

Yasmine Gabal^{1,2}, Heather Boyce², Wei-Jhe Sun², Manar Al-Ghabeish³, Ahmed Ibrahim⁴, Gary Hollenbeck⁴, Stephen Hoag⁴, AGM Mostofa², and Myong-Jin Kim²

¹Oak Ridge Institute for Science and Education

²Division of Therapeutic Performance II, Office of Research and Standards, Office of Generic Drugs, CDER, FDA.

³Division of Pharmaceutical Quality and Research, Office of Testing and Research, Office of Pharmaceutical Quality, CDER, FDA.

⁴University of Maryland School of Pharmacy

Purpose

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

Milling

- O/N tablets were milled by common household tools either:
 - Mortar & pestle (M&P) to test three strengths of the tablet (O/N = 40/20 mg, 20/10 mg, and 5/2.5 mg), n=2
 - Electronic pepper mill (EPG) with one or two turn gap settings (EPG-1 and EPG-2) to test the tablet strength (O/N = 40/20 mg), n=3

Sieving

- Milled tablets were sieved with a Sonic sifter to the particle range: 600–1000, 425–600, 300–425, 212–300, 106–212 and <106 μm

Characterization

- Determine for each particle size range:
 - $\% \text{ Yield} = 100 \times \frac{\text{mass of powder recovered from all sieve fractions}}{\text{Actual mass of intact tablets}}$
 - $\% \text{ Drug recovered} = 100 \times \frac{\text{drug content in total powder recovery}}{\text{theoretical drug weight from intact tablets}}$



Figure 1: Mortar & pestle



Figure 2: a) Electronic pepper mill, b) Gap settings.

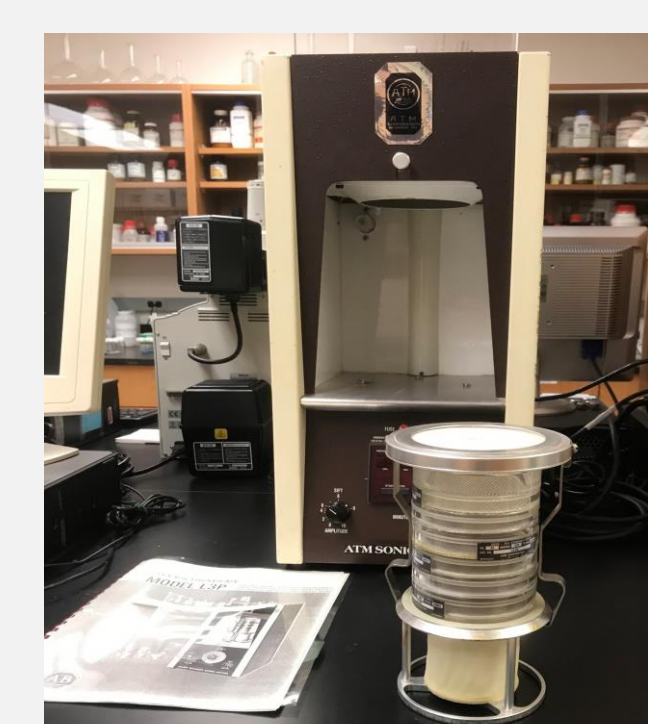


Figure 3: Sonic sifter

Results

Mortar & Pestle (M&P)

Effective method for milling the O/N tablets with a high %yield and %drug recovered as shown in Table 1.

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

Strength(O/N) Characterization	40/20	20/10	10/5
% Yield	89.7% ± 2.5	91% ± 1.9	92% ± 3.5
% Oxycodone recovered	91% ± 0.4	94.4% ± 1.8	97.5% ± 2.7
% Naloxone recovered	91.3% ± 0.1	94.8% ± 2.1	95.6% ± 1.5

- The weight distribution of particles was centered around 600 μm (40% ± 10%) of the weight of milled tablets) as shown in Figure 4.

Electronic pepper mill- 1 turn (EPG-1)

EPG-1 milled the O/N tablets into smaller particle sizes compared to the M&P.

- The weight distribution of particles was centered around 425 μm (39% ± 9% of the weight of milled tablets) as shown in Figure 4.

