Nanostructural control of the release of opioids prevents their abuse

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Introduction:

Analgesics represent a $23 billion per year industry in the Unites States [1]. Oxycodone, an opioid, is currently administered using controlled release tablets. Although this has led to gaining considerable control over pain management, the controlled release tablets have been misused. Emergency rooms treated an estimated 5,261 people from January to June 2000 for abuse of a controlled release form of oxycodone [2]. Measures to curb illicit use of the drug have not yet been successful. Thus, there is a considerable interest in the development of alternative controlled release methods that are abuse-proof. Herein, we propose that by incorporating the medicine in a nanostructurally optimized delivery material, release concentrations will be achieved that cannot exceed therapeutic target levels even when the carrier material would be crushed.

Methods:

Dextromethorphan, an inactive opioid with the same molecule weight of oxycodone, was used as a model drug. Silica xerogels were synthesized by using acid-catalyzed hydrolysis of tetramethyl orthosilicate (TMOS-98%, Aldrich) as nanostructural delivery materials (pore channels less than 2 nm). After mixing TMOS, DI water and 1N HCl, a sol was formed and corresponding amounts of dextromethorphan - methanol solution were added. The drug loads was varied from10, 20, 50 to 80 mg/g. The nanostructure was altered by varying the ratio of water to alkoxide (R). Values of 4, 6, and 10 were used. The sols were cast into 1"-polystyrene vials (1 ml in each vial), sealed, allowed to gel and then to age for 3 days. The vials were unsealed and the gels were dried at room temperature till constant weight. The resulting xerogel discs were crushed and particles of three different size ranges, 200-500, 40-70, and 20-40 μm, were produced by sieving.

The release studies were conducted in phosphate buffered saline solution (PBS) at pH 7.4 and 37 °C, and shaking on a shaker table rotating at 100 rpm. The particles were immersed in PBS at a ratio between weight and solution volume of 5 mg/ml and the solutions were exchanged daily. The concentration of released dextromethorphan was measured spectrophotometrically at 280 nm.

Results / Discussion:

The effect of particle size on in vitro release of dextromethorphan from xerogels (80 mg/g, R4) as a function of immersion time is shown in Figure 1. The data demonstrates that both large (200-500 μm) and fine (20-40 and 40-70 μm) particles showed time-dependent release of dextromethorphan. Although the release from smaller particles was noticeably faster than from larger ones, the finer particles did not show any burst release. Specifically, by one day of immersion, only 2% of the original load was released from fine (20-40-μm) particles of 80 mg/g-xerogels. The release continued in a controlled manner with immersion time. By seven days, 17% of the original load was released from the fine particles of 80 mg/g-xerogels. . The data so far demonstrate that a delivery material can be synthesized that achieves controlled release of therapeutically relevant doses.

The experiments also document that the principle of misuse resistance can be accomplished. First, there is no burst release associated with the controlled release sol gel materials. This finding is valid independent of the size of the controlled release particles. Thus, it is not feasible to dissolve the drug and obtain large quantities sufficient for recreational use in a reasonable time frame. Second, the controlled release carrier can be made in a small particle size useful for injection (40 – 70 μm). Reducing this particle size further to a 20 – 40 μm size is very difficult, and regardless, does not lead to an important increase of the release or a burst effect. One could envision making the product in a 20 – 40 μm particle formulation. This, however, only strengthens the misuse resistance concept. Reducing the size of 20 – 40 μm particles further is not a realistic undertaking.

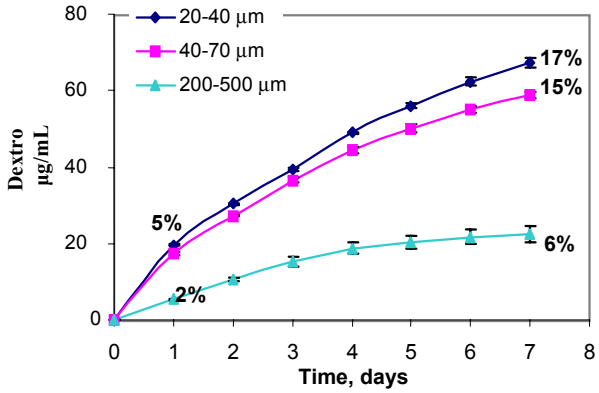

Figure 1. Mean cumulative release of Dextromethorphan from 80 mg/g-xerogels as a function of immersion time in PBS. The % release at various time points is also indicated (n=3, error bars represent standard deviation – by virtue of their small size, they are not clearly visible).

Conclusions:

The novel sol gel controlled release technology offers a fundamental solution to the abuse issue of controlled release opioid tablets. The controlled release materials can be made as monoliths which cannot be crushed to sizes smaller than about 10 μm. This size is then still three orders of magnitude larger than the pore channels (about 2 nm) that can be created to contain the opioid.

Acknowledgments:

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References:

1. CSAT Advisory, Breaking News for the Treatment Field, April 2001, Vol 1, Issue 1
2. Oxycontin. How Stuff Works. September 2004. http://www.howstuffworks.com