EXPERT OPINION

Opioid extended-release tablets with improved tamper-resistant properties

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Objective: To prepare a polyethylene oxide-based tablet with high mechanical strength that would release an opioid for once- or twice-daily administration. This tablet would also create barriers against crushing and subsequent preparation steps for abuse and misuse that are not present in conventional opioid formulations.

Research design & methods: Innovative manufacturing processes were created by applying heat and force simultaneously, using tramadol HCl as model compound; production scale testing used oxymorphone HCl. Standardized *in vitro* crush force and extraction tests were performed.

Results & discussion: A production scale manufacturing process using hot melt extrusion of a strand, cooling, slicing and shaping the slices into tablet form produced stable oxymorphone extended-release (ER) tablets with *in vitro* dissolution characteristics similar to commercial oxymorphone ER. The tablets resisted crushing by spoons, pill crushers and a hammer and resisted extraction in a test battery of solvents. The standardized tampering methods used here do not include all methods an abuser might employ. Post-marketing data will be needed to determine the actual impact of tamper resistance mechanisms on opioid abuse rates.

Conclusions: This purely mechanical approach to tamper resistance may make a tablet less attractive for abuse without exposing compliant patients to new risks associated with opioid antagonists or aversive compounds. A compliant patient's risk of adverse events may be reduced by the tablet's resistance to accidental crushing.

Keywords: abuse, controlled release, mechanical properties, misuse, opioids, tamper resistant

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1. Introduction

Extended-release (ER) opioid tablets play an important role in modern therapy for chronic pain and allow convenient 'dosing by the clock' instead of symptomatic dosing upon the recurrence of pain. ER opioids with proven efficacy in patients with chronic pain include dihydrocodeine, hydromorphone, morphine, tapentadol, oxycodone and oxymorphone. Unfortunately, opioids are frequently abused because of their positive subjective effects, most notably euphoria [1]. Moreover, since ER opioids typically contain a larger amount of the drug compared with immediate-release formulations, the ER opioids are attractive to abusers but may also be associated with more negative consequences, such as overdose and death [2]. This is particularly true when the ER mechanism of an opioid is tampered with by crushing or dissolution in a liquid [3,4]. After crushing, the active ingredient is no longer released gradually, but instead becomes readily available for immediate release, thereby increasing its attractiveness for abuse by swallowing or insufflating the powder. After dissolution, the opioid can be injected.

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To discourage abuse, drug manufacturers have attempted to develop opioids with formulations designed to create obstacles to common methods of tampering, often referred to as tamper-resistant formulations (TRFs). To date, opioids employing three TRF strategies have been approved for use in the US (**Table 1**). Embeda® (morphine sulfate controlled release/naltrexone;) includes a sequestered opioid antagonist that is released if the product granules are crushed, neutralizing opioid effects. Oxecta® (oxycodone; King Pharmaceuticals Inc., Bristol, TN, USA), an immediate-release TRF, includes nonsequestered aversive excipients that cause mucosal irritation if the product is abused via inhalation and exhibit gelling properties that deter injection. Nucynta® ER (tapentadol ER; Janssen Pharmaceuticals, Inc., Titusville, NJ, USA), reformulated OPANA® ER (oxymorphone ER; Endo Pharmaceuticals Inc., Chadds Ford, PA, USA) and reformulated OxyContin® (oxycodone CR; Purdue Pharma L.P., Stamford, CT, USA) incorporate physical barriers to crushing and form a viscous gel upon dissolution in fluids [5-13].

Two of the three approved strategies for tamper resistance may have potential to compromise efficacy or tolerability in legitimate patients compared with non-TRF formulations. Sequestered opioid antagonists or aversive compounds are designed to compromise efficacy or cause adverse events when the tablet is tampered within certain ways. As a result, these formulations may create adverse events in patients who inappropriately crush or try to dissolve a tablet with no intent of abuse, for reasons such as dysphagia, pill phobia or a desire to take a partial dose. By contrast, the purely physicochemical approach makes such inappropriate tablet crushing difficult or impossible, thereby potentially reducing the risk of adverse events in legitimate patients compared with formulations that can be crushed. Of course, unintentional adverse events such as difficulty swallowing a tablet that gels or breaking a tooth trying to bite a crush-resistant tablet may occur.

