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REVIEW ON RECENT ADVANCEMENTS IN TECHNOLOGIES FOR OPIOID ABUSE-DETERRENT FORMULATIONS AND REGULATORY REQUIREMENTS

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ABSTRACT

Chronic pain arises from several diseases and conditions. The issue of inappropriate utilization of crucial opioid medicine has been a subject of significant discussion over the past two decades, particularly in relation to its use for long-term management of chronic pain. Abuse-deterrent formulations are essential components of comprehensive strategies for mitigating the dangers associated with opioids. These formulations reduce the attractiveness and addictive characteristics of opioids by limiting their ability to be absorbed by the body. This reduces the attractiveness and motivations for abusing modified opioid prescriptions, and also presents difficulties in extracting the opioid component for use in different ways. This article analyzes several regulatory measures, anticipated requirements for obtaining licenses for abuse-deterrent formulations, and ongoing efforts to develop opioid abuse-deterrent formulations as potential solutions to address the opioid abuse epidemic. Given the gravity of the worldwide opioid crisis, it is imperative for different regulatory bodies to collaborate in order to protect society from the opioid pandemic. This entails the implementation of a comprehensive policy for the prescription of opioid medications to patients, the conduction of evaluations to assess the probability of addiction, and the enhancement of efforts to approve only opioid drugs that are specially designed to mitigate abuse.

KEYWORD: Abuse, Abuse Deterrent Technology, Opioid, Overdose, Regulatory.

1. INTRODUCTION

Chronic pain disorders affect a greater percentage of the worldwide population, approximately 20-30%, than the combined prevalence of heart disease, cancer, and diabetes. Figure 1 provides a thorough representation of the global population's vulnerability to chronic pain. In the last two decades, substantial research in pain therapy has led to the discovery of groundbreaking opioid medications that efficiently address chronic pain and other therapeutic conditions. Prescription opioid analgesics are the primary method of using medication to treat pain, and they can be given in many forms and by various innovative methods.[1,2]

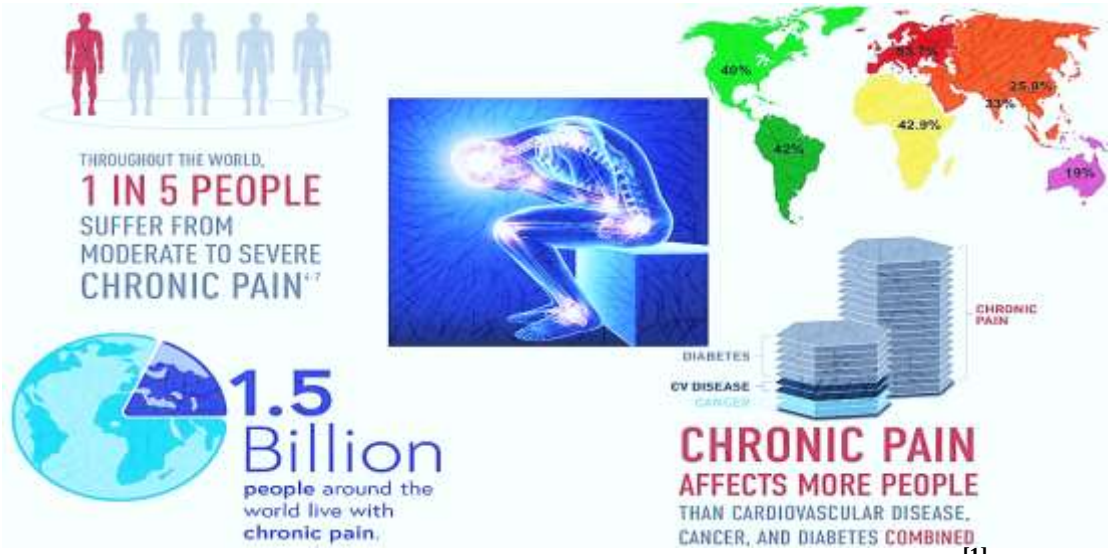

Fig. 1: Overview of chronic pain impact on global population.[1]

Credit for the figure: Patel J, Patel R. Advancement in Opioid Abuse-deterrent Formulation Technologies and Regulatory Expectation. Curr Drug Res Rev. 2023 Dec 19.

Chronic pain is a long-lasting medical condition that can linger for weeks, months, or even years. It is an outcome of various diseases and disorders, including cancer, surgeries, and other conditions. The problem of improper utilization of vital opioid medication has been a topic of intense deliberation during the last two decades, in conjunction with its application for the extended treatment of persistent pain. The initiation of this conversation was prompted by worries surrounding the potential deleterious effects of opioids, a dearth of comprehensive knowledge regarding their long-term ramifications, and the peril associated with their incorrect utilization and misuse. More precisely, the growth of the opioid market has led to increasing health problems and substantial socio-economic difficulties on a global scale. Drug consumption undermines the essential components of society, leading to death, abuse of

children, sexual and domestic violence, increased criminal behavior, and a lack of peace and security for women and children [Figure 2].[1,2,3,4]

Fig. 2: Societal impact of drug abuse crisis on society.[1]

Credit for the figure: Patel J, Patel R. Advancement in Opioid Abuse-deterrent Formulation Technologies and Regulatory Expectation. Curr Drug Res Rev. 2023 Dec 19.

