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Research Article:

Development and Characterization of Abuse-Deterrent Tablets Using Chlorpheniramine Maleate as a Surrogate

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Abstract

Background and Objectives: Drug abuse has become a worldwide problem associated with increased addiction and death, which led to encouraging the Food and Drug Administration and many companies to develop formulations that can prevent or decrease abuse. This study aimed to develop abuse-deterrent formulations using chlorpheniramine maleate as a model drug. The formulations were evaluated for their ability to resist crushing and injection, which are common methods of drug abuse. **Method:** The direct compression method was used to prepare tablets. Polyethylene oxide was used as a polymer at two concentrations (40% and 80%) and two molecular weights (300,000 and 4,000,000). Neusilin US2 and microcrystalline cellulose were added as tablet diluents. Half of the formulations were heat-treated in an oven at 80 °C. A full factorial experimental design was developed using Minitab software, resulting in 16 formulations. **Results:** The results showed that both the grade and concentration of Polyethylene oxide, along with oven heating, significantly affect almost all the tested properties of the tablets. However, altering the type of diluent only impacts some tablet properties, such as hardness. **Conclusion:** This study has shown the feasibility of using polyethylene oxide at a different grade to prepare abuse-deterrent dosage forms. Furthermore, the utilization of a diluent such as neusilin in the preparation of tablets introduces challenges in terms of crushing; this could help reduce drug abuse.

1. Introduction

Prescription drug abuse has become a global problem, leading to increased deaths. Over the past two decades (1, 2). Western countries have seen a rise in opioid prescriptions for non-cancer pain, which has unfortunately also led to increased illegal use, misuse, and overdoses of these drugs (3-5). A national survey carried out in the United States of America found that 2 million more people began abusing prescription opioids, and this percentage is still rising every year (6). Certain drug classes, such as opioids (e.g., hydrocodone, oxycodone and fentanyl), CNS stimulants (e.g., methylphenidate and amphetamines), and CNS depressants (e.g., benzodiazepines and barbiturates), are more prone to abuse (7). The US Food and Drug Administration (FDA) is focused on encouraging the development of abuse-deterrent formulations (ADFs) for tablets and considers it a public health priority to combat the abuse of opioids (8-10). Extended-release formulations are more likely to be abused than immediate-release formulations due to the higher dosage. As a result, the FDA recommends developing abuse-deterrent properties for extended-release formulations (11). Purdue Pharma's reformulated OxyContinTM (oxycodone HCl) extended-release tablet received FDA approval in 2010.

ADFs are designed to prevent the misuse of prescription drugs by making it harder to alter or tamper with the medication (12). Abusers often crush, dissolve, or heat these drugs to inject, inhale, or ingest them, which increases the potential for abuse (13, 14). The goal of ADFs

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is to reduce the effectiveness of these manipulation techniques and minimize the euphoria or high desired by abusers (15). While ADFs aim to be resistant to all known methods of abuse, it is rare for a single formulation to address every possible abuse scenario. Therefore, ADFs are often designed to combat the specific abuse methods prevalent in different regions (16). Future developments may include over-the-counter products with abuse-deterrent features to address issues such as the misuse of pseudoephedrine and cough medicines containing dextromethorphan (7). The FDA has approved ten abuse-deterrent dosage formulations (ADFs) (17). Nine of the approved products are extended-release and one immediate-release (IR), which include Hysingla ER, MorphaBond ER, Xtampza ER, Arymo ER, Vantrela ER, RoxyBond (IR), Embeda®, Targiniq ER, Troxyca® ER, and OxyContin® (18-21). Among these, three use a combination of agonists and antagonists, while seven employ physical or chemical barriers to prevent abuse (22-24). These barriers, which account for about 70% of approved ADFs, create gels or increase mechanical strength to prevent manipulation (6, 25). Commonly used excipients include foaming agents, carbomers, xanthan gum, polyethylene oxide (PEO), sucrose acetate isobutyrate, and hydroxypropyl methylcellulose (26), with PEO being the most frequent. PEO, also known as Polyox™, is favored for its chemical and physical barrier properties, creating viscous gels that resist extraction and injection (27-29).

PEO is known for its stability, compressibility, and ability to form gels upon hydration or heating, making it a multipurpose ingredient in various pharmaceutical applications, including ADFs (30). Previous works focused on evaluating the effect of PEO and other polymers on the abuse-deterrent properties using different grades of polymer (31-34), while there is limited information available regarding the effect of different diluents such as Neusilin US2 (NEU) and microcrystalline cellulose (MCC). In addition, there is limited information on the use of large particle diluents such as NEU in ADFs. Furthermore, the present research investigation focused on producing abuse-deterrent extended-release opioid tablets with excipients acting as physical barriers to reduce the risk of opioid abuse. In this work, we aimed to prepare an abuse-deterrent dosage form through direct compression utilizing excipients to serve as physical barriers. The design of experiments (DOE) method was used, utilizing Minitab software to create a full factorial design and analyze the impact of each variable on the abuse deterrent properties. PEO was utilized as a polymer, and NEU and MCC were used as diluents. The DOE included four variables, each with two levels: the molecular weight (M.wt) of PEO (300K and 4M), the concentration of PEO (40% and 80%), the type of diluent (MCC and NEU), and the thermal process (untreated and treated).

Material and Method

1.1. Materials

Pure drug chlorpheniramine maleate (CPM) and microcrystalline cellulose MCC (Avicel PH 102) were provided by Samaraa drug company (Iraq); magnesium alumino-metasilicate (Neusilin) was provided by Fuji chemical industry (Japan), PEO 300,000 and PEO 4M were purchased from Hyperchem company (China), and magnesium stearate was provided from Mosul college of pharmacy.

2.2. Method

2.2.1. Characterization of chlorpheniramine maleate

2.2.1.1. Determination of melting point

The melting point (m.p) of CPM was measured using the capillary tube method. A glass capillary tube with one end sealed was filled with dry powder, creating a column 3 mm high at the closed end of the tube through gentle tapping on a hard surface. After that, the tube was put in a melting point apparatus, and the temperature gradually began to rise. After that, the melting of the samples was visually observed (35-37). Melting point was measured in triplicate.

