BIOAVAILABILITY OF Δ⁹-TETRAHYDROCANNABINOL (Δ⁹-THC) FROM DIFFERENT DOSAGE FORMS CONTAINING ITS PRODRUG Δ⁹-THC-VAL-HS (NB1111)

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ABSTRACT

A prodrug of Δ⁹-THC (Δ⁹-THC-Val-HS; NB1111) was prepared and formulated in three different pharmaceutical dosage forms, namely; suppositories, transmucosal delivery systems, and eye drops. The suppository dosage form was tested in rats at 3.67 and 7.9 mg/kg doses, the transmucosal delivery system was tested in a swine model at 5,10 and 20 mg doses, and the eye drops were tested in the rabbit in a 0.6% solution in Tocrisolve. All animal studies were performed using University of Mississippi IACUC approved protocols. Blood levels of Δ⁹-THC, 11-OH-Δ⁹-THC, and 11-Nor-9-Carboxy-Δ⁹-THC were measured after suppository and transmucosal delivery system administration while only Δ⁹-THC was measured in the different eye tissues after the eye drops administration. The data suggest that NB1111 is a good candidate for development in these formulations to deliver Δ⁹-THC both systemically and topically. None of the data presented here was published or presented previously.

INTRODUCTION

Previous work has shown that Δ⁹-THC is not absorbed from suppositories[1,2]. In pervious communications, we have shown that the Δ⁹-THC-Hemisuccinate (THC-HS) prodrug was able to deliver Δ⁹-THC with consistent bioavailability in animal models (monkeys[2] and dogs[3]) and humans[4-6]. Figure 1 shows a dose response curve in humans, and Figure 2 shows a comparison of Δ⁹-THC blood levels for the Δ⁹-THC-HS vs. Δ⁹-THC oral (Marinol®). In this presentation, we have prepared the amino acid derivative of Δ⁹-THC (Δ⁹-THC-Val-HS) and studied the bioavailability of Δ⁹-THC from different dosage forms using this prodrug. These formulations included suppositories, transmucosal delivery sytems, and topical eye formulations.

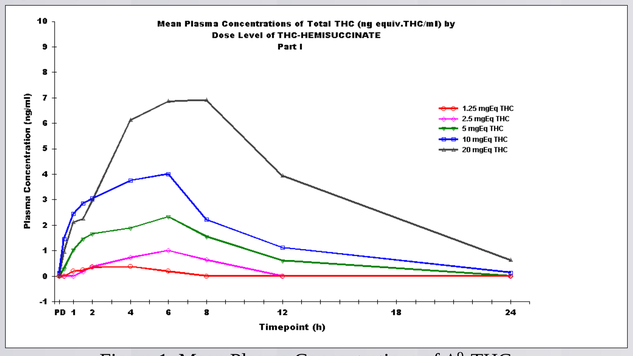


Figure 1. Mean Plasma Concentrations of Δ⁹-THC

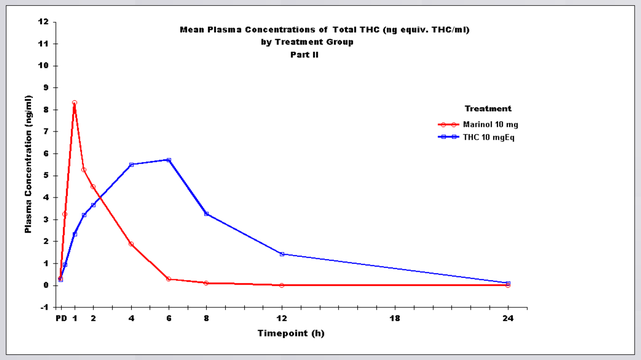
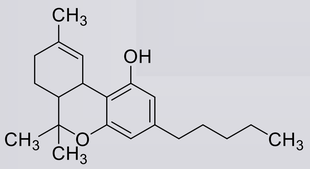
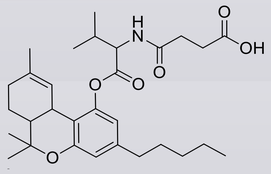


Figure 2. A Comparison of Δ⁹-THC Plasma Concentrations from the DHS Suppository versus Marinol®

STRUCTURES



Δ⁹-THC



Δ⁹-THC-Val-HS

EXPERIMENTAL

Suppositories: Δ⁹-THC-Val-HS was formulated in WECOBE w lipophilic base at two dose levels. Bioavailability was carried out in a cannulated rat model and plasma samples at different times. Theses samples were analyzed using LC-MS/MS for Δ⁹-THC, 11-OH-Δ⁹-THC, and Δ⁹-THC-COOH. The results are shown in Figures 3 and 4.

