Towards a Long-Acting Injectable (LAI) Formulation For Maraviroc

Lee M. Tatham[a], Andrew Dwyer[b], Alison C. Savage[b], Marco Siccardi[a], Trevor Scott[c], Manoli Vourvahis[d], Steve P. Rannard[b] & Andrew Owen[a]

[a]Department of Molecular and Clinical Pharmacology, University of Liverpool, UK, [b]Department of Chemistry, University of Liverpool, UK, [c]ViiV Healthcare, Five Moore Drive, Research Triangle Park, North Carolina, USA, [d]Pfizer, 235 East 42nd Street, New York, New York, USA.

483

Introduction

The introduction of antiretroviral therapy (ART) has significantly reduced HIV-associated morbidity and mortality and has transformed HIV infection into a manageable chronic condition[1]. However, strict adherence to daily oral ART remains essential in maintaining viral suppression, preventing the emergence of resistance and reducing the risk of HIV transmission[2,3]. Pre-exposure Prophylaxis (PrEP) has been shown to be effective in the prevention of HIV acquisition in individuals identified as being at risk of infection[4]. MVC has particular appeal for use in PrEP[5,6]. It is readily absorbed into relevant tissues and has a unique resistance profile compared to other ARVs meaning resistance is rare[7,8]. Studies have shown a clear dose-response relationship between protection and adherence[9]. The challenges presented by daily oral dosing and the requirement for life-long maintenance of such dosing has driven interest in the development of Long-Acting Injectables (LAIs), a technology well established for antipsychotic-therapies and contraception[10]. **Here, we describe the use of emulsion-templated freeze-drying (ETFD) in the development of oil-blended MVC Solid Drug Nanoparticles (SDNs) as potential LAI MVC nanomedicines for use in PrEP.**

Results

SDN Production and Characterisation

An ETFD screen was used to produce and optimise soybean oil blended solid drug nanosuspensions of MVC, achieving up to 70 wt.% drug-loading. Formulations progressed to *In vitro* release rate studies are outlined in Table 1.

Dichloromethane-in-water emulsions were prepared via sonication, consisting of: (i) a 6:1 ratio of MVC and soybean oil within the dispersed organic phase, and (ii) combinations of polymers and surfactants within the aqueous continuous phase. Rapid freezing and drying of the emulsions gave SDNs dispersed within a solid matrix of hydrophilic polymer and surfactant stabilisers, which were subsequently dispersed in water to yield aqueous nanodispersions and used for pharmacological assessment.

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

MVC Nanodispersion	MVC loading (wt.%)	Z-average size (nm)	PDI
1	50%	115	0.210
2	50%	160	0.254
3	50%	145	0.213
4	60%	155	0.149
5	60%	170	0.169
6	70%	175	0.165

In vitro MVC Release

Understanding a formulation's release rate can be used to predict the rate of drug release from an intramuscular depot.

