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Existing and emerging mitigation strategies for the prevention of accidental overdose from oral pharmaceutical products

Review

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Abstract

Misadventure with pharmaceutical oral medication has been on the rise, with the opioid crisis playing a major part. Drug overdose related to opioids has become such an issue, that it has been labelled a worldwide crisis. This review explores the mitigation strategies currently in place to prevent accidental overdose from oral pharmaceuticals, categorising the options based on whether they are relevant before, during or after the consumption of a toxic drug dose. To prophylactically prevent an overdose before consumption, governments and medical boards provide guidelines and implement policy, such as prescription monitoring, for the use of heavily abused medication. Some opioids have also been formulated as abuse deterrent formulations (ADF) which make it difficult for an individual to tamper with the medication. However, this does not prevent accidental overdose and only a few novel formulations were found to have multi-dose preventative properties. After an overdose has occurred, the situation is usually dealt with by first responders and hospitals using antidotes or medical procedures to limit the absorption of the drug. As pharmaceutical scientists, therein lies an opportunity to produce novel formulations that could limit the chances of accidental overdose. One approach could be to harness the physiological properties within the gastrointestinal tract (GIT), especially the enzymatic degradation of macromolecular matrix formulations. The ideal formulation will deliver a therapeutic dose but prevent or limit further release from consequent dose forms if a toxic quantity of drug is consumed.

Keywords: overdose; prevention; formulation; drug release; enzymes

1 Introduction

The development of modern medicine has been immense in the advancement of humankind. Pharmaceutical products in particular have helped the fight against diseases by eradicating and/or minimising the associated symptoms (1). This in turn has led to an increase in human life expectancy and overall health (2, 3). Even with the multitude of benefits, there are unfortunate downsides which have become more apparent since the turn of the millennium. As stronger medications, especially those used to treat pain, are developed, they also heighten the risks associated with addiction, with the worst cases leading to accidental drug overdose. Unfortunately, most research suggests that drug overdose has seen a substantial increase in incidences worldwide (4, 5). Defined as having an excess and dangerous dose of drug, overdose often leads to negative side effects which could lead to loss of life.

The classes of prescription drugs commonly associated with unintentional overdose include opioids, benzodiazepines and stimulants. Over-the-counter (OTC) medication such as paracetamol, ibuprofen and antihistamines can also be dangerous when taken incorrectly. Opioids, including morphine, oxycodone and codeine, have caused worldwide headlines due to the rise of drug-related deaths. They are an important tool in the management of chronic pain that OTC medication cannot resolve (6). However, at high doses, they provide the user a feeling of euphoria which leads to addiction and over-dependence on the medication.

Overdose can encompass numerous scenarios; some intentional while others accidental. For example, overdoses could occur by an elderly patient misreading labels, a curious child in the family medicine cabinet or an unfortunate suicide attempt (7). This highlights the broad nature of the problem and indicates that a single solution cannot solve it; rather that further research and greater public awareness is required. The research within this review will focus on accidental overdose relating to prescription opioids and common orally administered household medications and perspectives on how drug formulation can potentially add a lot more opportunities to reduce the risk of overdose through accidental or intentional multiple dose administration.

1.1 *Pharmaceutical opioids*

Opioids have been causing worldwide headlines due to the rise of drug-related overdose (**Figure 1**) (8, 9). Much of this increase arises from the misuse of prescription opioid

medication (e.g. oxycodone, morphine etc.). Prescription opioids are currently formulated as oral tablets and capsules with multiple modes of modified-release ranging from immediate-release (IR) to recently developed extended-release (ER) formulations. Transdermal patches for specific opioids (fentanyl, buprenorphine) have also been created as it allows for more controlled plasma concentration in patients while avoiding first pass metabolism (10). Reports have shown that opioid-related deaths from prescription drugs are a leading cause of premature mortality among middle-aged adults following only that of alcohol and tobacco (11). This has led to the Centre for Disease Control and Prevention labelling prescription overdose as a national epidemic in the USA (12). Numerous methods have been trialled to address this trend with many attributing the cause to excessive and inappropriate prescribing by physicians, doctor shopping and employee diversions (13).

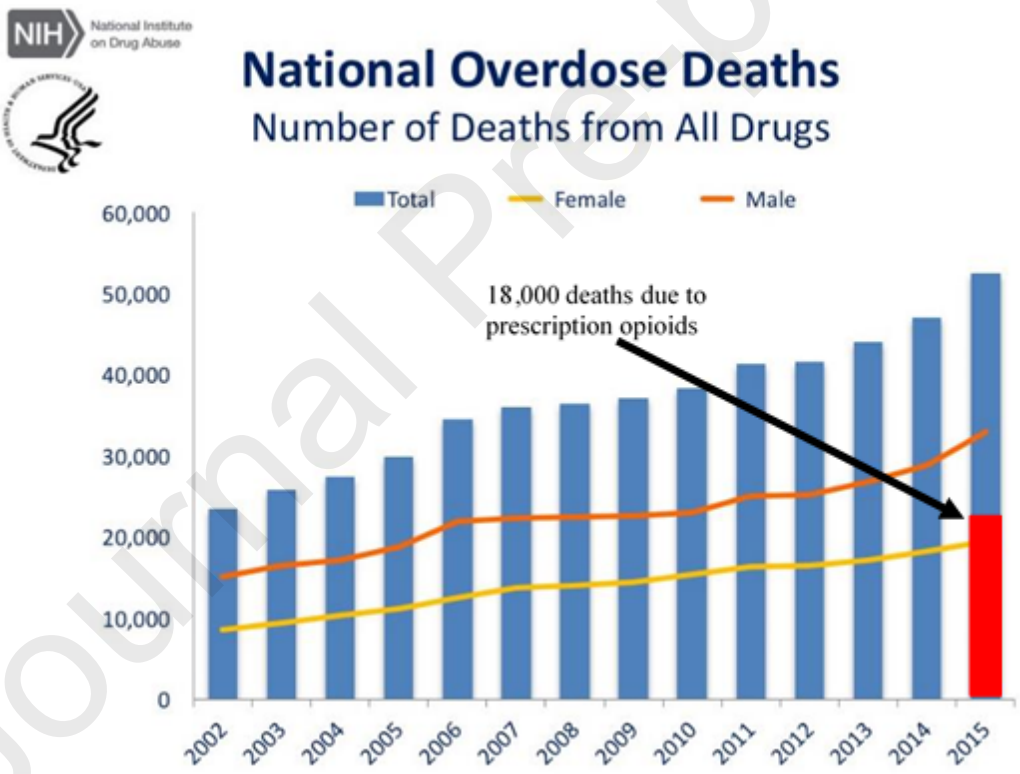

Figure 1. *National overdose deaths from prescription opioids in the USA. A large portion is in result of dangerous quantities of opioid consumption. It highlights the need for another solution to current methods as each year deaths are rising. Adapted with permission from National Centre for Health Statistics (NCHS) brief written by Hedegaard, H et al. 2017 (8).*

