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Oral pharmacokinetics of the anti-HIV efavirenz encapsulated within polymeric micelles

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ABSTRACT

Aiming to improve the pediatric pharmacotherapy of the human immunodeficiency virus (HIV) infection, our group has recently developed a concentrated formulation of the first-line antiretroviral efavirenz by means of encapsulation within polymeric micelles. The aqueous solubility of the drug was increased more than 8400 times (up to 34 mg/mL) and preliminary preclinical data suggested the significantly greater oral bioavailability with respect to an extemporaneous suspension and an oleous solution (similar to the only "commercially available" pediatric formulation). As the preamble to a bioequivalence trial to evaluate the micellar system in adult healthy volunteers, the present work investigated the effect of parameters such as dose per body weight and drug concentration on the oral pharmacokinetics of the drug. The non-linear pharmacokinetics of the drug was confirmed for all the formulations. Despite the drug concentration and dose, micelles consistently resulted in significantly greater absorption rates, PK parameters increasing up to 3-fold. For example, C_{max} values increased from 687, 1789 and 2657 ng/mL for the oily system to 1145, 2856 and 7056 ng/mL for the micellar one, for EFV doses between 20 and 80 mg/kg. Data clearly showed that the smaller the micellar size, the higher the bioavailability attained. The effect of micellar size was also assessed. In addition, a comparison between *in vitro* dissolution rates of EFV for the different micelles and AUC values suggested that micelles releasing faster *in vitro* lead to a less pronounced absorption *in vivo*. These findings would suggest the involvement of additional absorption mechanisms.

1. Introduction

The Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS), the most deadly infection of our times, affects approximately 35–40 million people worldwide [1]; 60% of the patients live in the sub-Saharan region (sSR) and 2.5 million succumb to the disease every year. The number of infected children is 2.5 million [1]. Owing to the High Activity Antiretroviral Therapy (HAART), the disease has become manageable [2]. A successful pharmacotherapy involves the chronic administration of high and frequent doses of, at least, three antiretrovirals (ARV) and it demands compliance and adherence greater than 95% [3]. Otherwise, the chances of therapeutic failure grow substantially. Pediatric HIV has been almost eradicated in the developed world by preventing the mother-to-child-transmission (MTCT) [4]. Conversely, approximately 1000–1500 children get HIV-infected every day in emerging countries [5]. Only 10% of the HIV-infected children have timeous access to any medication, this level dropping to less than 2% in the sSR [6]. Without treatment, approximately 30% and 50% of the pediatric patients will die before the first and second birthday.

The limited number of ARVs approved by the regulatory agencies for pediatric administration [7] together with the reduced commercial availability of liquid formulations [8–10] are the most remarkable hurdles towards a highly compliant pharmacotherapy. The massive development of safe, proven and effective pediatric medications constitutes a pending agenda in HIV/AIDS and other neglected diseases [11].

Efavirenz (EFV) is a highly lipophilic (intrinsic water solubility = 4 μg/mL) non-nucleoside reverse transcriptase inhibitor

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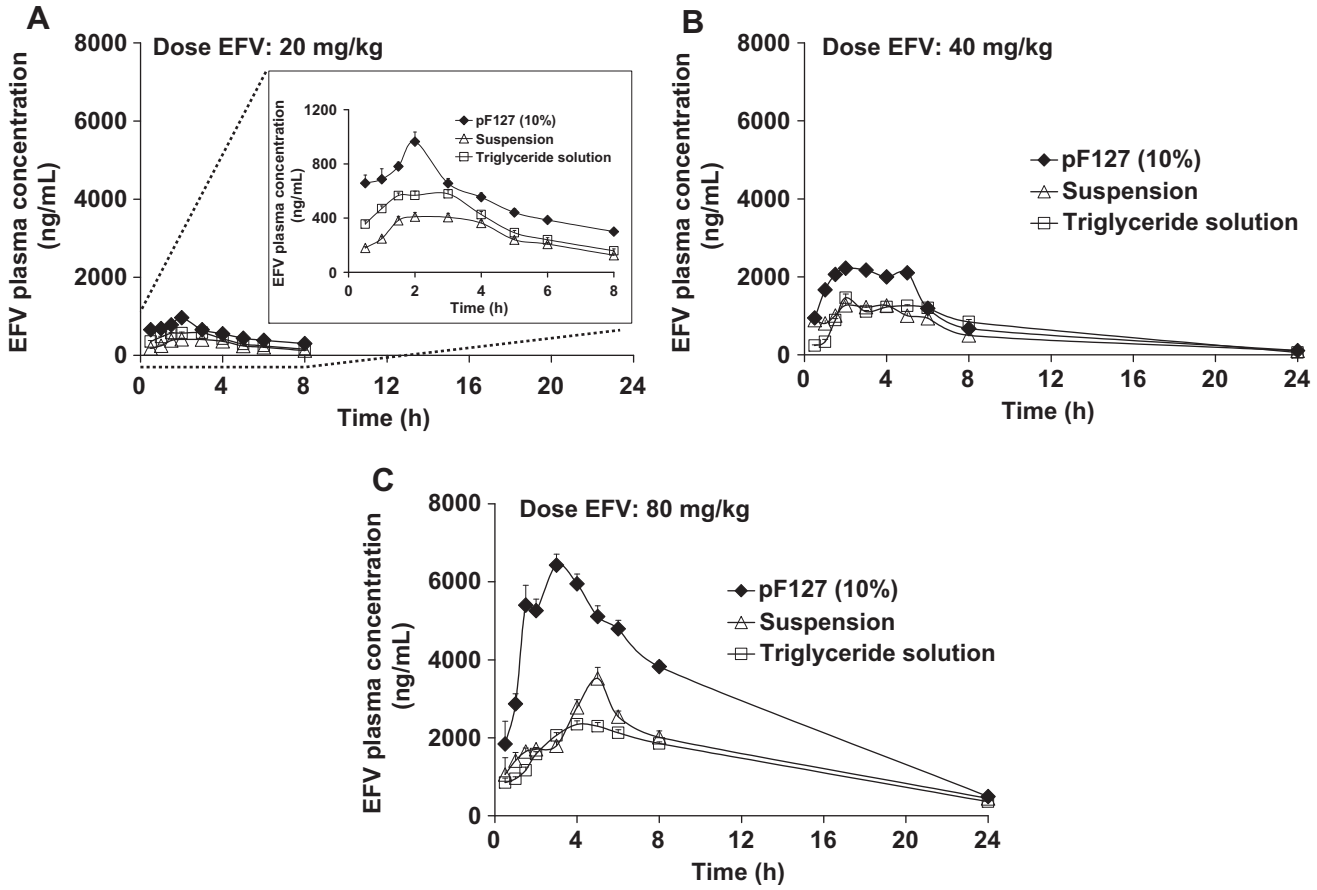