This paper details the development of opioid tablets formulated using a polyethylene oxide (PEO) matrix that resists crushing while allowing controlled release of the opioid from the tablet over a 12-h dosing interval. The manufacturing process development was carried out with the opioid tramadol HCl used as a model compound since this opioid is not scheduled by narcotic law in Germany. Thus, tramadol was easier to handle in development environments. To verify the suitability for commercially available scheduled opioids, the PEO matrix was combined with oxymorphone HCl (a schedule II narcotic in the US) with the goal of developing an ER tablet (Oxy-PEO) bioequivalent to the existing commercially marketed oxymorphone ER (Oxy-PSH) that was formulated with a polysaccharide hydrogel (PSH) matrix (TIMERx®, Endo Pharmaceuticals, Chadds Ford, PA, USA). The intent of this study was to test whether Oxy-PEO has improved tamper-resistant properties compared with Oxy-PSH, by virtue of being more difficult to crush. Benchtop experiments were conducted to test the tablet's resistance to tampering.

2. Materials and methods

2.1 Materials

Tramadol hydrochloride, EP, was manufactured by Grünenthal, Aachen, Germany; Oxymorphone hydrochloride, USP, was supplied by Mallinckrodt, St. Louis, MO, USA; Polyethylene oxide 7 Mio, USP/NF (Polyox WSR303), was supplied by Dow Wolff Cellulosics GmbH, Bomlitz, Germany; Hypromellose 100,000 mPas, USP/NF was supplied by Shin-Etsu, Tokyo, Japan, as well as by Colorcon, Dartford, UK; Macrogol 6000, EP, was supplied by Clariant, Muttenz, Switzerland; Butyl hydroxy toluene was supplied by Merck KGaA, Darmstadt, Germany; Magnesium stearate was supplied by Peter Greven, Bad Münstereifel, Germany; α-tocopherol was supplied by BASF, Ludwigshafen, Germany; OxyContin CR tablets were bought in 2009 in the US and imported under Narcotic Law; Opana ER tablets were provided by Endo Pharmaceuticals, Inc. in 2009 and imported under Narcotic Law.

2.2 Manufacturing process development

2.2.1 *Matrix concept*

The proposed tablets were to be manufactured by compressing mixtures of drug substance with PEO in a molten state followed by solidification during cooling. However, no suitable manufacturing process had previously been described. The challenge with respect to manufacturing was that PEO of high molecular weight exhibits a crystalline melting point in the range of 62 – 67°C, as detected by DSC and X-ray [14], which is close to the range of the chemically similar polyethylene glycols (PEG) of lower molecular weight. In contrast to PEG, PEO does not melt into a liquid when heated above 70°C but forms a sticky lump. Because of this atypical melt, a procedure like casting a molten formulation and solidifying it by cooling was not possible.

2.2.2 *Conventional tableting trials*

The first trials were carried out using tramadol hydrochloride as the model compound. Compositions of trial formulations are presented in **Table 2**. Conventional compression of formulation A in an eccentric tablet press (Korsch EK0) resulted in ER of tramadol hydrochloride but not in a tablet of high mechanical strength. Thus, the interaction among the PEO particles did not grow strong enough by simple compression to allow the formation of a firm scaffold in the tablet. Consequently, there was a need for a processing step that would lead to stronger cohesion inside the tablet.

2.2.3 *Experimental process for tablet-manufacturing principle [15]*

In an initial manufacturing trial, the upper and lower punch as well as the die of the eccentric press tableting tool was heated to 80°C in an oven. The lower punch was manually inserted in the die, the mixture of formulation A was poured into the chamber of the hot tool and the die was closed by manual insertion of the upper punch. The punches were pressed against each other by

Table 1. Approaches to making drug formulations less attractive for certain routes of abuse*.

Approach/route of abuse	Multiple doses, swallowing intact	Chewing	Snorting	Injecting
Niacin				
Emetic				
Pro-drug				
Bittering agent				
Dye				
Capsaicin				
Naloxone				
Naltrexone (sequestered)				
Gelling				
Hardness				

*This table indicates the intention or potential for each approach to drug formulation to present obstacles to abuse and is not intended to suggest that evidence of success in deterring these specific routes of abuse or abuse in general has been achieved for any the products discussed.

Table 2. Composition of tramadol hydrochloride formulations*.

Formulation ingredient	A (mg)	B (mg)	C (mg)
Tramadol hydrochloride	100.0	100.0	100.0
Polyethylene oxide, MW 7 Mio	200.0	200.0	167.8
Hypromellose, 100,000 mPa s			33.5
Magnesium stearate		8.3	
Macrogol 6000			33.5
Butyl hydroxy toluene			0.2
Total weight	300.0	308.3	335.0

*All formulations were tablets of 10-mm and 8-mm radius of curvature.

clamping the whole arrangement in a bench vise and twisting with a torque wrench set to 70 Nm. After 10 min, the tablets were taken out of the tool. The resulting tablets were of the desired high mechanical strength and intended *in vitro* dissolution profile (see results).

