Preparation and characterization of physically manipulated abuse-deterrent formulation of an opioid product prepared for nasal insufflation studies

Yasmine Gabal[1,2], Heather Boyce[2], Wei-Jhe Sun[2], Manar Al-Ghabeish[3], Ahmed Ibrahim[4], Gary Hollenbeck[4], Stephen Hoag[4], AGM Mostofa[2], and Myong-Jin Kim[2]

[1]Oak Ridge Institute for Science and Education
[2]Division of Therapeutic Performance II, Office of Research and Standards, Office of Generic Drugs, CDER, FDA.
[3]Division of Pharmaceutical Quality and Research, Office of Testing and Research, Office of Pharmaceutical Quality, CDER, FDA.
[4]University of Maryland School of Pharmacy

Background

Abuse-deterrent formulation (ADF) is a strategy to mitigate the abuse of prescription opioid products. An example is oxycodone HCl ((O) opioid agonist) and naloxone HCl ((N) opioid antagonist) extended-release (ER) tablets. In abuse, the O/N tablets are physically manipulated to smaller particles for nasal insufflation. A change in the agonist and antagonist content at each particle size range may occur and limit the antagonism action and the overall effectiveness of the ADF. The goal of this study was to standardize a milling process of O/N tablets and to characterize the milled tablets to be used in nasal pharmacokinetics (PK) studies

Methods

- O/N tablets were milled by common household tools as:
  - Mortar & Pestle (M& P) to test three strengths of O/N tablet (40/20, 20/10, and 5/2.5 mg), n=2.
  - Electronic Pepper Grinder (EPG) with one or two turn gap settings (EPG-1 and EPG-2) to test O/N tablet of strength (40/20 mg), n=3.
- Milled tablets were sieved with a sonic sifter to particle size ranges: 1000–600, 600–425, 525–300, 300–212, 212–106, and <106 µm.
- The percent yield of milled O/N tablets and the percent recovered of O and N for each method were determined as follow:

$$\%\ \text{Yield} = 100 * \frac{\text{mass of powder recovered from all sieve fractions}}{\text{Actual mass of intact tablets}}$$

$$\%\ \text{Drug recovered} = 100 * \frac{\text{drug content in total powder recovery}}{\text{theoretical drug weight from intact tablets}}$$

- One- and 3-month stability studies of EPG-2 milled O/N tablets was conducted under standard conditions (25 C, 60% RH) using storage vials with two lid materials (Teflon and Polyethylene (PE)).

Results

The three tested methods (M&P and EPG-1, EPG-2) milled O/N tablets to safe and tolerable particles of size range (100–1000 µm) for nasal insufflation PK studies. All tested milling methods resulted in a mass percent of particles (<500 µm) >10% and a constant ratio of O/N (2:1) at all particle size ranges.

The EGP-2 milled the O/N tablets into coarser particle sizes compared to the EPG-1 but smaller particle sized compared to M&P. This milling method had the highest % yield (93.3% ± 1%), produced the lowest weight fraction (2.8% ± 0.4%) of fine particles (<106 µm), and recovered the highest amount of drug (O: 95.6% ± 1%, N: 96.2% ± 1.2%). Therefore, EPG-2 was chosen for milling O/N tablets (40/20).

Milling the tablets with EPG-2 did not affect the stability of O or N after 1- or 3-months storage in vials covered with either Teflon or PE lid.

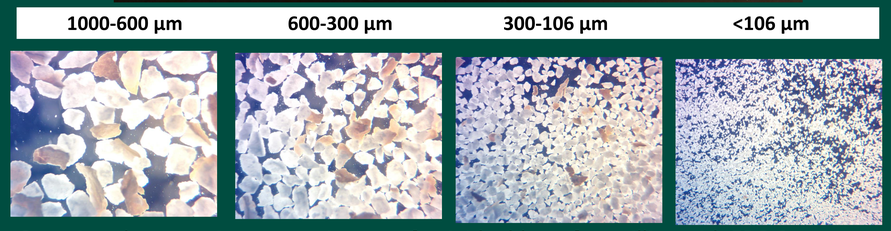
Conclusion

EPG-2 is a reproducible and reasonably scalable method for milling O/N ER tablets for a nasal insufflation PK study that aims to evaluate the abuse-deterrent effectiveness of this opioid product after nasal insufflation.

FDA U.S. FOOD & DRUG ADMINISTRATION

The electronic pepper grinder (EPG) is a representative household method for grinding opioid tablets for nasal insufflation PK studies.

