Stability Study to Ensure Abuse-deterrent Properties During Shelf Life of Abuse-deterrent Formulation of Opioids

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BACKGROUND

Abuse of Opioid drug products has become a national health crisis in the US. These drugs are being abused in several ways by administering either oral, nasal or parenteral routes that potentially increases the mortality rates. To deter abuse, a number of drug products with abuse-deterrent (AD) properties have been approved by the US Food and Drug Administration (FDA) (1). For AD labeling, various strategies including physical barriers, chemical barriers, antagonists, aversive agents, and prodrugs have been investigated (1). To deter abuse effectively, it is critical to maintain AD properties during product shelf life. However, no information on the stability of AD properties during product shelf life is publicly available. To support the development and safe use of abuse-deterrent formulation (ADF) of Opioids, this study is designed to evaluate the stability of AD properties of surrogate ADF of Opioids at various storage conditions.

Potential Routes of Abuse of Opioid Drug Products

- Ingestion (Oral)
- Injection (Parenteral)
- Insufflation (Nasal)
- Smoking/Vaping (Inhalation)

To combat opioid crisis, polyethylene oxide (PEO) polymer is being used for the development of AD products. PEO provides abuse deterrence by exerting physical barriers via enhancing hardness and viscosity of the formulation.

Mode of action of PEO to exert AD property

Difficult to Cut/Crush

Difficult to Inject

MANUFACTURING OF ABUSE DETERRENT TABLETS

Surrogate extended release (ER) AD tablets were prepared by direct compression using Diltiazem HCl (model drug), PEO polymer and suitable excipients followed by curing at 70°C for 30 mins. Following the FDA Guidance (2), *in vitro* characterization and evaluation of AD properties of tablets including physical manipulation using coffee grinder, particle size distribution, drug extraction potential in solvents at room and elevated temperatures, syringeability/injectability etc. have been performed. The stability study was conducted at 25°C/60% RH and 40°C/75% RH following the ICH guidelines (3).

Powder Blend

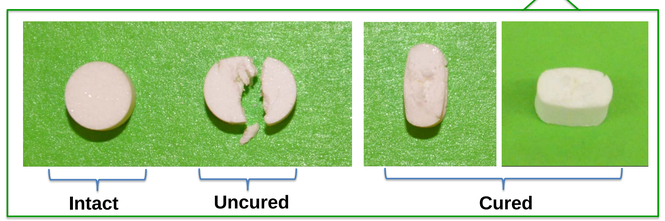
Direct Compression

Curing
(70 °C, 30 min)

Stability Study

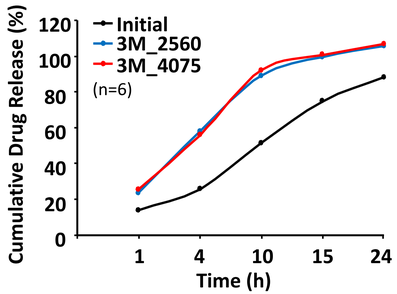
CHARACTERIZATION OF AD TABLETS

	Tablet ID	Diameter (mm)	Thickness (mm)	Weight (mg)	Hardness (kP)	Friability (NMT 1%)
Uncured		8.00	4.54	253.92	7.19	0.11%
Cured	Initial	7.97	5.05	253.36	ND	0.002%
	3M_2560	7.96	5.04	253.11	ND	0.035%
	3M_4075	7.99	5.07	256.5	ND	0.311%



ND: Not Determined

Drug Release Profile :



Drug release profile changes with storage time

AD PROPERTIES (PHYSICAL MANIPULATION)

Tablet

Coffee Grinder

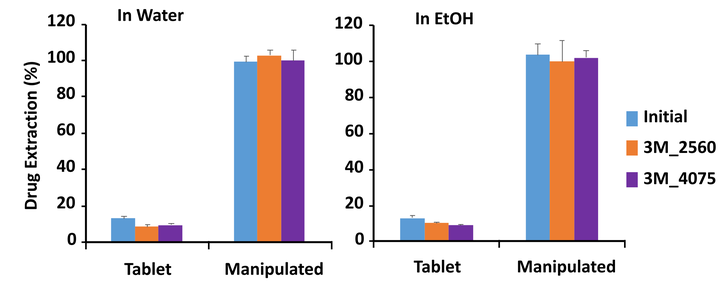
Manipulated

Particle Size Distribution :

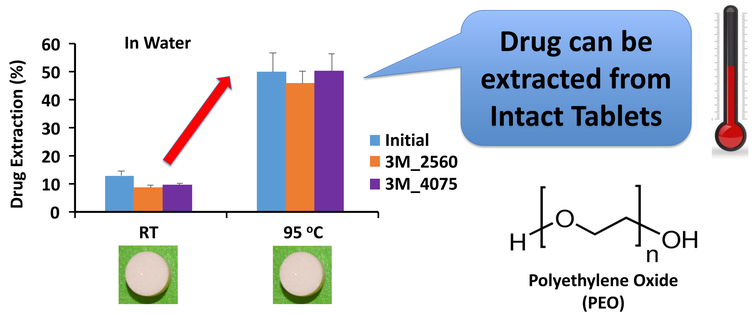
Size	Unit	Initial	3M_2560	3M_4075
D10	µm	3.51	2.96	3.46
D50	µm	158.07	163.62	147.74
D90	µm	364.42	352.97	354.41
0-500 µm	**%**	**99.69**	**99.67**	**99.77**
0-1000 µm	%	100	100	100

Tablets can be manipulated using a coffee grinder in <5 min at RT to a size ~500 µm

Drug Extraction: (Effect of Manipulation)



Drug Extraction: (Effect of Temperature)



CONCLUSION

- Curing PEO-based tablets substantially increases hardness of the tablets.
- Cured tablets can be manipulated using a coffee grinder in <5 min at room temp (RT) to a size <1 mm, dictates risk threshold for nasal route of abuse.[2]
- Physical manipulation enhances drug extraction in solvents (Water, EtOH).
- Cured tablet surface morphology changes with storage time, prompts drug release (data not shown).
- Once tablet is manipulated, hydration of manipulated sample in water eases syringeability, and increases the possibility of potential drug abuse by IV route (data not shown).

References

1. Maincent J, Zhang F. *Int J Pharm*. 2016;510(1):57-72. **2**. General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products: Guidance for Industry, 2017. **3**. ICH guidelines, Q1A(R2), 2003.

Acknowledgements

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