This initial trial proved that simultaneous application of heat and force in principle can transform a mixture of PEO and drug substance into a hard tablet of the desired properties, but the manufacturing process needed about a quarter of an hour to manufacture one tablet. Hence, for commercial manufacturing, a more efficient manufacturing process based on application of heat and force had to be developed. Three different manufacturing approaches were subsequently designed and investigated for their suitability to deliver the intended product properties and scale up potential to commercial scale.

2.2.4 *Post-tableting heating and compression principle [16]*

The first manufacturing process was based on conventional manufacturing of PEO matrix tablets by a rotary tablet press as the first step, followed by heating and compression in the hot stage to achieve the high mechanical strength of the tablets. In a prototype setting, the heating and compression could be achieved using a laboratory sealer (Kopp SGPE 20) that is typically used to seal foils or small numbers of blister packages. A format tool with a concavity of 10 mm diameter and a radius of curvature of 8 mm that fitted the tablet was produced and attached to the SGPE20 instead of the sealing jaws. Formulation B (**Table 2**) included magnesium stearate to allow for conventional tableting. The mixture was compressed into tablets, which were later inserted one by one in the preheated (120°C) format tool and compressed with 500 N for 2.5 min. The resulting tablets were of the desired high mechanical strength and intended *in vitro* dissolution profile (see results).

2.2.5 *Ultrasound-assisted compression principle [17]*

For the second approach, a straightforward one-step powder-to-tablet manufacturing was found by employing the principles

Figure 1. The production scale manufacturing line.

of ultrasound welding that are commonly utilized in the plastics industry. The mixture of formulation A was filled into the die of a tableting tool closed at the bottom by the lower punch and then compressed by the sonotrode of an ultrasound welding device while applying ultrasound for about 0.7 s and holding the tablet compressed for about 3 s in total. The process resulted in tablets of high mechanical strength and the intended *in vitro* drug release (see results).

2.2.6 *Hot melt extrusion principle [18]*

The third approach was based on hot melt extrusion, a manufacturing process used in the plastics industry and that was introduced by BASF (now Soliqs, part of Abbott) to pharmaceutical manufacturing. A hot melt extruder can provide heat to melt the PEO while bringing the compound under pressure into intensive contact to allow forming of the intended strong structure of the tablets. Conventional melt extrusion processes yield a molten mass that can be extruded into a broad flat band by an extrusion head with a slit die and/or rolled out into a flat area and formed into the final tablets by means of a calender (Meltrex® Technology of Soliqs®). By contrast, the melt extrusion of high-molecular-weight PEO yielded a strong plastic strand of about 5 – 20 mm, depending on the extrusion nozzle, that could not be flattened or directly transformed into tablets. Thus, a new downstream process had to be developed.

In laboratory scale, this was achieved by hot melt extrusion of the PEO mixture through a nozzle of approximately 9 mm diameter, tearing strands of some 10 cm manually from the extruder, letting the strand cool at ambient temperature, slicing the strand into disks of defined lengths by means of a meat slicer with a rotating wheel knife, manually transferring the disks into the die of a tablet press and forming the final tablets by compression. Initial extrusion trials suggested that addition of PEG 6000 as a plasticizer, as well as the addition of hydroxypropyl methylcellulose (HPMC), improved the smoothness of extrusion. Since the mechanical shear stress of the extruder screws may cause scission of the long PEO chains, leading to oxidative reactive radicals, further addition of butylated hydroxytoluene (BHT) to the formulation on top of the small amount of BHT already contained in the commercially available Polyox WSR 303 as antioxidant appeared to be useful. BHT was added as an ethanolic solution to the PEG, dried off and then blended with the remaining compounds of the formulation.

Tablets of formulation C (**Table 2**) were manufactured by this process employing a planetary-gear extruder (Bohle BCG10). Extrusion was run under the following conditions: temperature setting of heating jacket 100°C, central screw running at 30 rpm, four planetary screws inserted and an extrusion rate of 10 kg/h. Cold extrudate strands were sliced into disks of 335 mg and formed by means of tablet tools in the Korsch EK0 press. The resulting tablets were of the desired mechanical strength and *in vitro* dissolution profile (see results).

2.2.7 *Design study for a production scale manufacturing line*

Although all three manufacturing approaches performed in laboratory scale led to the intended mechanical and dissolution properties, none of the processes had a production scale manufacturing line commercially available. Therefore, a decision had to be made about which manufacturing technology should be scaled up in collaboration with equipment manufacturers to achieve a viable manufacturing process for the product. Although the ultrasound welding itself was a fast one-step manufacturing process, it lacked available high-speed manufacturing equipment capable of delivering tablets at a rate comparable with that of a rotary tablet press. Moreover, designing and developing the necessary equipment in accordance with all GMP and workers' safety requirements were not considered possible in the time frame given for the intended development project.