In 1986 Portenoy *et al.* reported the successful chronic use of opioids to treat non-cancerous pain (14). This paper started a transition, making it more acceptable for physicians to prescribe opioid treatment for chronic pain (15). Patients with non-cancerous pain from USA, Australia and Canada are more likely to be given long-term opioid therapies compared to nations in

Europe (6). German guidelines indicate that when chronic pain is the main symptom, opioids should not be prescribed, whereas patients in the USA and Australia were often treated excessively with opioids (6, 16). In the past, health-care professionals were taught to aggressively treat acute and chronic pain with opioid medication (17). This practice is changing with more strict guidelines implemented. For example, general practitioners (GP) in Australia must undertake a comprehensive biopsychosocial-based assessment of the patient stipulated by the guidelines set by the Royal Australian College of General Practitioners (18), before making their decision. Leaving the judgement to clinicians may also leave patients without the correct medication due to the potential for abuse and misuse (19).

This crisis has also affected healthcare systems around the world, with hospitals having to bear the expenses of the opioid overdose patients. The average cost of the intensive care unit (ICU) admissions increased in the USA by 58%, from $58,500 USD to $92,400 USD (20). A recent study undertaken at the University of South Australia by Dr Jacinta Johnson analysed the costs associated with hospital admissions related to over-the-counter (OTC) codeine products. The study concluded that on average each admission was costing the tax payer $10,000AUD as some patients were taking 90 tablets a day (21). To combat this increasing dependence of OTC opioids the Australian Federal Government announced that all these medications would require prescriptions post 1st February 2018 (22).

Combination products with opioids also increase the chance for overdose complications. Instead of the absorbed opioid component being at dangerous levels, the combined ibuprofen and/or paracetamol can become the more acute hazard. The majority of these products contain a large non-opioid dose (e.g. 50 mg codeine + 500 mg ibuprofen), therefore as more tablets are consumed, there is high potential to overdose on the non-opioid component.

2 Mitigation strategies to prevent drug overdose with current oral medication

New formulations are being developed to decrease the risks of abuse along with improvements in the packaging and labelling of pharmaceuticals (23). The industry has recently been held to account as multiple companies have been prosecuted in lawsuits pertaining to their involvement in the opioid epidemic (24-27). This crackdown has been led by an increase in awareness due to greater media coverage and government education programs. Clinicians are also transitioning away from prescribing opioids unless necessary with stricter guidelines being

implemented by medical boards and colleges. Governments, with recommendations from clinicians, have introduced new regulations restricting sales of highly addictive drugs and have implemented programs to educate society about the risks associated with some prescription drugs.

Different strategies are used to mitigate death from drug overdose and can be categorised depending on timing in relation to when the medication is consumed (**Figure 2**). Strategies in play *prior* to consumption are those stipulated by governments or medical boards and colleges, including those in the left-hand box of Figure 2. *At the time of consumption*, the approaches involved the physical medicine itself (Figure 2, middle box) and include new drug formulation approaches and abuse deterrent formulations (ADF). New preventative formulations are intended to prevent multi-dose abuse, while abuse deterrent formulations are intended to prevent extraction of the drug for alternate administration such as injection or smoking. *After* an overdose situation has occurred, the responsibilities fall on first responders which use antagonist-based kits (e.g. Naloxone) and other emergency procedures (e.g. stomach pumping) to prevent loss of life (Figure 2, right panel).

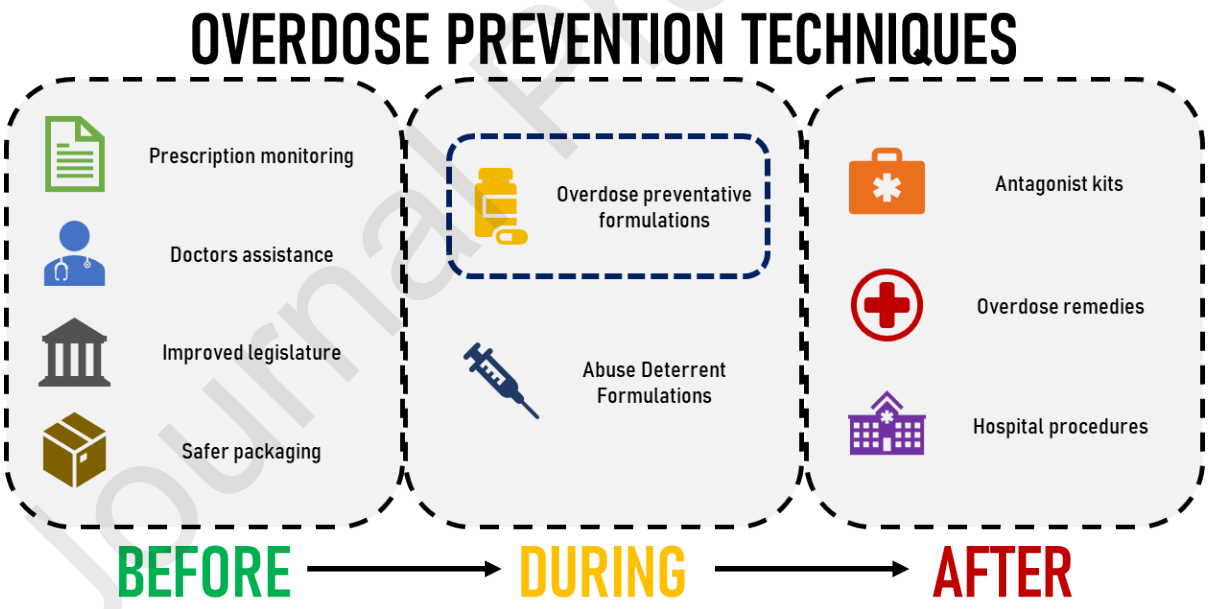

Figure 2. *Current overdose prevention strategies divided into categories; before, during and after consumption of the dangerous level of medication leading to overdose. A key focus of this review will be those formulations which have overdose preventative properties.*

2.1 *Before the consumption of medicine*

The main methods undertaken to prevent overdoses before consumption of the oral pharmaceutical product relate primarily to new government legislation, how clinicians are

handling prescriptions and smart packaging options which could prevent a patient from consuming a dangerous amount of prescription drugs.

