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# Use of a vertical diffusion cell for the in vitro assessment of abuse deterrence of comminuted abuse deterrent formulations

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## Purpose

It is challenging to evaluate in vitro the abuse deterrence of opioid formulations abused by the nasal route. While a vertical diffusion cell is commonly used to evaluate in vitro drug release from liquid and semisolid formulations, this study explored the application of the vertical diffusion cell (an artificial nasal absorption model) in the in vitro evaluation of the abuse deterrence of opioid formulation abused by the nasal route.

***Novelty:*** Dry comminuted particles retrieved from manipulated tablets containing polyethylene oxide (PEO) were loaded directly on the top of a wetted cellulose membrane and the release of API was measured.

## Methods

Thermally treated tablets made of PEO are known to be more difficult to be comminuted by grinding, milling, or chewing. In addition, PEO forms a gel upon contact with water, which helps retard the absorption in the nose. Thus, all the formulations used in this study contained polyethylene oxide. Opana® (OM), containing active pharmaceutical ingredient (API) oxymorphone HCl (MOR) and abuse deterrent OxyContin® (CD) containing oxycodone HCl (COD) were both used in this study. Tablets were also made with 30 wt% metoprolol tartrate (MTAR) with either 70wt% of 1,000,000$M_w$ (1) [red bars] or 7,000,000 $M_w$ (7) [black bars] PEO and compressed at 4 kN (H) (20% porosity) or 9.3 kN (L) (10% porosity). Metoprolol tartrate tablets were sintered for 30 minutes and allowed to rest for one day before they were comminuted.

***In Vitro Nasal Abuse Simulation Strategy***

***Step 1***: **Comminution of Tablets (3 methods)**

Cutting (C) - 5 minutes with diagonal pliers
Milling (M) - 1 minute in coffee mill
Grinding(G): - ground into a beaker with rotary tool until the tablet could not be held

***Step 2 Diffusion:*** Apply comminuted tablet to a wetted cellulose membrane to simulate a nasal abuse situation. Sampling: 6 ml aliquots at T= 15 min, 30 min, 1, 1.5, 2, 3, 4, and 5 hr

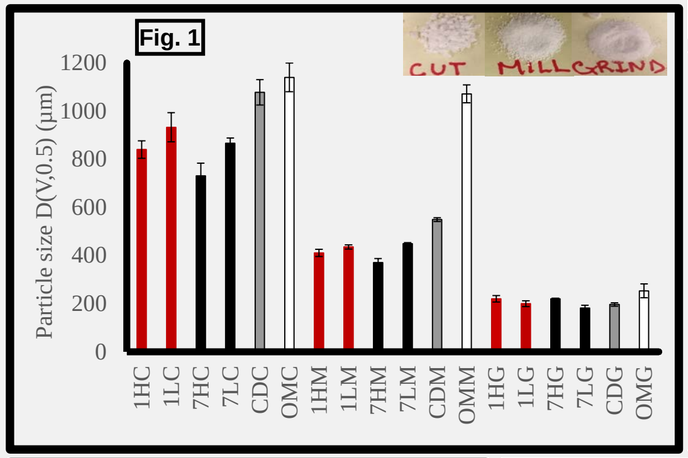
***Step 3 Quantitate:*** Release rate defined as the slope of the cumulative API release, Q, vs $\sqrt{Time}$ $where\ Q = \{C_n V + \sum_{i=1}^{n-1} C_i S\}/A$, and C is the concentration of API, V is the volume of the diffusion cell, A is the surface area of the membrane, and S is the sample aliquot.[1]

## Results:

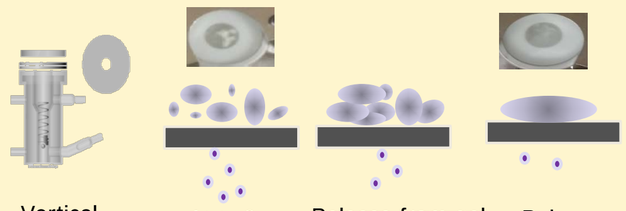
### Step 1: Particle size of Comminuted Particles (Fig. 1)

