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SELF-REGULATED ANTI-OVERDOSE CRUSH-RESISTANT DRUG DELIVERY SYSTEM DESIGNED TO ADDRESS THE OPIOID ABUSE CRISIS

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ABSTRACT

Background: The pharmaceutical opioid dosage form is frequently misused through the oral route, either in its original form by taking an excessive dose, or in a manipulated form by crushing the dosage form. It can also be misused through non-oral routes, particularly through injection or nasal administration, after manipulating the dosage form. **Objectives:** The objective is to evaluate the self-regulated anti-overdose characteristics of the crush-resistant drug delivery system by conducting in-vitro laboratory research on its crushing strength, extractability, and syringeability. **Methods:** The extractability of Metformin HCl drug particles, produced using various polymers, was evaluated in 25ml of water at room temperature (RT) and at temperatures exceeding 90°C. The assessment of crushing strength involved grinding the drug particles using a mortar-pestle and a coffee grinder for a duration of 1 minute. In order to assess the syringeability of the drug mixture, an effort was made to extract it using a 1ml Insulin syringe for a period of 1 minute. In order to evaluate the ability of self-regulation against overdose in both normal and overdose scenarios, we conducted in-vitro dissolving testing. This involved evaluating a single, unaltered capsule per dissolution vessel for normal settings, and four capsules per dissolution

vessel for overdose situations. **Results:** The presence of drug particles comprising polyox, natrosol, and blanose significantly reduced the extraction of the drug by more than 80% at room temperature and over 90°C. After grinding in a mortar-pestle and a coffee grinder for 1 minute, the crushed particles of thermally produced drug particulates containing polyox were able to be retained at a rate of over 99% on the ASTM 170# screen. The endeavor to extract the thick and sticky combination of drug formulation, which was mixed with 5ml of water, using a 1ml insulin syringe for a duration of 1 minute, did not succeed. During the dissolution trial, unaltered capsules exhibited a drug release of over 90% and significantly slowed down drug release by over 90% under normal and overdose circumstances, respectively. **Conclusion:** Laboratory experiments conducted in a controlled environment show that the newly created drug delivery system, which is designed to prevent overdosing and resist crushing, has the potential to discourage abuse through both oral and non-oral methods of administration.

KEYWORDS: Abuse Deterrent, Over Dose Abuse, Tamper Resistant, Opioid, Chronic Pain, Metformin HCl, Extraction, Syringeability, Crushing.

1.0 INTRODUCTION

Chronic pain impacts a significant proportion of the population, ranging from 20-30%, surpassing the combined prevalence of heart disease, cancer, and diabetes. Since the 1990s, revolutionary analgesic medications have been developed to address chronic pain. Prescription opioids remain the exclusive and unchanged primary treatment for chronic pain sufferers during the past ten years. Nevertheless, because to the ongoing expansion of the opioid market, drug misuse has emerged as a significant health and socio-economic concern on a global scale. Drug misuse undermines the fundamental pillars of society and leads to fatalities, child maltreatment, sexual and domestic aggression, a surge in criminal activities, and a dearth of tranquility and safety for women and children. An excessive amount of an opioid leads to the demise of the individual who abuses it.[1]

In 2017, almost 1.7 million Americans experienced substance abuse as a result of their addiction to prescribed opioid medicines. Currently, opioid overdose is the primary cause of mortality in the United States. In 2017, opioids accounted for 68% of all drug overdose deaths in the US, totaling 47,600 fatalities. According to the US Department of Health and Human Services, there were more than 130 daily fatalities due to opioid overdoses in both

2016 and 2017. The annual cost of this catastrophe to the United States exceeds $150 billion.[2,3]

Over 70% of those with addiction acquire opioids through means such as theft, illegal purchase, or borrowing from acquaintances or relatives. Individuals who abuse prescription opioids aim to achieve a state of euphoria by either consuming excessive amounts of tablets orally or by converting the medication into a powdered form and then inhaling, snorting, or injecting it. Numerous individuals who engage in abusive behavior try to manipulate the prescribed opioid formulation in order to make a concoction known as a "dump". Crushing extended-release opioids causes the complete dose to be released all at once, rather than gradually over a period of time. As a result, there is a more rapid rise in the maximum concentration of opioids in the bloodstream (Cmax) within a shorter period of time (Tmax). Altered pharmacokinetics leads to altered pharmacodynamics, which ultimately produces the desired "reward effect" of euphoria.[4,5,6]