2.1.1 Administration policy

Due to the rising death tolls and the increasing demand and cost placed on the healthcare systems of each nation, governments and policy makers have had to come together to find solutions to the opioid crisis. The success of each policy is hard to determine but a perspective about the policies in Massachusetts, USA written by Barnett *et al.* in 2017 suggested many of the policy changes or interventions did not have any significant effects (28). **Table 1** was reproduced from the same perspective and highlights some of the methods tested. Prescription drug monitoring programs (PDMPs) have been implemented in many countries with the key focus being to prevent a patient accessing multiple dispensing of the same high-risk medication, either through doctor-shopping or going to different pharmacies. The specifics in each program vary widely from nation to nation and in some regions, state to state, which can lead to differing degrees of success (29). Campaigns advocating and educating for the safe disposal of unwanted medicines is another action undertaken by regulatory boards or drug enforcement agencies around the world. Some examples of these programs are the TGA in Australia starting a twitter campaign using the #ReturnYourOpioids, while in the USA, the DEA periodically holding "National Prescription Drug Take Back Days" which has on estimate removed nearly 7000 tonnes of pharmaceuticals since its inception (30).

The implementation of new policy could unfortunately also have unintended effects whereby as GPs are more reluctant to prescribe opioids, there potential for legitimate patients to remain untreated. There have also been reports of patients who were heavy prescription opioid users, moving to illicit substances after prescription limits and monitoring where applied (31). However, even though there may be some negative outcomes, the general shift in modern prescribing methods is overall positive, albeit with difficulties in quantifying the benefit.

Table 1. *Evidence of effects of selected opioid-control interventions. Reproduced from Barnett et al. (28).*

Evidence for Effects of Selected Opioid-Control Interventions

Policy or Intervention	Description	Evidence for Effect
Prescription drug monitoring programs (PDMPs)	State-wide databases of all prescriptions filled for controlled-substances; allow clinicians to check for high-risk behaviours	Low rates of use by clinicians; reduced rates of overdoses, high-dose opioid use, and doctor shopping, but mostly in states with robust PDMP design and provider use mandates (32, 33)
Prescription limits	Policies or dispensing regulations that limit the time during which an opioid prescription can be filled or the quantity of opioids supplied	No significant effect on high-dose opioid use or doctor shopping among disabled Medicare beneficiaries (34)
Restrictions on doctor shopping	Policies that make it illegal for patients to withhold information from providers about prior opioid prescriptions	No significant effect on high-dose opioid use or doctor shopping among disabled Medicare beneficiaries (34)
Abuse-deterrent formulations	Reformulation of extended-release oxycodone to make it more difficult to crush pills into an injectable or inhalable form	Reduced prescribing of reformulated oxycodone, but with a concomitant increase in heroin use (35)
Notification letters for high-volume prescribers	"Informative letters" sent to physicians with the highest levels of opioid prescribing	In Medicare Part D, no significant effect on controlled-substance-prescribing in a randomised, controlled trial (36)

2.1.2 Packaging and intuitive labelling strategies

The key factors for effective packaging are a combination of well-defined labelling and having safety measures incorporated into the overall package. A simple but effective example is that of a child resistant cap, which usually requires some form of pressure to be applied to the lid before the twisting and opening motion can be applied (**Figure 3**). Correct labelling and clear dosing advice from medical professionals is also important for patients as there have been numerous reports of complications occurring due to confusion (37). An example of intuitive labelling is adding a day (Monday, Tuesday etc.) and time (morning, noon etc.) label directly onto a blister pack. This improves adherence rates and helps the patient in situations when they cannot remember if they have taken their medication, avoiding an accidental extra dose being consumed (38). Some pharmacies offer medication packaging services which are designed to organise medicines in a similar manner to ensure the correct pills are taken at the right time.

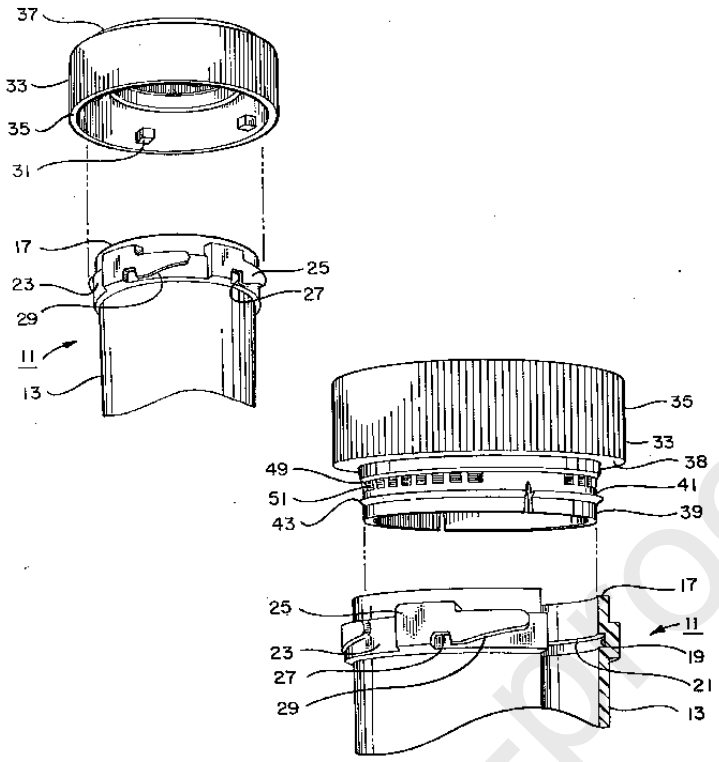

Figure 3. *Drawings from the original patent for a safety closure device for medicine containers invented by Ronald D. Kay. US4452364 (39)*

While these methods have so far been effective at preventing a magnitude of overdose situations, much of the responsibility is still placed upon the consumer. Some studies have shown that child-resistant caps can still be opened by children aged 6-8 and that these preventative measures cannot be solely relied upon to prevent overdose events (40). The next section will explore the possibilities of engineering the medication itself with fail-safe features to prevent overdose situations when consuming the medication.

2.2 *During the consumption of medicine*

Prevention of an overdose after consumption of medicine is a difficult task. The current reported methods all relate to oral dose forms. Increasing oral bioavailability has always been seen as important in the pharmaceutical industry, but prevention of overdose requires the opposite thinking – a need to prevent oral bioavailability above a single dose threshold. Here formulation concepts which could contribute to a decrease in prescription overdose complications are reviewed.

2.2.1 Abuse-deterrent formulations (ADFs)

In 2016, the US Food and Drug Administration (FDA) released an Opioids Action Plan in response to the crisis. The document outlined the strategies the agency will implement which

included expanding advisory boards and developing warning labels for immediate-release (IR) opioids. Incentives for manufacturers to develop ADFs were also announced (41, 42). ADFs are formulations which have properties that can deter the tampering of opioid medications (43). These formulations have unique physical and/or chemical barriers that can mitigate tampering while maintaining the drug's potency and efficacy. **Table 2** adapted from Maincent *et al.* 2016 (44), provides an overview of some currently FDA approved ADFs.

