M1310

# Development of an Accelerated *In Vitro* Release Testing Method for Naltrexone Microspheres

Nitin K. Swarnakar[1], Jie Shen[1], Wen Qu[2], Stephanie Choi[2], Yan Wang[2], Diane J. Burgess[1]

[1]-University of Connecticut, School of Pharmacy, Storrs, CT 06269

[2]-FDA/CDER, Office of Generic Drugs, Silver Spring, MD 20993

## OBJECTIVE

To develop a robust and reproducible accelerated *in vitro* release testing method that correlates with "real-time" *in vitro* release of naltrexone microspheres for quality control purposes.

## INTRODUCTION

Microsphere formulations such as naltrexone microspheres contain high amounts of potent therapeutics which are delivered continuously for weeks to months. Quality control testing, particularly *in vitro* release testing is important at every stage of formulation development to ensure product performance and safety. At present, various *in vitro* release testing methods (such as sample-and-separate, and continuous flow methods) are widely used for *in vitro* release testing of PLGA microspheres. In the present study, a robust and reproducible accelerated method for the approved and commercially available product containing naltrexone was developed that correlates with "real-time" *in vitro* release from naltrexone microspheres.

## METHODS

**Stability Study of Naltrexone**: The stability of naltrexone in different release media (*e.g.* 10 mM PBS + 0.02 % (w/v) Tween 20 + 0.02 % (w/v) sodium azide at different pH) at different temperatures was investigated prior to *in vitro* release testing. In addition, the effect of different concentrations (0.0625-1% w/w) of sodium ascorbate on the stability of naltrexone was investigated.

***In Vitro* Release Testing:** *In vitro* release testing of the marketed naltrexone microsphere product was investigated under both "real-time" (37°C) and accelerated testing (45°C) conditions using different release testing methods (*i.e.* sample-and-separate, and continuous flow). The reproducibility of these two release methods under different testing conditions as well as correlation between the obtained accelerated and "real-time" faction release were evaluated.

## RESULTS

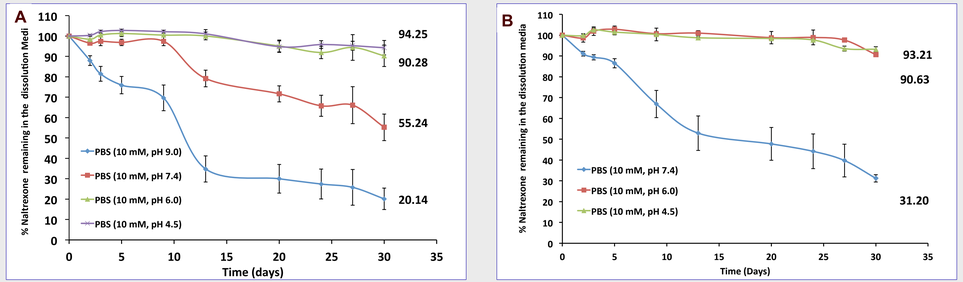


**Figure 1.** Stability of naltrexone under different pH conditions* in a water shaker bath at (A) 37ºC and (B) 45ºC.

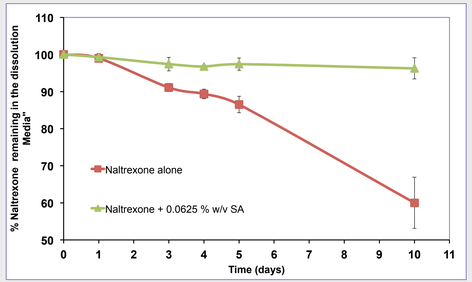


**Figure 2.** Stability of naltrexone solution in the presence of antioxidant (sodium ascorbate; 0.0625%w/v) at 37ºC (10 mM PBS, pH 7.4)*.

* Media contain 0.02% (v/v) Tween 20 and 0.02% (w/v) sodium azide.

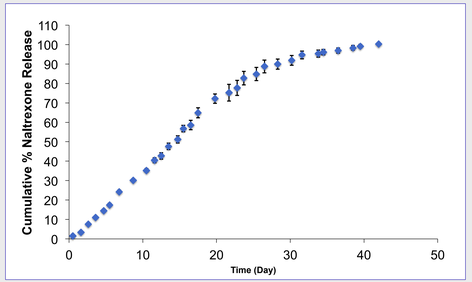


**Figure 3.** *In vitro* release profile of the naltrexone microsphere product in 10 mM PBS (pH 7.4)* at 37ºC using USP apparatus 4.
Note: dissolution media was replaced every five days.

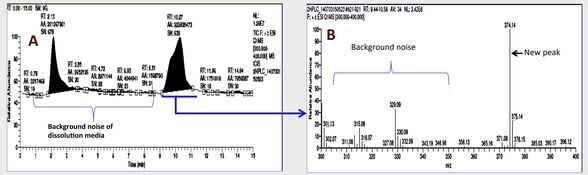


**Figure 4.** LCMS (A and B) chromatograms of major degradants following 30 days stability testig in 10 mM PBS pH 7.4* media using USP 4 apparatus at 37ºC. Image (B) represents different mass of components present in the peak (RT of 10.27 min) in image (A).

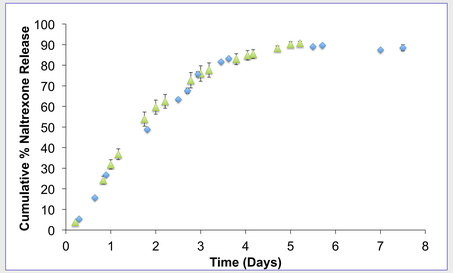


**Figure 5.** *In vitro* release profiles of the naltrexone microsphere product in 10 mM PBS (pH 7.4)* at 45ºC using USP apparatus 4. Test I (green): dissolution media without sodium ascorbate, the media was replaced every 12h. Test II (blue): dissolution medium containing 0.0625% (*w/v*) sodium ascorbate.

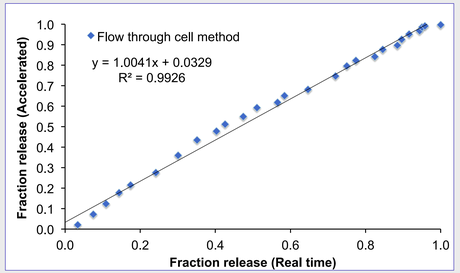


**Figure 6.** Comparative correlation of fraction *in vitro* naltrexone release obtained using USP apparatus 4 under "real-time" (37°C) and accelerated (45ºC) release conditions.
Note: Media with 0.0625% sodium ascorbate was used under accelerated test conditions.

## CONCLUSIONS

This work demonstrated that naltrexone degradation is pH- and temperature-dependent and is autocatalyzed by the oxidized degradation products. A reproducible accelerated *in vitro* release testing method using USP apparatus 4 was developed. An antioxidant was included in the media to negate the need for frequent media replacement. The developed *in vitro* method correlated well with "real-time" release. Accordingly, this method may be used to facilitate high throughput quality control testing of naltrexone-containing microsphere products.

## ACKNOWLEDGEMENT

This work was supported by the FDA/CDER, Office of Generic Drugs (1U01FD004931-01). Support from Sotax Corporation is highly appreciated.

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