Zero-Order Release of Hydrocodone from a Hydrophilic Matrix Tablet Containing Naproxen Sodium

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ABSTRACT SUMMARY
A novel hydrophilic matrix tablet formulation was developed which provided sustained release (SR) of a primary analgesic, hydrocodone bitartrate, for up to 12 hours. Introduction of a secondary analgesic, naproxen sodium, into the hydrophilic matrix modified the release profile of the primary analgesic from first-order release to zero-order release. Comparison of the hydrophilic matrix tablet to an immediate release tablet using a dog model demonstrated proof-of-concept for the hydrophilic matrix technology.

INTRODUCTION
Hydrocodone was the most commonly prescribed medication in the United States in 2011.¹ Hydrocodone is often formulated with other non-opioid compounds, such as acetaminophen or ibuprofen, to provide a possible synergy of analgesic effects between hydrocodone and the non-opioid compounds present. Due to concerns regarding liver damage from protracted use of acetaminophen at high doses, a government advisory panel voted in June 2009 to eliminate prescription drugs combining acetaminophen with opioids. Ultimately, The U.S. Food and Drug Administration (FDA) mandated that drug manufacturers limit the strength of acetaminophen in prescription drug products, which are predominantly combinations of acetaminophen and opioids, to 325 mg per tablet, capsule, or other dosage unit.²

Currently, there are no single active ingredient formulations of hydrocodone on the market. Despite recent development efforts, there are also no sustained release formulations of hydrocodone commercially available to patients suffering from acute or chronic pain.³,⁴ Due to the safety concerns associated with acetaminophen and the lack of a commercially available modified release dosage form, the goal of the current work was to develop a SR hydrophilic matrix tablet formulation of hydrocodone containing naproxen sodium as the secondary analgesic.

EXPERIMENTAL METHODS
Tablets were produced by dry-blending the active substance(s) and excipients together followed by direct compression. The hydrocodone and naproxen sodium (when present) were added together with the other excipients (Methocel K4M, Avicel PH-302, Ac-Di-Sol) in an HDPE bag. Blending was accomplished by manually mixing the contents of the bag for five minutes. Aliquots of the blend were massed out using an analytical balance and were compressed using a GlobePharma MTCM-1 hand tablet press. Lots without naproxen sodium were compressed using 0.3125-inch round, concave tooling, while lots containing naproxen sodium were compressed using 0.3750-in round, concave tooling. The compression force was varied until a tablet breaking force of 14-16 kPa was consistently achieved.

USP Apparatus 2, with a paddle speed of 50 rpm, was used for all dissolution testing of the prototype tablets manufactured. Dissolution was measured in 900 mL of pH 7.5 phosphate buffer maintained at 37°C. The dissolution samples were assayed for hydrocodone using HPLC with UV detection at 280 nm. Testing was completed on a Waters Alliance 2487 HPLC system using a Phenomenex Jupiter C18 column.

The dog PK study was conducted as a crossover design consisting of 6 dogs per leg with a one week washout period between legs. Male beagle dogs between 8-14 kg were fasted for four hours prior to dosing and gavaged with an HCl solution immediately following tablet administration. Blood samples were taken from the jugular vein of each dog at predetermined time-points and stored in vials with anticoagulant until analysis. All samples were analyzed using LC-MS/MS. A non-compartmental analysis was used to determine the PK parameters.

RESULTS AND DISCUSSION
The target release rate (80% in 10-12 hours) for the primary analgesic (hydrocodone) was achieved by formulating hydrocodone in a SR matrix containing Methocel K4M as the rate controlling polymer and Avicel PH-302 as the binder (Figure 1). In the absence of naproxen sodium, the hydrocodone demonstrated a first-order SR profile.

![Figure 1. Dissolution of hydrocodone from hydrophilic matrix tablets formulated with (red) and without (blue) naproxen sodium.](image-url)
Incorporation of naproxen sodium into the hydrophilic matrix had the novel and unexpected result of modifying the hydrocodone release rate from first-order to zero-order (Figure 1) while still maintaining the target SR profile of the primary analgesic.

To demonstrate proof-of-concept for the zero-order hydrophilic matrix tablet technology in vivo, a dog pharmacokinetic (PK) study was conducted to investigate the performance of the SR tablet compared to an immediate release (IR) tablet. The IR tablet was formulated by replacing the rate controlling polymer (Methocel K4M) with a superspersion polymer (Ac-Di-Sol). Dissolution data (Figure 2) confirmed immediate release of the hydrocodone (80% released within 30 minutes).

Due to the relatively short gastrointestinal transit time of the dog (6-8 hours total), the SR tablet formulation was modified in order to realize faster release of the hydrocodone. Dissolution data for the new SR tablet (Figure 2) confirmed that the target release rate (80% in 6-8 hours) had been achieved while maintaining zero-order release kinetics.

Results of the dog PK study demonstrated statistically significant differences between the IR tablet and the SR tablet containing naproxen sodium (Figure 3). As illustrated in the figure, the SR tablet had a significantly lower average $C_{\text{max}}$ (SR = 24 ng/ml; IR = 56 ng/ml) and longer average $t_{\text{max}}$ (SR = 4.3 hr; IR = 0.8 hr) than the IR tablet. Importantly, the SR tablet was able to blunt $C_{\text{max}}$ and increase $t_{\text{max}}$ without significantly decreasing the average dose normalized AUC$_{\text{IR}}$ (SR = 84.9 ng/ml; IR = 99.5 ng/ml).

**CONCLUSION**

A hydrophilic matrix tablet formulation was developed to achieve sustained release of hydrocodone for up to twelve hours. Incorporation of naproxen sodium into the hydrophilic matrix was demonstrated to modify the release profile of hydrocodone from first-order to zero-order while maintaining the target release rate. A dog PK study was conducted to demonstrate proof-of-concept of the hydrophilic matrix tablet technology in an animal model. When compared to an immediate release tablet, the hydrophilic matrix tablet containing naproxen sodium was shown to significantly reduce $C_{\text{max}}$ and increase $t_{\text{max}}$ without decreasing the overall exposure of hydrocodone.

**REFERENCES**