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Development of *in vitro* permeation method for nasally insufflated abuse deterrent formulations

Nahid S Kamal[1], Ahmed Zidan[1], Xin Feng[1], Xiaoming Xu[1], Dajun Sun[2], Ross Walenga[2], Heather Boyce[2], Celia N. Cruz[1], Muhammad Ashraf[1]

1. Division of Product Quality Research, Office of Testing and Research, Office of Pharmaceutical Quality,
2. Division of Quantitative Methods and Modeling, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD 20993, USA

Contact information: Nahid.Kamal@fda.hhs.gov & Ahmed .Zidan@fda.hhs.gov

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PURPOSE

To understand impact of particle size of physically manipulated abuse deterrent formulations (ADF) for intranasal absorption following insufflation using an in vitro permeation method.

OBJECTIVES

The objective of this study was to develop an in vitro permeation method to predict or mimic the intranasal absorption of manipulated ADF following insufflation. In this particular study we studied experimental conditions that may differentiate the permeation rate and extent based on particle sizes.

METHODS

An ADF formulation was prepared as a model drug product, where the composition is shown in Table 1. Metoprolol succinate is intended to act as a surrogate for oxycodone HCl because it has similar physicochemical properties and the analytical method has been previously established.

Table 1. Compositions of a surrogate ADF formulation with the model drug metoprolol succinate. succinate.

Component	Weight (mg)	Function
Metoprolol succinate	40	Active ingredient (model drug)
Polyethylene oxide	158	Release controlling polymer
Magnesium stearate	2	Lubricant
Total weight	200	

The surrogate ADF was prepared by blending the drug and the excipients, direct compression then curing the compacts at 80°C for 30 minutes. Tablets were then mechanically manipulated into fine and coarse particles to 100-500 µm and 500-900 µm size ranges by employing household coffee blender followed by sieving, respectively. Content uniformity (n = 10) was determined on each size fraction to evaluate drug recovery after manipulation. To understand the effect of formulation particle size on drug permeation by employing Franz diffusion cell (Figure 2), permeation studies (n = 6) were performed using the following parameters:

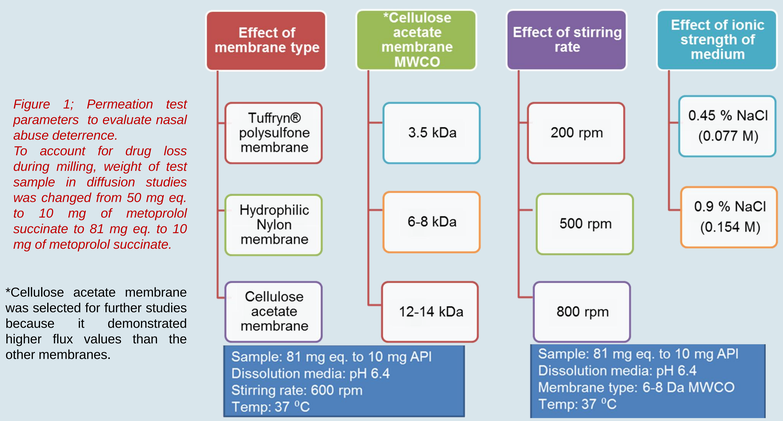

Figure 1; Permeation test parameters to evaluate nasal abuse deterrence. To account for drug loss during milling, weight of test sample in diffusion studies was changed from 50 mg eq. to 10 mg of metoprolol succinate to 81 mg eq. to 10 mg of metoprolol succinate.

*Cellulose acetate membrane was selected for further studies because it demonstrated higher flux values than the other membranes.

RESULTS

- Results of percent recovery of the manipulated ADF revealed that ~65% of metoprolol contents were recovered from all samples regardless of particle size (Figure 4). Distribution of the API between the airborne fines and the plasticly deformed polyethylene oxide (PEO) may have occurred during milling in blender. As a result, weight of test sample in diffusion studies was changed from 50 mg eq. to 10 mg of metoprolol succinate to 81 mg eq. to 10 mg of metoprolol succinate.
- Under all conditions tested and normalization for recovered amount of API after milling, an incomplete permeation of the drug from both fine and coarse particles was observed which may be attributed to membrane clogging by swelled polymer (Figure 5-7 and 3)
- A statistically non-significant ($p < 0.05$) difference was observed between permeation profiles of coarse and fine particles by the MWCO of diffusion membrane (Figure 5), agitation rate which may be explained by the vigorous swelling of PEO (Figure 3 and 6) and ionic strength from 0.1% to 0.9% (Figure 7).

