

Fighting a New Drug Epidemic

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Most of us are familiar with drug development research that is focused on getting a drug into the body, and ultimately to a target site, with the intent of achieving maximum drug efficacy. However, there has recently been much attention in designing drug delivery systems that, under certain circumstances, do just the opposite. This new field of research is spawning out of the growing need to combat prescription drug abuse. Every year, since 2002, there is an estimated 1.9 million Americans who become new abusers of prescription pain medications [1]. This problem has become so big the White House has referred to it as an “epidemic” and created a collaborative plan to help reduce the nation’s prescription drug crisis [2].

A variety of different dosage forms (e.g.; tablets, transdermal patches, nasal sprays) are known to be abused. However, prescription opioids analgesics along with central nervous system stimulants and depressants are the class of drugs most commonly associated with prescription abuse [3]. Abusers of these medications are commonly known to modify the original form of the product prior to administration. This “tampering” is typically done to enhance the speed and onset of drug absorption, to increase bioavailability, or to make the product suitable for alternate routes of administration (e.g.; nasal, smoking, injection) [4]. Crushing may also destroy the extended drug release mechanisms in long action tablets, allowing the entire dose to be dangerously released at once. More complex methods of tampering also exist that involve separating and extracting the active drug out of the other product components using a variety of solvents.

To help control tampering and misuse of prescription drugs, the pharmaceutical industry has begun to introduce what most call either abuse-deterrent or tamper-resistant formulations. These formulations are designed to prevent or impede common methods of tampering. These novel formulations utilize chemical and/or physical methods to provide deterrence to abuse [5]. Chemical approaches involve the use of drug antagonists, aversive agents (ingredients that produce unpleasant effects), prodrugs, and enzyme inhibitors. Physical approaches use physical barriers that either shelter the drug behind an insoluble coating, make the dosage form mechanically strong, use highly viscous semisolid materials, or add ingredients that form viscous solutions in an aqueous or hydroalcoholic media. Oral analgesics, particularly opioids, have been the drugs to first be incorporated into such formulations.

While a number of different abuse deterrent approaches have been studied or suggested, there are currently only a handful of approved products on the market. In the past, simple mixed agonist/antagonist products were the common way to make a product less favorable to abuse by alternate sites of administration. Today, the most recently approved products are more complex, and have been designed with specific physical characteristic that provide improved resistance to multiple forms of tampering. One of the first drug products to intentionally use physical approaches was the reformulation of Oxycontin[®]. Abusers quickly found that chewing/crushing the original tablet or co-ingesting it with alcohol allowed the entire drug load to be rapidly released. The newer formulation involves a manufacturing step that renders the tablet into a form that cannot be crushed into a fine powder and also prevents rapid dissolution in alcohol. Other currently approved products and their abuse deterrent mechanisms

include Embeda[™] (protected antagonist core which releases when crushed), Exaglo[®] (hard exterior shell and gelling agents), Oxecta[®] (gelling agents and nasal irritant), Opana ER[®] (crush resistant polymer matrix), and Nucynta ER (increased mechanical resistance to crushing) [6-8]. Additionally, many other products are still in development or in late stage clinical trials.

The development of abuse-deterrent formulations is not without its challenges. To start, the dosage form must be designed to be safe and effective when used appropriately, yet still provide a level of deterrence if misused. These products must therefore be tested for not only efficacy but for tamper and abuse resistance. In-vitro testing methods that can determine a product’s deterrence capacity to different forms of abuse is another challenge. Testing methods that may assess tamper resistance include evaluating particle size reduction methods using common household tools; extraction studies using water and other solvents of varying pH, composition and temperature; syringe ability studies to measure the ease of preparation and injection of a resultant drug extracted mixture; vaporization studies to observe if drug volatilization is impaired; and alcohol dissolution studies using hydroalcoholic solutions to observe the likelihood of accelerated dissolution [9]. Additionally, to specifically make the label claim of abuse deterrence, a product will most likely have to show post marketing clinical data supporting a decrease in abuse. Although costly and time consuming, this information may help determine which types of formulation approaches have the most effect in terms of lowering a products likelihood of being used for nonmedical purposes. To help with the above challenges, the FDA has recently issued a draft guidance outlining how studies should be performed, evaluated, and the label claims allowed based on the results of such studies [10].

The future looks bright for abuse-deterrent formulations as large scale initial research in the “real world” is showing that the prevalence of abuse and tampering is significantly less for these products [11,12]. Tamper-resistant formulations are also being utilized to help combat another national drug problem, the illegal manufacturing of methamphetamine from over the counter nasal decongestant medications [13]. There also lies a big opportunity for research in preventing overdoses resulting from the concurrent ingestion of an excess number of pills, as thus far no approach has yet been successful at this form of abuse. The field of abuse-deterrent formulations is therefore likely to continue growing as the nature of the problem rises, and public attention both in the United States and abroad becomes even further recognized.

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