- MVC release from the 6 formulations and a conventional MVC preparation (<5% DMSO) was assessed using Rapid Equilibrium Dialysis (RED) across a size selective membrane (8 kDa MWCO).
- The results in Fig 1. indicate a, 2.7-, 3.1-, 2.7-, 1.8-, 1.9- and 1.8-fold reduction in MVC release rate for the SDN formulations 1 through 6 compared to a conventional MVC preparation, respectively.
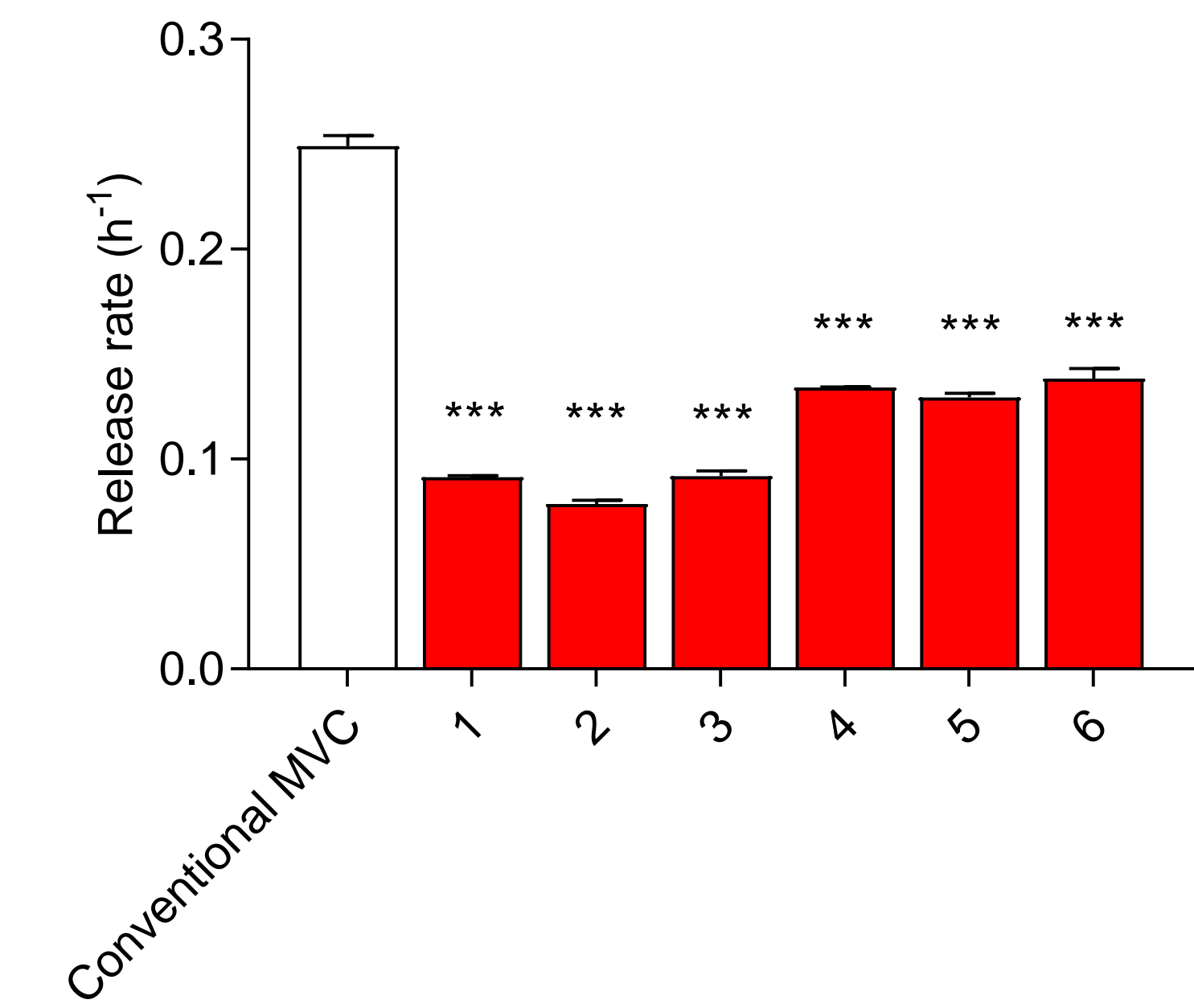

Figure 1. MVC release rate constant calculated over 6 h for both conventional and SDN formulated MVC. RED plates incubated at 37°C, 100 rpm. (P=<0.001; unpaired two-tailed t-test).

