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Commercial Abuse-Deterrent Dosage Forms: Clinical Status

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Abstract

Abuse of prescription medications is being combated with the advent of novel formulations designed to prevent or discourage tampering and misuse. The ability of these abuse-deterrent and tamper-resistant formulations to impact abuse, and the test methods used to determine their lowered abuse potential is becoming more important. There are three main reasons for the need to access these formulations, a) to determine if a formulation itself can impact abuse of a product, b) for standardized methods that can be used to support product labeling, and c) to evaluate both new and generic products for tamper-equivalence. The object of this review is to provide an overview and evaluation of the various types of premarketing tamper and abuse studies performed both in-vitro and by experienced abusers when evaluating a product's deterrence to abuse. To find and assess abuse liability studies of FDA approved products, a database search using Medline and Google Scholar with keywords "abuse deterrent", and "tamper resistant" was used along with information obtained from product innovator websites and regulatory documents from the FDA regarding each product. Results from our investigation revealed that studies evaluating of a products abuse deterrent properties could be separated into three main categories based on the state the product is in during the study. The three main categories are 1) solid state studies, 2) solution state studies, and 3) aerosol state studies. For each category, various study examples are discussed and assessed for factors that will have significant impact on the way the study is evaluated.

Keywords: Abuse deterrent; Abuse liability; Formulation; Tamper resistant; Opioids

Introduction

The treatment of pain and patients' access to needed opioid analgesics has always been in conflict with preventing the misuse and abuse of these potentially addictive medications. With prescription drug abuse growing to epidemic proportions in the United States, it is now becoming significantly important to find effective solutions that lower abuse. Recent strategies have been proposed and implemented with efforts to specifically help curb abuse of prescription medications. One strategy gaining increasing attention is the development of novel dosage forms that are engineered to be more resistant to tampering and abuse when compared to traditional formulations already on the market. These tamper-resistant and abuse-deterrent medications have recently entered the clinical setting over the last three years, and their effectiveness at deterring abuse in the real-world is now being examined.

The need to evaluate how these novel formulations perform is primarily fueled by three main reasons. The first, and probably the most obvious, is to determine if they have an impact on public health. Studies that can show these formulations are associated with less abuse, less "liked" by abusers, have lower street value or are associated with decreased overdoses and or deaths would define that a product's formulation plays a major role in preventing its abuse. Additionally, studies with positive outcomes may drive legislation that requires tamper-resistance to be incorporated into all prescription drugs having abuse potential. The STOPP (Stop Tampering of Prescription Pills) Act is one example of federal legislation that, if passed, would require pharmaceutical manufactures to produce tamper-resistant formulations of specific drugs, and would prohibit sales of previously approved non-tamper resistant formulations if a new safer version of the drug is approved by the Food and Drug Administration (FDA) [1].

The second need to evaluate these novel formulations is for product labeling; the ability to promote, advertise and state in product literature the abuse deterrent nature of a product. Product labeling refers to any written, printed, or graphical material on the product itself or accompanying the product [2]. Any information on the label must be informative, have no false or misleading statements, and be based on data from human experience whenever possible [3]. Therefore, to claim a product has abuse deterrent properties on its labeling, it must show supporting evidence. So far this has not been easy as the FDA is requiring epidemiological studies demonstrating a reduction in drug abuse [4]. However, preliminary findings are showing these products are associated with decreased abuse in the larger population [5,6]. Furthermore, a product which can show less abuse may have an advantage in the marketplace when it comes to the prescribing practices of physicians compared to its higher abused counterpart. Also, non-narcotic abuse-deterrent formulations may in the future qualify for exemptions that would allow them to be placed into a lower control substance schedule, increasing access to the drug due to less restrictions and limitations (e.g., ability to have refills, phoned into pharmacy).

