INTRAOCULAR PRESSURE LOWERING EFFICACY OF A Δ9-TETRAHYDROCANNABINOL PRODRUG, NB1111, IN A NORMOTENSIVE RABBIT MODEL

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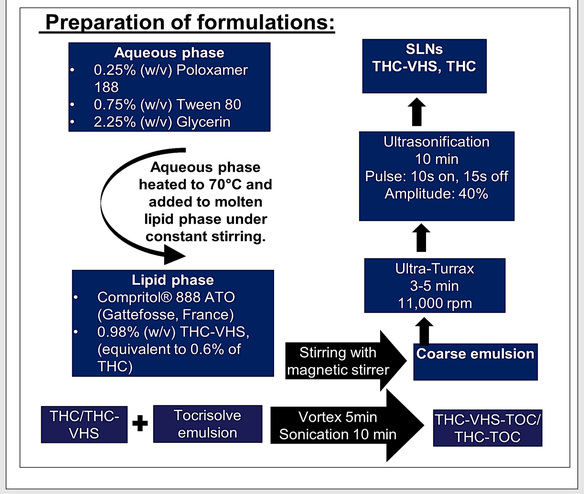
PURPOSE

- Δ9-Tetrahydrocannabinol (Δ9-THC) is the active ingredient of the plant *cannabis sativa*, and exhibits the intraocular pressure (IOP) lowering activity by acting on the cannabinoid receptors, CB1 and CB2.
- Δ9-THC-Valine-Hemisuccinate (THC-VHS; NB1111) is a relatively hydrophilic prodrug of Δ9-THC with improved ocular bioavailability.
- The aim of this study was to evaluate the effect of a single application as well as multiple day application of THC-VHS solid-lipid nanoparticles (THC-VHS-SLN), soybean-oil based emulsion (THC-VHS-TOC), and THC SLN on the IOP of normotensive rabbits, following topical application.
- The ocular disposition of THC-VHS was studied corresponding to the IOP drop at two time points.
- IOP lowering efficacy of a single application of THC-VHS-SLN was also compared to that of marketed ophthalmic formulations of Pilocarpine and Timolol Maleate.

METHODS



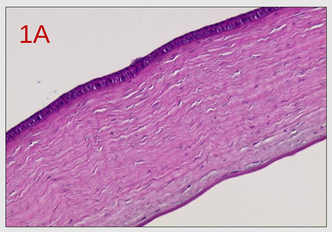
Multiple dosing regimen

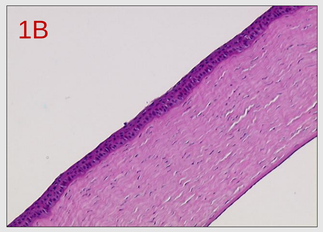
- Fifty microliters of SLN or Tocrisolve™, was instilled topically in the cul-de sac of the left eye of normotensive New Zealand White rabbits (n=6), twice a day, for five consecutive days.
- For the single day IOP-Time profiling, after the first application on Day 1 and Day 5, IOP was measured every 30 min till IOP returned to 90 % of the baseline, using a TONO-PEN VET™ (Reichert, Inc.).
- From Day 2 to Day 4, the IOP was measured 90 min before and after administration of the dose.
- On Day 6, the animals were sacrificed at two time points, the first time point which showed the lowest drop in IOP on day 5 and the second time point when the IOP returned back to 90% IOP from the baseline.
- All animal studies were conducted following IACUC approved protocols.