In vivo LAI Pharmacokinetics

Rats were dosed intramuscularly, into the left hind leg with 10 mg Kg^{-1} MVC either as a conventional MVC preparation (<5% DMSO) or as oil-blended nanodispersions.
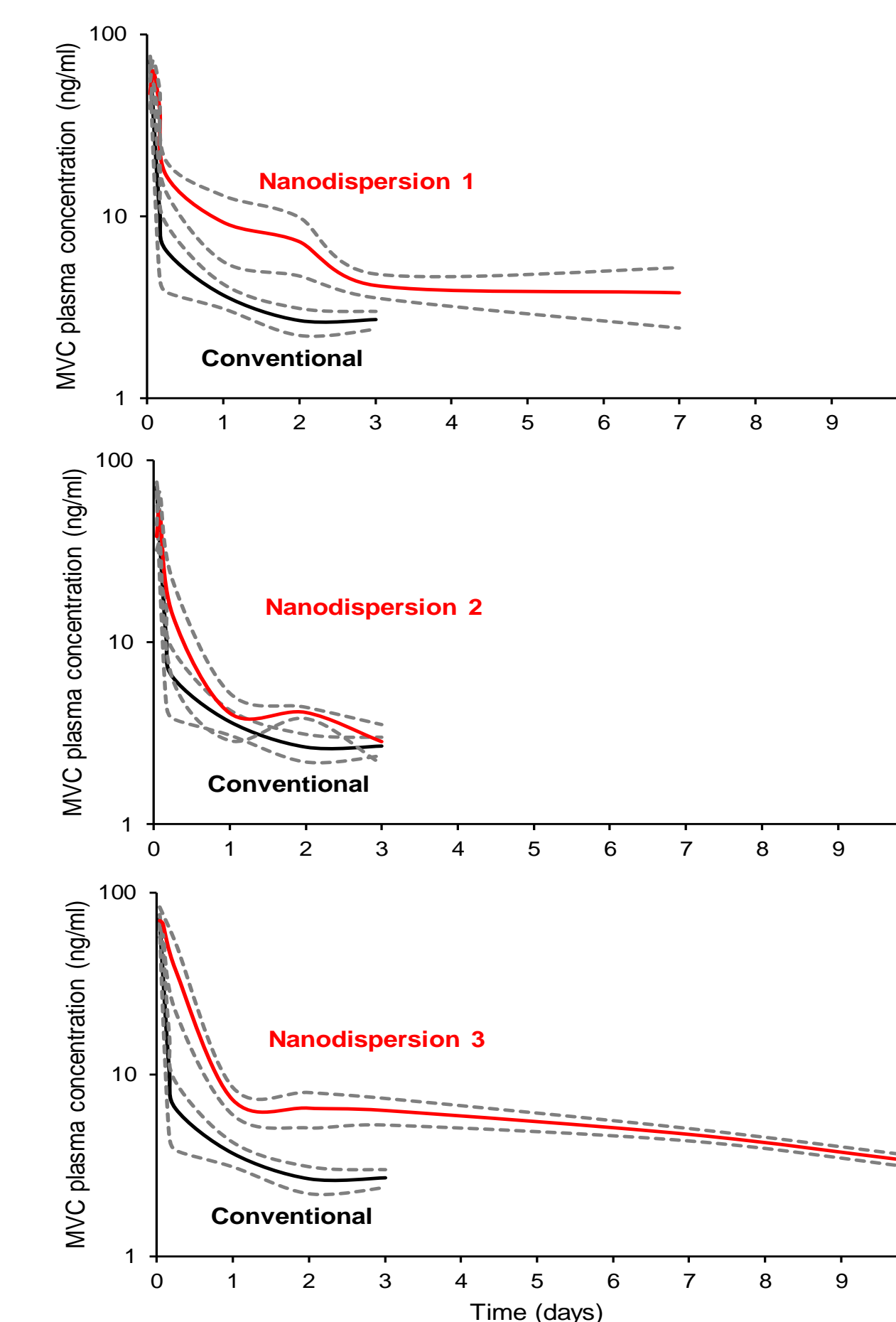

Figure 2. MVC exposure in adult male Wistar rats following a single intramuscular injection of either a conventional MVC preparation or each nanodispersion. n=3, ±SD.

Table 2. Pharmacokinetic parameters derived from Figure 2.

