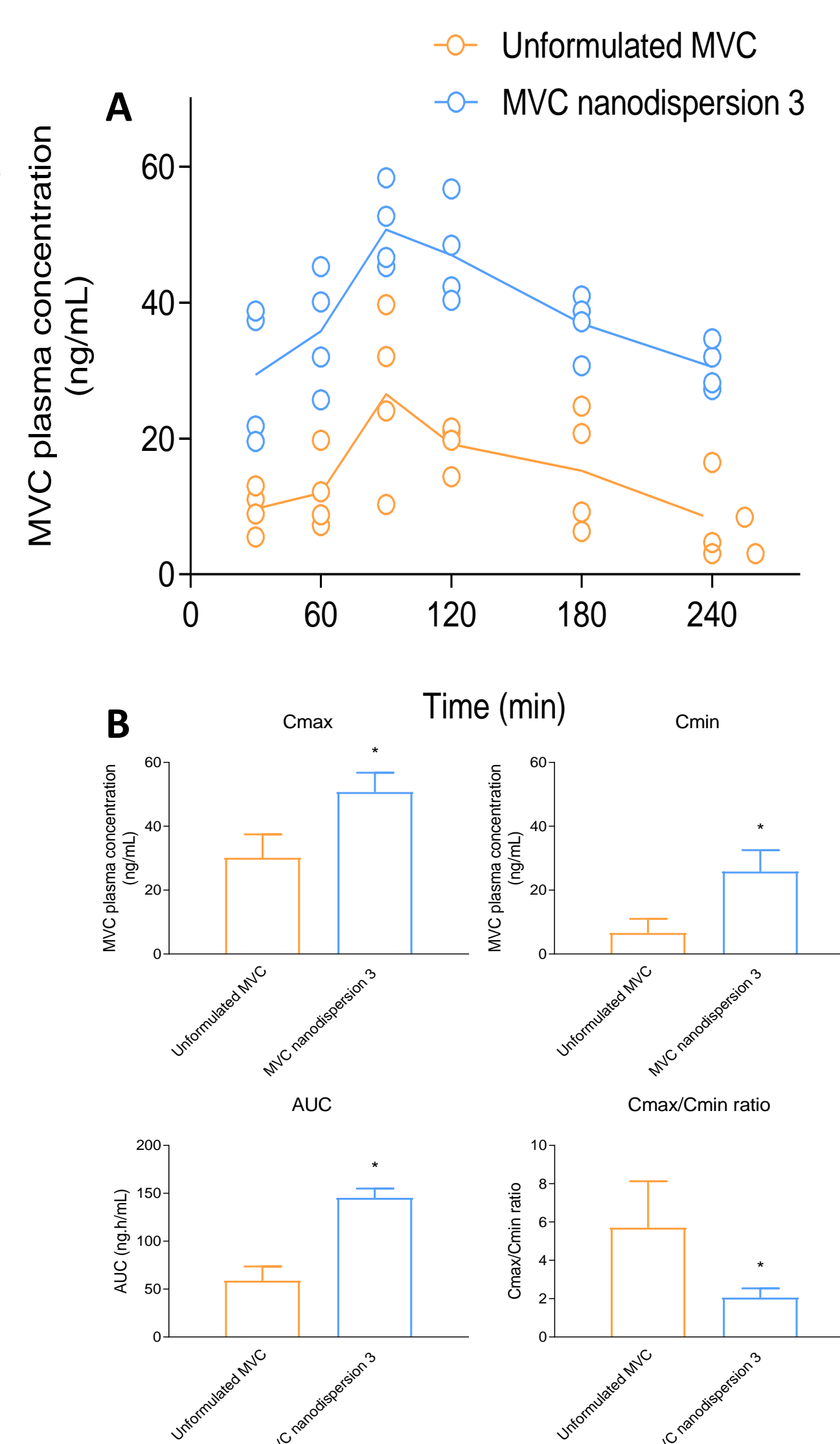


Figure 2 (A). MVC plasma concentration in adult male Wistar rats (280-330 g) dosed with either the lead drug-loaded SDN preparation or an equivalent unformulated MVC dose (10 mg/Kg MVC, 10 μ Ci/mg ³H activity) via oral gavage. **(B.)** PK parameters derived from the study (\pm SD, n=4).

