Optimization of a Smoking-Simulation Technique to Investigate Smoke-Ability of Opioids from Pharmaceutical Formulations

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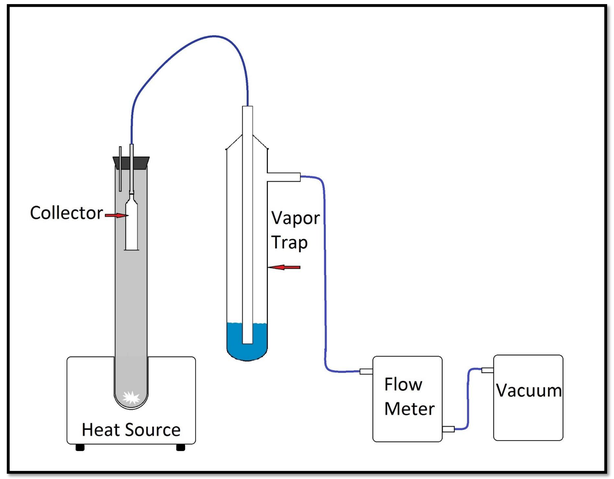
Background and Purpose

- Smoking is a common route of administration for abusers of opioids.
- The FDA 2015 final guidance "Abuse-Deterrent Opioids — Evaluation and Labeling Guidance for Industry" (April 2015)[1] listed abuse by smoking as one of the abuse-deterrent formulation (ADF) characteristics required to be evaluated by subjecting innovator opioid products to vaporization temperatures from melting point to degradation of the active pharmaceutical ingredient (API).
- The FDA 2016 draft guidance "General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products"[2] identifies 233 °C (the ignition temperature of paper) as the single temperature for evaluating generic opioid products for abuse by smoking.
- In this poster, we present our current optimization of a proprietary smoking apparatus, created by DRUGSCAN and PinneyAssociates, that simulates the smoking of opioid products via heat-induced volatilization and collection of volatilized API in a vacuum pump-induced air flow that mimics inhalation.

Materials and Methods

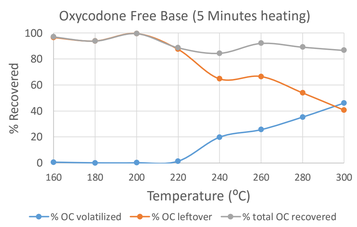
- The adjacent diagram illustrates the smoking apparatus developed in conjunction with PinneyAssociates and used in this study.
- To optimize the technology, we used two commonly abused opioids, Oxycodone (OC) and Hydrocodone (HC) in both pure base and pure salt forms.
- The API material loaded in the crucible tube, was heated from temperatures of 160 ^{o}C to 300 ^{o}C in 20 ^{o}C increments.
- The selected temperature range covers the melting points of the pure base and salt forms for both API opioid materials.
- The air flow, induced by a vacuum pump, is adjusted to a flow rate that simulates rapid inhalation by a healthy adult human.
- The material was heated for 5 or 10 minutes during which vaporized API is captured by a C18 column (the collector).
- The collected API is eluted from the collector, and any residual API is dissolved from the crucible tube.
- Both fractions are assayed for drug content on validated LC-MS/MS assays.

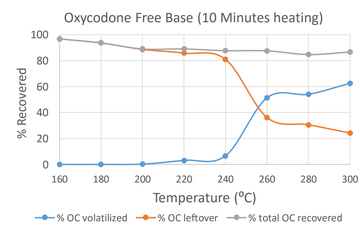
Simulated Smoking Apparatus

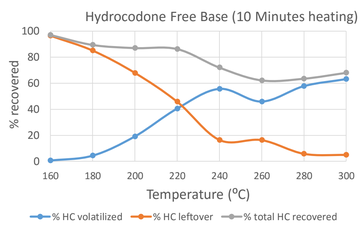


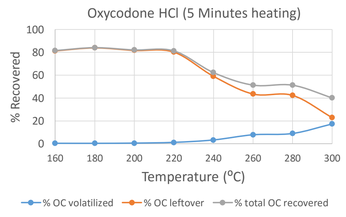
- Performance verification of the apparatus is performed with API (free base) to demonstrate that the collector efficiently and accurately collects API and the collector capacity is not exceeded (break-through).
- The amount of pure API (free base) trapped by the collector is measured by validated LC-MS/MS assay.
- The efficiency of the collector is determined by comparing the amount of collected API (free base) compared to the mass of pure API added.
- Break-through studies are conducted by heating 100 mg of API (free base) at appropriate temperature(s) and time(s). In this experiment, a vapor trap is added in-line between the collector and vacuum source.
- After heating the API, the contents of the vapor trap are tested for possible break-through from the primary collector.

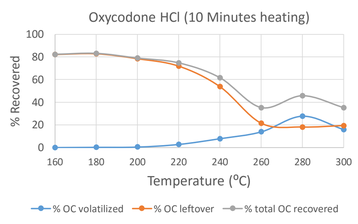
Results

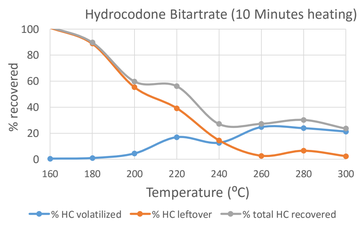












Conclusions

- As shown by the graphs, free base was more readily volatilized than the salt forms for both OC and HC.
- Total recovery (volatilized + residual) decreased proportionally at high temperatures - especially with the opioid salts.
- Charring of the material at higher temperatures and longer times correlates to lower total recoveries and possible API degradation.
- When heated for 5 and 10 minutes, about 46 % and 51 % of OC free base was volatilized at 300 ^{o}C and 260 ^{o}C respectively, and about 17 % and 28 % of OC salt was volatilized at 300 ^{o}C and 280 ^{o}C.
- About 63 % of HC base and about 25 % of HC salt were volatilized at 300 ^{o}C and 260 ^{o}C respectively.

Discussion

- These results indicate that a simulated smoking technique should be optimized at different heating temperatures and different times.
- The degradation of API in salt form is more apparent at longer heating times, which is readily observed in these experiments with Oxycodone HCl. Additional experiments to include higher temperatures and shorter heating time needs to be investigated.
- This data can serve as a bench mark for abuse deterrent opioid products under development.
- Once optimized conditions have been established, these conditions should be applied to the pharmaceutical product under investigation.

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.

2) Food and Drug Administration. Generic Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products Draft Guidance. March 2016. U.S. Department of Health and Human Services.

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