Table 2. *Overview of ADF categories established by the FDA. Examples of approved formulations are also provided. Table has been adapted from (44).*

Abuse-deterrent formulation approaches							
ADF Categories	**Physical/ Chemical barriers**	**Agonist/ Antagonist combination**	**Aversive substances**	**Unconventional opioid delivery**	**Prodrugs**	**Combination**	**Novel therapeutic**
What is it?	Resistance to mechanical alterations preventing extraction of opioid	Addition of opioid antagonist to block opioid effect	Unpleasant effect if substance released or excessive amount taken	Systems not commonly used for opioid delivery e.g. subcutaneous implants	Drug effect occurs only when enzymatically acted upon in the GI tract	Combination of previous approaches	Brand new approach
Examples	Physical: OxyContin® (PEO) Chemical: Xtampza® (fatty acid/ wax)	Troxyca® (Oxycodone/ Naltrexone)	Acurox® (Niacin)	N/A	Shire LLC has multiple formulations in Phase 2 clinical stage but none yet to be approved	Targiniq® (Oxycodone/ Naloxone) with PEO coating	N/A
Materials	PEO, lipids, foam forming agents, fatty acids (ion pairing)	Naloxone, naltrexone	Bittering, gelling, staining agents		Opioids covalently bonded to L-lysine, aryl carboxylic acids	Mixtures of any of the materials mentioned	
Abuse route prevented	Chewing, crushing, snorting, inhaling, injecting, multiple doses	Chewing, crushing, snorting, inhaling, injecting	Chewing, crushing, snorting, inhaling, injecting, multiple doses		Chewing, crushing, snorting, inhaling, injecting		

Physical and chemical barriers prevent extraction of the drug from the dose form, preventing the abuser from administering the drug using more direct methods such as IV and inhalation. An example of such a product is the reformulation of OxyContin®, which incorporates poly(ethylene oxide) (PEO) into the formulation, thereby allowing the product to resist damage from household tools (e.g. hammer, blender). The other categories of ADFs include agonist/antagonist combinations, addition of aversive substances, unconventional opioid delivery, prodrugs and a combination of any of these methods.

Although the development of ADFs for opioid analgesics is promising, they can often be overcome. Adding barriers and/or bittering agent to the formulation for example would not necessarily stop individuals from consuming more tablets. As such, novel strategies are needed to address this issue by rational design of oral based formulations through understanding of the physiological conditions in the gastrointestinal tract and their impact on drug release, solubilization and absorption.

2.2.2 Multi-dose abuse-preventive formulations

In recent years there has been some research reported exploring multi-dose abuse-preventive formulations. These formulations propose techniques which could stop the release of drug when multiple dosages are consumed. One approach designed by the Patel group utilises pH sensitive Eudragit® polymers to prevent release of drug when multiple doses were taken together. **Figure 4** shows the concept behind a loperamide multi-dose abuse formulation (45). The drug was hot melt extruded with gastric soluble polymers (Eudragit® EPO or Kollicoat® Smartseal 100P) and a base (L-arginine). The researchers hypothesised that if sufficient base was present when a dangerous quantity (15 tablets in their experiment) was consumed by co-lease with the initial amount of drug, then the pH of the surrounding gastric solution would increase to > pH 5, thus preventing further dissolution of the polymer and hence prevent further release of drug. Results indicated that when one dose was exposed to gastrointestinal fluid, release of drug equivalent to a therapeutic dose was achieved, but when multiple doses were taken only 2% of drug was released compared to the current marketed product Imodium®.

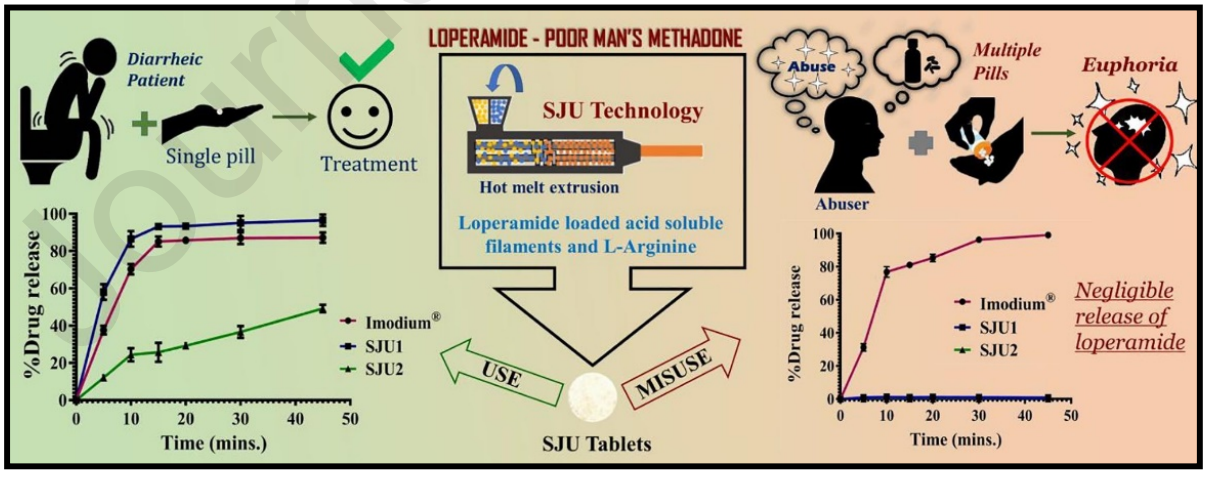

Figure 4. *Schematic of loperamide-loaded multi-dose abuse preventative systems. When multiple tablets are consumed the change in the pH environment would prevent the solubilisation of the outer*

polymer layer, thus preventing the release of drug. Reproduced with permission from the International Journal of Pharmaceutics (45). Copyright © Elsevier

Another concept explored was termed "overdose and alcohol sensitive immediate release systems" (OASIS) (**Figure 5**) (46). This formulation was designed to help prevent the exaggerated consumption of sleeping tablets which consisted of benzodiazepine or z-drugs (zolpidem, zaleplon and zopiclone) as the active component. The formulation has similar properties to the one in **Figure 4**, with reliance on an alkalizing agent to change the pH within the gastric environment to > pH 5 to prevent drug release when multiple doses are taken. However, this formulation included the added benefit of limiting release of drug when excessive alcohol was also consumed and subsequently released the antagonist at a faster rate. This was achieved by incorporating an additional antagonist payload loaded via a sustained release alcohol-soluble polymer. The materials used in the research were a combination of Eudragit® polymers, model agonist (metoprolol tartrate) and antagonist (hydrochlorothiazide) with a hot melt extrusion method in making the final OASIS formulations.