Fig. 1. EFV plasma concentration after the oral administration of (A) 20 mg/kg, (B) 40 mg/kg and (C) 80 mg/kg. Results are expressed as mean ± S.E. ($n = 8$). (D) C_{max} and AUC_{0-24} versus dose of the different formulations. Data of 40 mg/mL was adapted from Ref. [34].

Table 1
EFV oral pharmacokinetic parameters upon the oral administration of 20, 40 and 80 mg/kg ($n = 8$). The EFV concentration was 20 mg/mL.

Dose (mg/kg)	PK parameter	pF127 (10%)		Suspension			MCT solution		
		Media	CV%	Media	CV%	p	Media	CV%	p
20	C_{max} (ng/mL)	1145[b]	42.7	515	37.6	<0.01	687	29.8	<0.05
	t_{max} (h)	1.94	46.6	2.14	48.0	ND	2.19	32.2	ND
	AUC_{0-4} (μg/mL/h)	2.65[b]	39.8	1.50	46.5	<0.05	2.01	29.3	NS
	AUC_{0-24} (μg/mL/h)	7.22[b]	32.1	3.53	33.8	<0.01	4.79	36.5	<0.05
	k_e (h^{-1})	0.15	6.30	0.15	7.85	ND	0.16	10.2	ND
	F_r (%)	204.5	ND	100.0	ND	ND	135.7	ND	ND
40	C_{max} (ng/mL)[a]	2863[b]	28.3	1526	42.2	<0.005	1789	61.4	<0.05
	t_{max} (h)[a]	2.85	40.5	2.38	50.0	NS	2.42	53.0	NS
	AUC_{0-4} (μg/mL/h)	5.02[b]	12.8	3.91	39.2	NS	3.27	30.8	<0.05
	AUC_{0-24} (μg/mL/h)[a]	23.5[b]	37.1	15.1	55.2	<0.05	12.6	49.0	<0.05
	k_e (h^{-1})	0.14	13.4	0.13	16.9	NS	0.16	5.7	NS
	F_r (%)	155.6	ND	100.0	ND	ND	83.4	ND	ND
80	C_{max} (ng/mL)	7056[b]	21.3	3361	52.8	<0.001	2657	20.7	<0.001
	t_{max} (h)	3.69	31.5	4.67	17.5	NS	4.83	33.1	NS
	AUC_{0-4} (μg/mL/h)	22.3[b]	42.2	7.2	41.6	<0.001	6.5	9.8	<0.001
	AUC_{0-24} (μg/mL/h)	79.4[b]	24.1	39.4	38.8	<0.001	36.7	26.1	<0.001
	k_e (h^{-1})	0.12	13.6	0.11	23.9	NS	0.11	47.2	NS
	F_r (%)	201.5	ND	100.0	ND	ND	93.1	ND	ND

k_e: Elimination rate constant.
AUC0–4: Area-under-the-curve between 0 and 4 h.
AUC0–24: Area-under-the-curve between 0 and 24 h.
NS: Difference is not statistically significant with respect to the EFV-loaded pF127micelles.
ND: Not determined.
[a] Data taken from [34].
[b] Parameter of EFV-micellar system is significantly greater than that of the suspension and/or the MCT solution.