1.1 The extent of the problem

There has been a significant increase in the number of people misusing opioid prescription drugs and dying from lethal overdoses. The enumeration From 1997 to 2007, there was a 402% rise in the average dosage of prescribed opioids ingested by individuals in the United States, rising from 74mg to 369mg. In 2009, retail pharmacies dispensed 257 million opioid prescriptions, representing a 48% surge compared to the 174 million prescriptions dispensed in 2000. Nationwide surveys conducted in the last ten years have shown that the abuse of legally prescribed opioid medications has surpassed the abuse of heroin and cocaine. This demonstrates a substantial increase in the abuse of opioids within the same timeframe. The provided text is a list comprising the items 5 and 6. From 2002 to 2012, there was a significant increase of over four times in hospital admissions linked to opioid prescriptions. Likewise, from 2000 to 2014, the incidence of fatalities resulting from excessive doses of these drugs increased by approximately four times. Every day, more than ninety people in the United States die due to opioid overdoses.[1,5,6,7,8]

Globally, around 33 million people, accounting for approximately 0.7% of the total adult population, are involved in the improper use of opioids, either by using them with or without a legitimate prescription. In 2014, around 4.30 million individuals aged 12 years or older in the USA participated in the nonmedical consumption of prescription pain medications, representing approximately 1.6% of the total population. The opioid analgesic that was prescribed was the most frequently misused after marijuana. The misuse of opioid formulations acquired through medical prescriptions is primarily noticed in the United States. However, it is also acknowledged as a significant problem in other nations worldwide, including Europe, Canada, India, Australia, and Japan. During the 2010-2011 school year in Ontario, Canada, 15.5% of secondary school students and 6% of the adult population acknowledged the non-medicinal use of opioid analgesics prescribed by a doctor. Around 7.7% of respondents in Australia admitted to engaging in non-medical use of opioid analgesics at some stage in their lives, which involved using the medication in a manner that was not recommended by a doctor. Furthermore, regulatory authorities such as the European Medicines Agency and the European tracking Centre on Drugs and Drug usage expressly focus on tracking the incidence of heroin usage, rather than the rates of abuse of prescribed opioid analgesics. The existing evidence on the misuse of prescribed opioid analgesics in the European region is minimal. Nevertheless, recent data indicate that the recreational use of opioid analgesics obtained through a medical prescription is becoming increasingly concerning in this region. Reports indicate that 2.4% of the Japanese population has participated in the non-medical consumption of opioid analgesic prescription drugs at some stage in their lives. The annual societal cost of abuse, misuse, and diversion of prescribed opioid analgesics in the United States is estimated to be between $55.7 billion and $72.5 billion.[1,9,10]

Therefore, regulatory bodies and pharmaceutical companies are confronted with a substantial challenge in tackling the problem of opioid overuse. This article examines various regulatory approaches, anticipates the approval of abuse-deterrent formulations (ADF), and explores strategies for producing opioid abuse-deterrent formulations as effective ways to combat the opioid abuse problem.

2. Potential approach of the durg abuse

Figure 3 illustrates the various mechanisms by which drugs are misused, including oral, intranasal, intravenous intake, and additional routes, such as rectal administration.

The most direct and common method of drug addiction entails the simultaneous ingestion of many pills through oral delivery. To obtain the 'dose-dumping' effect of the extended-release medication, those who abuse it usually crush and consume the extended-release (ER) form, resulting in a sudden and powerful feeling of exhilaration. This is accomplished by optimizing the level of the opioid in the brain's reward circuit as rapidly as feasible, leading to a greater peak concentration (Cmax) in a briefer duration of time (Tmax). Substance abuse can manifest in different ways, including the process of pulverizing and ingesting a quantity bigger than recommended, inhaling the drug through smoking or snorting, or injecting it directly into the muscles, veins, or subcutaneous tissue after removing it from its original form. Manipulation techniques encompass the processes of grinding or crushing the complete dosage form into tiny particles or a fine powder, dissolving it in a solvent (such as alcohol or water), and extracting the medication by subjecting it to high or low temperatures. Oral intake is the main way in which prescription opioid medications are commonly misused, as reported by several sources. Subsequently, the substance can be inhaled (by smoking or snorting), ingested orally (either in its original state or after undergoing modifications such as chewing, crushing, or dissolving), and ultimately, injected. However, there is tremendous variation in the ways in which prescription opioid analgesic formulae are abused. For example, the method of abuse selected is probably impacted by how much each abuser is affected positively or negatively by a particular opioid composition. This can proceed in any orientation. Because extended-release (ER) formulations include higher levels of opioids compared to immediate-release (IR) formulations, they are more appealing to individuals who abuse substances. The method of substance use that exhibits the highest correlation with increased morbidity rates is the practice of intravenous injection and inhalation of the substance.[1,11,12,13]

Fig. 3: Potential approaches of the drug abuse.[1]

Credit for the figure: Patel J, Patel R. Advancement in Opioid Abuse-deterrent Formulation Technologies and Regulatory Expectation. Curr Drug Res Rev. 2023 Dec 19.

