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# Effects of excipients and curing process on the abuse deterrent properties of directly compressed tablets

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ABSTRACT

The objective of the present investigation was to understand the effects of excipients and curing process on the abuse deterrent properties (ADP) of Polyox™ based directly compressible abuse deterrent tablet formulations (ADFs). The excipients investigated were lactose (monohydrate or anhydrous), microcrystalline cellulose and hydroxypropyl methylcellulose. The ADPs studied were tablet crush resistance or hardness, particle size distribution following mechanical manipulation, drug extraction in water and alcohol, syringeability and injectability. Other non-ADPs such as surface morphology and tablet dissolution were also studied. It was found that presence of 50% or more of water soluble or swellable excipient in the ADF tablets significantly affected the tablet hardness, particle size distribution following mechanical manipulation and drug extraction while small amount (5%) of excipients had either minimal or no effect on ADPs of these tablets. Addition of high molecular weight HPMC (K 100 M) affected syringeability and injectability of ADF. Curing process was found to affect ADPs (hardness, particle size distribution, drug extraction and syringeability and injectability) when compared with uncured tablet. In conclusion, addition of large amount of excipients, especially water soluble ones in Polyox™ based ADF tablets increase the risk of abuse by various routes of administration.

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## 1. Introduction

Prescription drug abuse of opioids has reached epidemic proportions in America (Compton et al., 2015; Volkow et al., 2014; The White House Office of National Drug Control Policy, 2012). It can be gauged by mortality and morbidity data. Emergency room visits due to prescription opioid has more than doubled from 82.5 to 184 per 100,000 during the period 2004–2011 (Substance Abuse and Mental Health Services Administration. Drug Abuse Warning Network: national estimates of drug-related emergency department visits 2015). Furthermore, opioid drug poisoning has more than tripled from 1.4 to 5.1 per 100,000 during 1999–2013 period. In addition, deaths due to prescription drug abuse are more than 16,200, which are more than all the illicit drugs combined (Centers for Disease Control and Prevention. National Center for Health Statistics- Multiple cause-of-death data, 1999–2013, 2014; Han et al., 2015). Abuse of opioid analgesic is associated with huge economic cost in addition to cause of significant mortality and morbidity. The total societal costs of prescription opioid abuse in 2007 were calculated to be $55.7 billion, of which lost workplace productivity contributed $25.6 billion, health care costs contributed $25.0 billion, and criminal justice costs accounted for the remaining $5.1 billion (Birnbaum et al., 2011). Prescription drugs can be abused by ingestion (chewing or taking more than the recommended dose), inhalation (snorting, smoking or inhaling) and injection (intravenous, intramuscular, or subcutaneous administration). Mechanical manipulation, by which an abuser may use to facilitate the abuse of the prescription drug product, includes crushing or grinding the product into a powder or small particles, and dissolving in a solvent such as ethanol and water at ambient or hot and/or cold temperatures (Gasior et al., 2016).

Various steps are taken at state and federal level (education, prescription monitoring, naloxone distribution, aggressive law enforcement and medication assisted treatment etc.) (Spoth et al., 2013; Haegerich et al., 2014; Walley et al., 2013; Johnson et al.,

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2014; Mitchell et al., 2012; Schwartz et al., 2013) to combat prescription opioids abuse. Pharmaceutical manufacturers have come up with a novel concept of abuse deterrent formulations (ADFs) (Havens et al., 2014). These formulations are designed to deter the abuse of prescription opioids but will not provide resistance to abuse. These formulations are also referred as tamper resistant in the literature (Gasior et al., 2016; Gudin and Nalamachu, 2016), but this terminology is also used in relation to packaging requirements applicable to certain classes of drugs, devices, and cosmetics. FDA refers to these formulations designed to deter the abuse of prescription opioids as "abuse deterrent" rather than "tamper resistant". Various formulation approaches can be utilized to make ADFs. Some of the approaches outlined in the FDA guidance document "on Abuse Deterrent Opioids-Evaluation and Labeling" include; physical/chemical barrier, agonist/antagonists combination, aversion, delivery system, new molecular entities and prodrug, combination of two or more approaches and novel approaches. Currently, there are seven commercially available opioid formulations with abuse deterrent label claims. These products employ either physical/chemical barrier or antagonists/agonist combination approach to impart abuse deterrence to the formulation. Antagonists/agonist combination ADFs contain antagonist that blocks euphoric effect of opioid e.g. morphine-naltrexone, oxycodone-naloxone, and buprenorphine-naloxone (Food and Drug Administration, on Abuse Deterrent Opioids-Evaluation and Labeling 2015). Physical/chemical barrier approach based ADFs provided resistance to physical manipulation such as crush, break, dissolve and/or forming a viscous mass that resists passage through needle. These products are Oxycontin®, Targiniq™, Embeda®, Hysingla® ER, MorphaBond™ ER, Xtampza ER and Troxyca ER (Gasior et al., 2016; FDA Facts: Abuse-Deterrent Opioid Medications, 2016).