Pharmacokinetic parameter	Conventional MVC	Nanodispersion 1	Nanodispersion 2	Nanodispersion 3
C_{max} (ng ml^{-1})	71.67	62.88	50.58	69.85
$AUC_{0-\infty}$ (ng.h ml^{-1})	567.17	1720.51	628.62	2821.3
AUC_{0-24} (ng.h ml^{-1})	244.29	472.19	356.76	714.85
Terminal half-life (t½)	53.23	121.44	33.19	196.04
C_{24} (ng ml^{-1})	3.67	9.30	4.11	7.23
C_{48} (ng ml^{-1})	2.69	7.28	4.08	6.50
C_{72} (ng ml^{-1})	2.66	4.18	2.84	6.32
C_{168} (ng ml^{-1})	-*	3.81	-*	4.67
C_{240} (ng ml^{-1})	-*	-*	-*	3.30

(-*)=below limits of quantification

- The results in Fig 2. show MVC was detectable in plasma for up to 7- and 10-days for nanodispersion 1 and 3, respectively. Nanodispersion 2 displayed comparable exposure with the conventional MVC dose.
- The parameters outlined in Table 2 show a 3- and 4.9-fold increase in the $AUC_{0-\infty}$ for nanodispersions 1 and 3, respectively.
- Similarly, a 2.3- and 3.6-fold increase in the terminal half-life (t½) was observed for nanodispersions 1 and 3, respectively. Whereas a 1.6-fold decrease in MVC t½ was observed for nanodispersion 2.
- All *In vivo* work was conducted in accordance with the Animals (Scientific Procedures) Act 1986 (ASPA), UK Home Office.

1. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents What's New in the Guidelines? Key Updates What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient. https://aidsinfo.nih.gov/guidelines.
2. C. Trezza, S.L. Ford, W. Spreen, R. Pan, S. Piscitelli, Formulation and pharmacology of long-acting cabotegravir, Curr. Opin. HIV AIDS. 10 (2015) 239–245.
3. M.S. Cohen, Y.Q. Chen, M. Mccauley et al., Prevention of HIV-1 Infection with Early Antiretroviral Therapy, N Engl J Med. 3656365 (2011) 493–505.
4. R.M. Grant, J.R. Lama, P.L. Anderson et al, Pre-exposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men, N Engl J Med. 36327 (2010).
5. R.M. Gulick, T.J. Wilkin, Y.Q. Chen et al, Phase 2 Study of the Safety and Tolerability of Maraviroc-Containing Regimens to Prevent HIV Infection in Men Who Have Sex With Men (HPTN 069/ACTG A5305), J. Infect. Dis. 215 (2017).
6. R.M. Gulick, T.J. Wilkin, Y.Q. Chen et al, Safety and tolerability of maraviroc-containing regimens to prevent HIV infection in women, Ann. Intern. Med. 167 (2017) 384–393.
7. C.M. Perry, Maraviroc, Drugs. 70 (2010) 1189–1213.
8. J. Fox, J.M. Tiraboschi, C. Herrera et al, Pharmacokinetic/Pharmacodynamic Investigation of Single-Dose Oral Maraviroc in the Context of HIV-1 Pre-exposure Prophylaxis, JAIDS J. Acquir. Immune Defic. Syndr. 73 (2016) 252–257.
9. C.W. Hendrix, Minireview Exploring Concentration Response in HIV Pre-Exposure Prophylaxis to Optimize Clinical Care and Trial Design, Cell. 155 (2013) 515–518.
10. A. Owen, S. Rannard, Strengths, weaknesses, opportunities and challenges for long acting injectable therapies: Insights for applications in HIV therapy, Adv. Drug Deliv. Rev. 103 (2016).

l.tatham@liverpool.ac.uk

Discussion

- Oil-blended MVC nanodispersions were developed and investigated as LAI formulations.
- Pharmacokinetic studies in rat demonstrate up to 10-days MVC exposure.
- These data support development of a MVC LAI formulation with potential application in PrEP.