3. Regulatory action

The US Food and Drug Administration (US FDA) introduced a new Risk Evaluation and Mitigation Strategy (REMS) for long-acting (LA) and extended-release (ER) opioid formulations in July 2012. This decision was made due to the increased likelihood of misuse associated with these formulations in comparison to short-acting opioid formulations (immediate release). The LA and ER formulations contain higher concentrations of the drug per dose, rendering them more hazardous when subjected to abuse or misuse in comparison to the shorter-acting formulations. This measure was implemented as a response to the intensifying problem of opioid misuse and abuse in the United States. It was enacted as a component of a 2011 initiative by the Obama administration, with the objective of tackling the widespread problem of prescription opioid misuse in the country. REMS is a risk management approach that specifically targets structural hazards by going beyond the usual medicine prescribing information and emphasizing monitoring. The primary goal of the program is to ensure that patients who truly need opioid medication can obtain access to these opioids (specifically, extended-release and long-acting opioids), while also providing education to healthcare providers and patients about the proper and safe use of extended-release and long-acting opioids. Manufacturers are accountable for developing instructional programs and materials targeted at all prescribers who are registered with the DEA (Drug Enforcement Administration).[1,14,15]

The US FDA revised safety labeling as part of its ongoing efforts. The new labeling will include the revised indication, emphasizing the exclusive use of LA/ER opioids in patients with severe pain that requires continuous, long-term opioid treatment, when other medications are not enough. This change will be integrated as a constituent of the labeling revisions. In addition, the US Food and Drug Administration (US FDA) has recently mandated the inclusion of a new boxed warning on all long-acting/extended-release opioid pain medications. The purpose of this warning is to notify consumers that prolonged use of these medications by pregnant women can lead to the development of neonatal opioid withdrawal syndrome (NOWS). The user's text is incomplete and does not provide any information.[1,16]

4. Abuse-deterrent formulation techniques

The process of developing a novel drug abuse-deterrent formulation (ADF) is similar to the creation of a new opioid chemical compound. The primary goals of developing innovative Abuse-Deterrent Formulations (ADF) of opioids are to manufacture opioid medications that are both therapeutically secure and effective in treating the specific therapeutic condition in the intended population. Furthermore, it does not cause substantial harm to any potential addict, and it is essential for an opioid drug to be economically efficient. Abuse-Deterrent Formulations (ADFs) are typically altered iterations of opioid medications that aim to diminish the attractiveness and pleasurable benefits of the drug. This is accomplished by restricting the quantity of medication that may be assimilated by the body, hence reducing its appeal for misuse or tampering. ADFs also impede the extraction of the opioid pharmacological substance, hence hindering other routes of administration. ADFs diminish the allure or drug-liking characteristics of drugs, therefore restricting one or more types of drug abuse by.

a) Impeding the extraction of opioid substances,
b) Impeding administration via alternative routes,
c) Retard the bioavailability of the opioid, thereby reducing the euphoric effect, and
d) Making abuse of the manipulated opioid formulation less attractive or rewarding.

As shown in Fig. ***4***, the ADFs product can be formulated using any of the following types of drug abuse-deterrent methods.

Fig. 4: Methods to Fabricate Abuse-Deterrent Formulations.[1]

Credit for the figure: Patel J, Patel R. Advancement in Opioid Abuse-deterrent Formulation Technologies and Regulatory Expectation. Curr Drug Res Rev. 2023 Dec 19.

4.1 Implementing physical barrier

By incorporating physical barriers inside the ADFs, it would effectively hinder any attempts to tamper with the opioid formulation. This would prevent actions such as crushing, chewing, grinding, or extracting the medicine. Polyethylene oxide (PEO) is commonly used as a polymer to create a physical barrier that successfully stops tampering with the dosage form. To achieve tamper resistance, the dosage form (such as a tablet) containing PEO is exposed to a high temperature of at least 75°C for a minimum of 60 minutes, which is higher than the melting point of the polymer. Table 1 presents a succinct summary of abuse-deterrent formulations that are specifically designed to prevent misuse, with a particular emphasis on those that employ a physical barrier.[1,17,18]

Table 1: Marketed ADF formulation based on physical barrier.

Product	Technology	Characteristics	FDA Approval
OxyContin® (Oxycodone HCl Extended-Release Tablets)	Fabricated using proprietary thermal processing of high-molecular-weight polyethylene oxide (PEO): **Processing Steps:** Compression – Coating – Curing at 75°C for at least 60 minutes	It resists crushing, grinding, and chewing of the dosage form. When attempted to dissolve with a small amount of water, the manipulated product will form a highly viscous hydrogel that will be difficult to inject IV.	2010
Hysingla ER® (Hydrocodone) Extended-Release Tablets			2014
OPANA ER (Oxymorphone) Extended-Release Tablets			2011
NUCYNTA® (Tapentadol HCl) Extended-Release Tablets	Fabricated using a proprietary thermal manufacturing process (Hot Melt Extrusion) using high-molecular-weight polyethylene oxide (PEO): **Processing Steps:** Hot Melt Extrusion of a mixture of API with PEO at > 75°C – Cutting of Extrude – Shaping of extrude to form dosage form		2011
Arymo ER® (Morphine Sulfate) Extended-Release Tablets			2017

