Mesoporous silica controlled release nanoparticles for the delivery of analgesics

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Statement of Purpose: Mesoporous silica nanoparticles (MSNs) show great potential for use as controlled release drug carriers due to unique features. These include a network of ordered uniformly sized pores, a high pore volume and an easily modifiable silanol-containing surface [1]. These unique features facilitate the optimal control of the loading, incorporation of a large volume of active molecules and ease of surface fucntionalization for targeting specific tissue sites. These controlled release particles allow to obtain a quasi constant concentration of the drug close to the desirable concentration, as a result of which adverse effects associated with systemic concentration imbalance may be avoided [2]. The aim of this work was to synthesize bupivacaine-loaded MSNs, with the goal to develop a prolonged release form, and to study the *in vitro* release kinetics of bupivacaine from these particles. An additional goal was to study the effect of surface fucntionalization of MSNs on the release kinetics of the analgesic molecule.

Methods: The MSNs were prepared a follows: first, 1.00 g Cetyl trimethylammonium bromide (CTAB) was dissolved in 480 ml nanopure H_2O and the temperature raised to 75^oC. The solution was made basic by the addition of 3.5 ml of 2.00M NaOH; 5 ml Tetraethyl orthosilicate (TEOS) was added dropwise. The reaction temperature was maintained at 75^oC for 2h while white precipitates formed. The mixture was filtered in a centrifuge, then washed with deionized water and ethanol until the supernatant shows neutral pH (~7). The samples were left to dry in an oven for 2 days. For the preparation of dye functionalized MSNs, first fluorescein isothiocyante (FITC) was conjugated with aminopropyl (triethoxy) silane (APTES) then 1.25 ml solution of this conjugates in dimethylformamide (DMF) was added along with TEOS. The analgesic was loaded by stirring the functionalizaed/non-functionalized MSNs with an alcoholic solution of bupivacaine hydrochloride for one day. MSN morphology was characterized by TEM and XRD. FTIR was used to confirm the fucntionalization of MSNs. The porosity of MSNs before and after the drug loading was determined using BET. The release study was performed by placing 30 mg of the drug loaded sample in three different test tubes and adding 5 ml Phosphate Buffered Saline (PBS). The tubes were placed on a shaker in a 37^{oC} oven for the following times: 30 min, 1h, 2h, 4h, 6h, 8h, 10h, 24h, 33h, 48h and subsequent measurement was performed every 24h up to 14 days. After the samples were placed in the shaker for the allotted time, the supernatant was taken out and fresh 5 ml PBS was added. The drug concentration in the supernatant was measured using a UV-vis spectrophotometer.

Results: BET results (Fig.1a) showed a striking difference between the empty MSNs and drug loaded MSNs confirming the penetration of drugs inside the mesopores. *In vitro* release kinetics showed a controlled release of bupivacaine until 14 days with maximum release of 70 % of incorporated bupivacaine from non-functionalized MSNs, whereas the functionalized MSNs provides a controlled release with much slower rate of release up to 50% over 14 days period (Fig. 1b). This behavior is probably due to both steric hindrance and chemical interaction between bupivacaine and FITC functionalized MSNs.

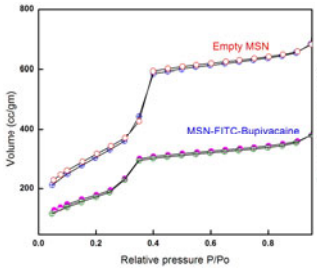

Fig. 1. (a)

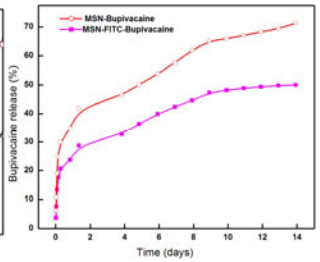

Fig. 1(b)

Conclusions: We have shown that mesoporous silica nanoparticles can be used for controlled release of analgesic bupivacaine for a time period up to 14 days. The rate of release can be controlled by the surface functionalization of MSNs.

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References:

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