Al-Rafidain J Med Sci. 2024;7(2):1-7.
DOI: https://doi.org/10.54133/ajms.v7i2.1277

Review Article

Abuse Deterrent Dosage Forms: Approaches, Advantages and Limitations

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Received: 30 July 2024; Revised: 10 September 2024; Accepted: 20 September 2024

Abstract

Background: Abuse-deterrent formulations (ADFs) are dosage forms designed to prevent or discourage the misuse of prescription drugs, particularly opioids. They achieve this aim by either minimizing the benefit of tampering with the dosage form or making it challenging to change this dosage form. Therefore, one of the priorities for public health is to develop dosage forms that have abuse-deterrent formulations. The escalation in the prescription of opioids has led to a surge in their abuse or misuse, resulting in a high mortality rate. ***Objectives***: This review article explores drug abuse methods among addicted individuals and lists the most frequently abused drug classes. Furthermore, this review concentrates on understanding the most prevalent technologies used to deter abuse of prescribed opioid drugs. ***Methods***: The search included online published databases from PubMed, Google Scholar, Research Gate, Science Direct, Elsevier, and others. The objective was to collect as much information as possible from articles using the keywords “abuse deterrent formulations and abuse deterrent technology." ***Conclusions***: Physical-chemical barriers and agonist-antagonist formulations are available as marketed drugs as well as aversive agents’ formulations. Each of these types can inhibit or reduce specific cases of opioid misuse. Although the success of these products mostly relies on robust formulation strategies, it also requires a thorough understanding of their benefits and broad adoption in the market.

Keyword: Abuse deterrent formulations, Abuse deterrent technology, Aversive agent, Drug abuse, Polyethylene oxide.

أشكال الجرعة الرادعة لسوء استخدام الدواء: النهج والمزايا والقيود

الخلاصة

الخلفية: التركيبات الرادعة لإساءة الاستخدام (ADFs) هي أشكال جرعات مصممة لمنع أو تثبيط إساءة استخدام الأدوية الموصوفة، وخاصة المواد الأفيونية. يتحقق هذا الهدف إما عن طريق تقليل فائدة العبث بشكل الجرعة أو جعل تغيير شكل الجرعة هذا أمرا صعبا. لذلك، تتمثل إحدى أولويات الصحة العامة في تطوير أشكال جرعات تحتوي على تركيبات رادعة لإساءة الاستخدام. أدى التصعيد في وصف المواد الأفيونية إلى زيادة في تعاطيها أو إساءة استخدامها، مما أدى إلى ارتفاع معدل الوفيات. **الأهداف**: تستكشف مقالة المراجعة هذه طرق تعاطي المخدرات بين الأفراد المدمنين وتسرد فئات المخدرات الأكثر تعاطيا. علاوة على ذلك، تركز هذه المراجعة على فهم التقنيات الأكثر انتشارا المستخدمة لردع تعاطي العقاقير الأفيونية الموصوفة. **الأساليب**: تضمن البحث قواعد بيانات منشورة عبر الإنترنت من PubMed و Google Scholar و Research Gate و Science Direct و Elsevier وغيرها. كان الهدف هو جمع أكبر قدر ممكن من المعلومات من المقالات باستخدام الكلمات الرئيسية "تركيبات ردع إساءة الاستخدام وتكنولوجيا ردع إساءة الاستخدام". **الاستنتاجات**: تتوفر الحواجز الفيزيائية والكيميائية وتركيبات مضادات الناهضات كعقاقير مسوقة بالإضافة إلى تركيبات عوامل مكروهة. يمكن لكل نوع من هذه الأنواع أن يمنع أو يقلل من حالات معينة من إساءة استخدام المواد الأفيونية. على الرغم من أن نجاح هذه المنتجات يعتمد في الغالب على استراتيجيات صياغة قوية ، إلا أنه يتطلب أيضا فهما شاملا لفوائدها واعتمادها على نطاق واسع في السوق.