A design study was conducted in collaboration with a special-purpose machinery manufacturer to explore the process of heating conventionally prepared tablets and compressing the hot tablets. The study revealed that the equipment required would be extremely complex and expensive and involve high energy consumption. Thus, the most straightforward and fastest approach seemed to be the use of hot melt extrusion combined with a newly designed downstream process [19].

Based on the laboratory-scale process, cooling and cutting equipment capable of producing 10,000 tablets per hour was designed in collaboration with partners from the food and plastics industries, including an upgrade of the equipment to GMP standard. To allow formation of the cut disks or rods in a rotary tablet press, special feeding units were designed in cooperation with a tablet press manufacturer. The entire equipment development process culminated in the manufacturing line that was qualified according to GMP and accepted by pharmaceutical inspection authorities. The final manufacturing process (**Figure 1**) consisted of the elements blending, extrusion, cooling, cutting and forming, optionally followed by coating.

2.2.8 Formulation development of a commercial product

2.2.8.1 Commercial product concept

The proposed innovative commercial product was to be a compound of the developed PEO matrix (INTAC)^{TM}, Grünenthal GmbH, Aachen, Germany with oxymorphone HCl (Oxy-PEO). The goal was to develop Oxy-PEO to be bioequivalent to the existing commercially marketed Oxy-PSH. Oxy-PSH was marketed in seven dose strengths: 5, 7.5, 10, 15, 20, 30 and 40 mg.

2.2.8.2 Commercial product compounding

The development of Oxy-PEO presented two main challenges. Firstly, the Oxy-PEO formulation had to be stable during manufacture and storage of the product. Secondly, the *in vitro* release profiles of all dose strengths of Oxy-PEO had to be similar to the corresponding dose strengths of Oxy-PSH to increase the likelihood that the two formulations would be bioequivalent and that Oxy-PEO would remain stable throughout its shelf life.

As PEO is subject to oxidative degradation and formation of radicals either by oxidation or by scission during extrusion, the addition of an antioxidant to the formulation was needed. Since α-tocopherol demonstrated superiority over BHT in protecting PEO during the extrusion process, it was also used for the new development process. Surprisingly, it was discovered that higher concentrations (1.5%) of α-tocopherol, which is commonly known as an antioxidant, increased the percentage of oxymorphone oxidation during storage more than did lower concentrations (0.2%). Thus, the optimal amount of α-tocopherol that protects PEO during extrusion and does not increase oxymorphone oxidation during storage needed to be determined. It was also found that the addition of acids, especially multicarboxylic acids such as citric acid, increased the stability of oxymorphone against oxidative degradation. A third provision against oxidative degradation was found in the addition of an oxygen scavenger to the bottle pack of the tablets. For details of this part of formulation development, see the examples in the patent application for the product [10].

Formulations of 5 and 40 mg oxymorphone with PEO, PEG, hydroxypropyl methyl cellulose, citric acid and α-tocopherol were blended, hot melt extruded, cooled, cut and formed into tablets of 325-mg weight for the 5-mg dose or 360 mg for the 40-mg dose and 10-mm diameter for both doses. A smaller tablet of 215 mg and 9-mm diameter was developed for both dose strengths with the difference in weight of oxymorphone compensated for using the excipients.

On the basis of dissolution testing, the smaller (215 mg, 9 mm) Oxy-PEO tablet was selected as most similar to Oxy-PSH. The 5- and 40-mg doses represented the brackets for the formulation of the remaining dose strengths. All intermediate dose strengths were also developed with the same tablet size and weight. Tablets for each dosage strength were assigned different colors that were applied using a nonfunctional color coat based on polyvinyl alcohol (Opadry II).

2.3 Product testing

2.3.1 Hardness testing

To gauge the mechanical strength of tablets produced by trial manufacturing methods, compression tests were performed at room temperature with a hardness tester applying 500 N of force (TBH 30, Erweka GmbH, D-Heusenstamm), with a mortar and pestle, and with a 500-g hammer.

2.3.2 *In vitro* dissolution

Tramadol hydrochloride tablets were tested in a paddle apparatus (apparatus II according to USP) at a paddle speed of 75 rpm in 600 ml phosphate buffer pH 6.8 (37°C) using ultraviolet detection at 271 nm.