The process of creating a novel drug abuse deterrent formulation (NDADF) is comparable to the development of a new opioid chemical compound. The primary objective of developing innovative drug abuse deterrent technology is to provide an opioid dosage form that is both safe and efficacious for the target patient population, while also minimizing harm to potential abusers who may attempt to misuse the opioid formulation. Additionally, the development of such technology should be economically viable. These formulations are specifically created to decrease the probability of an opioid substance being liked or abused by reducing its bioavailability, blocking the extraction of the pure opioid chemical from the dosage form, restricting administration through alternate routes, or making misuse less appealing. According to literature, there are several strategies that can be employed to create abuse deterrent opioid formulations. These strategies include creating new delivery systems, combining physical barriers (such as crush resistant barriers) and chemical barriers (such as gelling barriers), incorporating aversion agents (such as emetic agents), using a combination of agonists and antagonists, and utilizing prodrugs. The array Currently, there are only a limited number of products in the US market that are tamper resistant. However, none of these products have overdose abuse deterrent properties, meaning they do not prevent the act of swallowing multiple tablets or capsules at once in their original, unaltered form. This is the most common method of abusing opioid substances.[7,8]

The development of a pharmaceutical formulation that combines overdose prevention and tamper resistance qualities would be a noteworthy accomplishment in the field of Chronic Pain Medication. The objective of this study was to develop an innovative drug delivery system that addresses the issue of drug abuse in pharmaceutical formulations. This system aims to prevent oral overdose abuse, hinder the extraction of pure drug substance from the dosage unit, and prevent opioid abuse through parenteral or nasal routes. The primary aim of this study was to develop and analyze a new self-regulated drug delivery system that is resistant to crushing and prevents overdose. This system can be adapted to work with any existing or new drug molecule. Its purpose is to address the drug abuse crisis in pharmaceutical formulations, specifically by reducing opioid overdose and preventing tampering with the final product. Additionally, it aims to ensure that individuals who genuinely require these essential medications have access to them. The present study utilized Metformin HCL as the model drug which is a highly water soluble drug comparative to the opioid drug.[9]

2.0 MATERIALS AND METHODS

2.1 Materials

The following substances were obtained from various sources: Metformin Hydrochloride, Aerosil 200 (Colloidal Silicon Dioxide), Blanose (Sodium Carboxymethylcellulose, Crosspovidone, Microcrystalline cellulose and Magnesium Stearate) were received from Pyrrhic Pharma Private Limited. Polyox WSR 303 (polyethylene oxide), Opadary 85F and Methocel E5 (hydroxypropylmethyl cellulose) were received from Colorcon India. Klucel HXF (hydroxypropyl cellulose) and Natrosol 250HHX (hydroxyethyle cellulose) were received from Ashland. Eudragit EPO was received from Evonik. All solvents and remaining materials were obtained from a local vendor.

2.2 Methods

Currently, the field of drug abuse deterrence is in its early stages, leading to the rapid development of innovative technology aimed at preventing drug misuse. Abuse deterrent formulations are designed to specifically address the known ways in which drugs are abused, resulting in a decrease in overall drug abuse compared to traditional formulations. To tackle the problem of drug abuse in pharmaceutical formulations, we initially identified the main methods through which drugs are abused and then developed an effective strategy to prevent such abuse, as outlined in Table 1.[9,10]

Figure 1 illustrates a summary of a self-regulated drug delivery system that is resistant to crushing and prevents overdose: (a) drug particulates with a crush resistant core coated with a heat resistant coat that is surrounded by an outer acid soluble coat, (b) a pH elevating ingredient.

Table 1: Potential methods of drug abuse Vs Effective strategy to encounter the drug abuse.

Method of Drug Abuse	Strategy
Swallowed whole pills in multiple numbers at a time	pH Dependent Release Modulation: Release Modulation of the drug from the formulation depending on the pH of stomach fluid which will be governed by pH elevating ingredient and pH dependent soluble ingredient incorporated in the dosage form depending on the number of dosage form administered.
Crushed & snorted	Crush Resistant barriers: to prevent chewing, crushing, cutting, grating or grinding.
Crushed & smoked	
Crushed, dissolved and injected	Chemical Gelling Barriers: to resist extraction of the opioid using common solvents, such as water, alcohol, or other solvents.

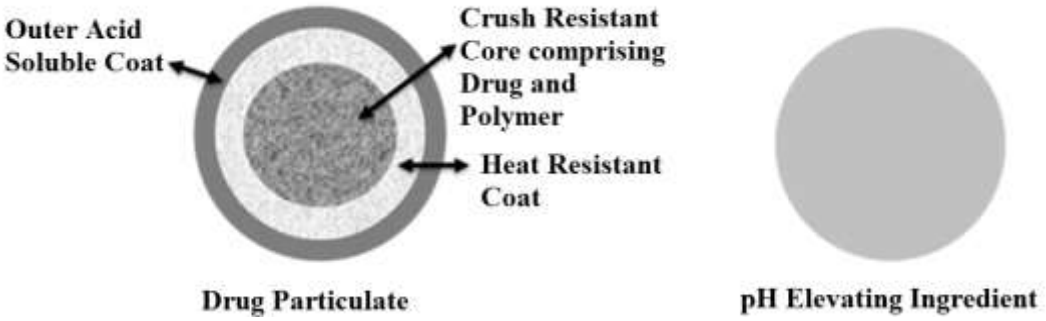

Figure 1: Overview of self-regulated crush-resistant drug delivery system to mitigate opioid overdose crisis.