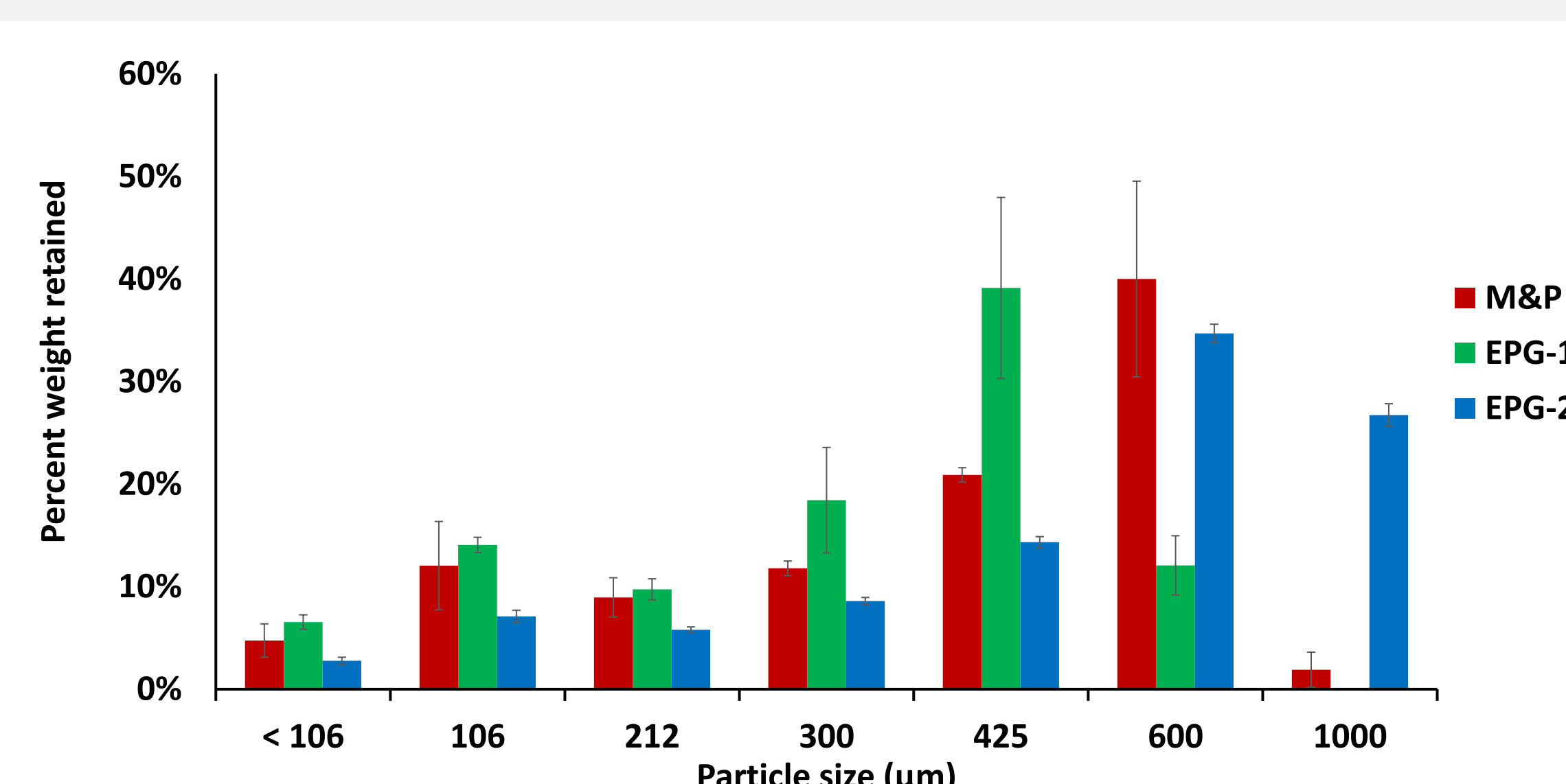


Figure 4: Weight distribution (mean ± SD) of particles resulting from milling O/N tablets (40/20) by M&P (n=2), EPG-1 (n=3), and EPG-2 (n=3) methods.

Electronic pepper mill- 2 turn (EPG-2)

EPG-2 milled the O/N tablets into coarser particle sizes compared to the EPG-2.

- The weight fraction of fine particles of size (<106 μm) significantly decreased from 6.5% ± 0.7% for EPG-1 to 2.8% ± 0.4% for EPG-2 (p<0.05) (Figure 4).

Conclusions

- The 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.
- 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%).

Results Cont.

- EPG-2 had higher %yield and %drug recovered of milled O/N tablet compared to EPG-1 as shown in Table 2.

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

Characterization Milling method	% Yield	Oxycodone	Naloxone
M&P	89.7% ± 2.5	91.1% ± 0.4	91.3% ± 0.1
EPG-1	84.4% ± 3.3	86.8% ± 3	86.7% ± 3.3
EPG-2	93.3% ± 1	95.6% ± 1	96.2% ± 1.2

- O/N tablets were milled to safe and tolerable particles of size range (100–1000 μm) for nasal insufflation PK study. The mass percent of particles (<500 μm) was >10% (Figure 4).
- The ratio of O/N was kept constant 2:1 at all particle size ranges (Figure 5).