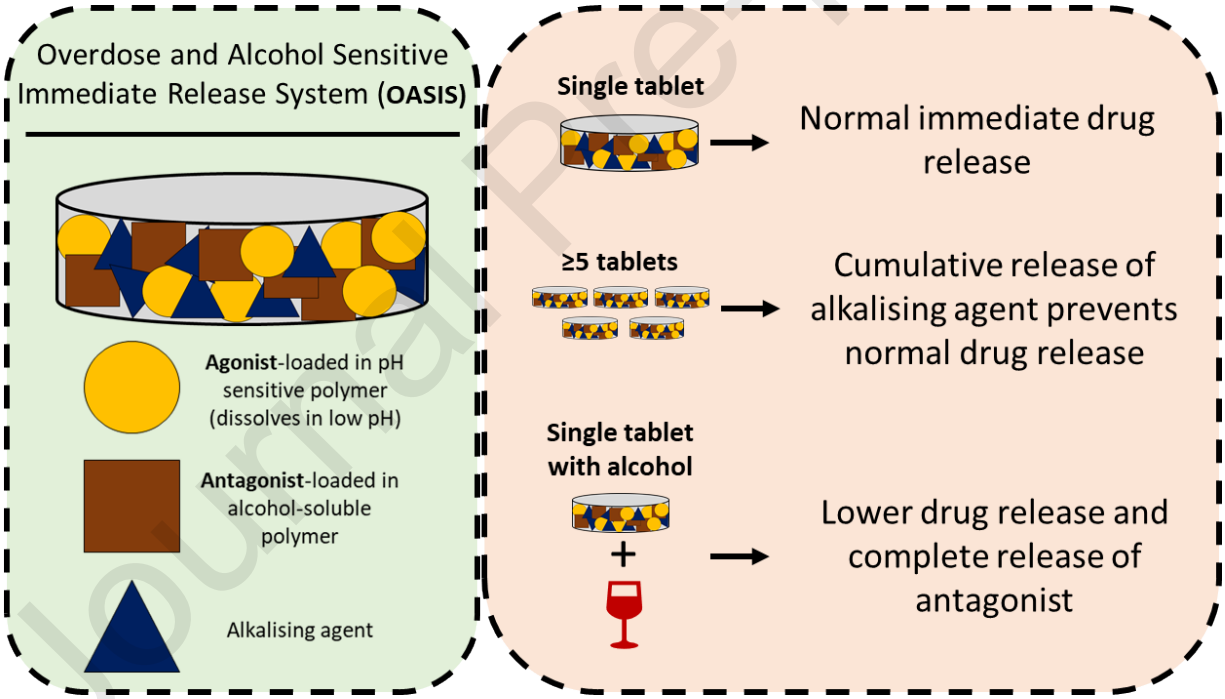

***Figure 5**. Schematic of the function of the OASIS formulation (46). Excessive consumption of the formulation decreased the release of the agonist (drug) through local increase in pH. When consumed with alcohol, the formulation would concurrently release the antagonist to prevent harm and abuse.*

A recent paper by Murshed *et al.* (47) describes an alternative concept of co-formulating drug with a lipase inhibitor within a solid lipid formulation, termed "lipase inhibitor controlled-release (LICR) formulations" (**Figure 6**). The formulations were created with a simple hot melt method with ibuprofen sodium salt used as the model drug, orlistat as the lipase inhibitor and

Gelucire® 43/01 as the lipid matrix. In order to release the drug payload, a LICR formulation must first be digested, with the paper suggesting that the body's own digestive system can be manipulated in order to prevent excessive drug release. It hypothesised that when multiple doses are consumed, the level of lipase inhibitor released into the surrounding aqueous phase would sufficiently inhibit the lipase activity and ultimately leading to a decrease or prevention of the overall drug release. The results indicated that above a threshold level of orlistat there was decreased digestibility of multiple doses of the LICR formulations, leading to reduced drug release. It also appears to be the only multi-dose abuse preventative system of this type to have been trialled *in vivo,* with LICR formulations dosed in capsules to rats. The pharmacokinetic study showed that the LICR formulations had the lowest exposure of ibuprofen, however further studies were required to optimise the system to obtain significance in the plasma exposure.

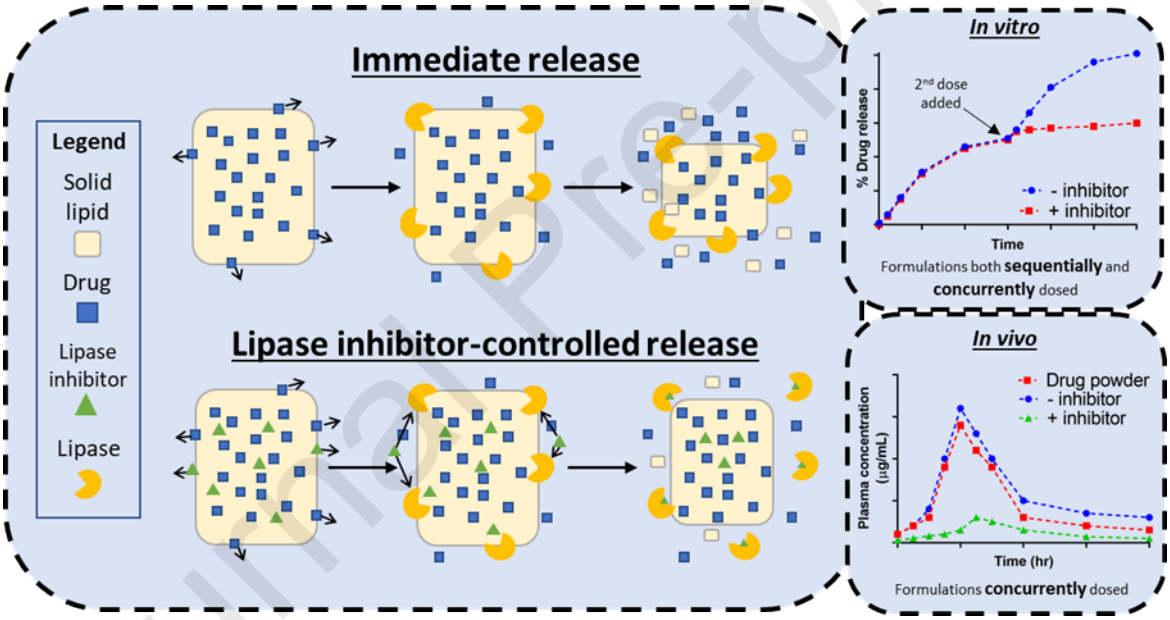

Figure 6*. Schematic of the lipase inhibitor-controlled release (LICR) concept along with hypothesised results from in vitro and in vivo experiments. As the lipase inhibitor is released, it inhibits the surrounding lipase preventing further breakdown of the solid lipid formulation, thus preventing excessive drug release. Reproduced with permission from the International Journal of Pharmaceutics (47). Copyright © Elsevier*

While the development of these type of formulations is in its early stages, these formulations are an advancement in the field where there are currently no alternative approaches. With more research conducted in this space, hopefully in the near future development of marketed products with these safety features will occur. However, currently, the only method of saving lives if someone has consumed a toxic dose is through the use of antidotes and in worst cases, hospital procedures.