The last reason that abuse liability studies are needed is when it comes to the drug approval process, particularly for generic versions of these tamper-resistant formulations. When the patent becomes expired on these new formulations, generic alternatives are likely to follow. The need for such generics to show bioequivalence as well as similar abuse equivalence is the trend that the FDA seems to be taking [7]. It is therefore expected that the types of studies as well as the interpretation of their results will be a major focus in both new and abbreviated drug applications. The FDA has already published a draft document that addresses the need to characterize the physicochemical abuse properties of the drug and dosage form as well as establishing

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a complete abuse potential assessment both pre-approval and post-marketed [8]. A more recent draft document was also introduced to address opioid medications that are specifically designed to be abuse-deterrent and the labeling claims that may be allowed based on the data generated from specific studies [9].

The development of abuse deterrent dosage forms is in its early stages and the study methods used to evaluate products that have gained FDA approval are few, and not always designed properly to show the effect of important variables. In addition to the typical drug safety, efficacy, pharmacokinetic, and performance studies of most products, abuse deterrent formulations are often first evaluated in-vitro for their resistance to physical and chemical tampering. These methods include how the product performs under stresses such as being crushed, grated, ground, mixed with solvents, frozen, heated, drawn up and out of a syringe, and the effects of ethanol on accelerating dissolution. Since different drugs and formulation types have been associated with very different probabilities in their routes of abuse and tampering [10], manipulation studies should focus on the most apparent abuse methods for a particular product.

The drug product may even be further tested in the hands of experienced abusers who perform their mastered techniques of manipulation often to extract the drug faster or make the product suitable for alternate routes of administration. Clinical studies that involve drug-liking behavior and the effectiveness of reducing abuse are then initiated to further support the in-vitro studies and gather further information for product regulatory submission. This step-wise approach to abuse-deterrent studies is mentioned by the FDA as four study categories or "tiers"; where the first categories influence the design, necessity, and evaluation of higher categories [9]. The first three categories are premarketing studies listed as category 1) laboratory-based in vitro manipulation and extraction studies, category 2) pharmacokinetic studies, and category 3) clinical abuse potential studies. Postmarketing studies are listed as category 4, and evaluate the products ability to decrease abuse in the general population.

The objective of this paper is to provide an overview and evaluation of the various types of premarketing tamper and abuse studies performed both in-vitro and by experienced abusers when evaluating a products deterrence to abuse for regulatory and product development purposes.

Methods

To assess abuse liability studies regarding product tampering and abuse, we looked at information submitted to the FDA regarding six currently approved products that have implied having formulations that are abuse-deterrent. Further information was gathered from the product innovator websites and a database search for literature using Medline and Google Scholar with keywords "abuse deterrent", and "tamper resistant" to identify relevant data. The six products investigated; along with their abuse deterrent formulation properties and other information are listed in (Table 1). For a more complete review of these formulations and other abuse-deterrent products and approaches in development, the reader is referred to the many review articles on the subject [11-13].

Results

The evaluation of a product for abuse deterrent properties was found to fit into three main groupings that we can easily categorize in terms of the state the product is in during the study. The three main categories are 1) solid state studies, 2) solution state studies, and 3) aerosol state studies. In the following section we discuss the various studies performed in each product state, and provide discernment into the testing methods used. A summary of studies that would typically be found in each of these categories and examples of the factors that should be taken into consideration for each experiment type are outlined in Figure 1.

Solid state studies

All of the FDA approved products found were solid tablet dosage forms with the exception of Embeda™ which is currently on voluntary recall. Since oral tablets make up the majority of these products, the testing of the dosage form in its native solid state and the ability to remain in this state is of importance to resist abuse.

Particle size reduction studies

The ability of a product to withstand reduction in particle size is significant in determining its potential for abuse. This is because almost all forms of tampering (e.g., snorting, intravenous injection, and smoking) start with the product being reduced into a fine powder. Additionally, accidental misuse of long-acting products such as being chewed for ease of swallowing or being crushed and administered via a nasogastric tube could lead to dangerous levels of the drug being released at once. Therefore, studies that show how the product behaves under manual and mechanical manipulation is important. The overall outcome of such studies should be to determine the ease of which a product can be defeated when compared to a similar commercial product without abuse-deterrent features.

