Abuse prevention by control release of opioids from micro to nano-structured silica xerogel delivery systems

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ABSTRACT

Analgesics are a multi-billion dollar pharmaceutical industry in the developed world. Studies have proven OxyContin to be effective in treating pains associated with arthritis, lower back conditions, injuries, and cancer. Controlled-release Oxycodone became a significant source of drug abuse and death-related opioid abuse increased during the 21st century and opioid poisoning was a common cause of death compared to cocaine and heroin. Measures to curb its illicit use have been unsuccessful so far. Interest in developing abuse-proof alternative controlled-release methods was generated and remains a key issue in resolving the drug abuse problem. This study proposes that release concentrations, of opioid, not exceeding therapeutic target levels can be achieved in a nano-structurally optimized delivery material. Dextromethorphan (Dextro-inactive opioid, mol wt. similar to Oxycodone) was used. Micro-sized to nano-sized silica xerogels particles were synthesized using silica precursors (TMOS/ TEOS), via hydrolysis and condensation reactions coupled with varying drug loads and water–to-alkoxide ratios. Particles were immersed in PBS and concentration of released Dextro was measured spectrophotometrically. The effect of particle size on *in vitro* release of Dextro from xerogels demonstrated that mocro to nanoscale particles showed time-dependent release of Dextro. This demonstrates that a delivery material can be synthesized to achieve controlled release of therapeutically relevant doses. Data indicates that the principle of misuse resistance can be accomplished. Particle size reduction might not lead to any important increase in the release or a burst effect. It is highly probable, therefore to fabricate a nano-sized particle formulation of the drug to strengthen the misuse resistance**.**

Key words: abuse, prevention, oxycodone, micro-to-nanoscale, controlled-release

1. INTRODUCTION

Analgesics represent hundreds of billions of dollars per year industry for the pharmaceutical companies, worldwide, and especially in the United States [1]. Recent statistics indicate that the prescriptions for opioids (oxycodone and hydrocodone) have sky-rocketed up to nearly 210 million by 2013, from around 75 million in 1991. Globally, the biggest consumer is the United States which accounts for up to 80% in the consumption of oxycodone and about 100% of hydrocodone [2]. The market consists of drugs used for the alleviation of pain due to injury, surgery, illness and chronic disease. In previous years, morphine and many opioids derivatives were widely used for the treatment of pain due to cancer or surgery. OxyContin is a semisynthetic opioid analgesic prescribed for chronic or long lasting pain. It contains between 10-160 mg of Oxycodone.HCl (active ingredient) in a time-release tablet [1]. Sales of OxyContin in the United States topped $1.2 billion in 2003 [3]. Recent studies have proven OxyContin to be effective in the treatment of various types of pain. It is most often prescribed for pain associated with arthritis, lower back conditions, injuries, and cancer. Treatment with oxycodone was effective for the management of moderate to severe chronic osteoarthritis-related knee pain, with substantially lower incidences of gastrointestinal-related TEAEs associated with treatment with oxycodone [4].

In 1996, controlled release OxyContin became available in 12 hour time release tablets in doses ranging from 10 mg to 160 mg per tablet [5]. The higher doses of 80 mg and 160 mg are administered to opioid (narcotic) tolerant

individuals. Unlike other analgesics like aspirin or acetaminophen with threshold to their effectiveness, OxyContin can potentially provide up to four times the relief of a non-opioid analgesic, such that the most severe degree of pain can be managed. The development of these controlled release tablets was a marked improvement over conventional tablets that only lasted 3 – 4 hours which required patients to swallow numerous pills per day in order to control their intense pain.

Although controlled release tablets have enabled patients to gain considerable control over their pain, OxyContin has become a significant source of drug abuse. From January to June of 2000, emergency rooms treated an estimated 5,261 people for abuse of OxyContin [6]. OxyContin is abused by crushing or dissolving the tablets and swallowing, snorting or injecting the drug contents released[5]. When abused, OxyContin can be dangerously addictive. Statistics indicate an increase in the negative consequences of opioid abuse, over recent years, tripling in the past 20 years [7]. It has also been reported that death-related opioid abuse started rising during the early part of the 21st century and that opioid poisoning was commonly listed on death certificates as the cause of death, in comparison with cocaine and heroin [8].