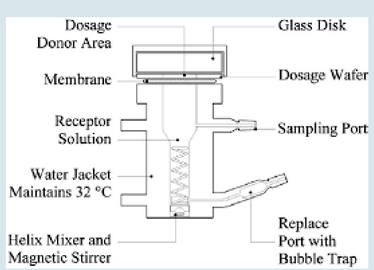

Figure 2: Configuration of diffusion cell

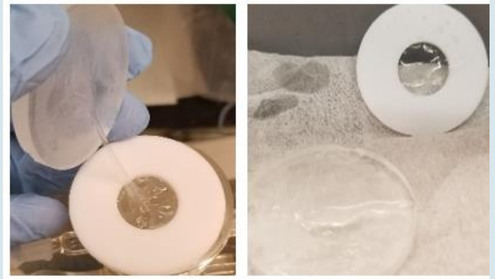

Figure 3: Swollen polymer on the membrane after permeation test

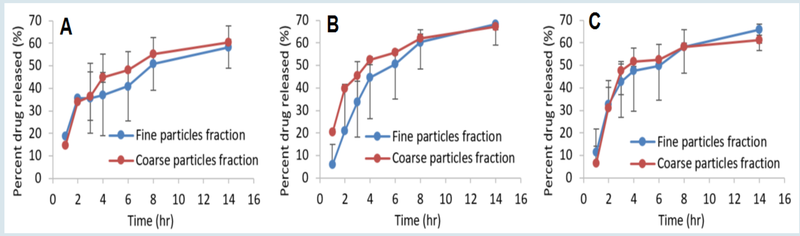

Figure 5. Release profiles of fine and coarse powders of manipulated tablets of metoprolol succinate obtained by diffusion cells as a function of molecular weight cut-offs of cellulose acetate membranes (A: 3-5 kDa; B: 6-8 kDa; and C: 12-14 kDa). Dissolution medium was phosphate buffer (pH 6.4) stirred by a magnetic bar at 600 rpm and maintained at a temperature of 37ºC. Error bars represent standard deviation of six replicates.

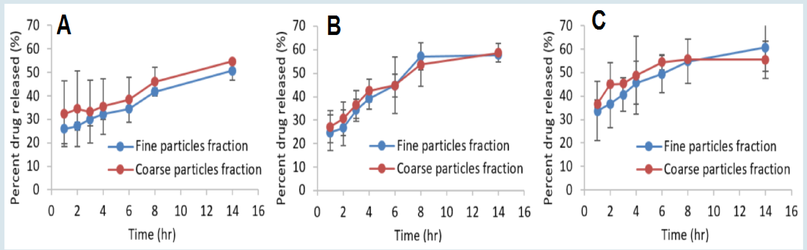

Figure 6. Release profiles of fine and coarse powders of manipulated tablets of metoprolol succinate obtained by diffusion cells as a function of stirring rate of the dissolution medium (A: 200 rpm; B: 500 rpm; and C: 800 rpm). Diffusion membrane was cellulose acetate of 6-8 kDa MWCO and dissolution medium was phosphate buffer (pH 6.4) maintained at a temperature of 37ºC. Error bars represent standard deviation of six replicates.

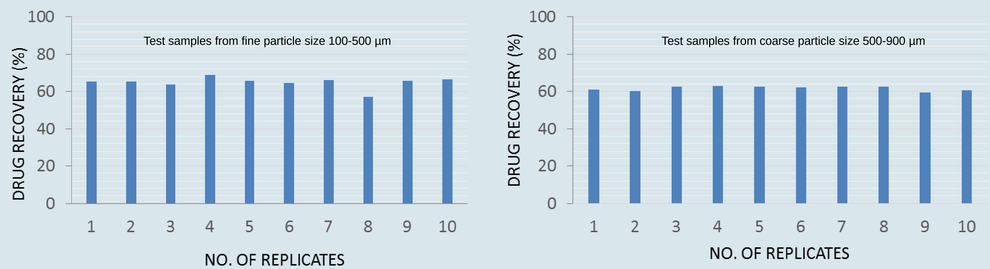

Figure 4: Percent drug recovery (n = 10) of manipulated surrogate formulations prepared from fine and coarse particle size

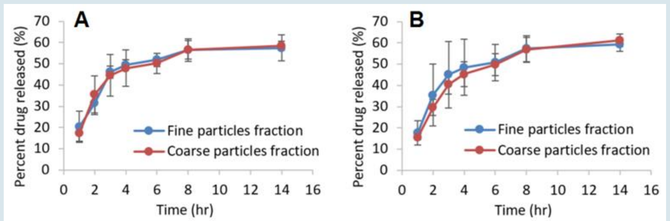

Figure 7. Release profiles of fine and coarse powders of manipulated tablets of metoprolol succinate obtained by diffusion cells as a function of ionic strength of the dissolution medium (A: 0.077 mol/L; and B: 0.154 mol/L). Diffusion membrane was cellulose acetate of 6-8 kDa MWCO and dissolution medium was phosphate buffer (pH 6.4) stirred at 600 rpm and maintained at a temperature of 37ºC. Error bars represent standard deviation of six replicates.

CONCLUSIONS

Diffusional release profiles of manipulated ADF formulations of different particle sizes depended primarily on the experimental conditions employed (e.g., stirring rate, type of supporting media, composition of the reservoir medium, etc.). However, this study showed poor discrimination based on particle size under these studied conditions. Identification of other membranes that can mimic the nasal barrier for drug absorption is in progress. Optimization of the permeation conditions will be critical for the generation of biorelevant permeation data of insufflated ADF products after manipulation.

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