Product	Abuse-deterrent property	FDA approval date	Sponsor Company
Oxycontin® (oxycodone CR Tab)†	• Mechanical resistance • Gelling in solvents	April 2010 (original formulation: December 1995)	Purdue Pharma
Nucynta® ER (tapentadol ER tab)	• Mechanical resistance	August 2011	Johnson & Johnson/Janssen Pharmaceuticals
Exaglo® (hydromorphone ER tab)	• OROS technology, hard outer shell • Gelling in solvents	March 2010	Mallinckrodt
Opana® ER (oxymorphone ER tab)	• Crush resistant • "Intac technology" by Grunenthal	December 2011	Endo Pharmaceuticals
Oxecta® (oxycodone tab)	• Gels in liquid • Nasal irritant • "Aversion technology" by Acura Pharmaceuticals	June 2011	Pfizer Inc. (formerly King Pharmaceuticals)
Embeda™ (morphine/naltrexone ER cap)	• Mixed agonist/antagonist • Sequestered antagonist	August 2009 (Voluntarily Recalled Mar. 2011)	Pfizer Inc. (formerly King Pharmaceuticals)

CR, controlled release; ER, extended release; † only product with approved abuse-deterrent labeling

Table 1: FDA approved products with properties expected to reduce abuse.

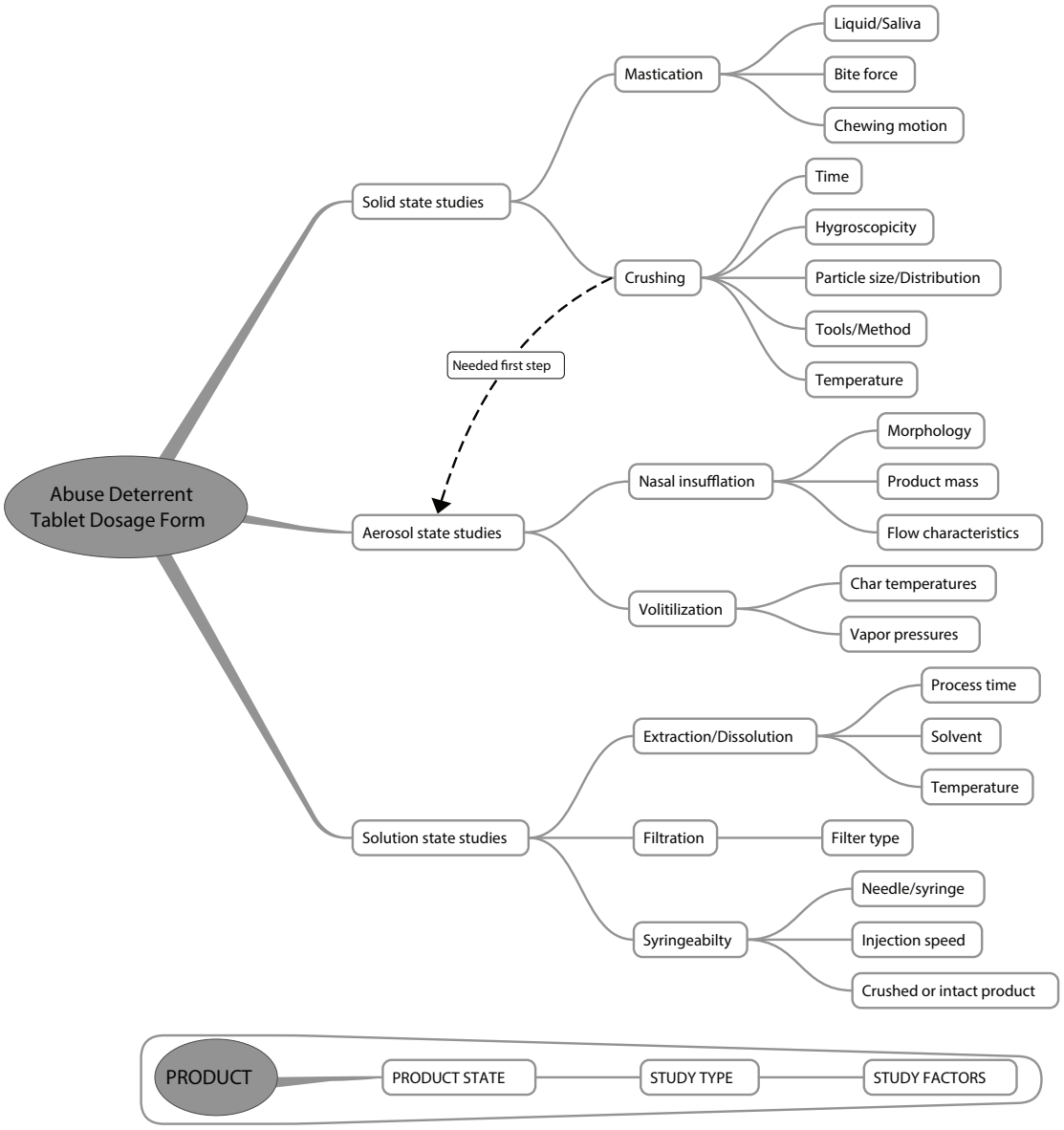

Figure 1: Examples of Category 1 laboratory-based in-vitro manipulation and extraction studies.

Various devices have been used to study the effect of a product to reductions in particle size (spoons, grinders, mortar and pestle). The items chosen for study should be easily obtainable by the average abuser so that it best represents real world abuse conditions. This would include household items that can crush, grind, grate, or otherwise help in reducing the product to a powder. For chewing studies, a method or device should be used that correlates with bite forcing and/or the chewing motion. The ability of product to resist being chewed should be determined not only in the dry state but should also be determined in the presence of a liquid that simulates saliva. For example, the Intac technology by Grunenthal, used to formulate Opana®ER tablets, shows it can resist forces over 500 N without rupture [14], way above the 220 N bite force. However the effect of saliva or other solvents on this strength is not mentioned. This is important as the product is highly composed of the water soluble excipients polyethylene oxide and hypromellose, and the ability to withstand forces may change in the presence of the mouth.