2. In vitro apparent permeability

The results in Figure 1. indicate that the formulation of MVC into SDNs increases the drugs apparent oral absorption up to 1.7-fold compared to conventional unformulated MVC. Suggesting a potential increase in the absorption of MVC from the gut and into the systemic circulation.

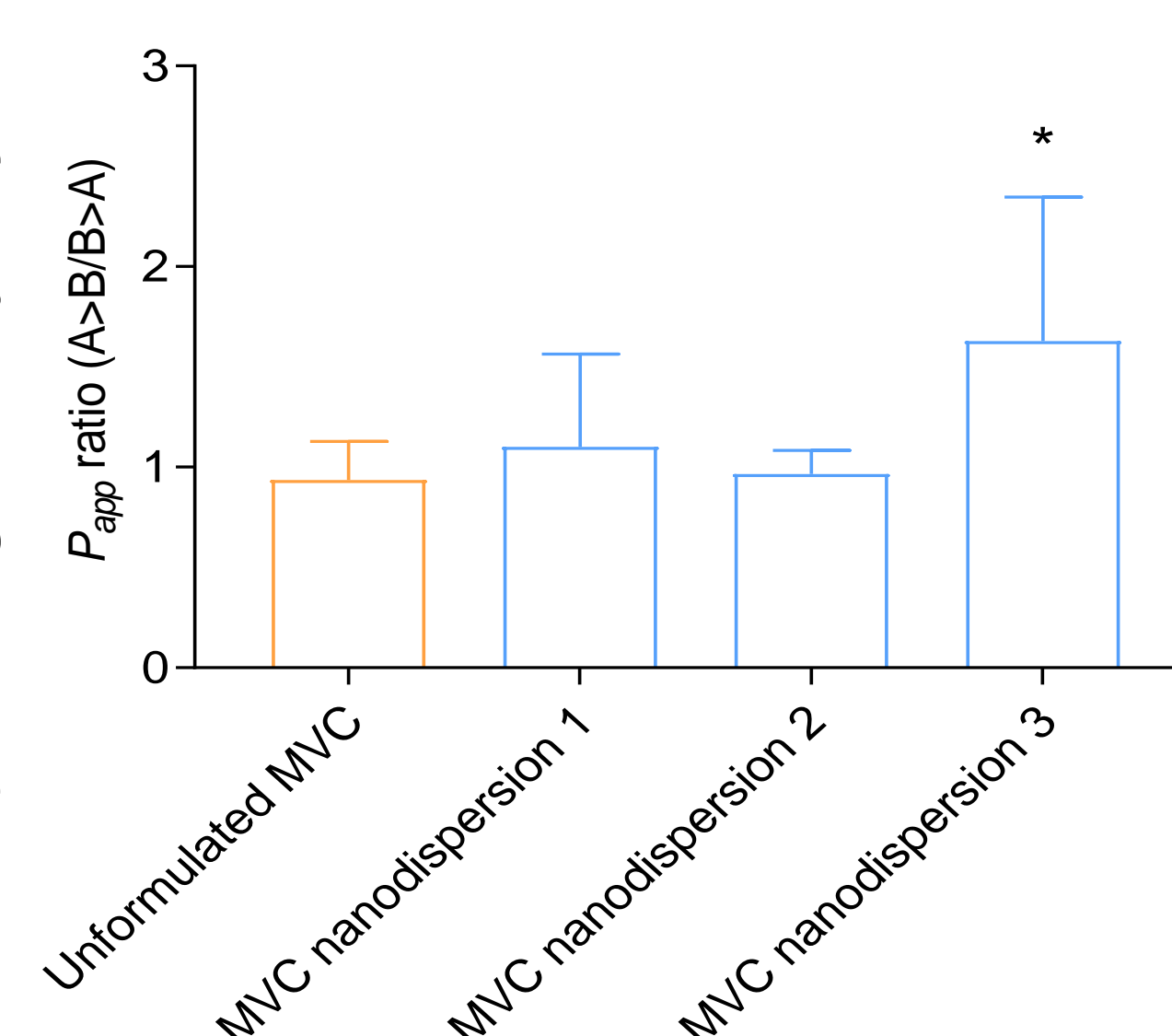


Figure 1. The Papp ratio of unformulated and SDN formulated MVC. Monolayers were incubated for 1 h at 37°C, 5% CO₂. *, P<0.05 (Two-tailed paired t-test) (\pm SD, n=4).