4.2 Implementing chemical barriers

The inclusion of chemical barriers in ADFs would limit the ability to extract pure opioid components from the dosage form using readily available solvents such as water, ethanol, or other organic solvents and chemicals. The main materials typically used to resist extraction are high viscosity water-soluble but alcohol-insoluble polymers, such as PEO, water and alcohol-insoluble compounds like fatty acids and waxes, or chemicals with wax-like

properties, as well as ion-exchange resin combined with medicinal molecules. Table 2 presents a concise overview of abuse-deterrent formulations that are presently available on the market. These formulations are specifically designed to hinder misuse by implementing a chemical barrier.[1,18,19]

Table 2: Marketed ADF Formulation Based on Chemical Barrier.

<table>
<tr><th>Product</th><th>Technology</th><th>Characteristics</th><th>FDA Approval</th></tr>
<tr><td>XTAMPZA ER® (Oxycodone HCl) Extended-Release Capsule</td><td>Wax microsphere containing yellow beeswax, myristic acid, carnauba wax, magnesium stearate, stearoyl polyoxyl-32 glycerides</td><td rowspan="8">• It limits the extraction of pure drug substances from the dosage form using conventional solvents readily available to abusers, such as water, alcohol such as ethanol, or other organic solvents and chemicals.
• It also resists crushing, grinding, and chewing of the dosage form.</td><td>2016</td></tr>
<tr><td>Remoxy® (Oxycodone HCl) Extended-Release Capsule</td><td>A highly viscous gelatine matrix comprising fully esterified sucrose derivative sucrose acetate isobutyrate is water insoluble and highly hydrophobic.</td><td>Not Approved</td></tr>
<tr><td>OxyContin® (Oxycodone HCl) Extended-Release Tablets</td><td rowspan="5">A tablet comprising highly viscous water soluble but alcohol insoluble polymer Polyethylene Oxide.</td><td>2010</td></tr>
<tr><td>Hysingla ER® (Hydrocodone) Extended-Release Tablets</td><td>2014</td></tr>
<tr><td>OPANA ER (Oxymorphone) Extended-Release Tablets</td><td>2011</td></tr>
<tr><td>NUCYNTA® (Tapentadol HCl) Extended-Release Tablets</td><td>2011</td></tr>
<tr><td>Arymo ER® (Morphine Sulfate) Extended-Release Tablets</td><td>2017</td></tr>
</table>

4.3 Integration of aversion agent

By incorporating aversion chemicals into the ADFs, the tampered opioid drugs will elicit an unpleasant response in persons who misuse them, hence reducing the likelihood of abuse. For instance, the inclusion of sodium lauryl sulfate and docusate sodium decreases the probability of nasal misuse by inducing nose discomfort when crushed tablet particles are breathed

through snorting or sniffing. Irritation can lead to symptoms such as excessive tearing, nasal congestion, dryness, throat irritation, and excessive nasal discharge, which successfully deters the misuse of medications through the nasal route. Table 3 presents a concise overview of abuse-deterrent formulations that are currently being sold and depend on aversion agents.[20,21,22]

Table 3: Marketed ADF Formulation Based on Aversion Agent.

Product	Technology	Characteristics	FDA Approval
OXAYDO® (Oxycodone HCl Immediate Release Tablet)	Based on Aversion technology, it includes sodium lauryl sulfate and high-viscosity PEO in small concentrations.	It limits nasal insufflation. It also limits syringeability using a small quantity of water as it forms a highly viscous mixture if tried to extract or add solvent.	2012

4.4 Delivery system

Opioid formulations can be created in novel formats, such as depot injectable formulations and subcutaneous implants, which are designed to inhibit overuse. Manipulating these drug delivery systems can be challenging due to their intentional design for controlled and progressive release of opioids over a specific duration. Regulating the delivery of medication using this unique technique becomes challenging once it is administered only by medical professionals. An important advantage of this distribution system is its limited accessibility to patients for home use; it requires in-person deposit only by medical personnel. At present, there is no officially sanctioned ADF formulation that employs this delivery technique.[23,24,25]

4.5 Agonist / Antagonist combination

Opioid agonists and opioid antagonists compete to bind to the opioid receptor. Because of its strong attraction to the opioid receptor, the opioid antagonist will have priority in binding to the receptor over the opioid agonist if both drugs are delivered at the same time. Therefore, opioid formulations may include an inactive opioid antagonist that cannot be released. This means that the antagonist only becomes clinically effective when the abuser attempts to manipulate the dosage form of the opioid. Table 4 presents a concise overview of abuse-deterrent formulations that have been brought to market and rely on a blend of agonists and antagonists.[26,27,28]

Table 4: Marketed ADF Formulation Based on Agonist / Antagonist Integration.