The evaluation of a product's resistance to crushing methods is typically evaluated by looking at particle size distributions after various tamper methods are performed on the product, and comparing it to a reference product manipulated in the same way. For example, a tamper-resistant formulation of Nucynta® ER was compared against an original non-tamper resistant formulation of Oxycontin® to determine ease of reducing each product's particle size [15]. Crushed products produced from each tablet by experienced abusers using any equipment they desired was ultimately passed through varying sieves for particle size analysis. It was determined that the tamper-resistant formulation produced fewer and larger particles compared to the reference product. For drug products likely

to be nasally insufflated, particle morphology and hygroscopicity may be assessed for the product in the crushed state if the flow properties of the resultant powder are thought to be affected by these factors.

Certain factors that can affect the ability of a product to be reduced in particle size should be taken into account and tested for to adequately determine a product's resistance to abuse. Temperature is a major factor that should be studied for its influence on making a product brittle or soft, particularly for products dependent on polymers for crush resistant properties. For example, freezing or submerging in liquid nitrogen a product may be sufficient to bring a polymer below its Tg and form a brittle product that can be easily fractured into small pieces. On the other extreme, high temperatures or even microwaving the product may result in the rubbery state of the polymer and turn the product into a more malleable form. Also, the factor of time should be taken into consideration. Different levels of abuse resistance can be inferred, for example, if two products can be reduced to fine particles of similar size distribution but one takes over an hour to reduce to a powder, and the other only minutes using the same method.