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Article citation: Mohammad HT, Omar TA. Abuse Deterrent Dosage Forms: Approaches, Advantages and Limitations. *Al-Rafidain J Med Sci*. 2024;7(2):1-7. doi: https://doi.org/10.54133/ajms.v7i2.1277

INTRODUCTION

Tablets are the most common type of solid oral dosage form, and they come in a variety of forms, from simple dosage forms with rapid release to complicated modified-release systems [1, 2]. All dosage forms have the potential for abuse, but oral dosage forms are the most commonly abused. This is not surprising, since the most commonly used dosage form is the tablet, which makes it simple for someone to abuse prescription drugs [3]. It's important to note that certain drug classes are more prone to drug abuse than others. The National Institute on Drug Abuse lists opioids, CNS stimulants such as methylphenidate and amphetamines, and CNS depressants such as benzodiazepines and barbiturates as the top three drug classes [4,5]. According to the US Food and Drug Administration (FDA), one of the priorities for public health is ensuring the development of solid oral dosage forms with abuse-deterrent formulations (ADFs) [6-8], which encourage pharmaceutical companies to create ADFs [9, 10]. Since prescription drug abuse and misuse have spread all over the world [11], resulting in a growing number of deaths [12,13], Western countries have seen an increase in physicians' willingness to prescribe drugs like opioids for persistent pain unrelated to cancer over the past 20 years [14,15]. Regrettably, the surge in opioid prescriptions has coincided with a surge in the following categories: illicit use or misuse (defined as any deviation from the prescribed usage of prescription medications) [16]; abuse (the deliberate possession and use of a

prescribed opioid for non-medical purposes, such as euphoria or altered state of consciousness) [17]. Both lethal and non-lethal overdoses of pharmaceutical opioids occur [14,18-22].

Strategies to Minimize Drug Abuse

Abuse and misuse of drugs are complicated, multifaceted issues. In order to promote the safe and effective use of drugs, addressing them necessitates a multiple risk management plan that incorporates every stakeholder, including patients, healthcare providers, employers, the Centers for Disease Control (CDC), the US Food and Drug Administration (FDA), pharmaceutical companies, and the federal, state, and local governments [23]. These strategies can include abuse deterrent formulations of ADFs, patient education, healthcare providers, programs for monitoring prescribed medications, programs for recovery from addiction, FDA guidelines for the ADFs industry, minimizing the availability of non-ADFs and healthcare policy [24].

Abuse Deterrent Formulations (ADFs)

Abuse-deterrent formulations (ADFs) are dosage forms that prevent prescription drug misuse by reducing the benefits of manipulating the dosage form or making it more difficult to alter the dosage form [12]. In order to change or manipulate the drug delivery properties of opioid drugs, abusers often crush or grind the medication into smaller particles or tiny powders, dissolve the medication or the manipulated medication in solvents like water and alcohol, or heat the medication above the point of vaporization temperature of the drug's active ingredient. These manipulative techniques make it possible to abuse drugs later on by injecting, inhaling, or ingesting them [25-29]. Making a product less prone to abuse and misuse is the main objective of an ADF [30]. Substances that can stop, deter, or lessen the euphoria, pleasure, or elevation that abusers are seeking can also fall under this category. Additional challenges include ensuring product safety and efficacy when used as prescribed. If possible, the optimal dosage form should be resistant to all established techniques of abuse and manipulation. It is unusual for a single dosage form to be equally resistant to every abuse scenario. Therefore, based on locally reported studies, a dosage form should at least address the established or predicted methods of abuse for the effective medication [31]. For instance, a formulation that is crush-resistant rather than one that inhibits parenteral injection would be more appropriate if a medication has been shown to be widely abused through sniffing [31]. In the future, there may be over-the-counter drug formulations with abuse-deterrent properties that can help combat the abuse of pseudoephedrine products and the recreational abuse of cough products containing dextromethorphan [4].

Abuse-deterrent Formulation Technologies

Drug formulation technology, an important component of pharmaceutics and healthcare, is essential for creating pharmaceutical formulations that deliver medications to patients in a safe and effective way [32,33]. Furthermore, the selection of dosage form is a critical factor in drug formulation, with tablets and capsules being the most commonly used orally [34]. These orally administered dosage forms are a mixture of active pharmaceutical ingredients (APIs) and excipients that need to be properly blended and/or granulated in order to assure the production of proper drugs [35,36]. As a result, formulation scientists rely on excipients to improve pharmaceutical formulations [37]. Similar principles apply when creating an abuse-deterrent formulation (ADF), with the main objective being the creation of a medication that is both safe and effective for the target market. A further requirement for the creation of an ADF is that it must prevent abuse by possible abusers by using additional components [33]. Furthermore, ADFs differ in their abuse-deterrent features because of variations in the technology and strategies used to develop them [23,38]. The Food and Drug Administration (FDA) has outlined six main groups of abuse-deterrent technology, just three of which are currently available on the market [7,39,40].