2.2.1.2. UV scan of CPM

A stock solution of 400 µg/mL was prepared by dissolving 20 mg of CPM in 50 mL of distilled water (D.W) (38). From this stock solution, 2.5 mL was taken and diluted to 10 mL with D.W to prepare a 100 µg/mL solution. In order to find the maximum wavelength absorbance (λmax) of the prepared samples, the UV-spectrophotometer was run within the range of 200 to 400 nm (39).

2.2.2 Preparation of abuse-deterrent dosage form

2.2.2.1 Design of experiments (DOE)

The DOE was developed using Minitab software 21. A two-levels full factorial design with four factors was chosen. These factors included the concentration of the polymer (40% and 80%), grades of the polymer (300,000 and 4M), type of the diluent (MCC and NUE), and thermal treatment (before and after oven), As a result, a 2^4 full factorial design was created and consisted of 16 formulas, in which every factor was examined at two different levels (low and high). To evaluate the abuse deterrence effectiveness for our prepared tablets, four responses (hardness, disintegration, syringeability and injectability) were measured for each batch. Stepwise regression analysis was carried out to

identify the main affecting factor and potential interactions between the factors. Therefore, the stepwise regression process that was chosen to identify the most significant factors for the model and eliminate the insignificant ones (40) The resulting formulas from this DOE were presented in **Table 1**.

Table 1. Design of experiment of abuse deterrent dosage form.

No. of formula	Conc. Of polymer	Grades of polymer	Thermal treatment	Type of diluents
1	40%	300K	Before	MCC
2	80%	300k	Before	MCC
3	40%	4M	Before	MCC
4	80%	4M	Before	MCC
5	40%	300K	After	MCC
6	80%	300K	After	MCC
7	40%	4M	After	MCC
8	80%	4M	After	MCC
9	40%	300K	Before	NEU
10	80%	300k	Before	NEU
11	40%	4M	Before	NEU
12	80%	4M	Before	NEU
13	40%	300K	After	NEU
14	80%	300K	After	NEU
15	40%	4M	After	NEU
16	80%	4M	After	NEU

2.2.2.2. Preparation of tablet

Tablets were made using a direct compression method with a target weight of 200 mg for each tablet; PEO was used as a polymer. Moreover, NEU and MCC were included as tablet diluents, in which NEU is a granulated synthetic, amorphous form of magnesium aluminum meta-silicate that has an adequate compressibility index and good flowability, while MCC is a white powder composed of agglomerated porous particles (41-43). Furthermore, magnesium stearate was used as a lubricant. Moreover, CPM was used as a model drug in this study.

For each formula in the design, the required amount of PEO, CPM, and diluent was weighed and blended for 10 minutes at 50 rpm using a V-shaped blender. Then, magnesium stearate (1% w/w) was added to the blend and mixed for an additional 2 minutes. Approximately 200 mg of each blend were weighed and compressed manually using a single-punch tablet press machine. The compression force was adjusted to be consistent for all formulas.

2.2.2.3. Thermal treatment process

Sixteen formulas were prepared, and half of these formulas were subjected to heat after compaction. These tablets were evenly placed on an aluminum foil inside the center of an oven at 80 °C for 1 hr. The selected temperature was above the melting point of PEO (65–70 °C) (44). After that, tablets were left to cool down at room temperature for a minimum of 24 hours before being subjected to further characterization.

2. Evaluation of tablets

All the tablets were evaluated using procedures as mentioned in pharmacopeia:

2.1. Tablet Crushing strength (hardness)

The hardness test was conducted on six tablets from each batch using a tablet hardness tester (YD-1, LPMIE, China) fitted with a 199 N load cell. The average hardness of six tablets was calculated with standard deviations. The tablets' hardness was considered as > 199 N if they did not experience diametric breakdown and only slight deformation from their initial shape when the instrument's maximum force was exceeded (34).

2.2. Friability

Friability test was carried out by randomly selecting ten tablets from each batch; the weight of all tablets was measured together. Then, these tablets were placed into the friabilitor (CS-3, China), which was operated at a speed of 25 rpm for a duration of 4 min. The tablets were subsequently taken off, dedusted, and re-weighted (45).

For the majority of oral tablets, the friability percentage is considered acceptable if it is less than 1% (46). The

following formula was used to determine the friability percentage (47):

$$\textbf{Friability } \% = \frac{\textbf{W1} - \textbf{W2}}{\textbf{W1}} * \textbf{100}\%$$

Where:

W1: Initial weight ; W2: Final weight

2.3. Disintegration time

Disintegration times of 16 formulas were recorded using a disintegration tester (BJ-2 Huanyu, China). Six tablets from each formula were randomly selected and placed in the disintegration tester using 900 mL of PH 1.2 (0.1N HCl) at 37 ± 0.5° C for 2 hours, then replaced with 900 mL of PH 6.8 phosphate buffer at 37 ± 0.5° C for 2 hours. The average time of disintegration for these six tablets was calculated with a standard deviation.

2.4. Syringeability and injectability

A quantity of formulation equivalent to 3 tablets (600 mg) was weighed and combined with 15 mL of D.W in a plastic container at room temperature (20-25 °C) (48). After that, in order to allow the polymer to dissolve completely, the preparations were agitated on a magnetic stirrer plate (HY-HS11, Korea) for an adequate amount of time (34). The resultant solutions were transferred to a 20 mL scintillation vial before the test. Then, each formulation was assessed for their syringeability (pulling force) and injectability (pushing force) by using a digital force gauge (AIDA engineering LTD, China) (48). All formulations were tested using a 10-mL syringe equipped with a 21-gauge needle (49), and Every test was performed with a new syringe and needle (44). Each formulation was examined three times. As another measure of syringe-ability, the volume withdrawn into the syringe was visually observed and reported.

2.5. Differential scanning calorimetry analysis (DSC)

Test was made on pure drug CPM, physical mixture of formulas (F3 and F11), milled tablet of untreated formulas (F3 and F11) and milled tablet of treated formulas (F7 and F15) using DSC (Shimadzu DSC-60, Japan). 2-3 mg of the samples were weighed and placed in an aluminum pan that was heated at a rate of 10°C per minute and temperature up to 300 (50). DSC offers descriptions on the physical characteristics of the samples, such as their amorphous state as well as the level of drug crystallinity (51).

