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Abuse-Deterrent Formulations (ADFs): Crush Resistance

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The rapid and widespread abuse of prescription medications within the United States from the late 1990s through the mid-2000s reached epidemic levels based on several national studies [1]. The largest contributor to this problem has been the use of opioid analgesics for nonmedical purposes. These powerful medications became overly prescribed, diverted, and popular among abusers. One product, Oxycontin®, became the most prescribed brand name medication for moderate-to-severe pain in 2001, and ranked high on the abused drug list due to its fast heroin like high [2]. To enhance these effects, this extended release product was frequently tampered with to release large amounts of drug all at once. Despite warning labels that such rapid release could be fatal, the drug was typically tampered by swallowing a chewed tablet, crushing to a powder followed by snorting, or extraction in water followed by injection [3]. It has also been shown overall that opioid pain medications are frequently tampering with and are most commonly abused by orally ingesting, injecting, snorting, or smoking [4]. Abusers may not only physically manipulate a drug product for abuse, but also co-ingest or combine with other substances to produce greater euphoria or other subjective effects. In one study looking at deaths associated with oxycodone, almost 97% of deaths were associated with another substance including other prescription drugs, cocaine, marijuana, or alcohol [5]. Therefore, preventing or decreasing prescription abuse involving all such activities will require multiple approaches and methods to obtain the greatest impact to public health.

One approach gaining considerable attention is the placement of drugs with high abuse potential into dosage forms that can resist, to a certain extent, common methods of abuse. The first generation type products combined active drugs with opioid antagonists (e.g. Talwin® NX) or aversive agents (e.g., Lomotil®) to discourage injection or overdose [6]. In contrast, the newer second generation formulations rely heavily on the properties of the excipient materials and manufacturing methods to produce products more resilient to abuse. Research in this new area focused largely on the development of formulations that could maintain their integrity under crushing and similar abuse stresses. Oral dosage forms having such properties started to become known simply as “crush resistant” products and were classified as having

physical barriers to abuse.

Since many common forms of abuse start with a product first being reduced into a fine powder, it is easy to understand where the desire to produce a tablet resistant to crushing might have begun. For example, abuse by nasal insufflation would require the tablet to initially be ground down into fine particles capable of being easily airborne before deposition into the nasal cavity. Likewise, preparing a tablet into a powdered form would speed drug dissolution and extraction efforts needed for intravenous injection. Additionally, the controlled release mechanisms of most tablets could be easily defeated when crushed. This allows a rapid and sometimes dangerous amount of drug to be released all at once in what is commonly referred to as “dose-dumping.” Products having crush resistance might therefore have the potential for decreasing all these forms of abuse. However, the difficulty comes not only in formulating such products but also in how to best initially demonstrate crush resistance in a laboratory setting.

The Food and Drug Administration (FDA) needed to at least address such concerns as products claiming crush resistance started to submit new drug applications. This was done in January of 2013 when the FDA released a draft guidance on how they would likely evaluate abuse deterrent features of a product and approve claims for labeling purposes [7]. According to this document, four different labeling claims or tiers, were established:

Tier	Claims that a product is/have:
1	Formulated with physicochemical barriers to abuse
2	Expected to reduce or block the effect of the opioid when the product is manipulated
3	Expected to Result in a Meaningful Reduction in Abuse
4	Demonstrated Reduced Abuse in the Community

The FDA stated they would evaluate extensive laboratory, as well as pre- and post-marketing clinical data to approve each claim.

For abuse deterrent products seeking tier 1 claims regarding crush resistance, in-vitro testing would have to demonstrate significant difficulty in rendering the product into an abusable state. For comparison, a marketed reference product devoid of abuse deterrent features but of equal comparison (e.g., drug, strength, dosage form) would need to be chosen in most cases. In general, the FDA guidance refers to such in-vitro tests as laboratory manipulation and extraction studies, or category 1 studies. The critical importance of conducting such studies, which help fully understanding a product's strengths and weakness with regards to being defeated are also mentioned. Even though category 1 tests are generally discussed, there is no in-depth discussion regarding the use of any standard testing methods or interpretation of results. It appears that most of this responsibility is left up to the investigators. This has created diversity in the methods, procedures, and equipment that manufacturers and researchers report when assessing crush resistance. This has also made it more difficult to compare one product resilience against another.