Chemical or physical barriers

The use of fats or waxes in the coating, or coatings that are either sparingly soluble or insoluble in ethanol, can create chemical barriers [41]. As a result, they prevent water, alcohol, and other solvents from penetrating and dissolving the active ingredient, making it more difficult to sniff or inject IV [38,42]. These barriers also serve to deter ethanol dose dumping, abuse, and solvent extraction [41]. Creating an extremely strong matrix from the dosage form, which can endure grinding and other attempts at particle size reduction [43] and damage from household equipment like coffee bean grinders [42], not only improves mechanical strength but also gives the dosage form resistance to extraction by forming a gel when its surface comes into contact with water or other solvents used for extracting the active pharmaceutical agent(s) [40,44] Manufacturers frequently use high-molecular-weight polymers like polyethylene oxide [45] and innovative manufacturing techniques like hot melt extrusion and curing to change the physical state of the dosage form. Strong coatings around internal particles, like drug-loaded granules, can also improve crush resistance [43]. The main focus of these methods is on using fillers like polyethylene oxide, sucrose acetate isobutyrate, lipids [46, 47], ion exchange resins, foaming agents [48], and ceramic nanoparticles. Many ADFs, including OxyContin® and Nucynta®, utilize the popular strategy of adding polyethylene oxide to the medication [49-51]. Finally, ADFs produced through chemical/physical barriers make it challenging to abuse through intravenous injection [52,53].

Agonist and antagonist

In an effort to make opiates less abused or reduce the euphoria caused by opioids when administered via IV injection or nasal snorting [54], naloxone was first added directly to the formulation in order to stop parenteral overdose. Moreover, the high first-pass metabolism of naloxone results in its extremely poor bioavailability, rendering it ineffective when taken orally. Despite the oral bioavailability of naltrexone and other opioid antagonists,

their absorption from the GI tract necessitates their isolation or sequestration in a formulation. Naltrexone has no major effect when taken in its intact form but has a considerable antagonistic effect when crushed or injected [55]. Non-abusers can safely take the medication as prescribed, as a sequestered antagonist only releases upon abuse. Techniques such as coating antagonists with polymers that impede their release and dissolution throughout the gastrointestinal tract can isolate and sequester the antagonist. If an ADF had orally bioavailable sequestered antagonists, it would effectively prevent nearly all efforts at drug abuse, in which the antagonist can be released and absorbed while the product's integrity is damaged. While the use of formulations containing antagonists with low bioavailability is primarily limited to the prevention of injection and nasal insufflation abuse, the antagonist's capacity to evaporate and enter the lungs is probably what determines how well it prevents smoking of any kind of product [43,56,57].

Aversive chemicals

They are substances that can be added to the ADFs that cause undesirable side effects if the dosage form is altered or exceeded; for instance, if crushed and snorted, the formulation may contain a material that irritates the nasal mucosa [40,58,59]. People frequently refer to these substances as "aversive agents." Typically, a formulation would enclose an aversive chemical, capable of producing the desired effect at extremely low dosages, and release it only in cases of improper manipulation. Researchers have suggested chemical agents like zinc sulfate, cephaeline (found in ipecac syrup), and ferrous sulfate as potential deterrents in ADFs. These substances can cause nausea or vomiting. Researchers have also investigated materials that irritate tissue and mucous membranes to prevent nasal insufflation. For instance, red pepper extracts containing capsaicin analogs or surfactants like sodium lauryl sulfate or poloxamers may cause a burning or stinging sensation when in contact with the nasal mucosa. If inhaled or injected parenterally, these discomforting effects can also occur in other tissues, such as the lungs or skin. Certainly, bitter-tasting chemical agents can serve as deterrents against the nasal and oral abuse of crushed tablets. Some examples of bitter aversive agents include menthol, peppermint/spearmint oils, sour citrus fruit flavors, denatonium benzoate, and sucrose octaacetate. These substances discourage misuse by causing an unpleasant taste experience [4,33,60-62]. Table 1 provides a summary of aversive agents [49]. Therefore, the primary objectives of aversion technology are to decrease the overconsumption of tablets and to intensify the challenge of extracting the active ingredient, thereby preventing its misuse via the IV route. When the tablet is crushed and snorted through the nose, it causes more burning and irritation to the nasal passages compared to previous formulations [33].

