Preventing Drug Overdose Through Deactivators and Self-Assembled-Monolayer-Forming Protectors Controlled Release by Evonik’s Eudragit

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Executive Summary

Many strategies to mitigate drug abuse have been reported, although none is directed towards preventing overdose of intact pills. The strategy proposed here to prevent drug overdose is to use deactivators and protectors controlled release by Evonik’s Eudragit polymer matrix. Under drug overdose, enough protectors are released from multiple drug pellets to form a protecting self-assembled monolayer on the deactivator which allows the deactivator to neutralize the drug’s agonistic effects. Using the Eudragit polymer matrix, controlled release of deactivators and protectors can be achieved to sufficiently neutralize the overdosed drug’s agonist effects.

Background

Prescribing pain relief drugs such as oxycodone comes with a risk of drug abuse due to its euphoric effects. In order to get the intense 'high', drug abusers typically crush the pills or dissolve them to take the drug via snorting through their nose or injecting it into their vein. The US Food and Drug Administration (FDA) now requires manufacturers to come up with a plan to mitigate this risk. This report presents a novel concept to prevent drug overdose using deactivator and protector controlled release by Evonik’s Eudragit polymer matrix.

Numerous patents have been filed addressing abuse-resistant dosage forms using Eudragit dating back as far as 2002. Strategies to mitigate abuse include sequestered aversive agents that causes irritation to abusers, sequestered drug antagonists that diminishes the euphoric effects, and physical barriers to crushing, chewing and solvent extraction. Although all three approaches have the potential to deter abuse and tampering, none is directed towards preventing abuse of intact pills by taking them in amounts that exceed the prescribed dose. The

problem of drug overdose expands beyond patients who abuse the drug for euphoric effects to other serious issues such as patients with suicidal thoughts.

**Deactivators and Protectors**

Deactivators and protectors (of the deactivators) will be added into the formulation of drug. When the drug is administered at the prescribed dosage, deactivators are released into the body along with protectors but they do not have any antagonistic influence because there is not enough protectors to protect the deactivators from degradation by the physiological environment. At a harmful dosage, enough protectors are released from multiple drug pellets into the body such that deactivators are protected from the physiological environment by the protectors, therefore they can induce antagonistic influence. The goal of this formulation is to activate deactivators to have antagonistic effects whenever a critical mass of intact pills is administered by the drug abuser, in which this critical mass have to be engineered to match the harmful dosage.

The protector molecule is designed to form a self-assembled monolayer around the deactivators to guard them from harsh physiological environments. If the drug is taken properly at the prescribed dosage, there will not be enough protectors to surround the deactivators and thus they will be degraded. When overdosage occurs, enough protectors are released from multiple pellets into the body such that the deactivators are protected and thus they can deactivate the drug’s agonistic effects. The schematic drawing below illustrates this mechanism.

<table>
<thead>
<tr>
<th>Overdose</th>
<th>Prescribed Dose</th>
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<tbody>
<tr>
<td>Deactivator is protected by the (blue) protectors</td>
<td>Not enough protectors to protect the deactivator</td>
</tr>
</tbody>
</table>

![Figure 1: Mechanism of self-assembled monolayer to protect deactivators from degradation.](image)

The protector’s molecular design must satisfy four main characteristics. Firstly, they must have an amphiphilic characteristic which can self-assemble in polar physiological environments. Secondly, the self-assembled monolayer of protectors must be able to protect the deactivators
from environmental degradations such as enzymatic cleavage and acidic or basic conditions. Thirdly, they must selectively chemisorb onto the deactivators, which means that the deactivator’s molecular design must also be taken into consideration. Finally, they must be biologically inert and can maintain their active form in the physiological environment they are released into.