Measures taken by manufacturers and traditional pharmaceutical companies to curb illicit use of the drug have not yet been successful. There is therefore, a considerable interest in the development of alternative controlled release methods that may be abuse-proof. We propose, in this study, 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 is crushed. This preliminary data represent an outstanding basis for achieving controlled release of OxyContin for pain relief over a long period of time, as well as, inhibiting its use for recreation.

Using silica precursors such as tetramethoxysilane (TMOS) or tetraethoxysilane (TEOS), silica sol gels are synthesized via hydrolysis and condensation reactions [9]. The hydrolysis reaction, which can be either acid or base catalyzed, replaces alkoxide groups with hydroxyl groups. Siloxane bonds (Si-O-Si) are formed during subsequent condensation. Alcohol and water are byproducts of the condensation reaction and evaporate during the drying phase. Theoretically, the overall reaction is stated as follows:

$$n\,Si(OR)_4 + 2n\,H_2O \rightarrow nSiO_2 + 4nROH$$

In reality, however, completion of the reaction and the chemical composition of resulting product depend on excess water above the stoichiometric H_2O/Si ratio of 2. A number of other sol-gel processing parameters (such as *pH* of the sol, type and concentration of solvents, temperature, aging and drying schedules, etc.) can also affect the composition, structure, and properties of the resulting product [10].

Drug molecules are incorporated in the nanosized pore channels and are released by diffusion through the aqueous phase that penetrates into these pores. In our research laboratory, we have developed a deep understanding regarding nanostructural control of the release properties of sol gels (2-4). The variation of processing parameters leads to variations of pore size (in the nanometer range) and porosity, which in turn affects the release rates of the drug molecules. This is summarized in a recent review paper entitled “Nanostructural control of implantable xerogels for the controlled release of biomolecules” [11].

The goals of this research are (i) to develop a sol-gel system for the release of an opioid compound from a sol-gel with the potential to provide sustained relief from post-operative pain over a period of time (from one to several weeks); (ii) formulate a drug carrying system that will be impervious to recreational use/abuse, either by crushing, or by dissolving in solution to obtain a burst release of the active ingredients. By using a model opioid such as dextromethorphan, it is possible to determine the feasibility of loading high concentrations (up

to 80 mg/g) of the drug into the xerogels; demonstrate the principle of preventing misuse of drug abuse by determining the effects of drug load (high versus low) and particle size (fine versus large) on the release profile of dextromethorphan from silica xerogels.

2. MATERIALS AND METHODS

In this first series of experiments, we used a model molecule, namely Dextromethorphan (an inactive opioid). The experimental design was based on the following assumptions: the use of low water/alkoxide ratio would prevent the burst release from finely crushed particles (the water to alkoxide ratio is a parameter associated with the synthesis of the nanostructure sol gel controlled release carriers); since solubility of dextromethorphan is low in water (15 mg/ml) and high in alcohols (up to 200 mg/ml in methanol), the use of alcohol solutions for the synthesis of drug-loaded xerogels would enable obtaining higher loads (up to 80 mg/g) of this drug.

Silica xerogels with water/alkoxide ratio of 4 and nominal dextromethorphan concentrations (W, %) of either 20 or 80 mg/g, were synthesized by using acid-catalyzed hydrolysis of tetramethyl orthosilicate (TMOS-98%, Aldrich). After mixing TMOS, DI water and 1N HCl a sol was formed and corresponding amounts of dextromethorphan - methanol solution were added. 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 was attained. The weight loss for both 20mg/g and 80 mg/g gels was about 70%. The resulting xerogel disks were crushed and particles of three different size ranges, 200-500, 40-70, and 20-40 μm, were produced by sieving. The smallest size was exceedingly difficult to produce.