Table 1: Summery of aversive agents

Type of aversive agents	Examples	Undesirable pharmacological effect
Bittering agent	Denatonium benzoate, Eucalyptus oil, Menthol, or Sucrose octaacetate	Reduces abuse through oral or inhalation by creating a bitter taste.
Emetic agent	Cephaeline Ipecac Zinc sulfate	Induces vomiting if consumed in excess of the recommended dosage.
Gelling agent	Carbomers Polyvinyl alcohol PEO	Induce irritation in the nose when they gel and come into contact with mucous membranes.
Irritant agent	Capsaicin Citric acid Surfactants	Causes discomfort and irritability to the abuser's respiratory passageway tissue and/or mucous membrane
Laxative agent	Aloin Bisacodyl, Casanthranol, Castor oil, or Senna	Involves increased bowel movements and/or loosening of stools if more than the recommended amount is consumed.
Staining agent	Beta-Carotene Food Drug and Cosmetic Color Other dyes and lakes	When handling or administering a staining agent, stain the tissues that come into contact with it.
Vasodilator	Niacin	Produce effects of itchiness, sweating, and a hot flushes syndrome.

Nontraditional drug delivery methods

Some drug delivery systems, like depot injections and implants, are designed to be abuse-deterrent [63]. For instance, a depot injectable formulation with sustained release or a subcutaneous implant can be challenging to alter for abuse\misuse [64] and difficult to work with once placed internally by medical professionals [42].

Prodrugs or new molecular entities

Prodrug technology has been used for opioid analgesics as well as for controlled drugs that have the potential to be abused [65-67]. This strategy specifically seeks to restrict the release of the active medication in the gastrointestinal (GI) tract. The active drug's release is limited when administered parenterally (via intranasal, inhalation, subcutaneous, or intravenous administration), as this avoids exposure to GI tract enzymes.

The active drug could only be formed through oral administration. If the gastrointestinal enzymes responsible for releasing the active medication can be fully used, the conversion of an inactive prodrug to its active form may be restricted, thereby preventing oral overdose [59,68,69]. Figure 1 illustrates the characteristics and actions of the perfect opioid prodrug that deters abuse [70].

Combinations

To produce greater deterrence, a single formulation can incorporate different strategies. For example, combining a gel-forming substance and nasal irritant with high mechanical strength would result in a product that is resistant to extraction, hard to crush, and discourages nasal insufflation [43].

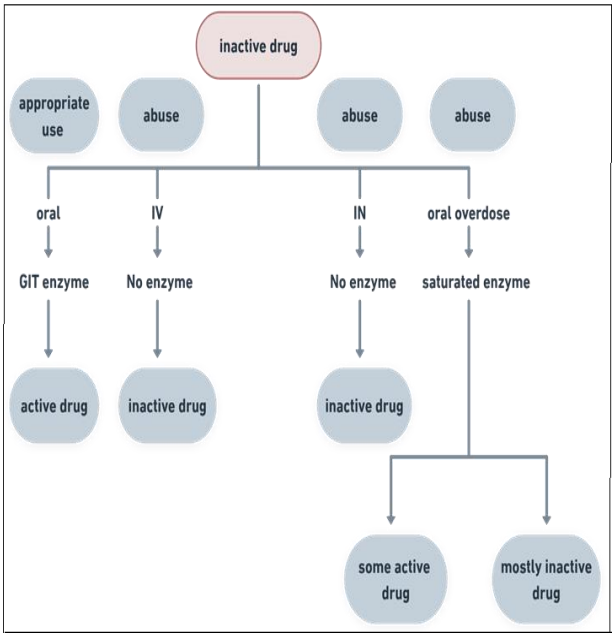

Figure 1: Actions of abuse deterrent prodrug.

Advantages and Limitations of ADFs Technology

Each ADF technology has its own set of advantages and limitations. Physical-chemical barriers could prevent the chewing, crushing, or solvent extraction without side effects in normal patients but fail to avoid the misuse of whole tablets. Furthermore, agonist/antagonist combinations can be designed to exhibit clinical activity only when subjected to manipulation such as crushing, chewing, or dissolving but fail to avoid the misuse of whole tablets [52]. Adding aversive substances to opioids can induce undesirable adverse effects when the opioids are manipulated or taken in higher doses; therefore, it may deter abuse by grinding or chewing, but the presence of an undesirable effect may not be enough to discourage a determined abuser. Furthermore, delivery systems can provide resistance against abuse, but they may still be able to remove the opioid from the formulation. Finally, a prodrug could be undesirable to abuse via IV or inhalation routes if a prodrug has no opioid activity until it becomes active in the GI tract. It's still simple to take too much medication orally [71].