Solution state studies

An ideal tamper-resistant formulation must be able to withstand tampering that result in the product being manipulated by methods that cause easy extraction of the drug or turn the product into a form suitable for other routes such as intravenous injection. Studies that test the resistance of a product under conditions of a solvent are categorized into solution state studies.

Syringeability

Tampering with drug products to heighten and enhance their euphoric effects by administering directly into the blood stream through intravenous injection is well known. For this tampering, the product is often first crushed and mixed with an aqueous solvent, then the resultant mixture may be heated, filtered, and finally drawn up in a syringe for injection. One objective of syringeability studies is to determine the relative difficulty in dissolving and readily forming a solution from a product that can be drawn up through a needle. The quantitative measurement of the force needed to draw up and inject a parenteral product has been a standard measurement for developing a patient friendly product. Similarly, the relative difficulty in drawing up and injecting an extract from an abuse-deterrent dosage form is used as a measure of the product's deterrence capabilities. Also, viscosity measurements of the resultant extract from a product may be appropriate if they can be correlated with syringeability or less likelihood of injection.

The syringeability or "glide-force" determines the ease of the product to be drawn into a syringe and injectability refers mostly to the pressure (force) needed to inject and the behavior of the mixture during this process [16]. For abuse-deterrent studies, the force required for injection of a solution made from the drug product is determined for a given injection rate, through a specific needle gauge and length. Additionally, studies may report only the volume that was able to be drawn up into a syringe or extruded. The study may also go further and determine the drug concentration in the volume obtained. For example, a study of crush resistant oxymorphone ER tablets (Opana® ER) looked at the ability of experienced abusers to make the product into a form abusable by intravenous injection using as much tools, time, and materials they requested [17]. The extract, if produced, was collected by the investigators and the percent yield of extracted oxymorphone was determined as the primary outcome.

Various factors that affect syringeability need to be defined in the study method for accurate determination of syringeability, and for the capability to compare products. These factors include the needle gauge, length, syringe size, injection speed, solution viscosity, and solution temperature. Because these studies involve the drug being mixed first with a solvent, various other factors arise. First, the particle size of the product before the solvent is added must be controlled. Second, the time and agitation used to help dissolve the crushed product needs to be stated. Third, the volume and type of solvents used to extract the drug should vary and be composed of those common in this form of abuse. And last, because the resultant mixture is often filtered to remove undissolved excipients, the effect of syringeability when using different filtering techniques (e.g., cotton plug, cigarette filter, filter needle) can be evaluated for a complete parenteral performance of a product's resistance to this type of tampering.

Extraction and solubility

Abusers use various solvents to extract and concentrate the abusable active ingredient from undesirable components in the dosage form. Therefore, it is required to determine the ability of a dosage form to resist having the active ingredient and components needed for tamper resistance from becoming soluble and extracted from each other. Based on the type of abuse-deterrent formulation under investigation, it may be necessary to test the ease of separating out, neutralizing, or other means known of inactivating sequestered components in the product such as an opioid antagonists or added aversive agents [18].

Test methods may be simple dissolution studies using various solvents and agitation rates. The solvents should have a range of pH, ionic strength, temperature and polarity and include common solvents such as water, vinegar, ethanol and isopropanol [9]. In evaluating the reformulated Oxycontin's® ability to withstand extraction in water, the researchers evaluated the effects of solvent temperature (near boiling and room temperature), particle size (three different fractions), and time (10 min, 60 min, and ≥ 18 hrs) [19]. Additional studies were conducted using aqueous medium at different pHs, household solvents, and more multistep extraction procedures using aqueous and organic solvents. Also, the co-ingestion of prescription drugs, whether intentional or unintentional, with ethanol has been known to accelerate dissolution of active ingredient and been taken advantage of by abusers looking to produce a fast high. The sensitivity to ethanol of certain formulations can be seen with Embeda®, which was shown that in the presence of 40% ethanol the Cmax of morphine was increased 2-fold and tmax shortened from 9 to 4 hours [20]. Therefore, the solubility and behavior of the active drug and excipients to hydroalcoholic solutions should be investigated on these novel formulations.