2.3 *After the consumption of medicine*

Methods used to combat overdose after the consumption of a toxic dosage are usually performed by first responders or medical professionals. In the event of an overdose, antidote kits and/or medical procedures such as a gastric lavage are utilised.

2.3.1 Pharmaceutical antidotes

The creation of pharmaceutical antidotes was a major accomplishment in preventing death from prescription drugs (48). Antidotes are given during an overdose to counteract the effects of the poison and in many cases can prevent the loss of life. The antidotes for commonly abused drugs are usually carried by first responders and are now also being found in emergency first aid kits at prominent public locations (e.g. shopping centres). One of the first antidotes used for poisons was activated charcoal. Sometimes referred to as the "universal antidote", activated charcoal binds to a multitude of drugs, preventing their absorption into the systemic circulation (49). However, more specific antidotes have been discovered/produced, especially those used against opioid overdoses. Some examples of opioid antagonists that function as antidotes are naloxone, naltrexone and nalmefene. The most commonly administered opioid antidote is naloxone, which is a synthetic opioid antagonist that can be injected or administered via the nasal cavity into overdosing patients (50). It is extremely fast acting with many clinicians also precautionarily co-prescribing naloxone when a strong opioid treatment is required. Naloxone is a competitive opioid receptor antagonist which has the highest affinity at the μ-opioid receptor (μ-OR). It was communicated in the book *Biological Research on Addiction*, that a 2 mg dose of naloxone administered intravenously produced a μ-OR inhibition of 80, 47, 44, and 8% at 5 min, 2, 4, and 8 h after administration, while a 1000-fold decrease in dose (naloxone 2 μg kg^{-1}) resulted in μ-OR blockade of 42, 6, 33, 10% at the same time points (51). Since its introduction, naloxone has been a success with many studies suggesting that naloxone programs directly led to a reduction of overdose mortality in the community (52). Other antidotes, not just for drugs of abuse, exist such as the N-acetylcysteine for paracetamol liver toxicity and chelating agents which are used when the ingested concentrations of heavy metals are high (48).

2.3.2 Medical procedures

Gastric lavages are an invasive form of overdose prevention post drug consumption. They involve the contents of the stomach being aspirated usually via a nasogastric tube. Some clinicians believe this method should only be used in absolute necessary cases as numerous

complications can arise (e.g. aspiration pneumonia) (53). A slightly less invasive method is inducing emesis using syrup of ipecac. The ipecac drug can cause irritation in the stomach while also activating the chemoreceptor trigger zone, causing vomiting usually within 10-30 min in the patient (54). However, a position paper by Höjer *et al.* (55) stated that they found "no convincing evidence from clinical studies that ipecac improves the outcome of poisoned patients."

Both antidotes and medical procedures have mostly been effective at decreasing the death toll from overdose situations but they can only be used after the consumption of medicine; scientists should be striving to create safer medication, and in the next section, we explore new opportunities to formulate oral drugs, especially those of abuse, to potentially prevent overdose scenarios.

3 Opportunities for novel formulation approaches to address the increase in oral overdose

The oral route is well established as one of the more common and preferred delivery techniques of pharmaceuticals. The majority of formulation research focuses on enhancing the bioavailability of drugs (56-58), rather than attempting to mitigate drug toxicity issues during an overdose situation, and therein lies an opportunity for researchers to produced novel formulations to address the increase in oral overdose. The formulations described in section 2.2.2 clearly indicate the potential of utilising the conditions in the gastrointestinal tract (GIT) and smart chemistry to achieve this goal, so formulation scientists and innovators must be armed with a strong understanding of the conditions in and function of the gastrointestinal tract.

3.1 *Drug delivery through the gastrointestinal tract*

The first steps in approaching the issues surrounding the increase in oral overdose is to understand the process an oral formulation undergoes once consumed. As an oral dose form is administered, it transits the GIT through the mouth, stomach and then into the intestines (59). There is a delay between the drug reaching the intestines from the stomach, which is known as gastric emptying (60, 61). In this time, the stomach contents is held in the acidic environment for a varied amount of time, depending on whether the patient is fasted (up to 2 hrs) or fed (up to 6 hr) (59, 62). If the dose form is a tablet, unless enterically coated to prevent dissolution of the coating polymer, the tablet will disintegrate rapidly into small drug particles from which the drug can dissolve. Some drug absorption can occur in this region but due to the small

surface area and impact of the acidic environment on the ionization of the drug, the absorption is usually minimal. The major site for drug absorption by the oral route is usually the small intestine due to the presence of blood vessel rich villi and microvilli, which offers approximately 30 m^2 of surface epithelia across where transfer can take place (59, 63). The alkaline environment present in this area also helps push further absorption as weakly basic drugs will tend to ionise under these conditions. The primary function of the large intestine is water absorption and the removal of waste products from the body, however some drug can also be absorbed in this area, albeit usually less than the small intestine, due to the lower surface area present. **Figure 7** highlights some key physiological factors to consider when designing new formulations. They include luminal pH, bowel transit times and the variation of mucosa and microbiome. Oral drugs are formulated with these factors in mind and are often created with matrix materials which allow various advantages.