2.6. Powder X-ray diffraction (PXRD)

The PXRD of CPM, a physical mixture of formulas (F3 and F11), milled tablets of untreated formulas (F3 and F11), and milled tablets of treated formulas (F7 and F15) were measured by a diffractometer (AERIS research edition, Netherlands) with a Cu Kα radiation source at 40 kV and 30 mA, with the 2 Theta (2θ) value ranging from 10° to 70° with a step size of 0.02°. The scanning rate was 2 s per step (28).

2.7. Dissolution study

The *in vitro* dissolution test of CPM was performed using dissolution test apparatus II (Copely, U.K), which is made up of six vessels; each vessel is filled with 500 mL of D.W. The temperature was set at 37 °C ± 0.5 °C and paddle speed of 50 rpm. Samples of 5 mL were collected from each vessel at 0.5, 1, 2, 3, 4, 5, 6 hrs, and 24 hrs as an infinity point to be considered as a reference for cumulative release of the drug. To maintain a total volume of 500 mL in each vessel, 5 mL of dissolution media was added to replace each withdrawn sample. Every extracted sample was passed through a 0.45 µm membrane filter and examined using a UV-spectrophotometer at a 261 nm wavelength to measure drug concentration. The total amount of drug was plotted against the period of time to achieve a cumulative drug release plot. The dissolution test was conducted three times in order to ensure accuracy and reliability.

2.8. Statistical analysis

Statistical analysis was performed using Minitab software 21, applying a factorial design analysis. The data were expressed as mean ± standard deviation using Excel (2016). Differences were considered statistically significant if the p-value was ≤ 0.05 and non-significant if p > 0.05.

4. Results and Discussion

4.1. Characterization of Chlorpheniramine maleate

4.1.1. Determination of melting Point

The m.p of CPM was 135 °C, which falls within the range of reported reference (52, 53). This means that the used drug is pure.

4.1.2. UV scan of CPM

The diluted solution of CPM in D.W was scanned by a UV-visible spectrophotometer at a wavelength range of 200–400 nm using a 1 cm quartz cell. A spectrum with a maximum absorbance (ƛ max) of 261 nm was obtained, and this is similar to the reported results (54).

4.2. Preparation of abuse-deterrent dosage form

4.2.2. Preparation of tablet

The abuse-deterrent tablets, which were composed of sixteen formulas, were prepared by the direct compression method. The direct compression method was preferred over tableting method because it requires fewer processing steps than other processes, making it the simplest and least expensive method for manufacturing of tablets (55-57). Since there are no intermediate steps involved, the approach of directly tableting the physical mixture after blending ensures unaltered API quality and low production costs (58).

4.2.3. Thermal treatment process

Thermal treatment was performed on half of the prepared formulation using an oven. The thermal process's temperature of 80 °C was higher than the polymers' melting point, which improves tablets strength and reduces their susceptibility to human manipulation through crushing (31). Using PEO as a matrix along with thermal treatment to produce tablets with high crush strength and gel-forming properties is a common manufacturing process for extended-release, abuse-resistant formulations (27, 59). According to Meruva *et al.* (2020) heating PEO above its melting point enhances the mechanical strength of the dosage form and this makes the tablets more resistant to crushing or grinding, which are common methods used to abuse medications (34). Furthermore, Tocce *et al.* (2020) performed the M.wt analysis on pure PEO compacts and observed that the polymer did not significantly degrade after 60 minutes of heating at 80°C (44).

4.3. Evaluation of Tablets

4.3.1. Hardness

One of the most important performance factors for oral ADFs made with physical barrier techniques is tablet hardness. While there are no established standards for tablet hardness to be considered abuse-deterrent, observations from research indicate that a tablet hardness of about 500 N offers adequate resistance towards the drugs manipulation (31, 60). The traditional formulations are not tough enough to withstand crushing; thus, the fine powder that is produced can be easily snorted through the nose (33). Therefore, ADFs with crushing prevention features are frequently made using a blend of excipients (such as high M.wt of polymer) and manufacturing techniques (such as thermal treatment) that improve mechanical characteristics (31). However, using a diluent like NEU is important in preventing abuse by inhalation. NEU US2 has a larger average particle size (about 100 microns), which makes it less likely to be inhaled. Smaller particles can easily become airborne and be inhaled, but larger particles are less prone to this (61).

The hardness value of untreated formulas varied from (41.9) to (101.6) N for MCC and (121.31) to (141.3) N for NUE. While the hardness value of treated formulas varied from 119.08 to >199.9 N for MCC and 143.7 to >199.9 N for NUE. tablets of formulations (F6, F8, F15, and F16) were resistant to breaking but could only be distorted instead of breaking by the apparatus beyond the maximum hardness level >199.9 as shown in **Figure 1**. this would indicate a plastic behavior due to the thermoplastic character of the polymer which is characterized by its ability to soften when heated and solidify upon cooling (62). Therefore, allowing the tablet to deform plastically rather than fracture and this observation similar to previous works (31, 33). These formulations may be regarded as crush-resistant, like OxyContin®, Hysingla™ ER, MorphaBond ER™, and Xtampza ER (49).

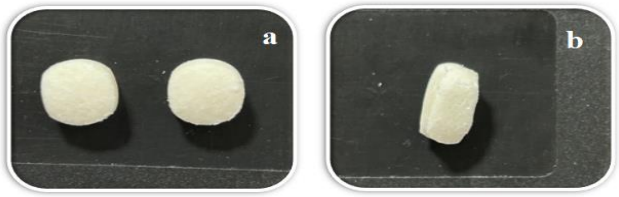

Figure 1. Shape of tablet: (a) at 199.9 N. (b) beyond the maximum level of apparatus (more than 199.9 N)

