Novel Crush Resistant Microspheres: Applications for Enhanced Safety and Abuse Deterrence


Collegium Pharmaceutical, Inc., Canton, MA, 02021, USA
afleming@collegiumpharma.com

ABSTRACT SUMMARY

Novel, crush-resistant microspheres have been developed. The patented microsphere formulation platform (DETERx®) has utility where patients or other individuals may intentionally or inadvertently crush, break or chew their dosage form either to facilitate swallowing (in legitimate patients) or to subvert the time release mechanism (in drug abusers seeking an immediate release dose).

In vitro and in vivo studies have been conducted to characterize the crush-resistant nature of the microspheres. These studies have demonstrated robust resistance of the microsphere formulation to physical manipulations such as breaking, crushing or chewing relative to conventional tablets or commercially available crush-resistant tablets.

The DETERx platform technology is being applied to other drugs of abuse such as opioids and amphetamines. The platform also has utility to create an extended release product for other compounds where unintentional dose dumping due to physical manipulations may result in adverse events.

INTRODUCTION

Extended release (ER) dosage forms are designed to release drug at a controlled rate over time. The time-release mechanism of many conventional oral ER dosage forms can be compromised when the tablet or capsule is broken, crushed or chewed. In some instances patients alter their dosage forms to facilitate administration (e.g. to overcome a swallowing difficulty). In other instances individuals intentionally alter dosage forms by “tampering” to accelerate the release and obtain the full dose of drug instantaneously; such tampering is reported for medications with abuse liability such as opioids. In fact, tampering followed by oral or intranasal administration is a well-documented and serious issue with many ER opioid formulations. Due to such unintentional and intentional manipulations, many ER dosage forms carry warnings that crushing, breaking or chewing can destroy the time-release and cause adverse events.

Tablets with crush-resistant properties have been approved for marketing in the U.S. While these tablets are more difficult to crush, particle size reduction with a variety of household tools has been reported.

Novel crush-resistant microspheres with unique physiochemical properties have been developed as an alternative to crush resistant monolithic tablets. These microspheres have a small starting particle size, such that efforts to further reduce the size does not dramatically enhance the available surface area for dissolution. Furthermore, the particles are fabricated from waxy materials that tend to fuse on application of pressure rather than crack. The utility of these microspheres to provide crush-resistance has been demonstrated for an opioid product (Oxycodone DETERx®) currently in clinical development.

EXPERIMENTAL METHODS

Particle size reduction (PSR) studies were carried out on Oxycodone DETERx microspheres and a marketed tablet formulation of oxycodone with crush resistant properties (comparator tablets). Ten different commonly available household tools were used in an attempt to reduce the overall size of the respective dosage forms. Contents from a 40 mg oxycodone DETERx capsule or intact comparator tablets were removed and subjected to each crushing technique for 2 minutes.

The particle size of Oxycodone DETERx microspheres were characterized before and after particle size reduction studies using laser diffraction. Crushed material from individual dosage units was pooled to produce ~2.5 g of sample. Particle size analysis (PSA) on pooled sample was conducted for oxycodone DETERx using Laser Diffraction with a Dry Powder Feeder. PSA was not carried out for the crushed reference product samples as particle size reduction was visually evident. Mathematical modeling (assuming Fickian diffusion) was used to predict the impact of particle size reduction on the dissolution profiles of both comparator tablets and DETERx microspheres for the most effective methods of crushing identified for each product.

The actual impact of particle size reduction on the dissolution profiles of both comparator tablets and DETERx microspheres was determined by conducting dissolution in a media appropriate for
each product. Dissolution was conducted using USP Apparatus II (Paddles) @ 50 RPM with collection of samples at 0.25, 1, 2, 4, 8, and 12 hours. Drug was quantified using a validated HPLC method.

The impact of particle size reduction was tested in vivo for Oxycodone DETERx. In an open label, active-controlled, single-dose, cross-over, naltrexone-blocked pharmacokinetic study, 44 subjects were enrolled and randomized to receive DETERx 40mg intact or crushed treatments in the fed state. Capsule contents were crushed for 2 minutes utilizing previously established, optimized crush methodology.

RESULTS AND DISCUSSION

Particle size reduction studies were conducted and the resulting powders were characterized visually and quantitatively. No apparent PSR was observed for oxycodone DETERx by visual analysis. Quantitative analyses showed minor changes (reduction) in particle size relative to the control microspheres for 5 of the 10 PSR tools used. Application of the other 5 PSR tools did not result in a reduction in particle size. For comparator tablets, visual impact was observed for 7 of the 10 PSR tools used. For 6 of these tools, the comparator product was reduced from a single tablet to smaller pieces consisting of chunks, and, in some cases, small particles.

The impact of particle size reduction on the drug release rate of Oxycodone DETERx microspheres and comparator tablets was determined by conducting dissolution studies. The largest increase in dissolution relative to baseline observed for Oxycodone DETERx was ~20% at 2 hours. In contrast, PSR with 5 of the tools tested resulted in a substantial increase in release rate (>50% at 2 hours).

The dissolution profiles of intact and crushed DETERx microspheres and comparator tablets were modeled based on the particle size pre- and post-crushing. The diffusion based model confirms the lack of effectiveness of even the most aggressive crushing tool at adversely affect the dissolution of the DETERx microspheres. The model shows that the comparator product behaves as an immediate release after application of the most effective crushing tool, also confirming the results observed in dissolution studies.

In order to determine the impact of particle size reduction on the pharmacokinetic profile, studies were conducted in healthy volunteers comparing intact administration to administration of microspheres crushed using the tool previously established as most effective. The in vivo studies demonstrated that physical manipulation does not increase peak plasma exposure ($C_{max}$) or overall extent of exposure ($AUC_{(0-\infty)}$) (Table 1). The crushed DETER microsphere treatment was bioequivalent to the intact DETERx treatment (90% confidence intervals within 80-125%)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LSMean Ratio (%)</th>
<th>90% Confidence Interval (Lower)</th>
<th>90% Confidence Interval (Upper)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{max}$</td>
<td>92.48%</td>
<td>85.96</td>
<td>99.51</td>
</tr>
<tr>
<td>$AUC_{(0-\infty)}$</td>
<td>97.82</td>
<td>92.66</td>
<td>103.27</td>
</tr>
</tbody>
</table>

Table 1: Bioequivalence analysis for crushed DETERx microspheres relative to intact microspheres administered in capsules

CONCLUSION

In vitro studies and associated modeling of drug release rates demonstrated that crushed oxycodone DETERx microspheres retained the ER properties and did not dose dump. The in vivo study showed that crushing DETERx does not compromise the ER mechanism; intact and manipulated treatments were bioequivalent. These results demonstrate the utility of the DETERx microsphere formulation in the development of products with robust crush resistance properties. The platform is currently being applied to abuse-deterrent formulations and may have utility for other compounds where unintentional dose dumping due to physical manipulations may result in adverse events.

ACKNOWLEDGEMENTS

This study was sponsored by Collegium Pharmaceutical, Inc.