4. Tissue distribution

Increased MVC concentrations were observed in most of the dissected tissues obtained from the SDN dosed rats compared to the unformulated MVC dosed animals (Figure 3.A.). Figure 3.B. shows increased MVC accumulation in the brain, lung, intestine, kidney, spleen and liver with an average 1.6-fold increase. Analysis of the heart and brain suggested slight reductions in MVC accumulation in these tissues. Animals were humanely culled, 4-hours post-dose, using an overdose of anaesthetic and all animal work was conducted in accordance with the Animals (Scientific Procedures) Act 1986 (ASPAs) implemented by the UK Home Office.

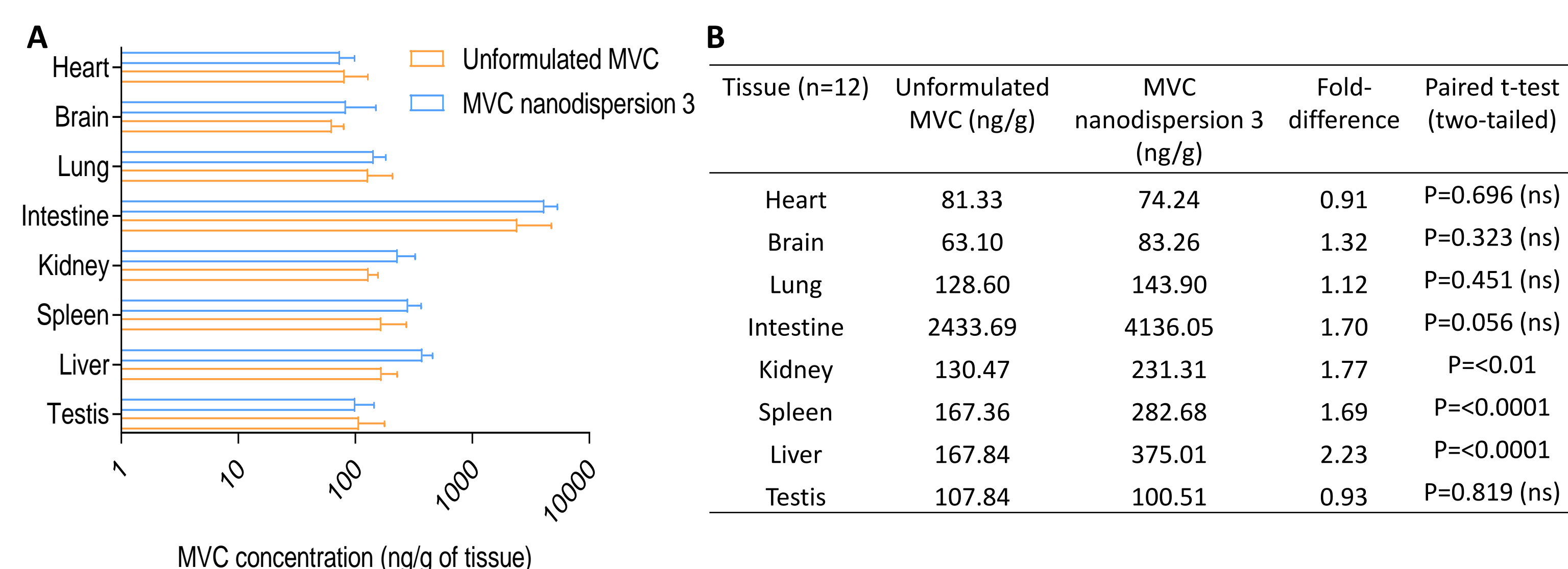


Figure 3 (A & B). MVC tissue concentrations (ng/g of dissected tissue) in adult male Wistar rats (280-330 g) dosed with either the lead drug-loaded SDN preparation or an equivalent unformulated MVC dose (10 mg/Kg MVC, 10 μ Ci/mg ³H activity) (\pm SD, n=4).

Discussion

- An emulsion-templated freeze-drying screen was employed to prepare and optimise MVC SDNs with up to 70 wt.% drug-loading.
- Enhanced permeation of SDN formulated MVC was observed across differentiated Caco-2 monolayers, highlighting the potential for improved oral absorption.
- Oral in vivo analysis suggested improved pharmacokinetic exposure and enhanced tissue accumulation.
- This study highlights the potential for improved MVC PK characteristics and the scope for dose reduction using SDN technology.

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