2.2.1 Investigation of effects of different polymers on hindering extractability of drug from the dosage form

We introduced different water-soluble gelling polymers, as listed in table 2, into the drug particles and examined the level of polymer concentration at which it hinders the extraction of the drug using conventional methods. Specifically, we aimed to replicate the process of extracting the active ingredient from the composition at both room temperature and higher temperatures. In table 2, we have selected five distinct water-soluble gelling polymers: Klucel HXF (hydroxypropyl cellulose), Polyox WSR 303 (polyethylene oxide), Methocel K100M (Hydroxypropylmethyl Cellulose), Natrosol 250HHX (Hydroxyethyl Cellulose), and Blasol (Sodium Carboxymethylcellulose).[10,11,12]

Drug particulates, specifically minitablets, measuring 1.8mm in size, were manufactured utilizing each polymer in the following manner:

• Step 1: All components, excluding Mg. Stearate, were passed through a 30# ASTM screen and blended for a duration of 10 minutes.

• Step 2: Magnesium Stearate was passed through a 60# ASTM Screen and combined with the components from step 1 for a duration of 5 minutes. The resulting mixture is subsequently compacted using 1.8mm equipment to attain a hardness of 1.5 to 2.5 kiloponds in a rotary tablet press.

The drug particles from formulations F1, F2, F3, F4, and F5 were individually placed in five separate glass beakers, each labeled as M1, M2, M3, M4, and M5. Additionally, 25ml of water was added to each beaker. The beakers were manufactured in two batches. A group of M1, M2, M3, M4, and M5 beakers were placed on a hot plate and heated to a temperature exceeding 90°C, while another group of M1, M2, M3, M4, and M5 beakers were maintained at ambient temperature. The impact of temperature on physical and chemical findings was documented at two time points: T = 0 minutes and T = 5 minutes. The physical observations were principally assessed based on three predetermined criteria: Does the drug particles disintegrate into extremely minute particles? Does the water soluble polymer separate from the drug particles? And is there any noticeable increase in the viscosity of the drug solution? The presence of the drug in the beaker was determined through chemical analysis using UV spectrophotometry. The amount of drug extracted was then measured as a percentage.

Table 2: Effects of different polymers on hindering extractability of drug from the core system.

No	Ingredients	Concentration (%w/w)				
		F1	F2	F3	F4	F5
1	Metformin (*Eq. to 116.48mg Metformin HCl)*	32.36	32.36	32.36	32.36	32.36
2	Hydroxypropylmethyl Cellulose (Methocel K100M)	62.73	-	-	-	-
3	Polyethylene Oxide (Polyox WSR 303)	-	62.73	-	-	-
4	Hydroxypropyl Cellulose (Klucel HXF)	-	-	62.73	-	-
5	Hydroxyethyl Cellulose (Natrosol 250HHX)	-	-	-	62.73	-
6	Sodium Carboxymethylcellulose (Blanose)	-	-	-	-	62.73
7	Colloidal Silicon Dioxide	1.00	1.00	1.00	1.00	1.00
8	Magnesium Stearate	1.00	1.00	1.00	1.00	1.00
Total		**100.0**	**100.0**	**100.0**	**100.0**	**100.0**

** Target weight of each uncoated minitablets: 6mg and unit dosage form comprises 50 minitablets eq. to 100mg Metformin (Eq. to 116.48mg Metformin HCl)*

2.2.2 Investigation of different manufacturing process to attain desired crushing strength

In order to assess the effect of the manufacturing process on the crushing strength, only the drug particles from batches F2, F4, and F5, which demonstrated strong resistance to extraction at both room temperature and temperatures exceeding 90°C, were subjected to further curing at temperatures over 75°C for a duration of 1 hour. Before the curing process, a heat resistant coating of HPMC-based Opadry 85F was applied to the drug particles, as indicated in table 3. This coating was used to prevent the minitablets from sticking together due to the molten polymer at the curing temperature.