As with other studies, effect of time should be determined in the ability of the product to withstand extraction. The nature of the product (intact, crushed, etc.) and the effect this has on the study results should also be determined in such studies.

Aerosol state studies

The prevention of an abusable dosage form to nasal insufflation and volatilization is important as these are common methods of abuse. Studies in this category relate to how the product acts to tampering that result in the product being made into a vapor, or into a suspension of fine solids or liquid particles in a gas.

Nasal insufflations'

In our search, nasal insufflation studies were seen only in humans with no in-vitro studies discovered. It is feasible however, to determine in-vitro, the flow characteristics of a crushed and powdered dosage form either by its free-flow characteristics or its flow under a vacuum of constant force similar to the force of inhalation. These studies would eventually need to be correlated with actual nasal inhalation studies later in development. Insufflation studies should determine the effect of particle size and mass of the dose inhaled. For example, Oxecta® was studied to determine the relative abuse potential and safety of the product when abused by nasal insufflations [21,22]. The study was a randomized, double-blinded, 2 way crossover design conducted using 40 non-dependent recreational opioid abusers. Subjects intranasally administered 15 mg of oxycodone, using two 7.5 mg Oxecta tablets and three 5 mg active control tablets (Roxicodone®). The endpoints of the study were to measure drug liking (using a visual analogue scale) at the moment the dose was administered and both overall drug liking and taking drug again, 8 hours post dose. The results of the study showed crushed and nasally administered Oxecta, when compared to the active control product of oxycodone, resulted in lower drug liking scores and more reports of nasal irritation. However, the FDA review cited the study was inadequate as the powder from crushed Oxecta tablets were almost three times the weight of control to the point that unblinding could have occurred, as well as a sequence effect being observed. What was noted was the inability of most subjects to entirely insufflate the Oxecta dose most often because of the nasal passage being blocked with the crushed material. It still remains unanswered if the excipients themselves or the increased mass of powder insufflated lead to the increased adverse events reported for the product. Because a formulation is being tested as it enters the nasal cavity and interacting with the nasal mucosa, any short or long term effects on the nasal tissue from the active component or excipients in the formulation should be considered.

Vaporization

Vaporization of a drug product can be done by first crushing the product, and then placing it onto something that can carry heat but is flame resistant (e.g., aluminum foil) and place this over a heat source such as lighter or candle. As the temperature of the powder increases, the drug is eventually volatilized and smoked. To test product's deterrence to being smoked by vaporization, the ability of the dosage form to either prevent drug vaporization or increase the vapor pressure of the active ingredient must be determined. Therefore, the vaporization temperature compared to the temperature the product begins to char and degrade should be compared, and the formation of harmful pyrolytic substances identified. Vapor pressures may be analytically determined using various methods such as gas chromatography/ mass spectrometry [23].

Discussion and Conclusion

The complete characterization of an abuse-deterrent formulation should be individualized to the specific drug and formulation type. This evaluation should be based on the most common methods of abuse suspected for the drug, and involve testing methods that similar formulation approaches were found susceptible to. Furthermore, as the product becomes marketed and in the hands of abusers, new tampering methods are bound to be developed and the formulation should constantly be tested for its resilience to any new methods. Abusers also develop new ways to administer the drugs (e.g., rectal, parachuting [24]) in their quest for euphoria. These routes and techniques should also be explored if the product becomes highly abused in these fashions. There also still exists a gap in formulations that can deter the most common form of abuse, which is taking multiple tablets and once, such as overdosing. In the future, more novel formulations may develop, and new studies added to the list for abuse liability determination.

With the growing number of abuse-deterrent formulations coming to market, there is now becoming a need for standardized test methods both in-vitro and clinically to help draw conclusions from studies and better determine a product's performance in real world abuse environments.

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