Marketed Products

FDA approval has been granted for ten abuse-deterrent dosage-form product formulations [72]. Nine of these formulations feature extended releases, while only one is available for immediate release (IR). The drugs include Hysingla ER, MorphaBond ER, Xtampza ER, Arymo ER, Vantrela ER, RoxyBond (IR), Embeda®, Targiniq ER, Troxyca® ER, and OxyContin® [9,73-77] (Table 2).

Table 2: A list of abuse deterrent drugs

Drug [23,73, 93,40]	ADF technology	Approval year	Pharmaceutical company
Oxycodone			
OxyContin® [59,94]	Physical and chemical barriers	2010	Purdue Pharma L.P.
RoxyBond® [95]	Physical and chemical barriers	2017	Inspirion Delivery Sciences, LLC, USA
Troxyca® [96]	Agonist/antagonist (naltrexone) combination	2016	Pfizer, New York, USA
Targiniq® [49]	Agonist/antagonist (naloxone) combination	2014	Purdue Pharma L.P.
Xtampza® [97,98]	Physical and chemical barriers	2016	Collegium Pharmaceuticals, Canton. USA.
Hydrocodone			
Hysingla® [99]	Physical and chemical barriers	2014	Purdue Pharma L.P.
Vantrela® [49]	Physical and chemical barriers	2017	Teva Pharmaceutical, North Wales, PA, USA
Morphine			
Arymo® [100]	Physical and chemical barriers	2017	Egalet, Wayne, PA, USA
Embeda® [59]	Agonist/antagonist (naltrexone) combination	2014	King Pharmaceuticals
MorphaBond® [101,102]	Physical and chemical barriers	2015	Daiichi Sankyo, NJ, USA.

Out of the ten approved ADFs, three are combinations of agonists and antagonists, and seven depend on the physical/chemical barrier principle [78-80]. As a result, approximately 70% of the pharmaceutical products that are currently approved prevent abuse by using physical barriers [51,60,81], and these barriers offer resistance to manipulation via the production of viscous gels in the presence of a solvent (alcoholic or aqueous), which decreases the efficiency of solvent extraction or increases the mechanical strength [40,44]. Some of the excipients that have been used to make chemical or physical barriers are foaming agents, carbomers, xanthum gum, polyethylene oxide, sucrose acetate isobutyrate, and hydroxypropyl methylcellulose [49]. Among these, polyethylene oxide, also known by its brand name Polyox®, is the excipient that is most frequently used in ADF products. It provides the formulations with chemical and physical barrier properties. Of the ADF products that have been approved, three are based on Polyox® (OxyContin®, Hysingla® ER, and Arymo® ER) [82-84]. Polyethylene oxide (PEO) is a non-ionic, non-toxic [85], not absorbed via the gastric and intestinal tract, and hydrophilic polymer with a molecular weight range of 100,000 to 7,000,000 [86-88]. PEO is thermoplastic, free-flowing, and has excellent compressibility. PEO has a melting point that ranges from 63 to 72 °C based on its molecular weight. When hydrated, PEO possesses an extensive capacity for swelling and creates viscous gels quickly, and when heated over its point of melting, PEO softens and creates a viscous stickiness mass. When this mass cools down, it will solidify into a solid composite with increased hardness and smashing strength [89]. When solvent extraction is applied to PEO, its gel-forming characteristics result in the creation of a viscous

gel that hinders injectability and syringebility [84,90,91]. PEO is a frequently used ingredient in pharmaceutical manufacturing because of its physical, chemical, and thermal stability, such as in osmotic pumps, controlled-releasing, gastro-retentive systems, hydrophilic matrices, and now abuse-deterrent formulations [92].

Conclusion

Some pharmaceutical companies are developing brain-affecting drugs, such as opioids, which encourage drug abuse. If physicians want to provide better care for patients who suffer from persistent nonmalignant pain, for example, they must be aware of the properties of these drugs. Therefore, it is of interest to develop pharmaceutical formulations that are both safe and effective and possess the ability to deter drug abuse. Different formulation technologies have been developed that include the use of chemical\physical barriers and drug agonist\antagonist techniques. Using antagonists has proven to be a successful strategy, leading to the introduction of several drugs containing them into the market. However, the use of aversive substances has sparked some debate because of the associated risks for patients. Furthermore, prodrugs mitigate the effects of ingesting large doses by saturating the enzymes that facilitate their activation. However, each type of formulation technology presents its own set of challenges and limitations. Finally, one of the most common excipients used in abuse formulations is a polymer, such as polyethylene oxide.

Conflict of interests

No conflict of interests was declared by the authors.

Funding source

The authors did not receive any source of fund.

Data sharing statement

N/A

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