In order to examine the resistance of drug particles to crushing, cured and uncured drug particulates from batches F2, F4, and F5 were pulverized using a mortar and pestle as well as a coffee grinder for a duration of 1 minute. We also assessed the "Crushing Strength" to differentiate the pulverizing intensity of the medication particles across several batches. According to the specified standards, the crushing strength should be sufficiently high to withstand pulverization. This means that when the coated drug particles are placed in a coffee grinder for approximately 5 minutes, only 10% or less of them should pass through a #170 mesh screen.

The drug particulates' crushing strength was measured by sieving the pulverized particles using an ASTM #170 mesh sieve (100 micron) after 5 minutes of pulverization in a coffee grinder. The ASTM #170 screen mesh size is utilized to measure the quantity of particles smaller than 100 microns in the pulverized dosage form. This is necessary because drug formulation necessitates a particle size below 100 microns to ensure effective delivery to the lungs through nasal insufflation.[13,14,15]

Table 3: Heat resistant coating composition for drug particulates.

No.	Ingredients	Concentration (%w/w)		
		F2	F4	F5
1	Minitablets of Metformin HCl	97.09	97.09	97.09
2	Opadry 85F Coat (HPMC Based)	2.91	2.91	2.91
3	Water	q.s.	q.s.	q.s.
Total		**100.00**	**100.00**	**100.00**

** Target Weight of each heat resistant coated minitablets: 6.18mg*

2.2.3 Incorporation of self-regulated over-dose abuse deterrent properties in the developed crush-resistant drug delivery system

The developed crush-resistant drug particulates are designed with overdose abuse deterrent properties by incorporating a pH-dependent release feature and a pH elevating feature. These features enable the drug to be released from the formulation based on the pH of the surrounding stomach fluid, which is controlled by the pH elevating ingredient and the number of dosage forms administered. The formulation included an outer acid soluble coat (consisting of Eudragit EPO and magnesium stearate) to provide a pH-dependent release feature. This coat surrounded the heat resistant coat of the drug particulate. Additionally, a pH elevating ingredient was included in the drug delivery system in the form of particulates, as shown in figure 1 and table 4.

A coating dispersion of Eudragit EPO and Magnesium stearate was produced using a solvent mixture of water and IPA in a ratio of 90:10. The Metformin HCl minitablets, which are resistant to heat, were coated with a coating dispersion in a small-scale laboratory coater. The coating parameters were adjusted to produce a target weight increase of 21.35%.

The pH elevating ingredients were selected in a 75:25 ratio of sodium bicarbonate and magnesium oxide due to their specific properties. Sodium bicarbonate dissolves rapidly and immediately raises the pH of the media. On the other hand, magnesium oxide dissolves slowly but can sustain the elevated pH above 6 for a longer duration. The dosage unit of the pH elevating ingredient was determined based on the molecular weight of selected ingredients, such as sodium bicarbonate and magnesium stearate. The goal was to ensure that when a patient takes a single dosage unit, the pH of the stomach fluid does not exceed 5. This allows for the dissolution of the outer acid soluble coat of the drug particles in the stomach fluid, leading to the release of the drug and the desired therapeutic effect. Simultaneously, the quantity should be adequate to prevent the outer acid-soluble coating from dissolving in the stomach if the abuser takes 4 or more dosage units at once to achieve euphoric effects. This is done by increasing the pH of the stomach fluid above 5, which inhibits the release of drugs from the drug particles.[16,17,18]

According to the molecular mass, a total of 567mg of sodium bicarbonate and 91mg of magnesium oxide are needed to neutralize or increase the pH of 900ml of 0.01N HCl (with a pH of 2, equal to the pH of the stomach) to a value of 6. In order to activate the self-regulated anti-overdose property, we have distributed 567mg of sodium bicarbonate and 91mg of

magnesium oxide. This amounts to 141.75 mg of sodium bicarbonate and 22.75mg of magnesium oxide per dosage unit. The total quantity of sodium bicarbonate and magnesium oxide in 4 or more dosage units should be sufficient (567mg or more of sodium bicarbonate and 91mg or more of magnesium oxide) to effectively raise the pH of at least 6 or more of 900ml 0.01N HCl from pH 2.0. Table 5 displays the makeup of pH increasing particles that were produced using the following method:

- Step 1: Sodium bicarbonate, magnesium oxide, cross-povidone, microcrystalline cellulose, and aerosil were sifted through ASTM# 30 while magnesium stearate was sifted through ASTM # 60.
- Step 2: Step 1 sifted materials were blended for 10 mins at 25 RPM.
- Step 3: Step 2 blended material was compressed into particulates using a 1.8mm size multi-tips punch.

Capsule Filling: 375mg of drug particulates and 300mg of pH elevating particulates were filled into the "00" size capsule.

Table 4: pH dependent release composition for drug particulates.

