Hedaya and Aldeeb, J Pharma Care Health Sys 2014, 1:1
DOI: 10.4172/2376-0419.1000e102

Journal of Pharmaceutical Care & Health Systems

Editorial Open Access

The Need for Tamper-Resistant and Abuse-Deterrent Formulations

Mohsen A. Hedaya* and Dana Aldeeb

Department of Pharmaceutics, Faculty of Pharmacy Kuwait University, P.O. Box 24923, Safat 13110, Kuwait

Abbreviations: CNS: Central Nervous System; IV: Intravenous; ADF: Abuse-Deterrent Formulation; ER-Extended Release

The abuse of prescription central nervous system (CNS) active drugs has been increasing with abusers persistently trying to experience the maximum effect of these drugs. The most commonly abused prescription drugs as stated by National Institute on Drug Abuse include CNS depressants (such as barbiturates and benzodiazepines), CNS stimulants (such as amphetamines and methylphenidate), and opioids and morphine derivatives [1]. Although every dosage form has a potential for abuse, oral medications in the form of tablets and capsules are the most popular type of dosage form that are abused and therefore easily available to those looking to abuse prescription drugs [2]. To achieve the maximum drug effect, abusers usually tamper with drug products prior to administration. Prevalent tampering methods of abused prescription drugs include crushing and extraction to make the active ingredient suitable for use by alternative routes such as chewing (mastication), snorting (insufflation), inhalation, and intravenous (IV) injection, so euphoria is enhanced. Tampering methods that reduce particle size such as crushing will allow faster dissolution that makes IV administration possible and will allow easier nasal insufflation. Extended release (ER) prescription drug products intended to treat chronic pain is very attractive to abusers because these dosage forms contain large dose of the drug as they are designed to deliver the drug over extended period of time [2]. However the controlled release mechanism can be destroyed by crushing or chewing the tablet leading to releasing most of the drug contents over a short period of time and leading to high maximum blood drug concentration that can achieve the abuser's desired "reward" of euphoria. Another known tampering method is extraction of the desired pharmaceutical ingredient (s) by mixing the product with a suitable solvent (e.g. water, soda, alcohol), allowing the drug to solubilize, and to be separated from the other undesirable and insoluble components. The extracted drug can be injected or administered by inhalation, smoking or snorting. Tampering with dosage forms followed by administration of the drugs in large quantities can create rapid increase in systemic drug concentration and lead to various health hazards or even death from overdoses, accidents, illness, and other causes [3]. Therefore, new regulatory and pharmaceutical companies efforts are directed to develop formulations that are less convenient or less desirable to abusers. Drug abusers are different in their experience with drug tampering ranging from the novice who only abuses the drug in its original dosage form to the experienced who knows the physicochemical properties of the drugs and can manipulate all dosage form including the tamper resistant formulations. So, the need is to intensify the effort for designing formulations that can deter abuse, and to resist common methods of tampering by as many drug abuser as possible.

The concept of developing an abuse-deterrent formulation [ADF] is similar to that of developing new formulation. General goals include producing drug products that are safe and effective for the intended population, produce no serious harm to the potential abuser, and economically feasible medication. The only additional component added to the development of an ADF is that it must also deter abuse by potential abusers [4]. The inherent characteristics of some drug formulations or methods of drug delivery support the intention of deterring abuse such as the extended release oral formulations, sustained-release depot injectable formulations, subcutaneous implant, and transdermal patches because they usually achieve low systemic drug concentration and produce mild drug effect which is usually not desired by abusers. However, many formulations have been specifically designed to resist tampering and deter abuse and are currently in the market with few more are in the pipeline. There are two main formulation approaches for manufacturing tamper-resistant and abuse-deterrent CNS active drug products. The first approach involves modification of the formulation physical characteristics to produce products with rigid structure, products with insoluble coating, and products that cause gel formation. While the second approach involves modification of the formulation contents by using agonist/antagonist combination, prodrugs, enzyme inhibitors, and aversive agents strategies.

