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In Vitro Method to Assess Performance of Abuse Deterrent Formulations (ADFs) for Nasal Route of Abuse

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Background & Objectives

Abuse deterrent formulations (ADFs) are designed to deter misuse and abuse of prescription narcotics and other drugs prone to abuse. One technology to develop an ADF is to incorporate a physical barrier, to increase the tablet strength, thereby reducing ease of tablet chewing, grinding, cutting and crushing. Increasing the tablet strength could be accomplished by several approaches including, but not limited to, incorporation of polyethylene oxide (PEO) in the formulation. PEO will also form a gel when exposed to moisture and retard the release of the drug.

If an abuser is able to mechanically manipulate the tablet and snort it, the resulting powder will be exposed to moisture in the nasal passage. The PEO in the powder matrix will form a gel and maintain a controlled release of the active pharmaceutical ingredient (API). To develop ADF formulations, it is valuable to have an *in vitro* method that can provide an assessment of how well an ADF can inhibit the release of a drug under simulated nasal conditions.

Objective:
To develop and assess an *in vitro* technique to measure the performance of an ADF for the nasal mode of abuse.

Methods

- Materials:
  - Active Pharmaceutical Ingredient (API): Metoprolol Tartrate (MT)
  - Polymer: Polyethylene Oxide (PEO) (DOW Chemical, 2,000,000MW)
- Diffusion Cell: In Line Diffusion Cells (PermeGear)
- Membrane Barrier: Cellulose Membrane (MW cutoff 12,000 to 14,000)
- Receiver Media: PBS solution pH 6.4
- Temperature: 37°C
- Temperature & Humidity Monitor Pyrobutton data loggers
- Sampling Points: 1, 3, 6, 9, 12 hrs
- Quantitative Assay: UV-VIS

Tab 1. Diffusion Cell Sample Loading

Sample Type	Sample Loading on Membrane	Mass of API in Sample
API Powder (N =4)	25 mg	25 mg
API in Solution (N = 4) (0.3 ml PBS buffer)	0.3 ml	25 mg
30 wt% API + 70 wt% PEO Powder (N = 6) (Physical Mixture)	25 mg	8 mg

Fig 1. Gelling of the API + Polymer blend during diffusion study

Results

Fig 2

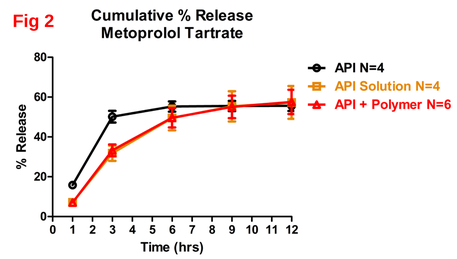

Fig 3

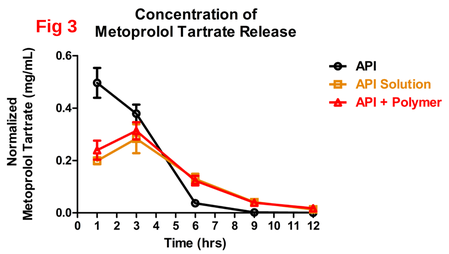

Fig 4

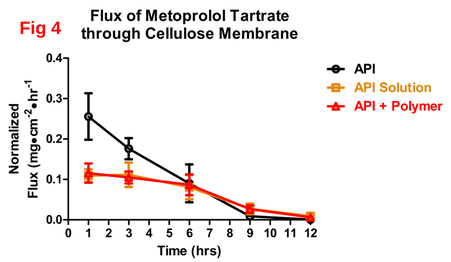

Fig 5

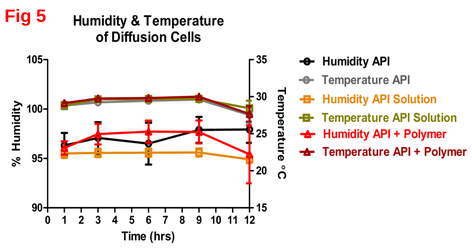

Figure 1 shows the progression of gelling on the membrane during the diffusion experiment of the API + Polymer sample. At T=0, the sample is powder. By T=1 hr, gelling has initiated. By T=12hrs, the sample has fully formed a gel.

Figure 2 shows that at 1 hr the API Powder diffused through the membrane faster than the API Solution and API + Polymer mixture. At 3 hrs, 50% of the API Powder had diffused across the membrane whereas only 30% of the API diffused through the membrane for the API + Polymer and API Solution samples. The cumulative release profile demonstrates differences in how the material diffuses across the membrane based on the sample presentation,

The API Powder demonstrates a C_{max} at T= 1 hr whereas the API Solution and API + Polymer mixture exhibited a C_{max}= 3hr (Fig 3). Figure 4 shows the flux to be greatest for the API powder. However, all samples showed maximum flux at T=1 hr. Finally, figure 5 shows the temperature and humidity of the sample cells remained consistent for the duration of experiment.

Initially we thought the API Solution would exhibit similar diffusion as the API Powder. We also expected to see less error in the API Solution measurements due to the consistent administration of the sample to the membrane. Based on the data presented, though, the error for the cumulative release of the API Solution was markedly higher than for the API Powder samples. It is possible that the API Solution slowed the release of MT by creating a stagnant layer at the membrane barrier since the donor compartment was not able to be stirred. Therefore, the diffusion of the API from solution is most likely attributed to experimental design. Therefore, we would not consider the API Solution to be a suitable comparator. A direct comparison of the diffusion profile for the API + Polymer mixture compared to just the API Powder sample shows discreet differences in diffusion that could be used to determine if a dosage form exhibits abuse deterrent protections. The data shown indicate that diffusion studies may be appropriate to detect differences in formulation effects on the diffusion of MT through a cellulose membrane.

Conclusions

Metoprolol tartrate blended with polyethylene oxide showed different diffusion profiles to that of the API Powdered samples. These differences demonstrate that the diffusion cells have the potential to be a suitable in vitro assessment to determine if a formulation is able to deter nasal abuse of the drug product. Additionally, no significant differences in temperature and humidity for each cell were observed.

Future Directions

Much literature on the topic of mathematical modeling of percutaneous absorption of topical vehicles[1] exists, but the idea of monitoring the diffusion of powdered particles across a membrane barrier is novel. Scheuplein and Ross[2] studied the mathematics on the diffusion of solvent deposited solids, but this would not work with solids that form a gel when exposed to moisture. It would be of interest to understand the more complex diffusion kinetics of the polymer blend as diffusion could be imagined to occur in 3 stages: before the polymer gels, as it gels, and after the gel has fully formed. Using suitable mathematical modeling we may be able to capture significant in vitro parameters that could be correlated to in vivo parameters of a real life abuser to truly assess the abuse deterrent nature of a formulation.

References

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