CONCLUSION

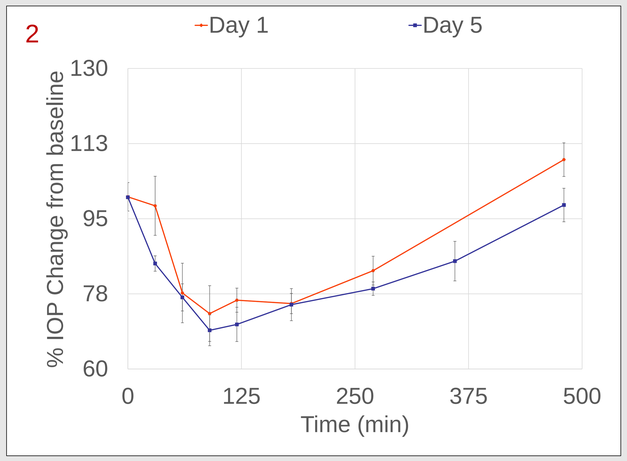
- THC-VHS SLN formulations were observed to produce a considerable drop in IOP and the duration of effect was significantly longer than the marketed formulations containing Pilocarpine or Timolol in normotensive rabbits.
- THC-VHS in the emulsion (Tocrisolve™) formulation produced only a slight decrease in the IOP.
- THC in the SLN or Tocrisolve™ formulations did not produce any effect on the IOP of normotensive rabbits.
- The corresponding THC-VHS concentrations in the ocular tissues were significantly higher with the SLN formulations demarking improved tissue penetration.
- Corneal histology studies showed that the formulations did not induce any toxic effects on the rabbit corneas.