As the science of formulating abuse deterrence products progresses and grows more complex, creating standard in-vitro testing methods also becomes more difficult and raises more questions. For example, it becomes difficult to answer whether all products should go through the same in-vitro testing or if testing should change based on the nature of the formulation, drug, or the abuse condition. These questions are certainly becoming more evident as products begin to enter the market and gain abuse deterrent labeling.

Several formulations and technologies exist with features to deter abuse [8,9], however only four products are currently FDA approved with labeling indicating such claims or described in its labeling; Oxycontin[®], Hysingla[™] ER, Oxaydo[™] (formerly Oxecta[®]) and Embeda[®]. With the exception of Oxaydo[™], each product has extended or controlled release properties where such mechanisms may be susceptible to destruction when crushed. Embeda[®] is not made to be crush resistant as it contains the opioid antagonist naltrexone, which is released upon crushing to decrease the effects of the active drug morphine. All other formulations use similar primary excipients and manufacturing processes to make the product more difficult to crush and break. Additionally, another product named Opana[®] ER was reformulated using analogous crush resistant methods in its formulation but was denied abuse deterrent labeling. This was in part due to the fact that the formulation couldn't maintain its extended release properties after being crushed; even though the product was robust to certain crushing methods compared to the original formulation [10]. This emphasizes the fact that changes in manufacturing methods or in-vitro testing may cause, in one way or another, gain or loss of abuse deterrent labeling. Furthermore, the fact that almost all products having abuse deterrent labeling address crushing to some extent, illustrates the importance of this formulation characteristic.

To adequately test crush resistant features and aid in formulation development and optimization, in-vitro crush resistant testing

has to advance. This starts with eliminating or at least expanding the common definition of "crush resistance" to include chewing, cutting, grating, and grinding. This is in direct response to what abusers may actually do to a product when trying to crush or break the product into smaller pieces. Going further, the definition of crush resistance should also include what tools have been used and if such tools were manual or mechanical in nature. The concept of pretreating a tablet using such methods as heat, microwave, or freezing temperatures before crushing adds more to the complexity of testing and crush resistant definitions.

The most common crush resistant testing involves mechanical methods of manipulating a tablet. Such testing may involve equipment as simple as two spoons, mortar and pestle, hammer, dropping weight, or worm-drive house clamp to more complex electrical devices such as a blender, coffee grinder, or rotary grinding tools (Figure 1).