Hardness increases significantly after thermal treatment, as shown in the main effect plot, **Figure 2**. Bartholomaeus *et al.* (2012) have observed that thermally treated PEO tablets exhibit high resistance to crushing (63). Rahman *et al.* (2016) have found that heating improves hardness and

also demonstrated that tablets that do not break at lower rates may break at higher compression rates (48). Meruva *and Donovan* (2019) have observed that tablets treated at 80°C exhibited a significant increase in hardness, exceeding the instrument's testing limit. These tablets did not break under load but instead deformed, suggesting that the thermal treatment at 80°C made them more plastic and less brittle (30). A possible reason for this enhancement is the melting, fusion, and bridge formation of the polymer particles (60). In contrast, M.wt had no significant effect on the hardness value, as demonstrated in the main effect Figure 2, which aligns with findings from Meruva *and* Donovan (2020); this is because PEO of different M.wt exhibits similar compaction behavior (34). While there is a slight decrease in hardness with increasing polymer concentration in untreated formulas, this difference is not significant. However, when the polymer concentration is increased in thermally treated formulas, there is a significant effect on hardness value, as illustrated in **Figure 3**. Similar research evaluating the abuse deterrence of thermally treated formulations has shown that crush resistance increases with the concentration of PEO (33, 40). Rahman et al. (2017) have observed that the hardness of the treated tablets, which contained higher amounts of PEO (73.9-78.9%), was significantly higher than the measurable range of the hardness tester in comparison with a lower amount of PEO (60). The polymer concentration in treated formulations determines their hardness. When heated, the PEO polymer melts, forming fusion and/or bridges between the polymer and the other components in the formulation. It solidifies into a stronger matrix that resembles plastic as it cools. Although the tablets still retain some strength, they do not fully solidify into a matrix resembling plastic when the polymer content is low Moreover, hardness values increased significantly with NUE due to its high tensile strength, which allows for the production of hard tablets with relatively low compression force, suggesting high bonding strength (64, 65). Finally, according to tablet hardness results, M.wt and the concentration of PEO had little effect on the hardness of untreated formulas. This observation is consistent with previous work, which found that M.wt and the amount of PEO do not affect the tensile strength of placebo PEO tablets that are directly compressed (66, 67). This could be attributed to the fact that PEO with varying M.wt exhibit similar compaction characteristics (66).

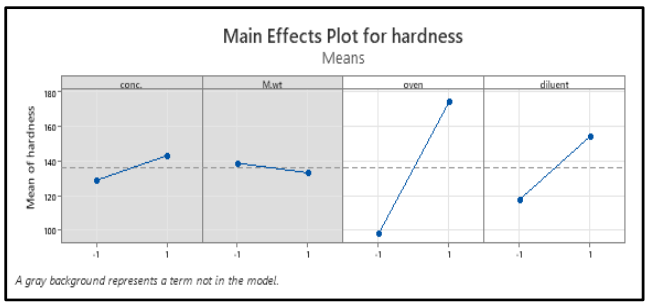

Figure 2. The main effects plots indicate that the thermal process and the type of the diluent had a significant effect on the hardness

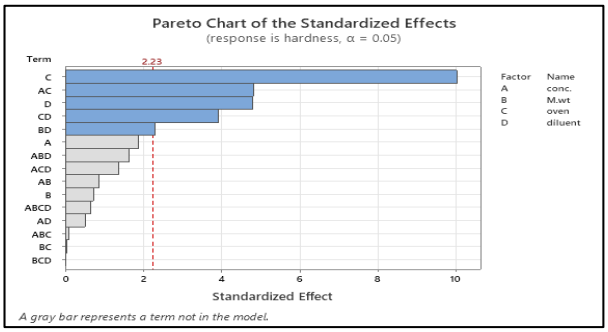

Figure 3. The Pareto chart indicated that the type of diluent had a significant effect on hardness. Additionally, the interaction of concentration and the thermal process significantly influenced tablet hardness.

4.3.2. Friability

The friability test measures the tablet's resistance to abrasion and loss of mass during packing, dealing with, and transportation (68). The friability test was conducted by randomly choosing 10 tablets and putting them in a friability tester. Subsequently, the percentage of friability was determined.

All formulas had an allowed friability percent that was within the acceptable limit (which is lower than 1%). This means that all tablets do not have a dust tendency while they are very hard. Usually hard tablets tend to form dust more than the same tablets with less hardness (69, 70). Adding highly compactible diluents, such as NEU producing tablets with high hardness (with relatively not high compression force) and less friability.

4.3.3. Disintegration time

The disintegration time is defined as the duration it takes for a tablet to break down and transform into smaller

particles. The process may initiate early when the oral tablet comes into contact with water that is consumed with it, even prior to reaching the stomach.

All formulas with 4M PEO have disintegration times of more than 4 hrs. and did not depend on the concentration of the polymer, thermal treatment, and type of diluent. **Figure 4**. shows the swelling of tablets after 4 hrs. Formulas with 300K PEO had different disintegration times of less than 4 hrs. However, disintegration time decreased after thermal treatment for formulas with 300K PEO. Therefore, the disintegration time of the prepared tablets depends mainly on M.wt of PEO, as illustrated in **Figure 5** and 6.

Figure 4. Swelling of tablets after 4 hrs of disintegration test

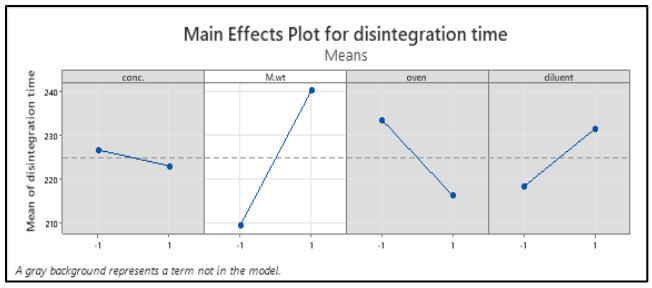

Figure 5. The main effects plot indicates that only the molecular weight of the polymer significantly affected the disintegration time.

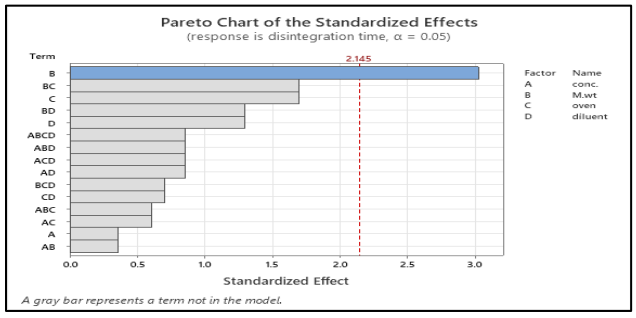

Figure 6. The pareto chart of the disintegration time

4.3.4. Syringeability and injectability:

Syringeability is the ability of the suspension or solution to get through a hypodermic needle before injection, while injectability is the ability of the solution to be pulled out of the syringe (60).

The parenteral route is another common method of drug abuse, which involves extracting a drug in a small volume of solution and then injecting the solution intravenously. (71 ،49). Therefore, these tests are essential for ADF in order to prevent drug abuse or misuse via the parenteral route (48). Moreover, ADFs tablets with PEO as a polymer can absorb water and form a viscous solution, making it challenging to draw up and administer via the IV route (44, 72).