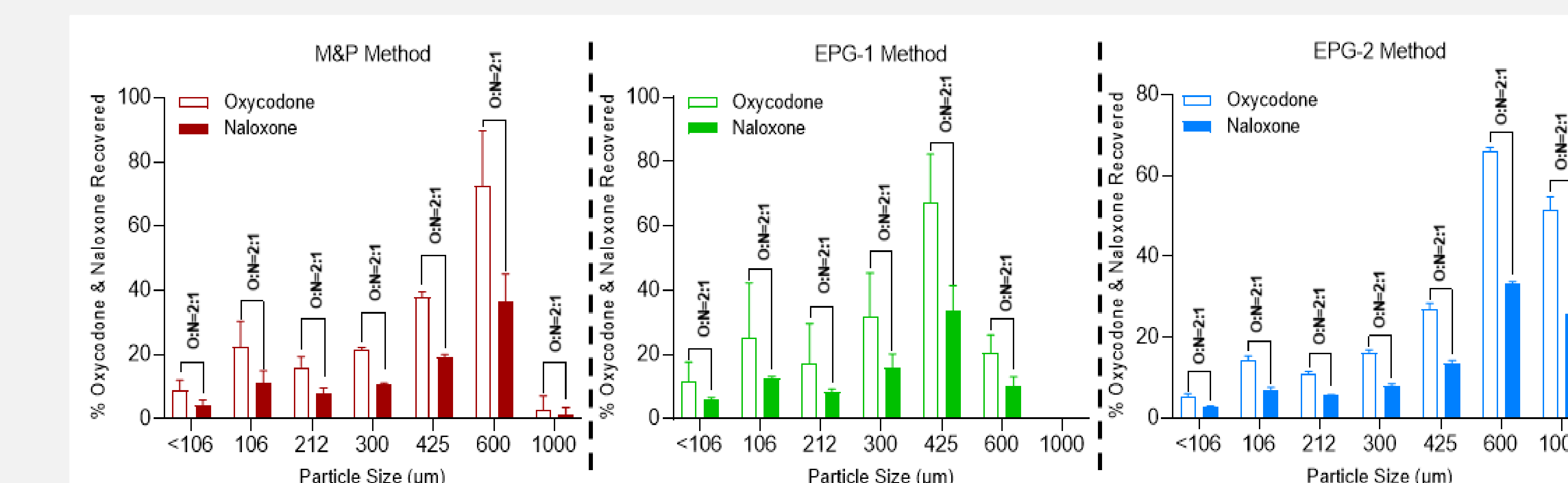


Figure 5: % Drug (O and N) recovered (mean ± SD) from milling O/N tablets (40/20) by M&P (n=2), EPG-1 (n=3), and EPG-2 (n=3) methods.

- Milling O/N tablets (40/20) using EPG-2 did not affect the stability of O and N after 1- or 3-months storage in vials covered with either Teflon or PE lid.

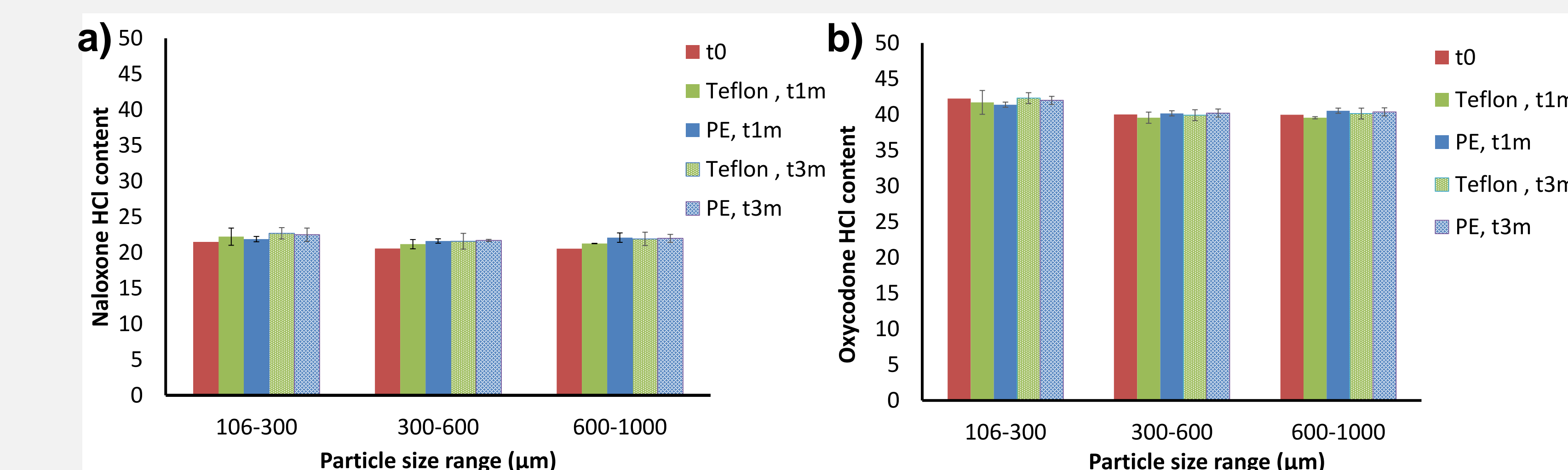


Figure 6: Drug content of a) N and b) O after 1- and 3-months storage of O/N milled tablets in vials with Teflon or PE lid.

Disclaimer & Acknowledgement

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