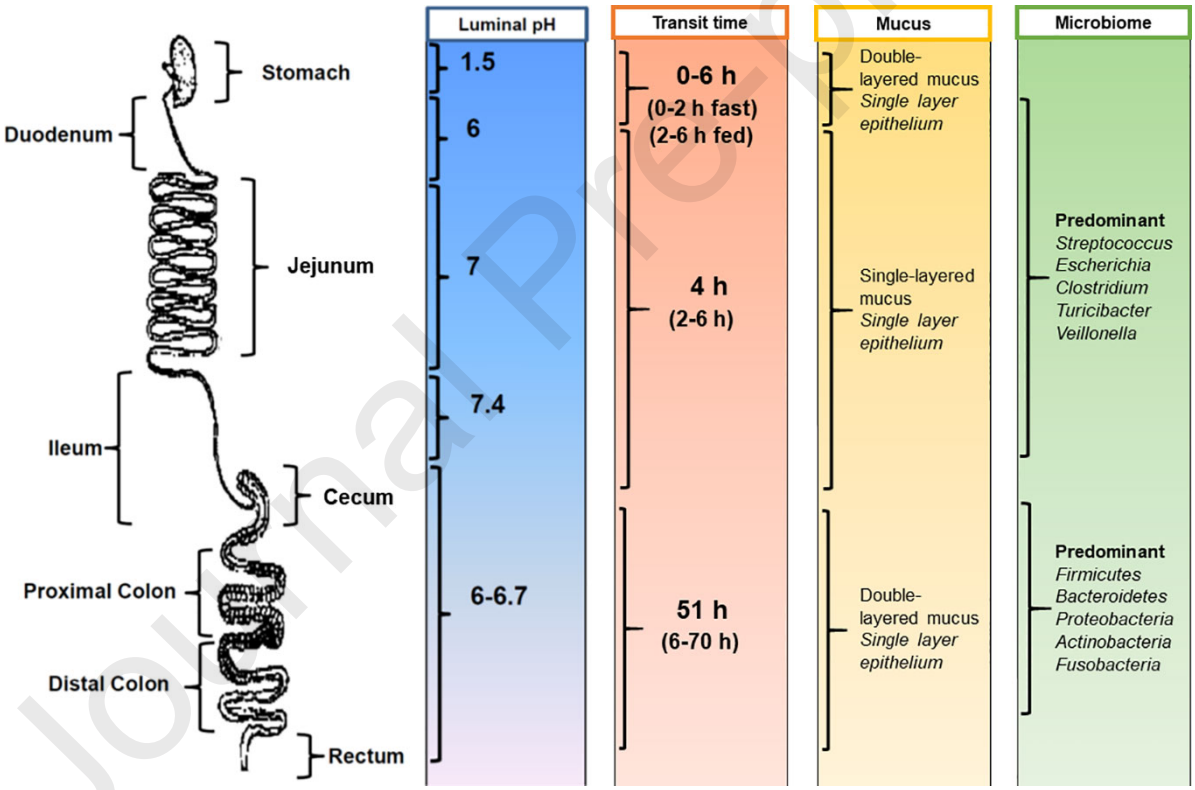

***Figure** 7. Physiological factors in the gastrointestinal tract that influence oral drug delivery. Reproduced with permission from Frontiers in Pharmacology (59)*

3.2 *Oral formulation matrix options*

A clear opportunity reflected in the systems described in section 2.2.2 is to encapsulate the drug in an environmentally responsive matrix the allows release under normal conditions, but arrests release when multiple dose units are consumed. Oral drug products can be formulated

with a multitude of matrix materials depending on the drug properties and the specific needs of the overall formulation (i.e. modified release, protection of active). There is a tendency to utilise biologically relevant macromolecules; lipids, proteins and carbohydrates, as they are usually considered safe and are easily accessible, although synthetic polymer systems have also been utilised (64).

Oral formulations utilising lipids (termed lipid-based drug delivery systems (LBDDS)) are common, as they can enhance the solubility and dissolution, and therefore the bioavailability of poorly soluble drugs, which constitute about 80-90% of the new drug candidates (65). Many different categories of LBDDS exist and these include suspensions, emulsions and self-micro and self-nano-emulsifying drug delivery systems (SMEDDS/SNEDDS). Further benefits of incorporating lipids within an oral formulation are to mask the taste, improve swallowability and to extend the shelf-life of products by protecting the drug (66, 67). Lipids also have the added benefit of possessing intrinsic abuse-deterrent properties with their addition to ADFs preventing crushing and solvent-based extractions. An example of such a use is Securel® technology from Relmada Therapeutics Inc. (68).

Matrices utilising protein and carbohydrates have also been explored. Naturally occurring protein from animals and plants are widely researched for oral drug delivery with various degrees of success (69-71). Seen as a sustainable and inexpensive material, proteins such as keratin, zein, collagen and spider silk can improve bioavailability and hold favourable structural properties for pharmaceutical applications (71). A review conducted by Paliwal *et al.* confirmed the vast array of applications of zein, a protein derived from maize (corn), suggesting that further exploration into the application of zein for targeted delivery and vaccines is required (69). Carbohydrates have also shown favourable traits as an oral formulation material with starch, alginate and chitosan being several of the most studied. Starch is a polysaccharide that is traditionally used in tablet formulation as an excipient. Specific starches can act as disintegrants, fillers and/or binders within the tablet (72, 73). Chitosan's are a family of polycationic derivatives of poly-N-acetyl-D-glucosamine (74). Their structure possesses positively charged units which plays an important role in mucoadhesion. Both proteins and carbohydrates can also be formulated into nanoparticle formulations where the particle size, surface area and surface properties all become modifiable (70, 75-77). A key attribute of these matrices is their ability to navigate the enzymatic activity of the GIT to resist degradation. This is important as it allows formulations to maintain their structural integrity,

however this process can also be manipulated to benefit drug delivery or for the case of drug overdose, its prevention.

As mention earlier, pH is one specific physiological handle that can be used to control dissolution of matrix components and drug release, specifically to prevent drug release by triggering a condition where it is unfavourable for the matrix components to dissolve (45, 46). Using pH as a trigger is useful but does have some downsides. Our GIT generally has a strong buffering capacity, meaning that an *in vitro* proof-of-concept may be difficult to translate to *in vivo*. The gastric emptying time is highly variable between individuals and even intra-patient, meaning the localisation of a specific pH condition with the dose form may prove difficult. Lastly, pH is of course a log scale with ionisation either side of the pKa requiring substantial shifts in hydronium concentration to make a strong impact on ionisation of matrix components and therefore dissolution. So, while opportunities certain are under investigation, translation to medicines has not been achieved for such a system. As an alternative we have proposed using enzymatic processes to control the degradation of matrix components (lipids, proteins and carbohydrates) to control drug release, explained in further detail below.

3.3 *Enzymatic digestion of matrix materials after oral administration*

Enzymes begin to act in the mouth however the majority of digestion occurs in the stomach or small intestine. For lipids, lingual and gastric lipase hydrolyse approximately 30% of the fat (78). This break down produces both diglycerides and free fatty acids which are subsequently further digested in the small intestine by pancreatic lipase. The pancreatic lipase plays the most crucial role in efficiently digesting triglycerides. Released by the pancreas, it acts by cleaving the triglyceride molecules into a *sn-2* monoglyceride and fatty acids. The enzyme hydrolyses the ester linkage between the fatty acids and the glycerol backbone at the *sn-1* and *sn-3* positions (79). Further enzymes found in the GIT are listed in **Table 3**. The presence of lipids in the small intestine acts as a signal to the gallbladder to release biliary fluid, which contains phospholipids, cholesterol and bile salts, to help with solubilisation and absorption of the active components (80, 81).