The syringing force for tablets prepared with MCC varied from 13.29 N (F1) to 19.93 N (F4) for untreated formulation and from 12.66 N (F5) to 18.35 N (F8) for treated formulation. On the other hand, the syringing force for tablets prepared with NEU varied from 10.46 N (F9) to 20.57 N (F12) for untreated formulation and from 9.3 N (F13) to 19.03 N (F16) for treated formulation. There is a slight decrease in syringing force after the thermal process and by changing the type of diluent. However, this difference is not significant (P>0.05) which means the syringeability mainly depends on the concentration of polymers and their M.wt as shown in **Figure 7** and **8**.

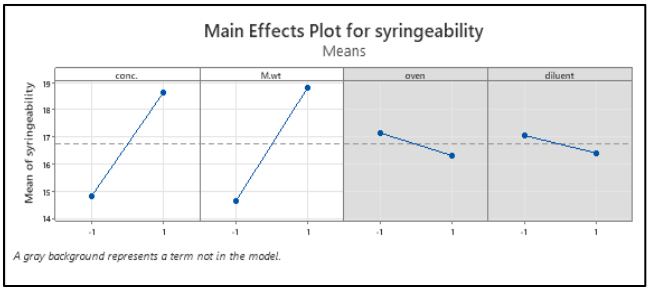

Figure 7. The main effects plot of syringeability indicates the significant effect of the concentration and the M.wt of the polymer

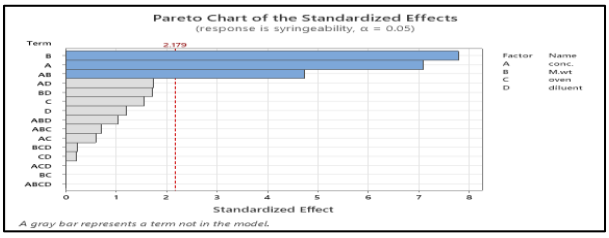

Figure 8. The Pareto chart indicated that both concentration and the molecular weight of the polymer had a significant effect on syringeability, and that the interaction between these two factors also significantly influenced syringeability.

Moreover, injecting force mainly depends on the concentration of polymers and their M.wt as well as the thermal process, as shown in **Figure 9** and **10**. Injecting force for tablets prepared with MCC varied from -14.89 N (F1) to -48.11 N (F4) for untreated formulation and from -14 N (F5) to 46.49 N (F8) for treated formulation. On the other hand, the injecting force for tablets prepared with NEU varied from -14.08 N (F9) to -49.18 N (F12) for untreated formulation and from -10.61 N (F13) to 45.18 N (F16) for treated formulation.

After thermal treatment, there is a decrease in syringing and injecting forces. While the decrease in syringing force is not significant ($P > 0.05$), the reduction in injecting force is significant ($P < 0.05$), which aligns with findings from previous work (49). On thermal exposure, PEO undergoes degradation into smaller molecular fragments (shorter chain length) (60, 73).

Higher M.wt is associated with increased syringing and injecting forces and requires a longer holding time, as demonstrated by Elizabeth *et al.* (2020) (44). This increased force results in a decrease in the volume withdrawn from the syringe. Therefore, greater M.wt PEO is much more viscous and challenging to pull or inject (74). Rahman *et al.* (2016) have observed that the volume of liquid withdrawn increased while the syringeability and injectability forces decreased in comparison to the corresponding untreated formulations, and the M.wt of the PEO in the formulation showed the strongest increase in syringeability, although they also discovered that the treated samples had slightly reduced forces than the untreated samples (48). See **Figure 11**. M.wt is therefore considered a significant variable for syringing and injecting forces, which is crucial for improving ADF features.

Additionally, as the concentration of the polymer increases; both syringing and injecting forces also increase, similar observation was found by previous research (49). Although there is a slight decrease in syringing and injecting forces with NUE, this difference is not significant ($P > 0.05$).

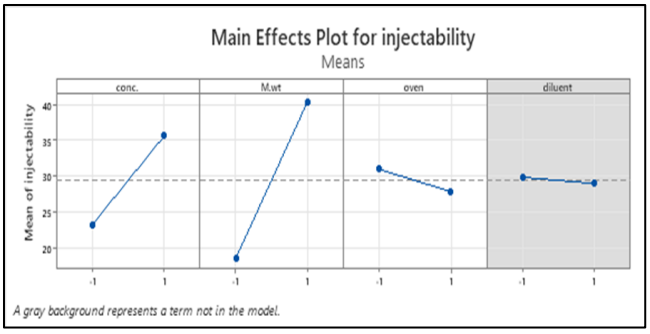

Figure 9. The main effects plot of injectability indicates that all factors had a significant effect except the type of the diluent

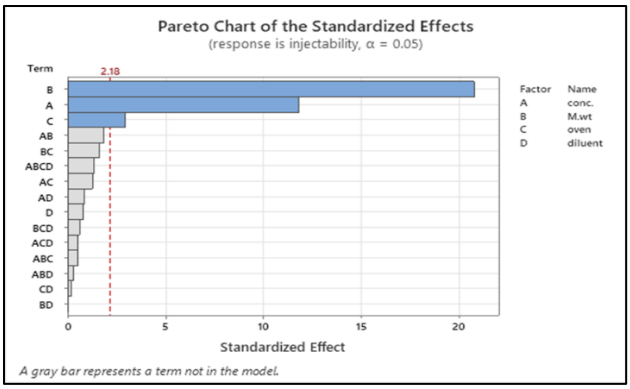

Figure 10. The pareto chart of injectability

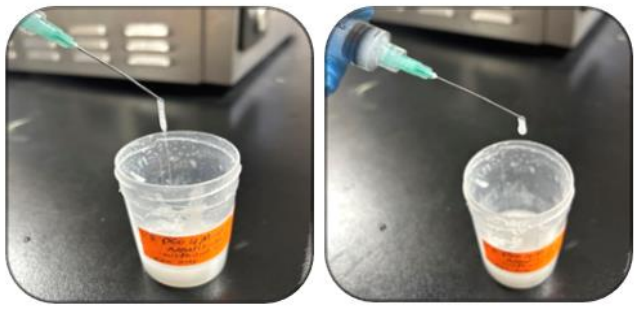

Figure 11. A viscous solution may discourage abusers from injecting extracts intravenously

4.3.5. Differential Scanning Calorimetry Analysis (DSC)

DSC reveals various endothermic and exothermic processes occurring in the sample as the temperature increases. DSC is capable of determining the m.p of crystalline substances, the glass transition temperature of amorphous polymers, and also degradation (75).

