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Exploratory in-vitro laboratory study to assess potential abuse-deterrent features of polyethylene oxide extended release matrices

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PURPOSE

- Abuse and misuse of prescription opioid products has created serious and growing public health concerns. One potentially important step towards the goal of creating safer opioid analgesics is the development of abuse-deterrent formulations.
- Hydrophilic polymers are preferred to formulate abuse-deterrent formulations due to their gelling behavior when in water. A Polyethylene oxide (POLYOX™) based matrix formulation has been developed with expected abuse-deterrence features.
- An exploratory, abbreviated Category-1 laboratory study was performed to assess the potential abuse-deterrent characteristics of the formulation.
- For this study, metoprolol tartrate was used as a model drug in an extended release (ER) matrix formulation and compared against an immediate release dosage form (Lopressor®) as a comparator with the same API. Uncured and cured (heat-treated) POLYOX extended release matrices were investigated.
- In this study we evaluated common routes of administration for opioid abuse listed in the FDA's Guidance for Abuse-Deterrent Opioids, Category 1: IV (syringe-ability), insufflation (sniff-ability) in addition to rectal administration (rectal plugging) using a novel technique developed by DRUGSCAN.

METHOD

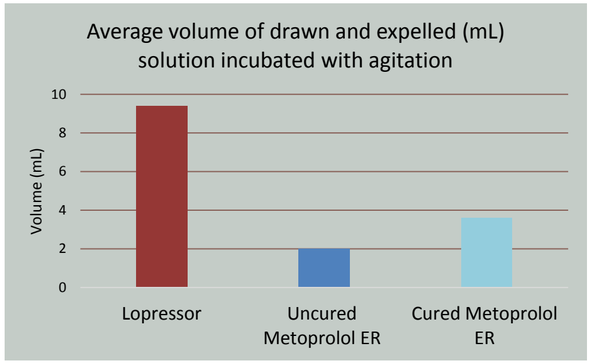
- The study included assessment of crushability followed by particle size characterization, extractability, syringe-ability, and dialysis as a surrogate test for rectal plugging.
- Reduction of the tablets to particles was performed using a mortar & pestle and Krups® coffee grinder followed by sieve analysis using a 500 µM sieve as a cut-off for sniff-ability of a powder.
- To assess syringe-ability, ground tablets were extracted in 10 mL of DI water for 10 minutes with and without shaking at 200 rpm.
- Volume of extract drawn into a syringe, equipped with 27 and 25 gauge needle, was measured.

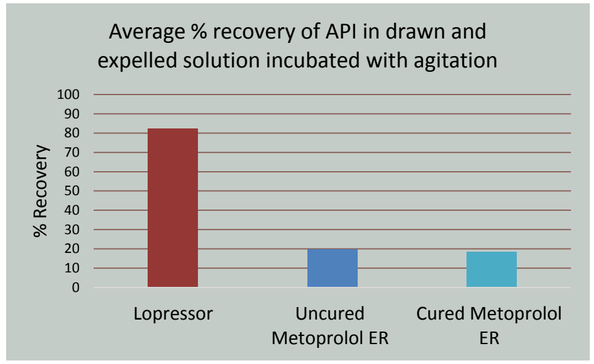
METHOD (cont.)

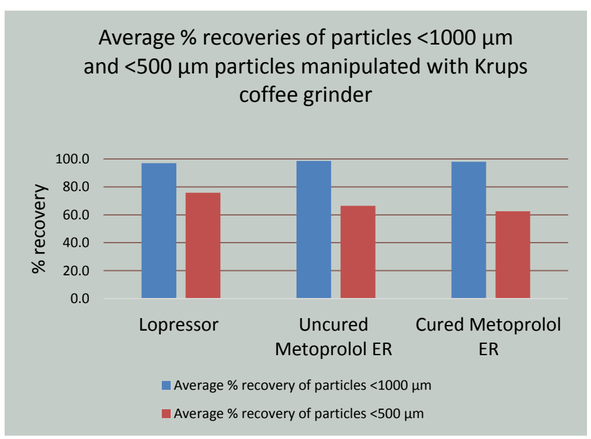
- Extractability was assessed by testing recovery of the API by dissolving ground tablet material in 10 mL of DI water and then incubating the solution in 350 mL of phosphate-buffered saline (PBS) for 60 minutes, while stirring at 200 rpm with aliquots taken at 9 time points.
- To simulate rectal plugging, ground tablet content was mixed in 10 mL of DI water and loaded into a dialysis bag and dialyzed against 350 mL PBS for 1 hr with dialysate analyzed at 9 time points.

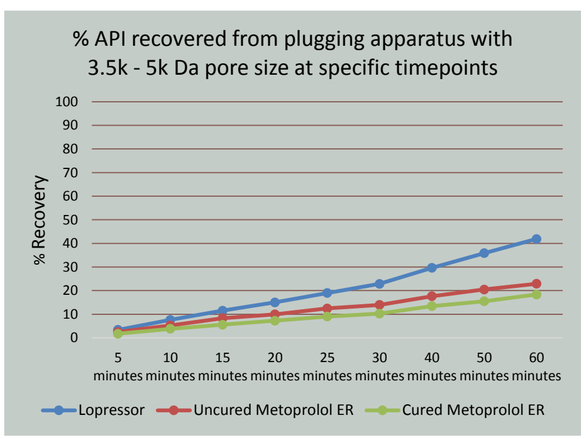
RESULTS

- With Krups® coffee grinder, % of powder that passed through the 500 µM sieve was about 76%, 66%, and 63% for Lopressor, uncured and cured investigational formulations respectively, but mortar and pestle was more efficient and produced about 99%, 92% and 91% of powders that passed through the 500 µM sieve.
- While more than 80% of the volume was drawn from Lopressor® solutions (with or without shaking), <10% and <20% of metoprolol ER formulations were syringe-able without and with shaking respectively



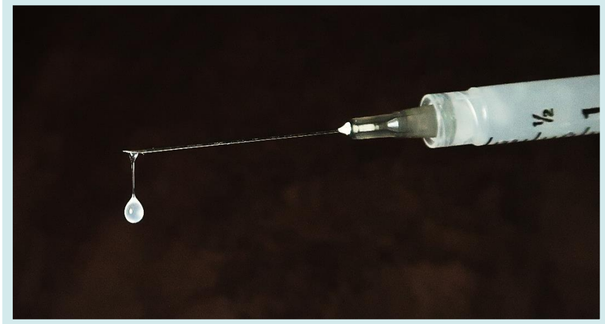






RESULTS (cont.)

- About 79%, 59% and 48% of API was recovered from reduced Lopressor®, metoprolol ER uncured and cured tablets after 10 min of stirring in 350 mL of PBS at 200 rpm, with no obvious change in % recovery over 60 minutes.
- When extracts were made from reduced tablets in 10 mL of DI water and dialyzed against 350 mL of PBS, API recovery gradually increased over time until it reached about 42%, 23% and 18% of Lopressor®, metoprolol ER uncured and cured nominal tablet contents, respectively.



CONCLUSION

- This exploratory study showed that metoprolol ER formulations may express abuse-deterrent features in terms of syringe-ability, sniff-ability of reduced products, extractability and rectal plugging. Further work on this promising technology is recommended

References

1. Food and Drug Administration. Abuse-deterrent opioids — Evaluation and Labeling Guidance for Industry. April 2015. U.S. Department of Health and Human Services.
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