Abuse-deterrent products with rigid structure are products that are so hard and unyielding to chewing and crushing into powder even by heavy hammer blows, and in addition to being hard products, they can also be insoluble in common solvents and turns into a viscous gel if mixed with liquid. This specific mechanical stability is created by the combination of specific excipients together with a unique manufacturing process. The technology used to formulate these products is called INTAC™ which is an advanced tamper-resistant formulation technology invented and developed by the German company "Grünenthal" and it is the leading tamper-resistance technology nowadays. INTAC™ is designed to deter non-oral routes of abuse such as intranasal and IV methods of abuse [5]. Oxymorphone (Opana®) is a newly approved abuse-deterrent formulation that contains oxymorphone HCl and has the Grünenthal Group INTAC™ Technology properties. This product preserves the ER characteristics of the medication while imparting crush-resistant properties [4].

Another strategy is to provide a physical barrier by using an insoluble coating or shell placed on the exterior of the product. Additionally, the whole product matrix can be formulated of a material that is relatively inflexible and stiff. Also, microparticles (10–3,000microns in diameter) that are composed of a material that is either slowly soluble or not soluble in water and contain the drug that is homogeneously dispersed within them can be used. This formulation design prevents quick release of a substantial portion of the drug even if the physical integrity of the formulation is compromised by chopping with a blade or crushing for the purpose of ingestion or inhalation. Also, easy extraction is limited by requiring a multi-step procedure using both aqueous and organic solvents [2]. Drugs that are suitable for this technology include those

***Corresponding author**: Mohsen A. Hedaya, Pharm.D., Ph.D. Department of Pharmaceutics, Faculty of Pharmacy Kuwait University, P.O. Box 24923, Safat 13110, Kuwait; Tel: +965 99004873; E-mail: mhedaya@hsc.edu.kw

Received April 23, 2014; **Accepted** April 25, 2014; **Published** May 05, 2014

Citation: Hedaya MA, Aldeeb D (2014) The Need for Tamper-Resistant and Abuse-Deterrent Formulations. J Pharma Care Health Sys 1: e102. doi:10.4172/2376-04191000e102

that are currently formulated as sustained or controlled release such as oxycodone [6]. An oral prolonged-release formulation of morphine sulfate for once-daily dosing has been developed by Egalet company in Denmark. This is an abuse-deterrent, prolonged-release erodible matrix (ADPREM®) covered by water-impermeable non-erodible shell [7].

Products that cause gel formation aim to prevent the CNS active ingredient from being abused parentally by adding substances that form gelatinous mixture when the tablet is mixed with a common solvent such as water or alcohol. Examples of these gelling agents are acacia, alginic acid, bentonite, and gelatin. The formation of this gelatinous mixture makes the process of extraction and drawing the drug into a syringe for parenteral administration difficult. Capsules with high viscosity matrix that is water insoluble can also be used for the same purpose [4]. Studies suggested that formulations prepared using this strategy exhibit certain characteristics that make them less attractive to abusers [4,8]. Oxycodone Controlled Release products are very popular among recreational drug abusers for use orally, by inhalation or smoking. The Oxycodone product (Remoxy®) was formulated as a hard gelatin capsule of high viscosity matrix that is water insoluble. The studies of this product suggested that it is safe, effective and deter abuse [4,8]. Also, OxyContin® is an oxycodone product in the form of extended release tablet with a plastic-like polymer that transforms into a viscous gel in the presence of common solvents.

Combining CNS active drug agonist with its antagonist in one formulation is an approach used for deterring abuse. The antagonist is selected to have poor bioavailability after oral administration or is formulated to be released slowly from the intact dosage form, but rapidly released if the dosage form is crushed or chewed. The role of incorporating the antagonist is to prevent tampering with the product to inject the agonist. This is because when the agonist/antagonist combination is injected, the effect of the antagonist is no longer impeded by low oral and low sublingual absorption, or slow release, and the antagonist effect will be sufficient to eliminate the euphoria or produce frank withdrawal symptoms. Suboxone® is a combination of the partial opioid agonist-antagonist buprenorphine and the opioid antagonist naloxone in 4:1 ratio. This product is available as sublingual tablets and sublingual film coated tablets. Buprenorphine has high sublingual bioavailability but poor oral bioavailability because of its extensive presystemic metabolism, while naloxone has no sublingual absorption and very little oral absorption [4]. Another example is Embeda® which is a formulation designed to deter abuse by offering a pharmacological barrier in the form of sequestered opioid antagonist. It consists of a combination of spheroidal pellets of morphine sulfate, an opioid receptor agonist, each surround an internal core of naltrexone hydrochloride, a μ-opioid antagonist, at a ratio of 100:4. The morphine pellets have an outer-most layer of an extended release polymer that provides the slow release of the opioid. The sequestration of naltrexone inside the pellets core prevents its unintentional release and subsequent absorption. Naltrexone does not have significant effect when taking the intact dosage form, while significant antagonistic effect is produced when the dosage form is crushed before ingestion or after injecting the extract [2,4,8].