Product	Technology	Characteristics	FDA Approval
EMBEDA® (Morphine Sulfate / Naltrexone HCl) Extended-Release Capsule	Opioid agonist pellets are surrounded with sequestered naltrexone, which will release only upon tampering with the dosage form.	If the dosage form is chewed, crushed, or otherwise altered, the orally bioavailable naltrexone will be released, reducing the euphoria expected from an opioid agonist. It limits tampering of dosage form for administration via altered routes such as parenterally.	2009
TROXYCA® (Oxycodone HCl / Naltrexone HCl) Extended-Release Capsule			2016
SUBOXONE® (Buprenorphine / Naloxone) Capsule	Due to significant first-pass hepatic metabolism, the oral bioavailability of naloxone is extremely low, resulting in a negligible effect when taken orally as prescribed. However, it becomes active only if the dosage form is tampered with for administration via an altered route, such as parenterally.	It limits tampering of dosage form for administration via altered routes such as parenterally.	2003
Targiniq® (Oxycodone / NaloxoneHCl) Extended-Release Capsule			2014

4.6 Prodrug

Prodrugs are inactive chemicals that can be metabolized in the body to produce the active form of the drug with pharmacological effects. Usually, this can be achieved by breaking down a group consisting of either an amide or an ester through hydrolysis. Prodrugs can be categorized into two main types: type I, which undergoes biotransformation inside cells, and type II, which undergoes biotransformation outside cells. Further subgroups can be distinguished by the precise extracellular position. For example, the gastrointestinal (GI) tract is classified as Type IIA. If a medication formulation needs to be in the gastrointestinal tract to become effective, then ideally, this should reduce the likelihood of misuse when the intranasal or intravenous routes are used. Although the discussion does not specifically address the problem of opioid abuse through several doses, the rate at which the gastrointestinal system metabolizes the drug will be the determining factor. This will lead to a diminished rise in the proportion of the medicine that is accessible for absorption. This occurs due to the overwhelming of enzymes in the gastrointestinal tract when a substantial amount

of opioids is delivered within a brief timeframe. Consequently, the medication's absorption will be postponed, which may result in a reduction of the highest concentration of the drug in the body (Cmax) and a prolongation of the time it takes to reach that maximum concentration (Tmax). This may reduce the profound sensation of joy that enhances the level of engagement. Currently, there is no officially approved ADF that employs a prodrug.[29,30,31]

Ensysce Biosciences, a California-based business, is presently working on the development of prodrug technology that employs trypsin-activated abuse protection (TAAP). The PF614 NCE is a biologically inert variant of oxycodone that can only be metabolized into its pharmacologically active form when administered orally. Trypsin is a proteolytic enzyme that facilitates the breakdown of proteins by breaking the chemical bonds between amino acids. Trypsin is produced in the pancreas as an inactive proenzyme and then released into the small intestine, where it is situated and performs its function. After being consumed, the opioid prodrug PF614, which is based on TAAP, is activated and released in the gastrointestinal system by the process of trypsin hydrolysis. PF614 must undergo metabolic transformation by trypsin in the gastrointestinal tract to access the oxycodone product, leading in the creation of an intermediate prodrug. The prodrug thereafter undergoes an autogenous chemical alteration process, which takes place within a defined timeframe. Injection, chewing, or snorting cannot activate the drug since the first activating enzyme (trypsin) is not present in the bloodstream or saliva. The FDA awarded fast-track development approval to PF614 in January 2018. Ideally, this medicine should exhibit resistance to misuse via all potential methods of administration, such as chewing, crushing, injecting, and inhaling. It is essential to recognize that PF614, like oxycodone and other abuse-deterrent opioid formulations, does not release any active drug when subjected to standard or advanced extraction methods. Extraction in isolation will not yield the desired opioid product. PF614 demonstrates resilience against common household chemical techniques often used to misuse pharmaceutical opioids.[32,33]

4.7 Implementing pH-Modulating release properties

In order to include self-releasing properties in cases of overdose, one can include a mechanism that increases the pH level and a mechanism that releases the medication based on the pH level in the dosage form. A pH-dependent release mechanism can be achieved by incorporating an opioid agonist into a matrix composed of a pH-dependent release polymer, such as Eudragit EPO, which dissolves when the pH is below 5. Alternatively, a pH-

dependent release coating, also made of Eudragit EPO, can be applied around an inert core that contains the opioid agonist. By adding substances like sodium bicarbonate and magnesium oxide to the dosage form, the pH level can be increased. The dosage unit is precisely prepared to contain a specified quantity of pH-elevating components. The dosage unit is modified to prevent the presence of pH-elevating components that would raise the pH of stomach fluid above six. This process is carried out to enhance the ability of a pH-sensitive soluble polymer known as eudragit EPO to dissolve, which in turn allows for the release of the opioid agonist contained in the dosage unit. Nevertheless, in cases of overdose where a substantial quantity of dosage units (e.g., four or more) are consumed simultaneously, the collective chemicals in these dosage forms that increase pH levels will neutralize the acidity of stomach fluid. This will lead to an elevation in the pH level of the stomach juice, surpassing 5 or 6. Consequently, the solubility of the pH-dependent soluble polymer (eudragit EPO) will be impacted, resulting in a delayed release of the opioid agonist included in the dosage units.[1,34,35]