The thermal characteristics of both the polymer and drug in physical mixtures and in milled tablets were examined using DSC. The DSC analysis of the physical mixture was conducted to establish a baseline and ensure that any observed changes in crystallinity were due to the formulation components rather than a result from the milling process. By comparing the DSC profiles of the physical mixtures and the milled tablets, it was possible to determine whether milling altered the polymer's melting behavior or if changes in crystallinity were intrinsic to the drug-polymer interactions.

The DSC analyses of pure drug CPM, physical mixtures (F3, F11), milled tablets of these mixtures (F3, F11), and milled tablets that are thermally treated (F7, F15) were evaluated and are illustrated in **Figure 12** and **Figure 13**. The DSC thermogram of the pure drug CPM exhibits an obvious endothermic peak at 132.7 °C, revealing its m.p. While all formulations thermograms did not exhibit a drug peak, indicating that CPM was entirely dissolved with the excipients and exists in both crystalline and molecular form (76). Thermal characterization performed by Meruva and Donovan (2019) indicates that the absence of the melting endotherm in the case of ketoprofen or dextromethorphan can be attributed to the drug dissolving in the molten PEO (30).

The DSC thermogram of the physical mixture (F3), milled tablets (F3), and thermally treated tablets (F7) shows an endothermic peak at 66.24 °C, 67.63 °C, and 61.20 °C, respectively. Furthermore, the DSC thermogram of the physical mixture (F11), milled tablets (F11), and thermally treated tablets (F15) exhibits an endothermic peak at 63.51 °C, 64.29 °C, and 59.88 °C, respectively. However, PEO has a crystalline m.p between 62 and 67 °C (77). Therefore, tableting of the physical mixture and milling had no obvious change on m.p. While thermal treatment at 80 °C results in a decrease of the m.p 3-5 ° C, this is consistent with the findings obtained by Meruva and Donovan (2020) and Rahman *et al.* (2016) (34, 48). This could be due to the breakdown of polymers into fractions with smaller M.wt, which may also be a factor in the observed decrease in enthalpy (78). Additionally, Boyce (2016) observed that after longer periods of sintering at 80 °C, the crystalline state of PEO gradually decreased (79). Furthermore, it has been noted that PEO, when stored at high temperatures for at least 24 hours, is susceptible to oxidative damage. This oxidation lowers PEO's M.wt (78, 80); however, the current study involves only a short period of time at elevated temperatures (1 hour).

4.3.6. Powder X-ray Diffraction (PXRD):

To study the state of CPM in the prepared tablets, the X-ray diffraction of pure drug CPM, physical mixtures (F3, F11), milled tablets of these mixtures (F3, F11), and milled tablets that are thermally treated (F7, F15) was conducted and shown in Figure 14 and Figure 15.

The diffraction pattern of pure CPM presented a complete crystalline state. The crystalline form of CPM was confirmed by exhibiting two sharp peaks at 2 theta equal to (19.29) and (20.26), indicating crystalline structure (81). F3 physical mixture, F3 after tableting, and F7 after thermal treatment exhibited two sharp peaks at 2 theta equal to 19 (with intensity = 4094.1) and 23 (with intensity = 5316.1), Also, **Figure 14**. clearly demonstrates that the XRD patterns of physical mixtures exactly match the XRD pattern of the prepared tablets.

Additionally, F11 physical mixture, F11 after tableting, and F15 after thermal treatment presented two sharp peaks at 2 theta equal to 18.90 (with intensity = 2313.2) and 23.04 (with intensity = 2675.5). In addition, Figure 15. shows that the XRD patterns of physical mixtures are the same as the XRD pattern of the prepared tablets.

Since both the peak widths (measure of crystallinity) and background intensity and shape (measures of % amorphous) are approximately the same for samples of physical mixture samples and for samples of the prepared tablets. CPM appears to be stable at the treating temperature. The sample did not appear to change phase, neither to amorphous degraded material nor to another crystalline (e.g., polymorphic) phase.

To sum up, the diffraction pattern of both pure CPM and all the tested showed sharp peaks, which indicated that CPM maintains its crystalline state after being prepared as tablets with or with no thermal treatment. Furthermore, the XRD patterns of the prepared tablets with and with no thermal treatment highly resemble the patterns of physical mixtures, indicating the stability of CPM at the temperature of thermal treatment.