No.	Ingredients	Concentration (%w/w)		
		F6	F7	F8
1	Heat Resistant Coated Minitablets of Metformin HCl	82.40	82.40	82.40
2	Eudragit EPO	10.00	12.60	15.00
3	Magnesium Stearate	7.60	5.00	2.60
Total		100.00	100.00	100.00

** Target Weight of each Eudragit EPO coated minitablet: 7.5mg*

Table 5: Composition for pH elevating particulates.

No.	Ingredients	Concentration (%w/w)
1	Sodium Bicarbonate	47.25
2	Magnesium Oxide	7.58
3	Cross-povidone	4.42
4	Microcrystaline Cellulose (MCC)	33.25
5	Aerosil	1.00
6	Magnesium Stearate	1.00
Total		100.00

** Target Weight of each pH Elevating particulates: 6mg*

2.2.4 In-vitro Dissolution Study

The in-vitro dissolving research was conducted at a temperature of 37°±1°C using 900ml of 0.01N hydrochloric acid in a USP Apparatus 1 operating at a speed of 100 revolutions per minute. The purpose of the in-vitro dissolve testing was to assess whether the dosage form would release the desired amount of medication in order to achieve therapeutic effectiveness. This testing involved placing one capsule in each dissolution vessel. In order to simulate an overdose situation in a laboratory setting, we conducted in-vitro dissolve testing on four capsules in each dissolution vessel. The pH of the dissolution media is measured after adding one dosage unit per dissolution vessel and four dosage units per dissolution vessel.

2.2.5 Determination of Extent of Resistant to convert minitablets in fine particles for nasal insufflation

10 capsules were subjected to pulverisation using coffee grinder for 5 mins and the resultant crushed particulates were sifted through a #170 mesh sieve. Further, the crushed particles passed through a #170 mesh size were mixed with 1ml of water.

2.2.6 Determination of Extent of Resistant to Injectability / Syringeability

5 capsules were subjected to pulverisation using a coffee grinder for 5 minutes and the resultant crushed dosage form was mixed with 5ml purified water. An attempt was made to withdraw the resultant mixture using a 1 ml insulin syringe for 1 minute.[19,20,21]

3.0 RESULT AND DISCUSSION

3.1 Polymer's intensity to hindering the extraction

Various literature and published patents affirm that any water-soluble polymer that can create a thick gel has the ability to hinder the extraction of drugs from the dosage form using traditional methods, so effectively resisting parenteral misuse. During our experiment, we noticed that all polymers, including Hydroxypropylmethyl cellulose (HPMC), a commonly used high viscosity polymer in pharmaceutical formulation, did not effectively prevent drug extraction.

At normal ambient temperature, we noticed that the majority of polymers were able to hinder the process of extracting drugs from drug particulates (as shown in figure 2). When the water temperature exceeded 90°C, the polymers HPMC and HPC, which are highly viscous water-soluble polymers found in the drug particulates of batches F1 and F3, respectively, underwent precipitation and disintegration into fine particles that are insoluble in water (as shown in

table 6). The results from chemical analysis confirms this conclusion, as it reveals that the F1 and F3 batches of the medicine have 88% and 95% of the drug available in solution form, respectively (figure 2). Through the application of a traditional filtration method, the drug solution can be readily isolated from the water-insoluble small particles of the polymers. The drug solution, after undergoing filtration, can be dehydrated to get a pure, dehydrated drug. This drug can then be misused by inhaling it via the nose or by injecting it directly into the body in liquid form, achieved by dissolving the dehydrated drug in small quantities of water, resulting in a pleasurable and euphoric sensation. The reason why Hydroxypropylmethyl cellulose (HPMC) and Hydroxypropyl cellulose (HPC) do not effectively prevent drug extraction at temperatures above 90°C is because their cloud point is lower. The cloud point for HPMC is between 55-65°C, while for HPC it is between 40-50°C.[19]

On the other hand, the minitablets from batches F2, F4, and F5, which contain polyethylene oxide, hydroxyethyl cellulose, and sodium carboxymethylcellulose respectively, maintain their structure at both room temperature and higher temperatures (table 6). They also impede the extraction of the drug from the drug particles (figure 2). Specifically, at room temperature, only 9%, 12%, and 16% of the drug is released, and at elevated temperatures (>90°C), only 14%, 17%, and 21% of the drug is released. This indicates that polyethylene oxide, hydroxyethyl cellulose, and sodium carboxymethylcellulose are more effective in preventing drug extraction at both room temperature and when heat is applied. Therefore, these substances have been chosen for further evaluation.[11,12,13,20]

Table 6: Physical Observation: room temperature Vs elevated temperature >90°C.