5. Regulatory Considerations and Expectations in adf approval process

The FDA guidance document, specifically Tablet 5, offers a detailed explanation of the three premarket studies that manufacturers are required to do in order to show the abuse-deterrent qualities of a formulation. Additionally, it provides suggestions for the techniques and approaches to carry out and assess these investigations, along with instructions on appropriately depicting the findings and their significance for labeling. After successfully completing the three premarket studies, the FDA will give approval for the ADF, which will require manufacturers to implement a REMS system. The Risk Evaluation and Mitigation Strategy (REMS) program, required by the Food and Drug Administration (FDA) Amendments Act of 2007, ensures that the benefits of an opioid agonist outweigh its risks. Aside from the three methods of pre-market research, a post-market evaluation is obligatory to examine the drug's efficacy in real-life scenarios.[36,37,38,39]

Table 5: FDA Guidance on Requirements of Premarket and Postmarket Study.

Category 1 (Pre-market Studies) - Laboratory-based in-vivo manipulation and extraction studies	At this stage of the evaluation process, the FDA may ask the drug product manufacturer to alter the drug formulation to the point where its abuse-deterrent properties are rendered ineffective and then compares the ADF version of the drug to non-ADF versions of the same drug. The syringeability of the formulation, which refers to how tampered drug formulation can be quickly drawn into a

	syringe and injected for intravenous use, is evaluated after the integrity of the formulation has been defeated or compromised. Grinding, crushing, cutting, or grating are some of the methods that can be used, as well as employing readily available various devices (like coffee grinders) at varying temperatures and employing readily available solvents under different conditions of temperature for variable time periods at varying pH and agitation.
Category 2 (Pre-market Studies) - Pharmacokinetics studies	At this stage of evaluation, in vivo pharmacokinetic properties of a newly developed ADF will be compared with its identical non-ADF opioid product under both intact and manipulated conditions, as well as for various routes of administration. Studies on the oral formulation are conducted with healthy volunteers who are given naltrexone HCl to block the pharmacodynamic effects of the opioids. These studies also occur under conditions where participants simultaneously consume food and alcohol. In-vivo studies on the administration of nasal drugs can be carried out on volunteers who have a history of abusing nasal drugs in the past. During these studies, the main pharmacokinetic parameters to be monitored are: Cmax Tmax AUC Half-life Adverse Event
Category 3 (Pre-market Studies) - Clinical potential studies	The likeability of a manipulated ADF is determined in this study by enrolling experienced recreational opioid abusers in randomized, double-blind, placebo-controlled, and positive-controlled crossover studies. These studies are conducted before the drug is available on the market. A comparison is made between the ADF and the non-ADF of the identical opioid drug at the same dose (and if the non-ADF does not exist, then using an opioid having similar pharmacologic properties), which is then compared with the placebo. These studies are carried out on participants who have already been prequalified to determine whether they can distinguish between the active drug and the placebo in a reliable manner. Those who have used drugs before and are familiar with their effects are in the best position to distinguish between them. The methods of substance abuse that will be investigated have been historically significant in terms of how the non-ADF has been used. These methods will almost always include inhalation through the nose and intravenous administration of the substance. The outcome measures include visual analog scales that assess how much a person likes the drug, as well as evaluations of whether or not they want to use it

	again.
Category 4 - A post-market assessment	A post-market assessment is obligatory in addition to the three forms of pre-market research. Studies in the fourth category, "postmarketing," will examine how the drug performs in the real world. Studies conducted after a drug has been approved are called postmarketing studies, and their purpose is to "determine whether the marketing of a developed opioid ADF reduces the meaningful abuse potential, misuse, and also related adverse clinical outcomes, e.g., overdose, addiction and any death of abuser in the post-approval.

6. Effect of adfs on misuse of prescription opioids

A study was done to assess the effects of the abuse-deterrent formulation (ADF) of OxyContin, which was approved by the FDA, on the usage of OxyContin and other opioids. The findings clearly show a substantial decline in the prevalence of oxycodone use as the primary substance of abuse. In contrast, there was a significant increase in the preference for other opioids, including hydrocodone, different oxycodone derivatives, hydromorphone, and fentanyl. Before the new OxyContin formulation was approved, OxyContin was one of the most often abused opioids for recreational use. Nevertheless, the frequency of heroin consumption increased by over two times after the implementation of the new formulation. Although 24% of patients acknowledged circumventing the abuse-deterrent mechanism, most patients switched to a different opioid. Although there was some limited evidence indicating that the ADF effectively decreased the utilization of the targeted substance, there was no definitive indication that users entirely ceased the misuse of opioids after transitioning to ADFs. Instead, individuals frequently transitioned to an other substance. The presence of abuse-deterrent dosage forms (ADFs) is expected to have a far more substantial effect compared to typical opioid formulations that do not have safeguards in place to prevent overuse. Legislation has recently been introduced to address the opioid problem, and the FDA is currently granted approval only to opioid formulations that are less prone to abuse.[40,41,42]