Table 3. *List of enzymes found in the human digestive system and corresponding enzyme inhibitors (82-86).*

Human digestive enzymes		**Enzyme inhibitors**	
Location	**Enzymes**		
Mouth	Lingual lipase Salivary amylase Lysozyme	**Lipase**	Alkaloids Carotenoids Glycosides Polyphenols Saponins Terpenes Orlistat
Stomach	Pepsin Gastric lipase	**Protease**	Ovomucoid Aprotinin Serpins Macroanions Dextran sulfate Carbenoxolone
Small Intestine	Trypsin Chymotrypsin Carboxypeptidase Elastase Pancreatic lipase Sterol esterase Phospholipase Nucleases Pancreatic amylase	**Amylase**	Various plant extracts Anthocyanin Alkylresorcinols Flavonoids

Protein breakdown begins in the stomach, as the acidic environment is favourable for denaturation. The release of pepsinogen from gastric chief cells in the stomach causes a reaction with hydrochloric acid, converting the pepsinogen into pepsin, an active non-specific protease (87). Pepsin partially degrades proteins into smaller fragments that are either absorbed or further degraded by a variety of pancreatic proteases (mainly trypsin and chymotrypsin) in the small intestine (88, 89).

Amylase is introduced in the mouth with the purpose of breaking down carbohydrates into disaccharides and trisaccharides. Both the salivary and pancreatic amylase found in humans are α-amylase, but differ in isomers at each location (90). α-Amylase breaks down carbohydrates by attacking the linear regions of amylose and amylopectin (90, 91). The carbohydrate chain length also impacts the rate of digestion and alters the degradation products from α-amylase. Oligomers with six or more glucose units tend to digest the fastest due to their affinity to the natural substrates of α-amylase (92, 93).

In a solid oral formulation, comprising lipids, proteins and/or carbohydrates as the matrix, the release of active is therefore dependent on the formulation design and its rate of enzymatic degradation in the GIT. Some macromolecules may readily diffuse into the aqueous environment, however, if the matrix has the appropriate characteristics: insoluble, digestible and remains solid at body temperature, formulations could be created which only release drug upon digestion. For the biological macromolecules discussed, it is possible to prevent the digestion process with compounds such as known as enzyme inhibitors, which presents an opportunity to control or prevent digestion and therefore release of the drug. Currently these types of inhibitors are used as standalone therapeutics as they bind to their respective enzymes decreasing their activity, but they have potential to be repurposed to act as a functional excipient, interfering with the digestion process.

3.4 *Enzyme inhibitors as functional excipients*

Enzyme inhibitors have the ability to decrease the activity of their corresponding enzymes through binding in certain biological pockets. Their effects can either be reversible or irreversible with reversible inhibitors slowly dissociating from the target enzyme (88). A wide variety of enzyme inhibitors exist throughout the with the inhibitors of the major enzymes described below.

Pancreatic lipase inhibitors prevent the activity of lipase secreted from the pancreas by binding in the triglyceride's binding pocket, preventing lipolysis (94). Without digestion, these fats cannot be absorbed into the circulation, therefore they are excreted through faeces (95). Lipase inhibitors have been marketed as anti-obesity drugs because of this function (94). Orlistat is an irreversible inhibitor of gastric and pancreatic lipase and has been used to effectively manage obesity in adults (95). It works by covalently binding with the active serine site of the enzymes, preventing them from hydrolysing triglycerides (96). Orlistat has been used previously to show controlled-release in lipid formulations (47, 97).

Protease inhibitors are antiviral drugs commonly used in the treatment of HIV and hepatitis C (98). The serpin class of proteins are one example systemic protease inhibitors. Serpin A1 (α-1 antitrypsin) inhibits various dietary proteases by forming a stable covalent complex (99). All serpins share common structural traits, they consist of three β-sheets, several α-helices and a reactive site loop exposed at one end of the molecule for protease binding (100). The Bowman-Birk protease inhibitor is an example of a natural anti-nutrient factor found in soybeans which

inhibits both chymotrypsin and trypsin-like proteases through the use of two distinct inhibitory domains (101).

Amylase inhibitors are also classified as anti-nutrient factors. Multiple varieties of α-amylase inhibitors exist as highlighted by Meng *et al.* in 2016. The paper showed that extracts from the plant *Hovenia dulcis* could behave as effective α-amylase inhibitors (102). Acarbose and miglitol are currently the only inhibitors available on the market and act as anti-diabetic drugs. These drugs are pancreatic α-amylase inhibitors that also target other α-glucosidases (103). The inhibitors function by forming a 1:1 stoichiometric complex with the α-amylase slowing down the rate of hydrolysis (104).

3.5 *Taking advantage of the GIT for multi-dose abuse preventative properties*

An orally consumed formulation must navigate the different environments through the GIT, including multiple regions of varying pH, ionic strength and enzymatic activity which facilitate digestion. Controlled-release formulations already exist which limit drug release by slowing down the breakdown of a matrix. However, this cannot prevent accidental overdose occurring from ingestion of multiple doses. As enzyme inhibitors have been shown to prevent this digestion process, an opportunity exists for incorporation of enzyme inhibitors into a macromolecular matrix formulation as a functional excipient. The large list of enzymes presented in **Table 3** could potentially be targeted with this approach although specific inhibitors are not available for all of the enzymes in the list.

As the proposed formulation is digested, drug and enzyme inhibitor would be concurrently released. In situations where the drug is being administered safety, the inhibitor concentration will be sufficiently low to allow release of a dose of drug, however if multiple doses are consumed, the increased accumulation of inhibitor would inhibit the surrounding enzymes, thereby preventing further digestion and ultimately further drug release.

Researchers should be looking into producing further innovative formulations which have a dose dependant ability to change drug release rate. It may not be necessary to completely inhibit release of second and subsequent doses to make a large impact on reducing overdose cases, as a significant reduction in exposure to the drug and reduced maximum plasma concentration may be sufficient to prevent the deleterious or fatal side effects from the same amount of drug consumed as immediate release tablets. This property could be then tailored to the toxicity for each specific drug, with the concentration of enzyme inhibitor altered. Such a concept was

recently reported by us (47) and our objective is for the formulation field to find inspiration from and further develop this concept, as the opportunity to design more precise formulation formats (e.g. 3D printing) will enable greater control over the release of the inhibitor relative to the drug.

4 Conclusion

The opioid crisis is the major factor in the increase in pharmaceutical medication abuse. It has been shown that even with tighter regulatory rules and a push to prescribe medicines that incorporate an abuse deterrent formulation, these initiatives cannot stem the constant increase in mortality rates. The opioid crisis is far from over and researchers should be focusing on making both less harmful medications and safer methods of oral delivery for those drugs deemed dangerous. There are largely unexplored innovative formulation approaches that have the potential to mitigate the effects of accidental oral overdose. The few attempts at producing multi-dose abuse preventative formulations are a step in the right direction, with their capability of preventing drug release after administration of multiple units crucial in preventing overdose scenarios. A unique opportunity exists for the creation of novel formulations which can show multi-dose abuse preventative properties by manipulation of the physiological factors within the GIT. Further research must be undertaken in this area, especially with greater emphasis on testing these new formulations in *in vivo* models, ultimately translating into human trials and products sold on the market.

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