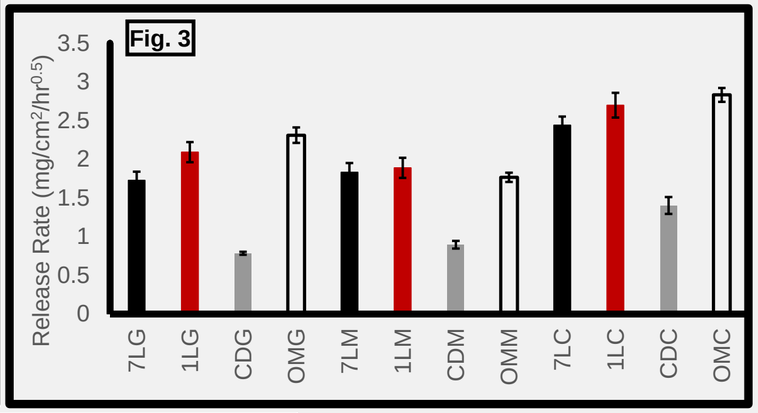
Tablets compacted at a lower solid fraction of 0.8 (H) produced smaller particles than those compacted at 0.9 (L) solid fraction. This effect was more noticeable with cutting, the lowest energy manipulation technique.

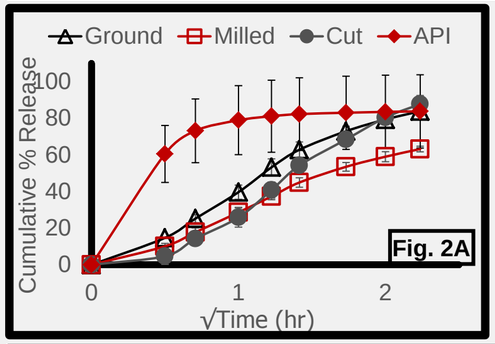
Opana® (white) and abuse deterrent OxyContin® (gray) produced the largest particles under manipulation; specifically milled Opana® produced a very large particle in comparison to the other milled samples. A large particle size after comminution implies the formulation is more resistant to physical abuse under the manipulation conditions in this study.

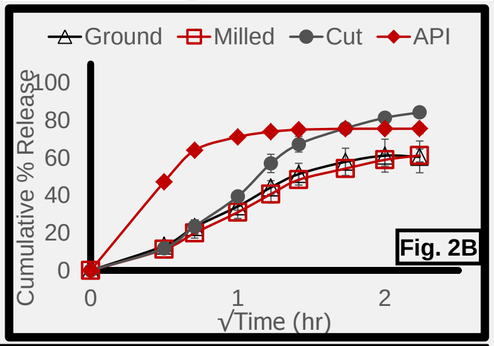



### Proposed Progression of Diffusion (Moving Boundary)[1,2]




### Step 2. Diffusion of API from dry particles (Fig. 2A-2B)

The release curves for the comminuted Opana® (2A) and metoprolol tartrate (2B) tablets demonstrate that the percent release from the comminuted tablets manipulated under all different conditions is much slower than that from the respective pure API. The ground and milled metoprolol tartrate particles exhibit similar percent release overall. Compared to the metoprolol samples, the differences in percent release due to manipulation method are evident for drug product Opana® between 15 min to 30 min. The reason why differences in release due to comminution exist may be due to manufacturing (sintering vs. hot melt extrusion) and/or the additional excipients in Opana®.

### Step 3: Release Rate (Fig. 3)

A higher release rate indicates the release of drug changes more over the 5 hr time period. This analysis does not demonstrate whether a formulation is abuse deterrent or not. Rather the release rate can be used to differentiate among different products, i.e. metoprolol tartrate, Opana® and OxyContin® , and grade of PEO used.

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## Conclusions

- A large particle size after manipulation demonstrates the tablet is more abuse deterrent; however, when more aggressive manipulation techniques are applied, the different dosage forms have similar particle size.
- Cumulative percent release curves show differences in API transfer from donor to receiver compartment are dependent on several factors involving thermal pre-treatment, comminution technique and/or formulation type.
- Release rate can be used as a way to quantitatively discriminate between formulation differences.
- Together, release rate, particle size, and cumulative release at early time points may provide a good indication of a formulations abuse deterrent capability.

## *References*

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## *Acknowledgements.*

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