7. Restriction of ADFS

Even opioids with features that reduce the likelihood of misuse can still be susceptible to overuse. The federal regulators appreciate the increasing scientific understanding in this field and the ongoing issues that remain unresolved. Recently, there has been an increase in comments on YouTube videos that offer guidance to viewers on different techniques for tampering with abuse-deterrent formulations (ADFs) of opioid medications. The altered

ADFs (Abuse-Deterrent Formulations) of Opana ER (oxymorphone) extended-release tablet, which hindered nasal inhalation but still permitted injection, were linked to an HIV outbreak in southern Indiana in 2015. The epidemic happened in 2015. Although there was a decrease in the improper use of the opioid formulation after the reformulated OxyContin (oxycodone) ADF was introduced, a study conducted on individuals who had previously misused OxyContin (oxycodone) and were entering treatment programs revealed that 25 to 30 percent of participants continued to use the new OxyContin ADF. This can be due to their finding a way to overcome the abuse-deterrent properties or their ingestion of the modified OxyContin pills by mouth. Furthermore, abuse-deterrent formulations do not offer safeguard against theft or accidental ingestion by infants or children. Importantly, a considerable proportion of persons who were discouraged by the new ADFs revealed that they switched to utilizing non-ADFs or heroin.[1,43,44,45,46,47,48,49,50,51,52]

8. CONCLUSION

The increasing number of deaths resulting from the fast expanding opioid pandemic necessitates the creation of abuse-deterrent opioid formulations. The abuse-deterrent platform technologies employed in the commercial production of abuse-deterrent opioid formulations are currently undergoing thorough investigation, and a number of advanced technologies are nearing regulatory approval. Post-marketing data on currently approved Abuse-Deterrent Formulations (ADFs) indicate negative results for ADF opioid formulations. This suggests that ADFs have the capacity to play a vital role in continuing and comprehensive efforts to decrease the risks associated with opioid use.

While the US FDA has authorized many tamper-resistant opioid formulations that effectively deter misuse through nasal and injection methods, the primary method of drug abuse, referred to as "oral overdose" (consuming numerous units of the drug simultaneously), continues to be an unresolved concern in the area. The prodrug approach has recently garnered considerable attention in tackling the issue of opioid overdose, while its efficacy is still being closely examined. Oxycodegol, also referred to as NKTR 181, is an Oxycodone derivative that was rejected by the AADPAC (Anesthetic and Analgesic Drug Products Advisory Committee) and DSaRM (Drug Safety and Risk Management Advisory Committee) of the USFDA (United States Food and Drug Administration). Although Nektar asserts that NKTR 181 is a selective mu-opioid agonist that provides long-lasting pain relief and has a decreased risk of abuse because of its delayed entry into the brain, the FDA committee voted against granting

approval for NKTR 181 due to apprehensions about the potential for drug abuse by injection or snorting.

Figure 5 demonstrates the effectiveness of current strategies to prevent various types of abuse. Each abuse deterrent tactic has unique advantages and limitations when it comes to different methods of drug abuse or routes of administration. We recommend integrating at least two or more strategies to develop a powerful opioid abuse-deterrent formulation that specifically targets the main method of drug administration. Figure 6 illustrates that a more practical method to effectively decrease opioid addiction, including instances of overdose, is to integrate two strategies: including pH altering release properties and employing an agonist-antagonist combination to develop abuse-deterrent technology. Researchers must investigate the possibility of developing complex formulations that can slow down or decrease the rate at which medications are released, depending on the dosage, by incorporating properties that regulate the acidity level of the surroundings. In order to reduce the probability of overdose incidents, it is not vital to entirely prevent the drug's release from the dosage form. Modulating the rate of opioid release from the dosage form, either by delaying it or prolonging a slower release, can also diminish the peak concentration of the medication in the bloodstream within a shorter duration. This may be sufficient to mitigate the detrimental or lethal adverse reactions of an opioid overdose, even when an equivalent dose of the medication is ingested in its rapid release formulation. Combining non-releasable opioid antagonists with opioid agonists will further reduce the abuser's desire to tamper with the dosage form in order to administer it through an altered route.

Although the use of opioid ADF does not entirely eliminate the risk of the opioid crisis, it is crucial to acknowledge that it substantially decreases the likelihood of abuse compared to typical non-ADF medicines that do not possess abuse-deterrent qualities. Consequently, this reduces the probability of improper use of opioid products. Therefore, it is crucial to enhance abuse-deterrent technology for opioid ADFs by developing safer, more varied, cost-effective, and stronger alternatives. In order to effectively tackle the severity of the worldwide opioid problem, it is recommended to implement a plan based on "universal precautions". This entails coordinating many regulatory bodies to safeguard society against the opioid epidemic. The objective is to create a policy that clearly defines the circumstances and procedures for prescribing opioid formulations to patients who truly need them. Furthermore, it is imperative

to evaluate the potential for misuse and only authorize the use of opioid drugs that have been specifically designed to dissuade abuse for medical purposes.

