Local and Sustained Drug Delivery for the Treatment of Cavernous Nerves Post-Prostate Cancer Surgery

Goyal R.[1], Patel N.[2], Salmasi A.[2], Kim I.Y.[2], Kohn J.[1]

[1]New Jersey Center for Biomaterials, Rutgers University, New Jersey, USA, [2] Cancer Institute of New Jersey, New Jersey, USA.

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Statement of Purpose: The probability of erectile dysfunction following radical prostatectomy (RP) is 20-80%.[1] Currently, there is no effective therapy to regenerate damaged cavernous nerves. The use of nanospheres (NSP) represents an innovative approach to increase the bioavailability, solubility, circulation time, and resistance to metabolic degradation of sildenafil (a PDE5 inhibitor) and rolipram (a PDE4 inhibitor). The NSP are synthesized from a family of fully-degradable, ABA-type triblock copolymers made of poly(ethylene glycol), oligomers of desaminotyrosyl-tyrosine esters and suberic acid.[2] These tyrosine-derived copolymers spontaneously self-assemble in aqueous media and provide the opportunity to deliver therapeutic agents that are hydrophobic, water-insoluble, and have poor bioavailability. These NSP have been shown to be nontoxic in vitro and in vivo.[2]

Methods: sildenafil citrate was used to prepare Sildenafil free-base (referred to as sildenafil) to make it more bioavailable. Sildenafil or rolipram loaded NSP were prepared using established protocols.[2] The NSP (with and without drug) were characterized for particle size, release profile, binding and loading efficiency. A dry formulation was prepared for the local delivery of sildenafil/rolipram encapsulated within NSP using a lyoprotectant under controlled freeze-drying conditions. Twenty-four male sprague dawley rats were randomly divided into 4 groups (n=6 for each group). Out of four, three groups received bilateral crush nerve injury (BCNI) and one group received no injury (SHAM, n=6). Of the rats that underwent BCNI, one group received no intervention (BCNI, n=6), while one group received sildenafil loaded NSP over site of induced crush injury bilaterally (BCNI+SIL+NSP, n=6), and the last group was treated with empty nanospheres after BCNI (NSP, n=6). After 14 days, each rat was analyzed for erectile function and immunohistochemistry of neurofilament in the penile dorsal nerve on mid penile cross-sections.

Results: The encapsulation efficiencies of sildenafil and rolipram into NSP were 58 and 63% respectively. Sildenafil citrate was incorporated in the NSP with the binding efficiency of only ~28%. These results indicate that the NSP are able to encapsulate the more hydrophobic drugs with higher efficiency. This is due to the fact that these NSP have hydrophobic core, which allows only hydrophobic drugs to encapsulate within the core.[2] The size of NSP was ~70nm (PDI~0.2) irrespective of the drug loading. The *in vitro* release data of 1% (w/w) sildenafil and rolipram loaded-NSP studied for 10 days in 1xPBS at 37 °C suggests that NSP provide an initial burst ~39% and 15% for sildenafil and rolipram respectively, within 2 h and releases up to 70% and 50% of sildenafil and rolipram respectively, in 24 h. At 10 day, the total release from NSP was ~81% and 85% for sildenafil and rolipram respectively (Figure 1). Depending on the targeted clinical doses, burst release of drugs can be beneficial. In this type of local drug application after prostate removal, this release profile can be helpful which provides an initial bolus to treat the injured nerve and thereafter releases slowly to maintain the drug concentration at the site of injury. Sildenafil loaded NSP significantly improved erectile function in rats compared to the BCNI group ($p<0.05$). Also, neurofilament staining was significantly higher in sildenafil loaded NSP group compared to the BCNI group ($p<0.05$) (Table 1). The results from rolipram group are pending analysis.

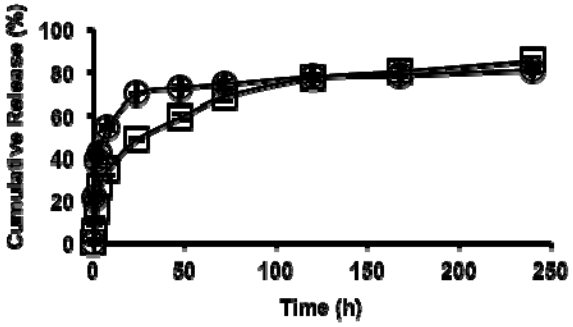

Figure 1. *In vitro* release of sildenafil (open circles) and rolipram (open squares) for 10 days in PBS (pH 7.4, 37°C) from 1% (w/w) drug loaded-NSP formulations.

Table 1. Quantitative analysis of immunohistochemistry images for NF and nNOS.

Group	Neurofilament (NF) (%)	neuronal Nitric Oxide (nNOS) Synthase (%)
Sham	12.92	0.96
BCNI	7.81	0.67
BCNI+NSP	7.24	0.66
BCNI+Sil+NSP	10.11	0.85

Conclusions: Sildenafil and rolipram were effectively encapsulated and released from the NSP. Local and sustained delivery of sildenafil to the site of injury using NSP technology showed improved erectile function, and neurofilament staining showed evidence of neuroprotection compared to the BCNI group. This therapeutic approach to localized drug delivery would benefit a large number of patients undergoing prostate removal and will help in cavernous nerve regeneration post-surgery.

References: 1. Nederlands tijdschrift voor geneeskunde 156, a4667 (2012).

2. Biomacromolecules 8, 998-1003, (2007).