Composition	**F1**	**F2**	**F3**	**F4**	**F5**
Initial Observation T = 0 min	Minitablets float on the surface of water in all 5 beakers				
Room Temperature Set 1 at T = 5 mins	Mini-tablets float in intact form on the surface of water, gelling layer observed on the outer surface of mini-tablets.				
After application of heat - Set II at T = 5 mins					
Does mini-tablets disintegrates into very small particles?	Yes	**No**	Yes	**No**	**No**
Does water soluble polymer precipitate out from the core of minitablets?	Yes	**No**	Yes	**No**	**No**
Does any observation of increment in viscosity of drug solution?	No	**Yes**	No	**Yes**	**Yes**

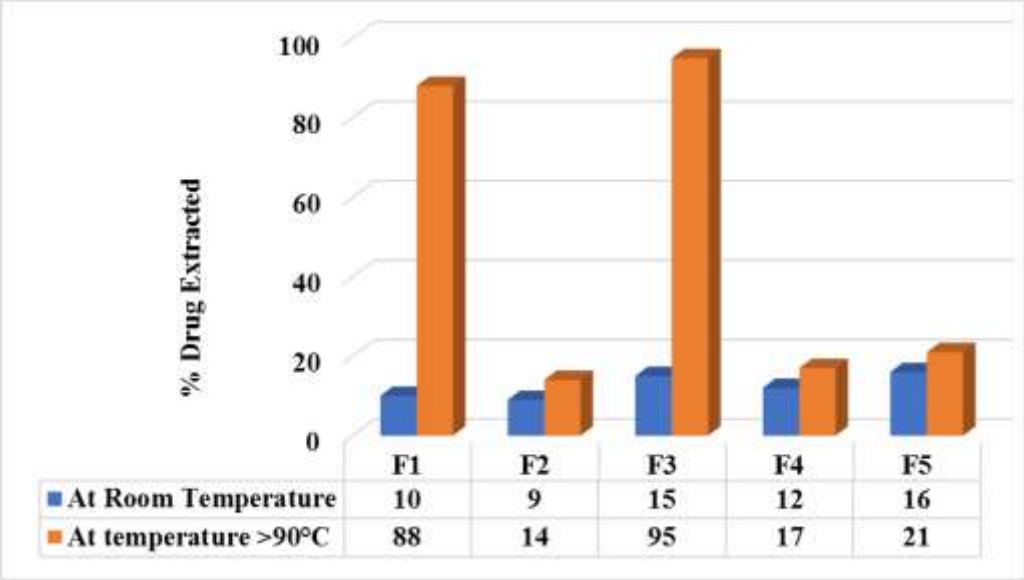

Figure 2: Chemical Observation: Percentages of drug extracted at room temperature Vs at elevated temperature >90°C.

3.2 Manufacturing Process

The drug particulates from batches F2, F4, and F5, which had not been treated, were readily pulverized into small particles using a mortar and pestle, as well as a coffee grinder, for a duration of 1 minute. Similarly, the drug particulates from batches F4 and F5 were easily pulverized into tiny particles using a mortar and pestle, as well as a coffee grinder, for a duration of 1 minute. On the other hand, the drug particles from batch F2, after being treated, proved to be highly resistant to crushing, both using a mortar-pestle and even when subjected to a coffee grinder for a duration of 1 minute. Figure 3 demonstrates that the uncured drug particulates from batches F2, F4, and F5 had a crushing strength failure. This occurred because the crushed particles of the drug particulates, which passed through ASTM #170 mesh size, exceeded 10%. Specifically, the percentages were 25%, 30%, and 36% for F2, F4, and F5 batches, respectively. These values surpass the predetermined limit of <10%. The cured drug particulates of batch F2 exhibited a much higher crushing strength compared to batches F4 and F5. Only 0.5% of the initial weight of pulverized particles from the F2 batch passed through ASTM#170 mesh, whereas it was 26% and 31% for batches F4 and F5, respectively. The fact that over 99% of crushed drug particles were retained on the ASTM 170# screen suggests that the cured drug particles from the F2 batch could be a strong deterrent against nasal insufflation. This is because particles must be smaller than 100 microns in order to be delivered to the lungs through nasal insufflation.[15,21,22,23]