For the deactivator’s molecular design, they must be able to induce antagonistic effects to the agonist of interest and they must be degradable by the environment they are released into. As an example, suggested antagonist for opioid include naltrexone, naloxone, and nalmephene.\(^5\) Investigation of their degradability is also an important consideration because the body should be able to digest or deactivate them once the deactivators have done their job. Another group of possible candidates is peptides that can sequestrate the agonists because peptides are susceptible to deactivation due to misfolding whenever they are not in the preferred environment. This misfolding characteristic of peptides can be utilized when the patient is administered the prescribed dosage, in which the peptides would be deactivated without the self-assembled monolayer of protectors.

Selecting appropriate molecules for the protectors and deactivators are challenging tasks because they must satisfy the mentioned characteristics. Tools in computational chemistry can be used to speed up the discovery process in a way that it has already been used in the drug discovery pipeline. Computational chemistry facilitates the team to make educated guesses of the appropriate molecules to synthesize and test.

<http://www.google.com/patents/US8182836>
Controlled Release by Evonik’s Eudragit

Controlled release of the deactivators and protectors is crucial to for the success of this overdose prevention strategy because releasing deactivators and protectors too quickly will neutralize the drug agonistic effects. At the same time, enough deactivators and protectors must be released to counter the possibility of overdosing. Using sustained-release polymer matrix formulation, such as Eudragit RS PO, the required controlled release can be attained. The specific polymer matrix chosen will depend on the targeted physiological area the drug is designed to be released.

The strategy of extended-release is more suitable for drug with moderate rates of absorption and elimination. For drugs with slow rate of absorption that have elimination half-lives above 10 hours, the sustained release dosage forms may cause accumulation effects because they are inherently long-acting and self-retarding. On the other hand, for drugs with fast absorption rate that have elimination half-lives below 2 hours, special development efforts is required because high fluctuation of plasma levels may cause drug inactivity. Examples of suitable drugs are oral opioids, such as morphine and hydromorphone, in which controlled release forms of oral tablets have already been released into the market.

As shown in the schematic of the formulation design above, the drug will be placed in an Eudragit polymer matrix as the outer layer and the deactivators and protectors are mixed in the inner layer Eudragit polymer matrix. The drug and the mixture of deactivator and protector are placed in a different compartment to allow the ratio of drug release to be engineered. The drug polymer matrix is placed on the outside because more drug will be released than the deactivators and protectors. The composition of the formulation will have to be optimized to ensure that appropriate amounts of the drug, deactivators and protectors will be released. An

appropriate amount means that when the prescribed dosage is administered, the patient receives the prescribed dosage of the drug with minimal antagonistic influence from the deactivators. This appropriate amount also means that when the patient overdose the drug, there is enough deactivators and protectors released to neutralize the drug’s agonist effects. In addition, the biological inert core is included to ensure structural stability and it can be made out of sugar or starch based pellets.

Polymer matrix formulations can be prepared by direct compression of Eudragit powders, in which Eudragit polymers serve as both the sustained release matrix former and binding agent. The relationship between compression force and release rate must be tested individually. To optimize the release profile of a particular drug, factors to be considered include particle size, dose strength and solubility of active ingredient, type and amount of matrix form, and the porosity and disintegration properties of the final tablets.

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Summary and Outlook

In summary, a novel concept to prevent drug overdose using deactivators and protectors controlled release by Evonik’s Eudragit polymer matrix is presented here. When the drug is overdosed, enough protectors are released from multiple drug pellets to form a protecting self-assembled monolayer on the deactivators which allow deactivators to neutralize the drug’s agonistic effects. If the patient administers the appropriate prescribed dosage, there is not enough protectors to form the self-assembled monolayer, and therefore the released drugs induce the normal physiological effects. Using the Eudragit polymer matrix, the controlled release of the deactivators, protectors and the drug allows successful deployment of the drug overdose prevention strategy.

Required further research and development efforts include determining the appropriate molecules to be used as deactivators and protectors and optimizing their compositions relative to one another and the drug. The choice of the Eudragit product is also dependent on the drug of interest. Furthermore, an interesting path to pursue is to combine this strategy with previous abuse-deterrent strategies such as making the pellet resistant to crushing, chewing and solvent extraction as well.8

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