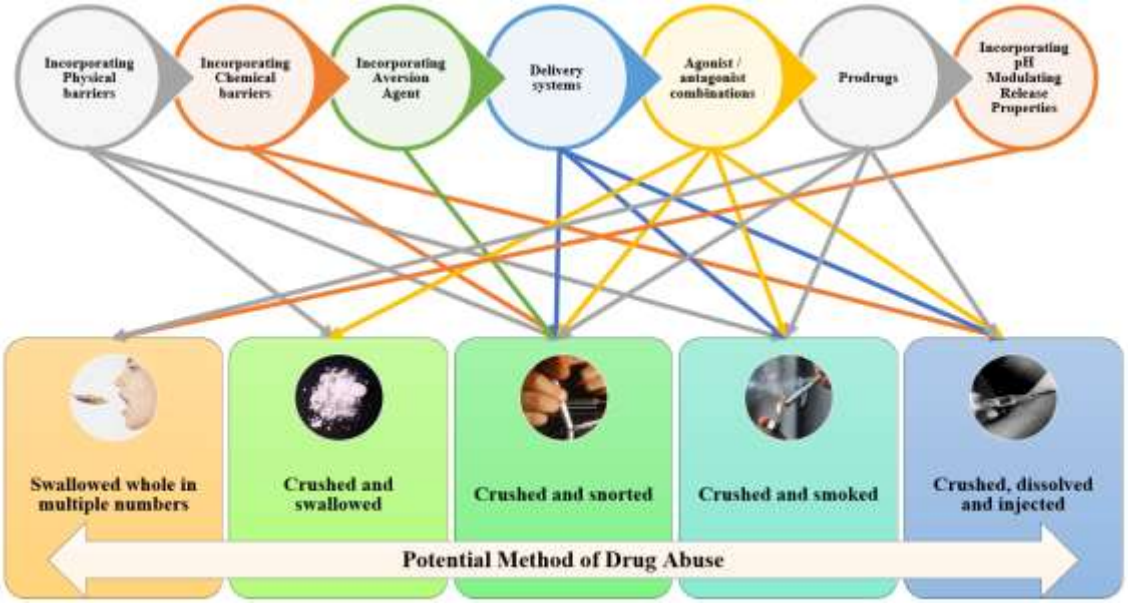

Fig. 5: Effectiveness of various abuse deterrent techniques against various methods of abuse.[1]

Credit for the figure: Patel J, Patel R. Advancement in Opioid Abuse-deterrent Formulation Technologies and Regulatory Expectation. Curr Drug Res Rev. 2023 Dec 19.

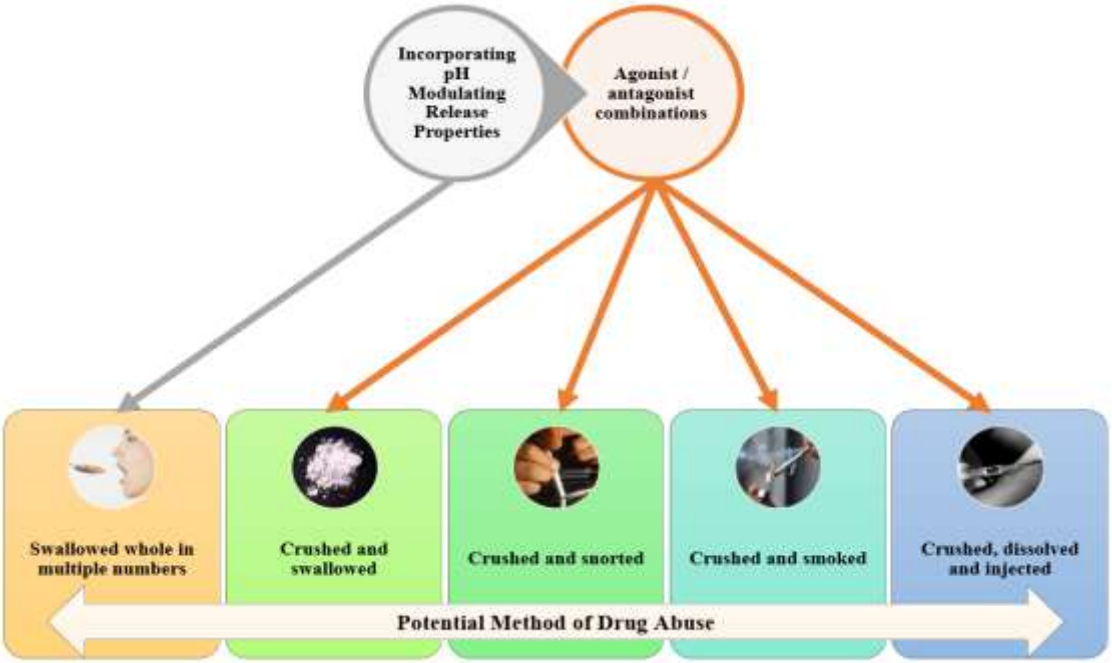

Fig. 6: Combining Two Potential Methods to Make Highly Effective ADF That Resist All Methods of Abuse.[1]

Credit for the figure: Patel J, Patel R. Advancement in Opioid Abuse-deterrent Formulation Technologies and Regulatory Expectation. Curr Drug Res Rev. 2023 Dec 19.

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