Table 1: A comparison between characteristic properties of Oxycontin and model opioid, Dextromethorphin

Property	OxyContin	Dextromerthophan
1. Molecular weight	351.83	370.30
2. Chemical Formula	$C_{18}H_{21}NO_4.HCl$	$C_{18}H_{25}NO.HBr.H_2O$
3. Physical properties:	White, odorless, crystalline	White, odorless, crystalline
4. Solubility		
a) In water	16g/100mL	1.5g/100mL
b) In alcohol	Slightly soluble in alcohol	Soluble 1 in 10 of ethanol (10g/100mL) Freely soluble in chloroform
5. pH		Of 1 % aqueous solution is 5.2 – 6.5
6. Chemical name	4, 5α-epoxy-14-hydroxyl-3-methyl-17-methylmorphinan-6-one hydrochloride	3 methoxy-17-methylmorphinan monohydrate
7. Type	Opioid analgesic (oxycodone is pure agonist opioid)	Synthetic compound; d-isomer of levophenol, a codein analogue and opioid analgesic
8. Drug name	Oxycodone hydrochloride	Dextromethorphan hydrobromide Dextromethorphan hydrobromium Demorphan hydrobromide
9. Trade name	OxyContin	Polistirex Exended Release Suspension
10. Therapeutic dosages	10, 20, 40 80 & 160 mg	10, 20, 30 and 60 mg

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.

3. RESULTS

In vitro release of dextromethorphan as a function of immersion time of 20mg/g and 80 mg/g xerogels is shown in Figs 1 and 2 respectively. The data demonstrates that both large (200-500 μm) and fine (20-40 and 40-70 μm) particles showed time- and load-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 4 and 2% of the original load were released from fine (20-40-μm) particles of 20mg/g- and 80 mg/g-xerogels, respectively. 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 both 20 mg/g- and 80 mg/g-xerogels.

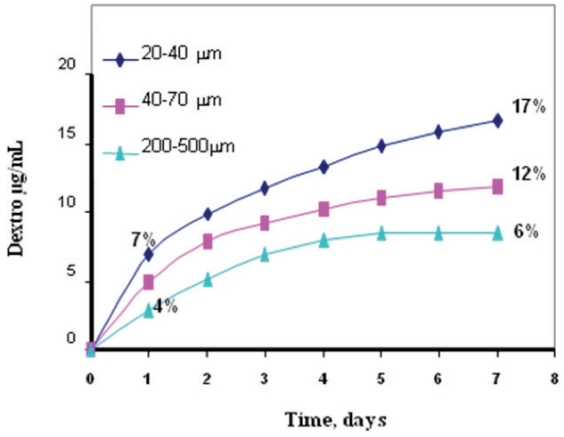

Fig.1. Mean cumulative release of Dextromethorphan from 20 mg/g-xerogels as a function of immersion time in PBS. % release at various time points is indicated (n=3, error bars represent standard deviation - by virtue of their small size, they are not clearly visible).

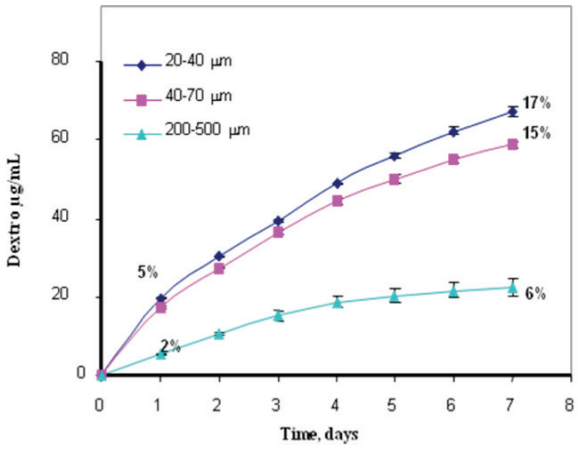

Fig.2. Mean cumulative release of Dextromethorphan from 80 mg/g-xerogels as a function of immersion time in PBS. % release at various time points is indicated (n=3, error bars represent standard deviation - by virtue of their small size, they are not clearly visible).

4. DISCUSSION AND CONCLUSION

We formulated our program based on the premise that the novel sol gel controlled release technology offered a fundamental solution to the abuse issue of controlled release opioids. The data so far demonstrate that a delivery material can be synthesized that achieves controlled release of therapeutically relevant doses. We have performed experiments for durations to 7 days and will continue with longer durations. 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. As such, 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.

The goal that we formulated at the outset was to control opioid release independent of the size of the pellet or powder in which the drug would be incorporated. We suggested that this can be achieved by encase the active substance in pore spaces that cannot be breached mechanically. This is achieved with the sol gels, as this class of 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. Herein we have reported the data for the proof of principle.

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