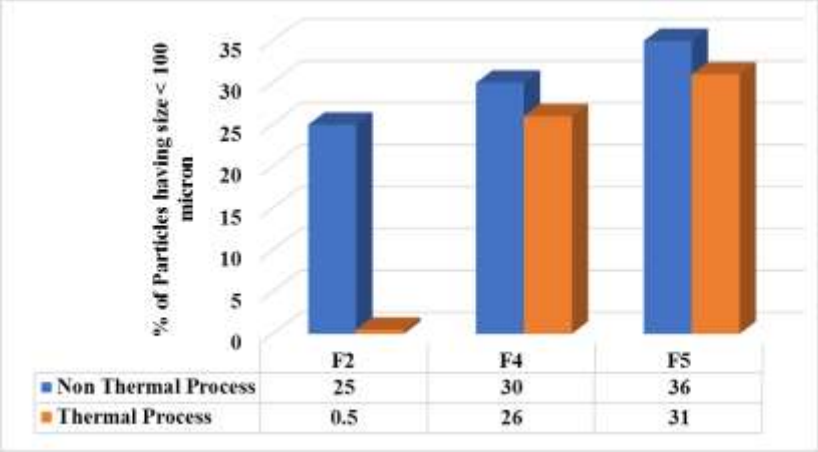

Figure 3: Crushing strength: Uncured minitablets vs cured minitablets.

3.3 In-vitro Dissolution Study

To assess the drug release characteristics of the dosage form in both normal and overdose scenarios, we conducted in-vitro dissolution testing. This involved placing a single capsule or four capsules in separate dissolution vessels and subjecting them to a temperature of 37°±1°C for 2 hours. The dissolution medium used was 900ml of 0.01N HCl, and the testing apparatus employed was a USP Apparatus 1 (basket) rotating at 100 rpm. Figure 4 demonstrates that, when taken as directed, a single dose of the medication released over 90% of the drug within 60 minutes from the different formulations (F6, F7, and F8) containing varying amounts of Eudragit EPO and magnesium stearate. This indicates that the pH-increasing particles in a single dose (141.75 mg sodium bicarbonate and 22.75 mg magnesium oxide) are not enough to raise the pH of the dissolution media above 5, as shown in figure 5. In an overdose scenario where four dosage units were used per dissolution vessel, the combined presence of pH elevating particulates in these units caused the pH of the dissolution media to rise above 5 (as shown in figure 5). This prevented the outer acid soluble coat of drug particulates from dissolving, thereby hindering the release of the drug from the dosage units. Specifically, less than 7% of the drug was released within a 120-minute period (as depicted in figure 4). Under typical dosing conditions, a patient will receive the desired therapeutic effect, while an abuser will not feel euphoria. This is because the drug delivery system changes the conditions in the stomach, specifically by increasing the pH of the gastric fluid to a level above 5. This prevents the drug from being released, as the outer acid soluble coat surrounding the drug particles remains undissolved in the dissolution media due to the elevated pH.

The primary objective of evaluating various ratios of Eudragit EPO and magnesium stearate is to ascertain the impact of the quantity of water insoluble fraction of the outer acid soluble

layer on the intensity of retarding drug release. Figure 4 demonstrates that an outer acid soluble coat with a higher proportion of water insoluble material (specifically, the amount of magnesium stearate in batch F6) has a greater ability to slow down the release of the drug. In fact, it was able to slow down more than 97% of the drug even after 120 minutes in cases of overdose. On the other hand, when compared to a lower proportion of water insoluble material (batch F8), which only slowed down 92% of the drug after 120 minutes in cases of overdose, the higher proportion released more than 90% of the drug within 60 minutes under normal dosing conditions. This finding suggests that the water-insoluble substance found in the outer acid-soluble coating needs to be optimized in order to achieve the desired level of drug retardation in the drug particles.

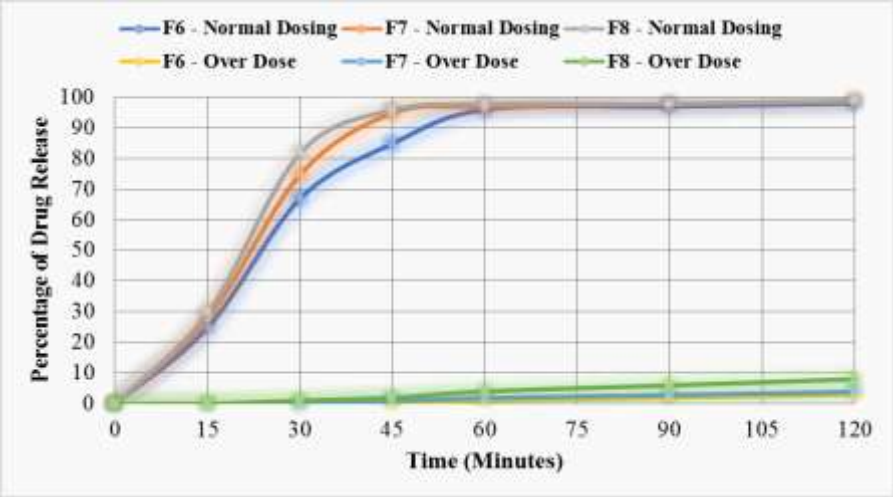

Figure 4: Dissolution profile comparison: normal dosing condition Vs overdose condition.

