A HIGHLY-LOADED NANOPARTICULATE FORMULATION OF PROGESTERONE FOR EMERGENCY TRAUMATIC BRAIN INJURY TREATMENT

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PURPOSE:
Progesterone is a water-insoluble steroidal hormone that is a promising therapeutic for treating traumatic brain injury (TBI) [1,2]. However, it is difficult to formulate the steroid into a feasible form for administration due to the physical properties of the steroid. In the literature, many different nanoparticulate formulations for progesterone have been described, but the highest concentration and drug loading reported remain low at 12 wt% of the particle solids, reaching 2.6 mg/mL progesterone in the aqueous dispersions [3]. We demonstrate the use of Flash Nanoprecipitation (FNP) to produce polymeric nanoparticles (NPs) with 24 wt% loading of progesterone at a base concentration of 10 mg/mL of the steroid.

METHODS:
Progesterone-loaded nanoparticles were made using only components that are classified by the FDA as GRAS (generally recognized as safe). A rapid precipitation method, FNP, was used to produce the NPs. Briefly, a water-miscible organic stream containing a dissolved amphiphilic block copolymer and a hydrophobic active of interest is rapidly micro-mixed against a larger water stream in a mixer of confined geometry. The formulation was optimized for particle size and drug loading.

RESULTS:
To achieve stable NPs with high loadings of progesterone, FNP with a 1:1 mass ratio of progesterone and α-tocopherol was necessary. The resulting nanoparticles were 300 nm in diameter with 24 wt% progesterone loading and active concentrations close to 10 mg/mL, of which approximately 80% was dissolved in the α-tocopherol. For prolonged stability, the nanoparticles were lyophilized with Pluronic F68. The nanoparticle suspensions were reproducibly reconstituted to the original size and at higher concentrations (3X concentration) by hand agitation for 1 minute. The reconstituted progesterone dispersion was readily expressed through a 25 gauge syringe needle.

CONCLUSIONS:
The Flash Nanoprecipitation process enables the formulation of progesterone using only GRAS components to produce NP suspensions with higher drug loadings and at higher concentrations than previously reported. The NPs can be kept in stable form and reconstituted in a convenient manner. This formulation can allow for administration of large amounts of progesterone in small volumes. Such a capability can be useful for emergency intramuscular administration, especially since administration of progesterone within 24 hours of the TBI produces the most benefit [4].
REFERENCES