Physical Manipulation of an Opioid Drug Product Containing Combination of Opioid Agonist and Antagonist

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BACKGROUND

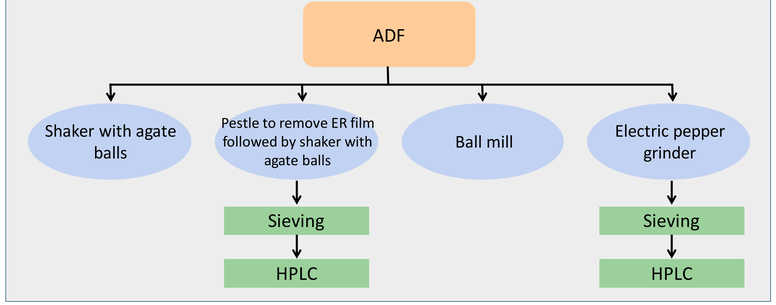
- Abuse-deterrent formulations (ADFs) of opioid drug products are developed as one of the intervention strategies to reduce abuse of opioid analgesics.
- One ADF design strategy is to incorporate an opioid antagonist in the formulation. Upon physical manipulation, the opioid antagonist becomes bioavailable and counteract the opioid agonist effect when these manipulated products administered such as via nasal insufflation.
- One of the marketed ADF opioid products contains opioid agonist and opioid antagonist in the ratio of 25:1. When the ratio of agonist to antagonist increases above 25:1, the reduction of abuse deterrent function of the product is expected.

PURPOSE

- The purpose of this work is to develop physical manipulation methods that can test the extent to which the opioid antagonist can be physically separated from an opioid agonist in a formulation that contains both substances when the ADF product is milled to the targeted particle size range.

METHODS

- The selected ADF product composed of opioid agonist and antagonist was physically manipulated using four strategies: (a) shaker with agate balls, (b) pestle to remove extended release (ER) film followed by shaker with agate balls, (c) ball mill, and (d) electric pepper grinder.
- After manipulation, specified particle size and amount of agonist and antagonist in each sieve fraction were obtained by sieving and high-performance liquid chromatography (HPLC) analysis, respectively.



RESULTS

(I) Shaker with Agate Balls

Figure 1. Photo of manipulated pellets using shaker with agate balls for 1 hours

- The shaker with agate balls did not provide sufficient external force to crush pellets.

(II) Pestle to Remove ER Film Followed by Shaker with Agate Balls

(a) (b)

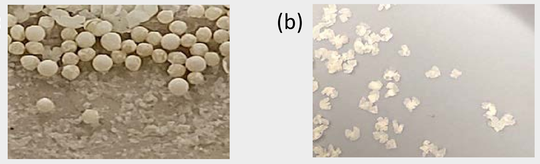


Figure 2. Photos of pellets using pestle and mortar to remove ER film. (a) Pellets without ER film, and (b) ER film

- The process of removing ER film resulted in a better separation of opioid agonist from antagonist after shaking with agate ball.

	Agonist (% of label claim)	Antagonist (% of label claim)	Agonist : Antagonist ratio
≥ 1000 µm	36.4	109.2	6.6 : 1
500 – 1000 µm	10.5	0	100 : 0
< 500 µm	15.6	0	100 : 0
Recovery (%)	62.5	109.2	

Table 1. Assay of agonist and antagonist in different particle size range after 30 minutes shaking with agate ball

- A high ratio of opioid agonist was obtained for particle size less than 1000 µm.
- About 38% of agonist was lost in the manipulation process.

(III) Ball Mill

(a) (b)

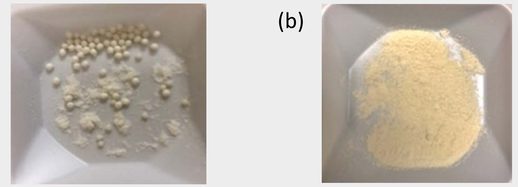


Figure 3. Photos of manipulated pellets using ball mill. (a) 30 minutes milling, and (b) one hour milling

- About 16% of pellets were pulverized after 30 minutes milling. Pellets were completely pulverized after 1 hour of agitation.
- Opioid agonist and antagonist were unable to be separated using ball mill.

(IV) Electric Pepper Grinder

	Agonist (% of label claim)	Antagonist (% of label claim)	Agonist : Antagonist ratio
≥ 500 µm	26.7	23.3	29 : 1
425 – 500 µm	9.9	19.5	12 : 1
300 – 425 µm	12.5	37.7	8 : 1
212 – 300 µm	7.9	14.1	14 : 1
106 – 212 µm	21.2	5.5	96 : 1
< 106 µm	5.4	1.3	104 : 1
Recovery (%)	83.6	101.4	

Table 2. Assay of agonist to antagonist within specified particle size

- A high ratio of opioid agonist in the milled particles could be obtained using an electric pepper grinder.
- A large ratio of opioid agonist to antagonist was obtained in fine particles , i.e., < 212 µm. Other size ranges below 500 µm, (i.e., 212 – 300 µm, 300 – 425 µm, 425 – 500 µm) produced significantly more quantities of antagonist.
- About 16% of agonist was lost in the manipulation process.

CONCLUSIONS

- A high ratio of opioid agonist in the milled particles could be achieved using the physical manipulation.
- The results indicated opioid agonist could be separated from antagonist with an adequate physical manipulation design. However, opioid agonist may be lost during the manipulation process.

DISCLAIMER

This study was funded through FDA Contract HHSF22301002T. Views expressed in this poster do not necessarily reflect the official policies of the Department of Health and Human Services, nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.

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