Maraviroc Solid Drug Nanoparticles with Improved Oral Pharmacokinetics

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Introduction

It was estimated that over 36 million people were living with HIV globally in 2016 with only 19.5 million receiving access to antiretroviral therapy (ART)[1]. Maraviroc (MVC) is an orally dosed entry inhibitor which targets the CCR5 co-receptor to prevent entry of CCR5-trophic virus into T-cells[2]. Oral dosing presents a simple route of self-administration but is often limited by low bioavailability. MVC is a substrate for P-glycoprotein (P-gp), limiting permeability. Additionally, it is estimated that over 60% of the absorbed drug is metabolised by CYP3A4, resulting in a bioavailability of ~33%[3]. Current MVC-containing ART regimens require twice-daily administration to maintain MVC plasma concentrations within the therapeutic range. Preferred ART regimens involve once daily dosing, but the MVC dose cannot be increased due to potential risk of postural hypotension, reported at C_{max}[4]. **The aims of this study were to develop MVC Solid Drug Nanoparticles (SDNs) using an emulsion-templated freeze-drying technique (ETFD)[5], with a higher bioavailability and a lower C_{max}:C_{min} ratio in rodent, potentially enabling a once-daily fixed dose combination product (FDC).**

Results

SDN Production and Characterisation

An ETFD screen was used to produce and optimise solid drug nanosuspensions of MVC, achieving up to 70 wt.% drug-loading. The lead formulations which showed enhanced permeability and progressed to *In vivo* studies are outlined in Table 1**.**

Table 1. MVC SDNs characterised using dynamic light scattering (Malvern Instruments, UK)

MVC Nanodispersion	MVC loading (wt.%)	Z-average size (nm)	PDI
1	70%	728	0.345
2*	70%	171	0.170

*Soybean oil blended formulation

In vitro Apparent Permeability

The results in Figure 1. indicate that formulation of MVC into SDNs increased the apparent oral absorption of the drug across Caco-2 monolayers. Specifically:

- Nanodispersion 1 increased the MVC P_{app} ratio over 1.7-fold compared to the conventional unformulated MVC.
- The soybean oil blended formulation, nanodispersion 2, increased the MVC P_{app} ratio over 4.3-fold.

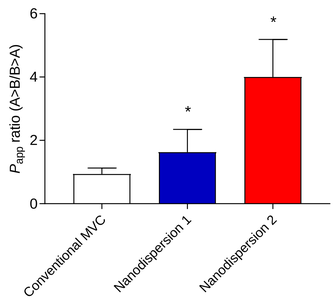

Figure 1. The P_{app} ratio of conventional and SDN formulated MVC. Monolayers were incubated for 1 h at 37°C, 5% CO_2.
*, P<0.05 (Two-tailed unpaired t-test)
(±SD, n=4).

In vivo Oral Pharmacokinetics

Enhanced MVC exposure was highlighted following the oral dosing of nanodispersions 1 (Fig. 2 A) and 2 (Fig. 2 B) compared to an equivalent conventional MVC dose in male Wistar rats.

The pharmacokinetic parameters in Table 2. highlight:

- A 2.4- and 2.5-fold increase in AUC_{0-4} and C_{ave}, respectively, and a 1.65-fold reduction in the C_{max}:C_{min} ratio for nanodispersion 1 compared to the conventional MVC preparation.
- A 2.4-, 2.8- and 4.5-fold increase in AUC_{0-4}, C_{ave} and C_{max}:C_{min} ratio, respectively, for the oil blended formulation, nanodispersion 2, compared to the conventional MVC preparation.

Table 2. Pharmacokinetic parameters of MVC following oral dosing. Parameters were calculated from the exposure curves outlined in Fig 2.

Pharmacokinetic parameter	Conventional MVC	Nanodispersion 1	Nanodispersion 2
C_{max} (ng ml^{-1})	26.52	50.74	130.31
C_{min} (ng ml^{-1})	8.16	25.83	8.88
AUC_{0-4} (ng.h ml^{-1})	58.71	145.33	146.24
C_{avg} (ng ml^{-1})	15.17	38.38	43.06
T_{max} (h)	1.5	1.5	1.0
C_{max}:C_{min} ratio	3.25	1.96	14.67

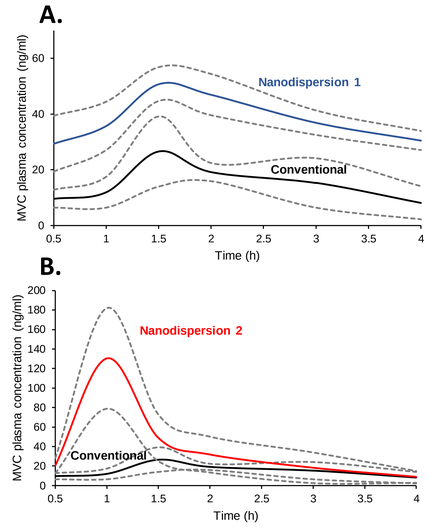

Figure 2. MVC plasma concentration in adult male Wistar rats dosed with either nanodispersion 1 (A.), 2 (B.) or a conventional MVC dose (10 mg Kg^{-1} MVC) via oral gavage. (±SD, n=4). All *In vivo* work was conducted in accordance with the Animals (Scientific Procedures) Act 1986 (ASPA) implemented by the UK Home Office.

Tissue Distribution

Increased MVC concentrations were observed in most tissues obtained from the nanodispersion dosed rats (Fig. 3). Specifically;

- A 2.2- (P=<0.001), 1.6- (P=<0.001) and 1.8-fold (P=0.0057) increase was observed in the liver, spleen and kidney, respectively, in the rats dosed with nanodispersion 1.
- A 3.8- (P=0.001), 2.4- (P=0.0227), 1.9- (P=0.0014), 4.6- (P=0.0040) and 1.6-fold (P=0.0173) increase was observed in the liver, spleen, kidney, lung and heart, respectively, in the rats dosed with nanodispersion 2.

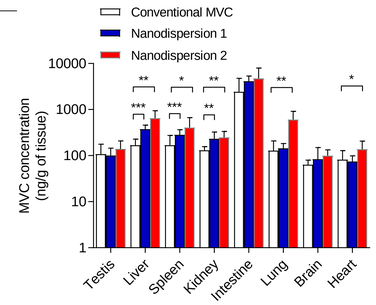

Figure 3. MVC tissue concentrations. *, P<0.05; **, P<0.01; ***, P<0.001 (Unpaired two-tailed t-test)
(±SD, n=4).

Discussion

The nanomedicines presented here have the potential to enable once-daily dosing of MVC, reducing the dose required for viral suppression and may enable the development of novel ART FDCs.

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