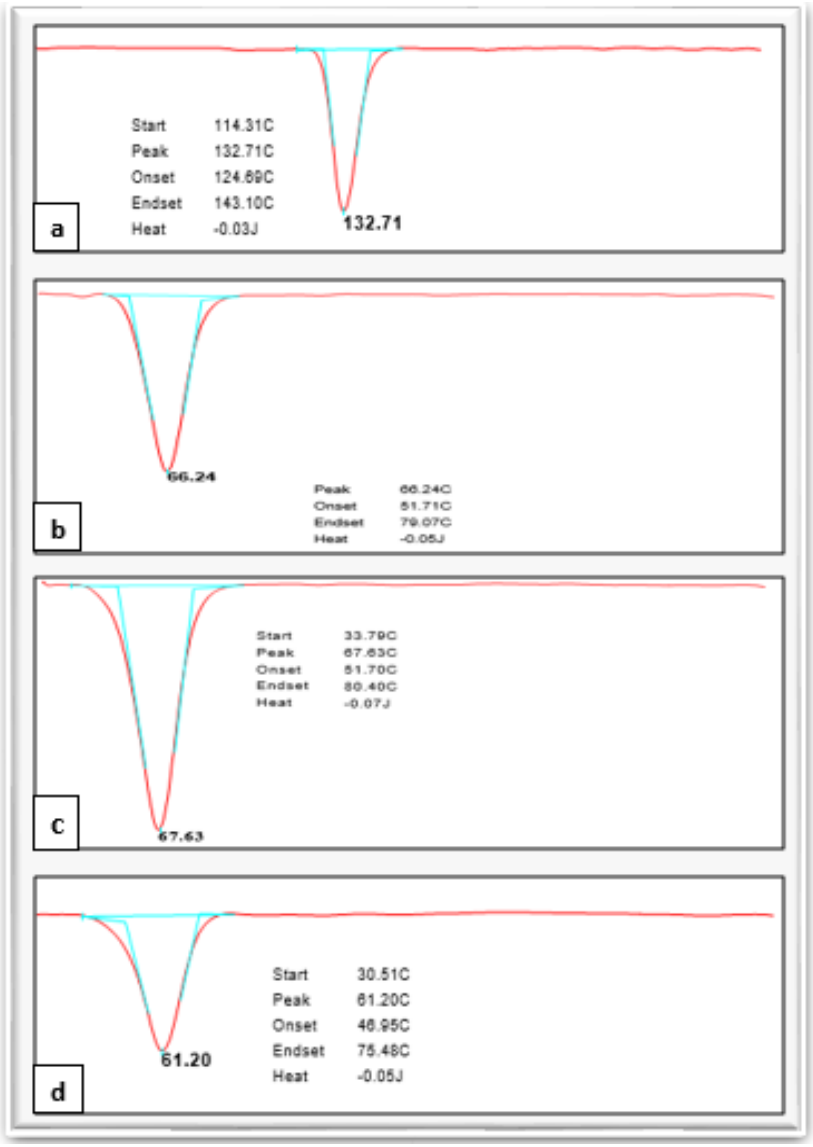

Figure 12. DSC of**:** (a) pure drug (b) Physical mixture of F3 (c) Milled tablet of F3 (d) Thermally treated milled tablet of F7

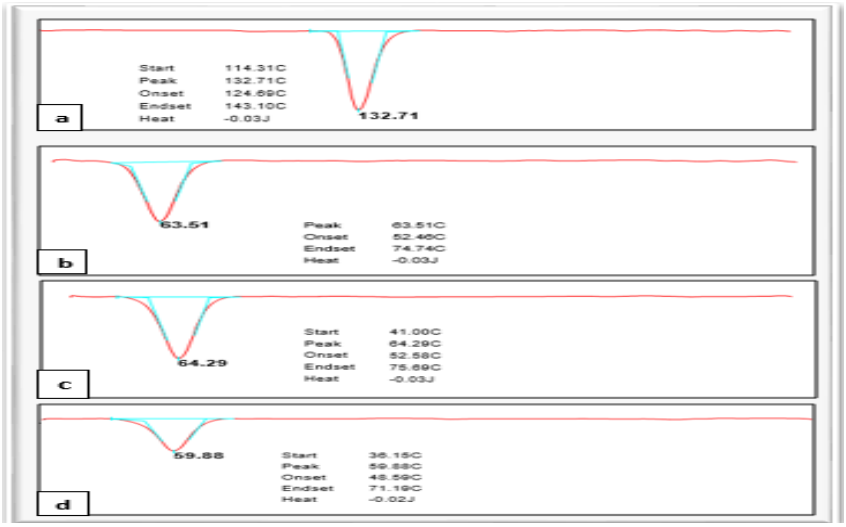

Figure 13. DSC of: (a) pure drug (b) Physical mixture of F11 (c) Milled tablet of F11 (d) Thermally treated milled tablet of F15

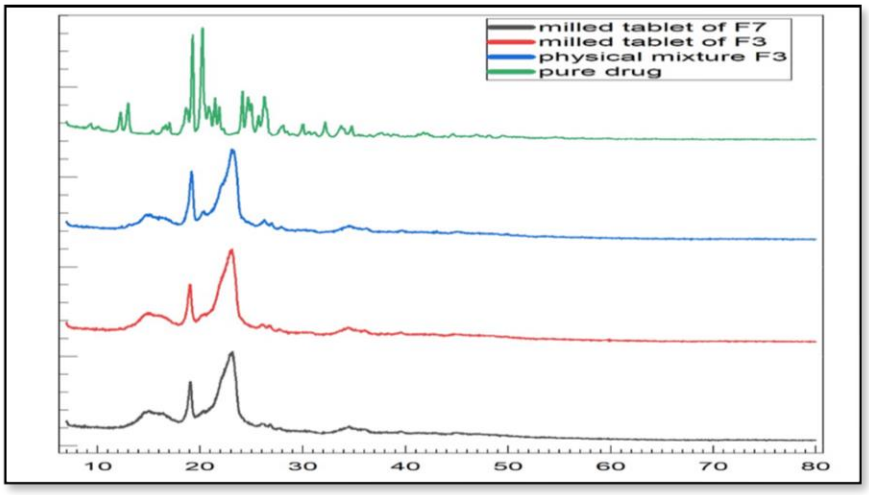

Figure 14. PXRD of CPM, physical mixture of F3, milled tablet of F3 and thermally treated milled tablet of F7

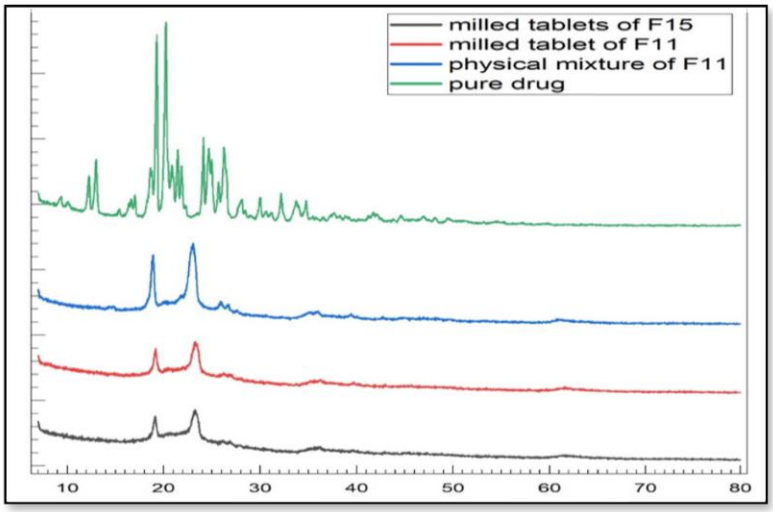

Figure 15. PXRD of CPM, physical mixture of F11, milled tablet of F11 and thermally treated milled tablet of F15

4.3.7. In Vitro dissolution study

Dissolution refers to the rate at which a drug dissolves in a liquid under specific and controlled conditions. It helps determine how long it takes for the drug to dissolve and begin working in the body (82).