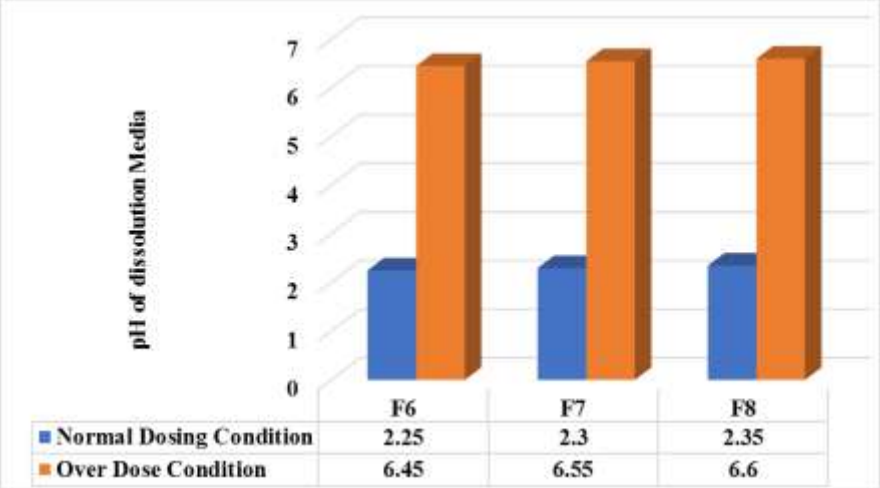

Figure 5: Impact on pH of dissolution media: normal dosing condition vs overdose condition.

3.4 Demonstration of deterrence to nasal insufflation

Only 0.4% of the initial weight of the dosage form consisted of the crushed particles that went through the #170 mesh filter. It is important to mention that over 99% of the crushed minitablets particles were captured by the ASTM 170# screen. Therefore, it can be concluded that the self-regulated anti-overdose crush resistant drug delivery system has a high level of crushing strength, as only 0.4% of particles are able to pass through ASTM 170#. This system effectively prevents nasal insufflation, as discussed earlier, because the particle size needs to be less than 100 microns for efficient delivery to the lungs via nasal insufflation. In addition, when the crushed particles of the dosage form pass through the ASTM # 170 screen and come into contact with a small amount of water (1 ml), they form a thick gel. This means that if someone tries to snort these crushed particles, it will cause irritation in their nasal passageway. This is because the crushed particles will start to form a thick gel inside the nasal passageway when they come into contact with the moisture of the nasal mucous membrane.[23,24,25,26]

3.5 Demonstration of Deterrence to Injectability / Syringeability

When the pulverized dosage form is combined with 5ml of pure water, it creates a highly thick slurry. The highly viscous mixture could not be withdrawn using a 1 ml insulin syringe for 1 minute, indicating that the self-regulated anti-overdose crush resistant drug delivery system effectively prevents injection or withdrawal of the medication.

4.0 CONCLUSION

A single dose unit dissolved completely within 60 minutes, releasing more than 90% of the drug. However, when four dosage units were dissolved together, more than 90% of the medication was still not released even after 120 minutes. This leads us to the important conclusion that the drug substance (Metformin HCl) released from the self-regulated anti-overdose drug delivery system will effectively treat the patient's therapeutic condition (chronic pain) when they take a single dose. However, if an abuser takes 4 or more doses at once, they will not experience euphoria. This is because the elevation of gastric fluid pH to a level greater than 5 prevents the outer acid soluble coat surrounding the drug particles from dissolving in the stomach fluid. As these particles pass into the intestinal tract, where the pH always remains above 5, the outer acid soluble coat continues to remain undissolved. This hinders the release of the drug from the drug particles throughout the gastrointestinal tract.

The self-regulated anti-overdose crush resistant drug delivery system may successfully prevent nasal insufflation by utilizing particles that are smaller than 100 microns, as just 0.4 percent of particles are able to pass through ASTM 170#. The endeavor to extract a highly thick mixture using a 1 ml insulin syringe was unsuccessful, suggesting that the self-regulated anti-overdose crush resistant drug delivery system may effectively prevent the mixture from being injected or drawn into the syringe.

The analytical data unequivocally showed that the newly created self-regulated anti-overdose crush resistant drug delivery system would effectively address the crisis of overdose abuse, as well as the abuse of drug formulations through non-oral routes such as nasal and parenteral administration. This would be achieved by preventing the crushing of dosage units into particles smaller than 100 microns and by impeding their ability to be drawn into a syringe or injected.

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