In our previous research paper, we reported on the effect of Polyox™; Polyox™ molecular weight and processing variables on the abuse deterrent properties (ADPs) of ADFs manufactured by direct compression method (Rahman et al., 2016). Formulations may contain additional excipients such as lactose, microcrystalline cellulose (MCC) and hydroxypropyl cellulose (HPMC) beside Polyox™. The effect of excipients on ADPs of Polyox™ based ADF was not reported in the literature to the best of our information. The present research focuses on understanding the effect of commonly used tablet excipients on the ADPs of ADFs. The ADPs evaluated were hardness/crush resistance, physical manipulation, particle size, syringeability, injectability and drug extraction in solvents (water and ethanol). Sotalol (STL) was selected as a model drug due to its physicochemical properties similarity with opioid drugs (Rahman et al., 2016).

## 2. Materials and methods

### 2.1. Materials

Sotalol (STL) (Abblis Chemicals LLC, Houston, TX), Polyox™ WSR 301 (polyethylene oxide, MW-4000,000), HPMC K 100 M and K 4 M (Colorcon, Harleysville, PA, USA), Lactose anhydrous (LA), lactose monohydrate (LM) (Foremost farms, Baraboo, WI, USA), MCC (Avicel® pH 101, FMC Biopolymer, Philadelphia, PA), magnesium stearate (MGS), butylated hydroxytoluene (BHT), octane sulfonic acid, acetonitrile and ethanol (200 proof) (Fisher Scientific, Pittsburgh, PA, USA) were used as obtained in this study. All other chemicals/reagents were of analytical grade.

### 2.2. Methods

#### 2.2.1. Tablet compression

Table 1 describes the composition of all tablet formulations investigated. The tablets were manufactured by direct compression method. A batch of 250 tablets was manufactured for each formulation. All ingredients, except MGS, were passed through ASTM sieve #50 and were blended for 20 min in Turbula® mixer for each formulation (Willy A. Bachofen AG Maschinenfabrik, Basel, Switzerland). BHT was added to Polyox™ in geometrical fashion before blending with the drug and excipients. Magnesium stearate was passed through ASTM sieve #50 and mixed with the formulation blends for 5 min. The final blend was compressed into tablets using Mini Press-1 (Globe Pharma, New Brunswick, NJ, USA) 10-station tableting machine with 8 mm flat die and punches (Natoli Engineering Company, Saint Charles, MO, USA). All tablets batches were cured at 75 °C in oven for 30 min (Rahman et al., 2016). Surface morphology of the tablets was determined by scanning electron microscopy (SEM, JSM-6390 LV, JEOL, Tokyo, Japan).

#### 2.2.2. Hardness

Pharmaceutical hardness tester (PTB 111E, Pharma Test Apparatebau AG, Hainburg, Germany) and texture analyzer (TA·XT Plus, Stable Micro Systems, Surrey, UK) were used for tablet hardness characterization. Both pieces of equipment were capable of exerting compression load of 50 kg on the tablet. Hardness test conditions selected for Texture analyzer were: compression mode, 2 mm/s pretest speed, 1 mm/s test speed, 10 mm/s post-test speed, target mode-force, 500 N force, 1N trigger force, 1N break sensitivity and break mode-rate. The measurements were done in six and three replicate for hardness tester and texture analyzer, respectively.

**Table 1**
Composition of abuse deterrent formulations.

| Formulation | Drug (mg) | MgS (mg) | BHT (mg) | Polyox 301 (mg) | HPMC K 100 M (mg) | HPMC K 4 M (mg) | Lactose monohydrate (mg) | Lactose anhydrous (mg) | Microcrystalline (mg) |
|---|---|---|---|---|---|---|---|---|---|
| F1 | 40 | 2 | 0.2 | 157.8 | – | – | – | – | – |
| F2 | 40 | 2 | 0.2 | 147.8 | 10 | – | – | – | – |
| F3 | 40 | 2 | 0.2 | 57.8 | 100 | – | – | – | – |
| F4 | 40 | 2 | 0.2 | 147.8 | – | – | 10 | – | – |
| F5 | 40 | 2 | 0.2 | 57.8 | – | – | 100 | – | – |
| F6 | 40 | 2 | 0.2 | 147.8 | – | – | – | – | 10 |
| F7 | 40 | 2 | 0.2 | 57.8 | – | – | – | – | 100 |
| F8 | 40 | 2 | 0.2 | 57.8 | 50 | – | – | – | 50 |
| F9 | 40 | 2 | 0.2 | 57.8 | – | – | 50 | – | 50 |
| F10 | 40 | 2 | 0.2 | 57.8 | 50 | – | 50 | – | – |
| F11 | 40 | 2 | 0.2 | 147.8 | – | 10 | – | – | – |
| F12 | 40 | 2 | 0.2 | 57.8 | – | 100 | – | – | – |
| F13 | 40 | 2 | 0.2 | 147.8 | – | – | – | 10 | – |
| F14 | 40 | 2 | 0.2 | 57.8 | – | – | – | 100 | – |