Electronic pepper grinder



Scanning electron microscope pictures of opioid tablets after milling with EPG-2

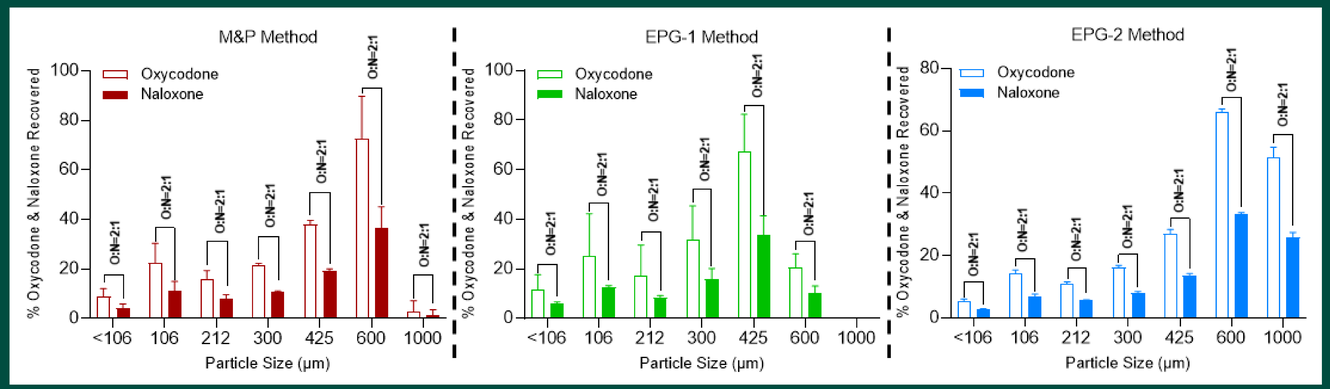


Figure : % Drug (O and N) recovered (mean ± SD) from milling O/N tablets (40/20) by M&P (n=2), EPG-1 (n=3), and EPG-2 (n=3) methods.

Get more information

Table 1: Characterization of O/N tablets at three strengths after milling by M&P. Data are presented as mean ± SD (n=2).

Characterization \ Strength (O/N)	40/20	20/10	10/5
% Yield	90% ± 2.5	91% ± 1.9	92% ± 3.5
% Oxycodone recovered	91% ± 0.4	94% ± 1.8	98% ± 2.7
% Naloxone recovered	91% ± 0.1	95% ± 2.1	96% ± 1.5

Table 2: Characterization of O/N tablets (40/20) after milling by different methods. Data are presented as mean ± SD (n=2 for M&P, n=3 for EPG-1 & 2).

Characterization \ Milling method	% Yield	Oxycodone	Naloxone
M&P	90% ± 2.5	91% ± 0.4	91% ± 0.1
EPG-1	85% ± 3.3	87% ± 3.0	87% ± 3.3
EPG-2	93%± 1.0	96%± 1.0	96% ± 1.2

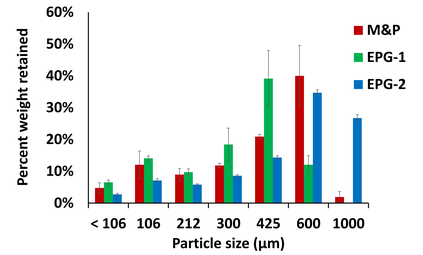


Figure 1: Weight distribution (mean ± SD) of particles resulting from milling O/N tablets (40/20) by M&P (n=2) , EPG-1 (n=3), and EPG-2 (n=3) methods.

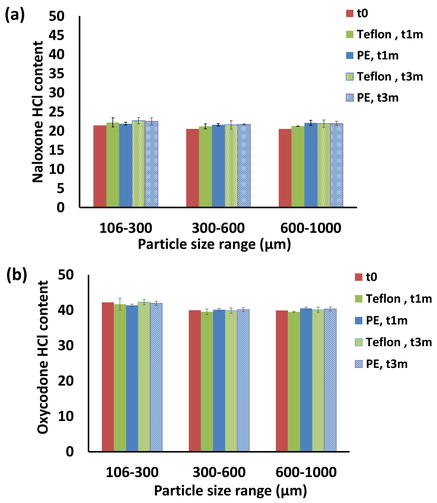


Figure 2: Drug content of a) N and b) O after 1- and 3-months storage of EPG-2 milled O/N tablets in vials with Teflon or PE lid.

Disclaimer and Acknowledgement

This poster reflects the views of the authors and should not be construed to represent FDA's views or policies. This work was supported to Yasmine Gabal, Oak Ridge Institute for Science and Education (ORISE) fellow, by an appointment to the Research Participation Program at CDER, administered by the ORISE through an interagency agreement between the U.S. Department of Energy and the FDA.