In this study, the dissolution study was not intended to achieve a full release profile but to understand the difference between the deference M.wt of PEO. However, formulas with the highest M.wt. and concentration (F4 & F12) as well as the lowest M.wt. and concentration (F1 & F9) undergo in vitro drug release testing. D.W was used as the dissolution medium. **Figure 16** illustrates the drug release percentage vs. time graph.

F1 and F9 release 95.42% and 88.25%, respectively, within 6 hours, while F4 and F12 release only 67.02% and

58.95%, respectively, demonstrating that formulas with the highest M.wt and concentration had delayed release in comparison with the lowest M.wt and concentration. Tocce

et al.'s similar study showed a significant variation in drug release and dissolution based on the PEO M.wt, with the lowest M.wt releasing the drug more quickly than those with higher M.wt (44). Furthermore, the type of diluent has an impact on the percentage of release. As a result, formulas containing NEU had a longer release time than formulas containing MCC. According to Sarabu *et al.* (2021), the in vitro dissolution test demonstrated that increasing NEU levels led to a reduction in dissolution but an improvement in stability (83).

When PEO comes into contact with water, it quickly hydrates, forming a gel-like structure around the dosage form. The strength of this gel structure depends on the polymer's M.wt and the presence of other additives. Higher M.wt and polymer concentration result in more viscous and robust hydrated gel structures. However, PEO-4M has a relatively high M.wt, which causes prolonged release of drug behavior and slower gel erosion. These effects translate into lower extractability (33, 84). As a result, drug release from PEO matrices can be regulated by polymer swelling, diffusion within the hydrated gel, erosion, or a combination of these processes, regardless of the manufacturing method used (85, 86). Different release profiles can be achieved depending on PEO's M.wt and the drug's physicochemical properties. Regardless of PEO M.wt, dissolution medium pH rarely affects drug release. However, drug solubility in different pH media may affect it (62). Some studies indicate that using PEO with HPMC is beneficial for achieving a slower initial drug release from matrices. Both PEO and HPMC are hydrophilic and non-ionic, which promotes quicker hydration of PEO and helps create a more durable gel layer. This combination reduces drug diffusion from the swollen matrix and lowers the erosion rate of the gel layer (33, 87).

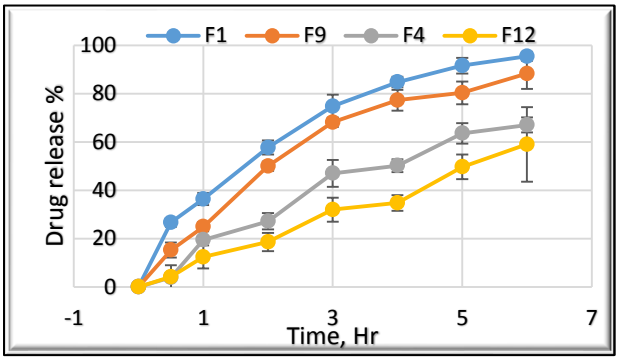

Figure 16. Drug release% of F1, F9, F4 and F12.

5. Conclusion

Abuse-deterrent tablets using simple tableting methods can be successfully manufactured. Subjecting the tablets to heat in an oven after preparation is an effective manufacturing technique that results in a significant increase in tablet hardness. However, thermal treatment at 80 °C results in a decrease of the melting point. It was additionally found that the concentration and M.wt of PEO were essential in providing the tablets' intended abuse-deterrent properties. Thus, the M.wt of the polymers utilized has the greatest impact on the disintegration of tablets, syringeability, injectability, and drug release. Additionally, NEU significantly increased the hardness of tablets and delayed drug release. Furthermore, this study demonstrated that the combination of several factors might have a significant effect on some characteristics of tablets. Hence, it is necessary to take into consideration the impact of factor interaction on our account. Finally, hot melt extrusion might be considered suitable equipment for preparing these tablets without the need for an oven.

Conflict of Interest:

There are no financial or non-financial interests to declare.

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Ethics statements:

This study does not need ethical approval from an ethics committee.

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تطوير وفحص الأقراص الدوائية المقاومة للإساءة باستخدام ماليات كلورفينيرامين كبديل دوائي

الخلاصة:

الخلفية والأهداف: أصبح تعاطي المخدرات مشكلة عالمية مرتبطة بزيادة الإدمان والوفاة، مما أدى إلى تشجيع إدارة الغذاء والدواء والعديد من الشركات على تطوير تركيبات يمكنها منع أو تقليل الإساءة. هدفت هذه الدراسة إلى تطوير تركيبات رادعة للإساءة باستخدام ماليات الكلورفينيرامين كدواء نموذجي. تم تقييم التركيبات لقدرتها على مقاومة السحق والحقن، وهي طرق شائعة لإساءة استخدام المخدرات. **الطريقة:** تم استخدام طريقة الكبس المباشر لإعداد الأقراص. تم استخدام أوكسيد البولي إيثيلين كبوليمر بتركيزين (40٪ و 80٪) ووزنين جزيئيين (300000 و 4000000). تمت إضافة ال Neusilin US2وال microcrystalline cellulose كمخففات للأقراص. تمت معالجة نصف التركيبات بالحرارة في فرن عند درجة حرارة 80 درجة مئوية. تم تطوير تصميم كامل باستخدام برنامج minitab، مما أدى إلى 16 تركيبة. **النتائج:** أظهرت النتائج أن كل من الوزن الجزيئي وتركيزالأوكسيد البولي إيثيلين ، إلى جانب تسخين الفرن، يؤثران بشكل كبير على جميع خصائص الأقراص المختبرة تقريبًا. ومع ذلك، فإن تغيير نوع المخفف يؤثر فقط على بعض خصائص الأقراص، مثل الصلابة. **الاستنتاج:** أظهرت هذه الدراسة جدوى استخدام أكسيد البولي إيثيلين بأوزان جزيئية مختلفة لإعداد جرعات رادعة لسوء الأستخدام. علاوة على ذلك، فإن استخدام مخفف مثل النيوسيلين في تحضير الأقراص يفرض تحديات من حيث السحق؛ وهذا يمكن أن يساعد في الحد من إساءة استخدام المخدرات.

الكلمات المفتاحية: منع سوء الأستخدام، إساءة استخدام الأدوية، أكسيد البولي إيثيلين، الحاجز المادي، تصميم التجربة.