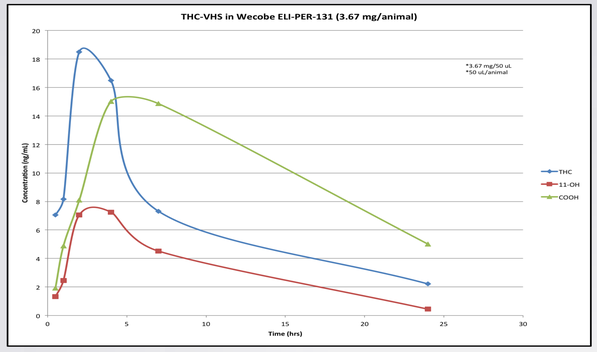


Figure 3. Δ⁹-THC-Val-HS in WECOBE ELI-PER-131 (3.67 mg/animal)

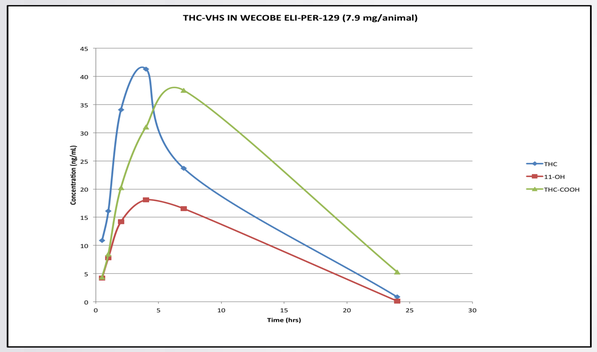
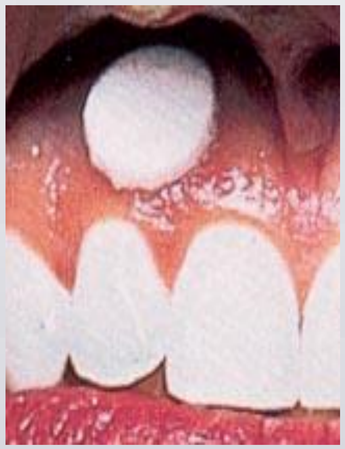
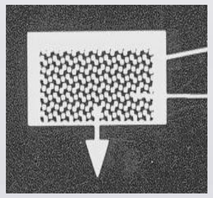


Figure 4. Δ⁹-THC-Val-HS in WECOBE ELI-PER-129 (7.9 mg/animal)

Transmucosal Delivery Systems: These samples were prepared using a hot-melt extraction process. Bioavailability was carried out in a surine model. The analysis of Δ⁹-THC and metabolites was carried out by LC-MS/MS. The results are shown in Figure 5.

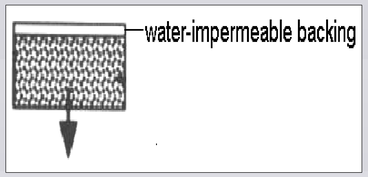


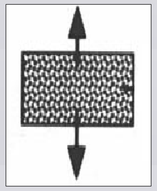
Prototype Transmucosal Matrix Patch (TMP) applied *in-vivo* (placebo)



Water-Impermeable Spray Coating

Bioadhesive + Drug + Excipients





Multi-Directional

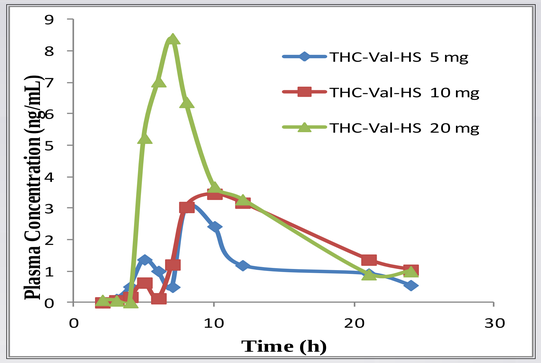


Figure 5. Δ⁹-THC-Val-HS in a Transmucosal Delivery System

Plasma Δ⁹-THC concentrations as a function of time and dose from Δ⁹-THC-Val-HS loaded HME patches. Data represents the mean value. The animals for maintained under anesthesia for the first 4 hours and were then allowed to come out of anesthesia and given access to food and water.

- In view of the superior stability and equivalent *in vivo* performance with respect to Δ⁹-THC-HG, Δ⁹-THC-Val-HS was selected as the most promising prodrug for transbuccal administration.
- A dose dependent plasma concentration time profile was then evaluated.

Topical Preparations for the Treatment of Glaucoma: Δ⁹-Δ⁹-THC-Val-HS was formulated in eye drops or optical films, and these were tested for their Δ⁹-THC level in different eye tissues in normal rabbits. The analysis of Δ⁹-THC in the tissues was carried out using LC-MS/MS. The results are shown in Tables 1 and 2. Furthermore, the effect of these preparations covering the intraocular pressure was tested in a rabbit model of glaucoma. The results are shown in Figure 6.