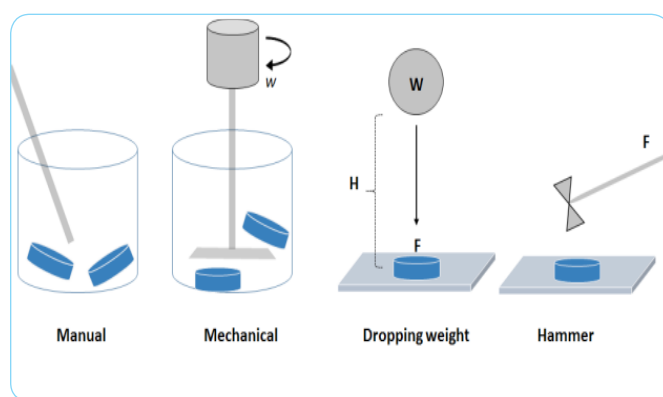


Figure 1: Example of in-vitro testing methods used to define crush resistance

At first, one may instinctively think that electrical tools would provide greater destruction and smaller particle sizes compared to more manual methods. However, this may not always be the case. With each technique, there are functioning factors that might change the result of the crushing process. For instance, in using a manual process such as a pestle & mortar, the person who is conducting the experiment, and not necessarily the number of tablets or the volume of the container may be the determining factor. With mechanical testing, the force of the motor, the number of tablets (crushing mass), volume and the shape of the container, as well as the design of the blade are all important. For instance, if one tablet is placed into a coffee grinder, it will likely be bounced around the container and impact the spinning blades every so often during its random movements. As particles start to break off, they may collect around the bottom or edges of the container and sit safely out of the way of the blades and never reduce more in size. The particle sizes produced will then likely depend on the empty space in the container that the blades do not touch. This will be in sharp contrast to placing multiple tablets into a coffee grinder where the blades may be in contact with a greater number of tablets or powder at all times. With a dropping weight method, the weight and weight height (the distance between the weight and the subject) are used together to qualitatively determine if the product is crushable. With using a hammer as the testing tool, the result would be extremely subjective and depend largely on the hammer, person conducting

the experiment, and the technique used. With all testing, duration of the tampering process will play a significant role and may become more complex when further considering how the nature of certain excipients may change during the crushing process. For instance, almost all abuse deterrent formulations contain poly(ethylene oxide) as the hardening and gelling agent that melts at around 70°C. One can expect a certain amount of heat to be generated over time during the crushing process, which may become sufficient to soften the polymer. If this occurs, the product will react in a ductile mode of fracture that enhances its resistance to particle size reduction.

The outcome variables being measured for most studies involving crushing are typically particle size and change in rate of drug dissolution or absorption. With regards to particle size, smaller particles are thought to have more abuse potential, although this assumption has yet to be adequately proven and can be easily challenged. Therefore, the goal of crush resistance should be to maintain an intact product or at most only produce very large particles under crushing. This outcome would likely prevent easy administration by unintended routes (e.g., nasal, injection), and thwart premature or accelerated drug release from controlled release products. In this order, the ability of a dosage form to resist particle size reduction would first be investigated before performing dissolution, extraction, or absorption studies on the resultant particles.

Mechanical crushing methods may be good for assessment of tablets formulated having rigid and tough mechanical properties that may fracture or shatter if a strong force is applied. However, formulations such as Oxycontin®, Nucynta® ER, and Opana® ER show properties that are more visco-elastic (plastic-like) and deform under applied forces. Therefore, smashing such a tablet with a hammer would create a flatter tablet and not so much multiple pieces. This tablet property is created by using high molecular weight polymers such as poly(ethylene oxide) that can be heated up to a molten state with an abusable drug to create a drug embedded matrix upon cooling. Such products may not show significant particle size reduction by chewing, crushing in a mortar and pestle, or chopping in an electrical blade device. This would ordinarily suggest crush resistance, but these tablets may effectively be reduced to fine particles by cutting, grating or grinding. Therefore a set of new in-vitro tests might need to be performed on such formulations to adequately determine their resilience of maintaining product integrity and drug release. Such testing methods have not been published but are certainly needed for determining the abuse deterrent nature of products manufactured via thermal processes such as hot melt extrusion or heated compression.

Overall, in-vitro testing methods for crush resistance should state how testing procedures closely mimic conditions that an actual abuser might perform. However, emphasis should also be placed on the use of testing methods that eliminate variability and decrease standard error. Furthermore, a testing method must be designed such that differences between various formulations can be easily differentiated.

The ability to make a tablet crush resistant may make it less desirable to abusers and produce a product associated with less

abuse or abuse related events. However, this will not stop or inhibit all forms of abuse including that of extraction or overdosing. Therefore, other actions such as the implementation of new federal and state regulations, the use of prescription monitoring programs, and prevention and treatment programs can work with abuse deterrent formulations to address this epidemic [11]. It is also important to realize that when a product states or claims features related to crush resistance, it is imperative that the nature of the test and dosage form be examined. Prescribers may not be aware of ambiguity in testing methods and put greater faith in such products before knowing how they were tested. Therefore, stating “crush-resistant” does simply not indicate if the product is abuse-resistant.

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