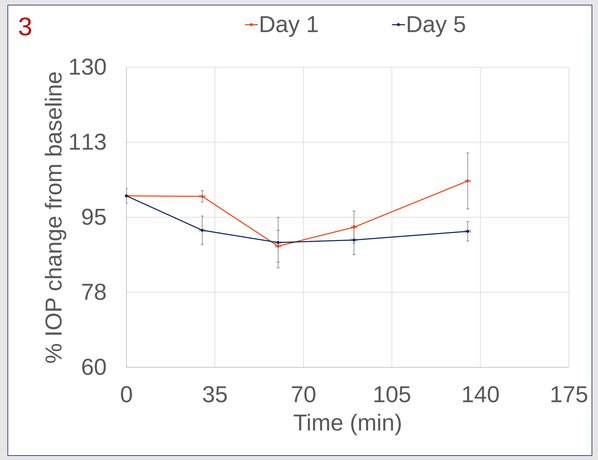
RESULTS

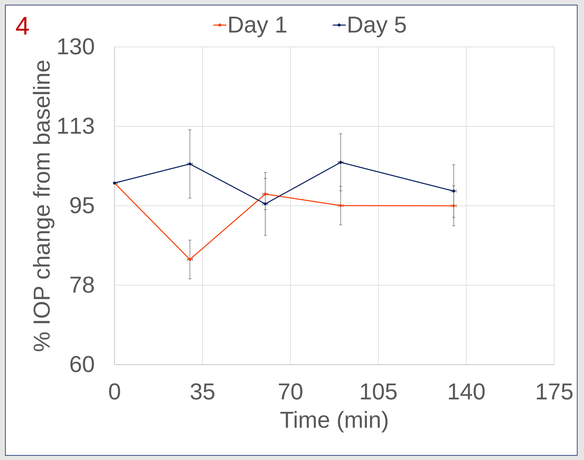


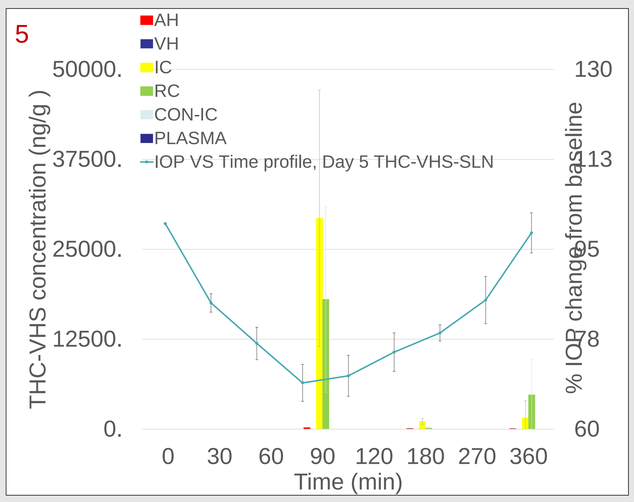


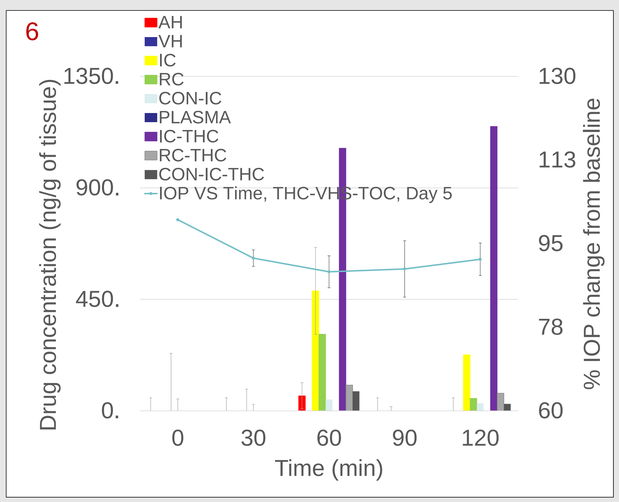
Figures 1A and 1B. depict the rabbit corneal histology after being dosed with the blank SLNs and IPBS respectively. The animals (n=3) were dosed with the formulations and the eyes were enucleated after 120 minutes. The corneas were isolated and fixed using neutral buffered formalin and stained Hematoxylin and Eosin. The corneas were mounted and studied under 10x magnification for possible toxicological effects.

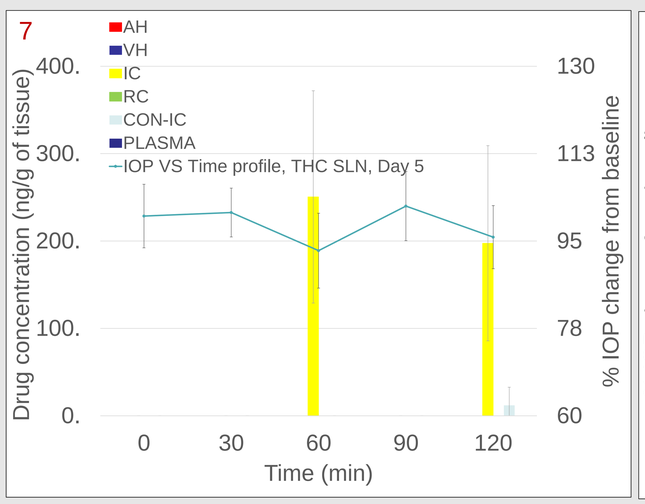


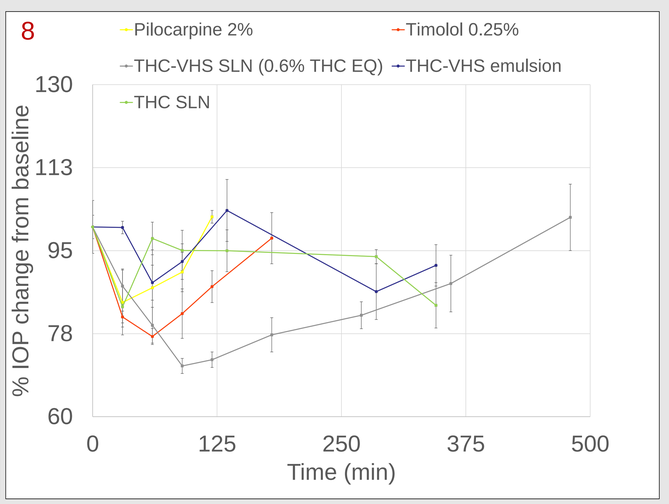












Figures 2., 3. and **4**. denote IOP vs Time profile for THC-VHS-SLN, THC-VHS-TOC, THC-SLN on Day 1 and Day 5 of the multiple dose dosing regimen. **Figures 5., 6.** and **7**. denote tissue concentrations of THC-VHS at 90 minutes (n=3) and 360 minutes (n=3), THC-VHS and THC at 60 minutes (n=3) and 120 minutes (n=3) and THC at 60 minutes (n=3) and 120 minutes (n=3), respectively, in aqueous humor, vitreous humor, retina choroid and iris ciliary, after dosing THC-VHS-SLN, THC-VHS-TOC and THC-SLN, respectively, corresponding to the % IOP drop vs Time profile on Day 5 of the multiple dose regimen. **Figure 8. illustrates** comparative IOP vs Time profile for THC-VHS-SLN, THC-VHS-TOC, THC-SLN, Pilocarpine and Timolol marketed formulations,

ACKNOWLEDGEMENT

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