Table 1. Ocular Tissue Distribution of Δ⁹-THC 1 Hour Post Topical Application of Free Δ⁹-THC

Tissue	THC		
	Light Mineral Oil	Emulsion	0.5% Cremophor RH 40 + 0.1% EDTA + 0.02% BAK + 0.5% HPMC
Drug Concentration in terms of THC (% w/v)	0.1	0.37	0.125
Cornea (ng/50 mg Tissue)	68.8 ± 14.5	300.6 ± 79.6	553.9 ± 87.4
Aqueous Humor (ng/100 µL)	ND*	ND*	ND*
Iris-Cilliary Body (ng/50 mg Tissue)	ND*	ND*	ND*
Vitreous Humor (ng/mL)	ND*	ND*	ND*
Retina-Choroid (ng/50 mg Tissue)	ND*	ND*	ND*
Sclera (ng/250 mg Tissue)	104.1 ± 36.1	171.1 ± 66.6	439.3 ± 280.2

ND* - Drug concentration below detection limit

Table 2. Ocular Tissue Distribution of Δ⁹-THC from Δ⁹-THC-Val-HS Applied Topically

Tissue	2.5 % HPβCD + 0.5% HPMC		0.1% Cremophor RH 40+ 0.02% BAK + 0.1% EDTA + 0.5% HPMC	Ocular Film	
	1 Hour	3 Hours	1 Hour	1 Hour	3 Hours
Drug Concentration	0.26 %w/v		0.25 %w/v	10 %w/w	
Dose (µg)	130		125	800	
Cornea (ng/50 mg Tissue)	1677.1 ± 172.1	1142.3 ± 415.9	1191. 7 ± 231.1	1634.5 ± 756.5	1043.4 ± 614.4
Aqueous Humor (ng/100 µL)	69.4 ± 16.7	38.3 ± 10.2	62.1 ± 12.6	61.3 ± 32.1	29.1 ± 14.2
Iris-Cilliary Body (ng/50 mg Tissue)	65.8 ± 15.9	57.9 ± 16.1	51.44 ± 19.5	86.03 ± 38.2	104.2 ± 41.2
Retina-Choroid (ng/50 mg Tissue)	ND*	ND*	ND*	355.5 ± 155.2	11.9 ± 4.9
Sclera (ng/250 mg Tissue)	882.2 ± 185.8	241.8 ± 106.6	913.4 ± 432.9	1891.2 ± 771.5	812.6 ± 501.4

ND* - Drug concentration below detection limit

EXPERIMENTAL (CONT.)

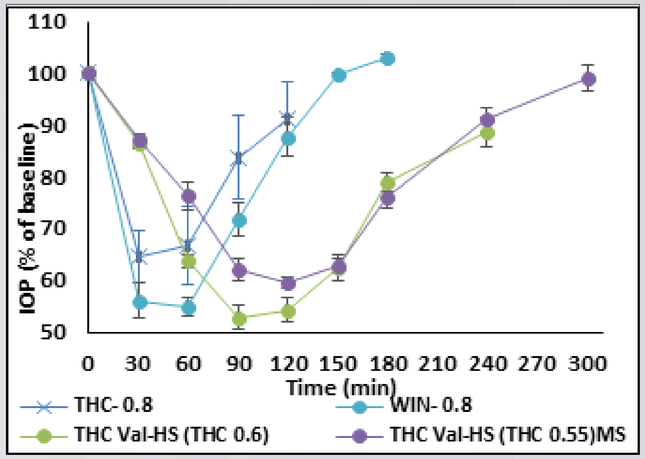


Figure 6. Δ⁹-THC-Val-HS in Topical Preparations for Treatment of Glaucoma

IOP-Time Profile in rabbit glaucoma model (Mean± SEM). THC-0.8: Δ⁹-THC in Tocrisolve (0.8 %w/v, 400µg), WIN-0.8: WIN in Tocrisolve (0.8 %w/v, 400µg), Δ⁹-THC-Val-HS (THC-0.6): Δ⁹-THC-Val-HS in Tocrisolve (Δ⁹-THC eq 0.6 %w/v, 300µg), Δ⁹-THC-Val-HS (THC-0.55)MS: Δ⁹-THC-Val-HS in micellar solution (Δ⁹-THC eq 0.6 %w/v, 275µg).

CONCLUSION

The prodrug Δ⁹-THC-Val-HS showed a high degree of bioavailability, delivering Δ⁹-THC, from the suppository formulation and transmucosal delivery system with dose proportionality. It also delivered Δ⁹-THC to the various eye tissues from topical preparations including micellar solutions, Tocrisolve, and occular films. The topical preparations resulted in significant reduction in intraoccular pressure in a rabbit glaucoma model.

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