Other pharmacological approaches that modify the formulation content include the use of prodrug which is a pharmacologically inactive moiety that can slowly form the active drug form in vivo after ingestion. Although the slow formation rate of the active form is enough for the drug to produce its desired effect for the treatment of chronic pain, these formulations are not attractive to abusers who are looking for intense drug effect after administration [9]. The hard capsule product, Vyvanse® (lisdexamfetamine dimesylate), approved for the treatment of attention deficit hyperactivity disorder, is a conjugate of dextroamphetamine and L-lysine by amidic linkage, which requires a biotransformation step to become active by being metabolized by first-pass intestinal and/or hepatic metabolism into dextroamphetamine. Another pharmacological approach involves the addition of a metabolizing enzyme inhibitor in formulations of drugs that are metabolized in vivo to more potent metabolite, such as oxycodone which is metabolized in the body to the active metabolite oxymorphone which is eight times more potent than the parent drug. The enzyme inhibitors (e.g. fluvoxamine is inhibitor for oxycodone metabolism) interfere with the metabolic activation of these drugs, which can prevent or reduce their abuse. Usually, the enzyme inhibitor would be sequestered in the formulation in the same way of how an opioid antagonist can be sequestered in a dosage form. So, the inhibitor will have no effect if the dosage form is used by ingestion, but the inhibitor effect will be significant if the dosage form is crushed or extracted with solvents. While the use of the aversion approach involves the addition of a substance that produces some type of unpleasant effect in addictive patients who ingest tampered CNS active-drug products [9]. Examples of these ingredients are emetic agent (ipecac), diuretic, flushing agents (niacin) or irritant (capsaicin). The aims of using these additives are to cause increased burning and irritation to the nasal passages when the tablet is crushed and nasally snorted, and to decrease multiple tablet swallowing as a consequence of experiencing uncomfortable symptoms [4].

It is crucial that manufacturers and researchers stay current with trends regarding which drugs are being abused, how they are being abused, and the tampering methods used to get "high". This is important for developing new designs, and utilizing new approaches in formulating abuse deterrent dosage forms. Abuse-deterrent products should never be considered abuse-proof, because sophisticated methods to "beat" these formulations are likely to be quickly found on the internet by those abusing prescription medications, almost as fast as they arrive on the market. Trying to stay one step ahead will help drive further research that may significantly impact prescription drug abuse. As ADFs for frequently abused medications become more available, prescribers can expect liability to change. Those who prescribe conventional products that are easier to tamper and abuse, may be forced to document why they prefer these over new, safer formulations.

Acknowledgments

I would like to thank pharmacist Dana Adeeb for providing valuable information while preparing this editorial.

References

1. National Institute on Drug Abuse, National Institutes of Health (2011). Commonly Abused Prescription Drugs Chart.
2. Mastropietro DJ, Omidian H (2013) Current approaches in tamper-resistant and abuse-deterrent formulations. Drug Dev Ind Pharm 39: 611-624.
3. National Institute on Drug Abuse, National Institutes of Health (2012) Easy to read drug facts.
4. Moorman R, Motycka CA, Inge LD, Congdon JM, Hobson S, et al. (2012) A review of abuse-deterrent opioids for chronic nonmalignant pain. Pharm Therap 37: 412-413.
5. Grunenthal Group (2012) INTAC™ technology fact sheet.
6. Hirsh JC, Fleming AB, Rariy RV, Klibanov AM (2004) Abuse-deterrent drug formulations. US patent 7771707.

7. Raffa RB, Pergolizzi JV, Mu˜niz E, Taylor R, Pergolizzi J (2012) Designing opioids that deter abuse. Pain Res Treat: 1-10.

8. Raffa RB, Pergolizzi JV Jr (2010) Opioid formulations designed to resist/deter abuse. Drugs 70: 1657-1675.

9. Nathaniel K (2008) Abuse-deterrent opioid formulations: Are they a pipe dream?. Curr Rheumatol Rep 10: 11-18.