Oxymorphone HCl tablets were tested in a paddle apparatus (apparatus II according to USP) with sinker (Sotax S2) at a paddle speed of 50 rpm in 900 ml phosphate buffer pH 4.5 (37°C) using reverse-phase high-performance liquid chromatography. Comparison was made of the experimental tablets versus commercial Oxy-PSH tablets.

2.3.3 Long-term stability

Tablets produced by the third commercial-scale manufacturing trial were investigated in a stability study under long-term conditions of 25°C/60% relative humidity (RH) for up to 24 months and accelerated conditions of 40°C/75% RH for 6 months. Tablets for each condition were packed in amber glass bottles with a PE stopper and in a blister pack of opaque polyvinyl chloride (250 µm) coated with Diophan (40 g/m^2) sealed against aluminum (25 µm).

2.4 *In vitro* tampering

At present, there is no standardized, validated battery of *in vitro* tests to assess tamper resistance or potential abuse deterrence. In the absence of an established protocol, tests performed on tablets manufactured using the hot melt extrusion principle were selected because they could be standardized and deliver objective results. The tests were not intended to exhaustively represent all conceivable tampering methods that might be employed by abusers.

2.4.1 Crush resistance

An independent external laboratory (Phast GmbH, Saarbrucken, Germany) following standard operating procedures performed tests attempting to crush Oxy-PSH and Oxy-PEO tablets between two spoons, with a mortar and pestle, with a plastic pill crusher intended for home use, with a professional die-cast metal pill crusher (Ocelco Pill Crusher, Ocelco, Inc., Brainerd, MN, USA)), and with a pharmacopeial breaking force tester with a testing range up to 1000 N (HT1, Sotax, CH-Allschwil). In addition, tablets were pounded with a standardized hammer apparatus (Coesfeld Dart-Tester, Article No. 40-550-011) mimicking a stroke with a 500-g hammer to simulate efforts at product

Table 3. Simulated beverages for extraction.

Test medium	Volume (ml)	Simulates
40% ethanol in water	30	Distilled beverages (e.g., vodka)
12% ethanol in water	150	Wine
5% ethanol in water	360	Beer
0.001 N hydrochloric acid in water	360	Carbonated soft drinks
Water	360	

tampering. Details on the apparatus are given in Section 3.2.1 on crush resistance testing. Tests were performed at room temperature and repeated after freezing the tablets in liquid nitrogen. *In vitro* dissolution characteristics of the tablets were measured after each attempt at tampering.

2.4.2 *Resistance to chemical extraction*

Another method of tampering, especially among recreational abusers, is extraction of the drug from either intact or crushed tablets using alcoholic or nonalcoholic beverages, followed by drinking of the resulting solution. Therefore, following standard operating procedures, the same independent external laboratory studied intact tablets and tablets tampered with a professional pill crusher by shaking them vigorously for 15 min in simulated beverages (**Table 3**). The extraction liquid including the tablet was then put into a vessel of an *in vitro* dissolution apparatus and filled to a total volume of 900 ml with phosphate buffer. Release of the drug from the tablets exposed to alcoholic media was followed for up to 14 h and compared with release of drug from tablets exposed only to an aqueous medium (control).

Some abusers, sometimes called 'kitchen chemists,' try to extract drug formulations by dissolving the tablet in an acidic or alkaline media or an organic solvent and then separate the product by letting the solvent evaporate. Such attempts were mimicked by extraction of oxymorphone tablets with vigorous shaking of a tablet for 1 h in 30 ml of different solvents (0.1 N sodium hydroxide, 0.1 N hydrochloric acid, acetone, ethanol 40%, ethanol 96%, ethyl acetate, isopropanol, methanol, corn oil and water). Aliquots for analytical testing were also taken after 15 min. Release of the drug from tablets exposed to various media was compared with drug release from tablets exposed only to an aqueous medium (control).

3. Results

3.1 Product testing

3.1.1 *Hardness testing*

The pilot tramadol tableting trial (conventional compression of formulation A in an eccentric tablet press, Korsch EK0) did not produce a tablet with high mechanical strength. By contrast, tramadol tablets produced by the initial manufacturing trial and all three commercial-scale trials resisted crushing in a hardness tester applying 500 N, the maximum force achieved by the test apparatus available at that time. The tablets could not be crushed by mortar and pestle or by hammer. Under mechanical stress, only plastic deformation but no crushing or pulverization could be observed.

Similarly, the Oxy-PEO tablets did not break in a hardness tester applying 500 N, could not be crushed by mortar and pestle or by hammer, and exhibited only plastic deformation without crushing or pulverization.

3.1.2 *In vitro* dissolution

The tramadol tablets produced by the pilot tableting trial, the initial manufacturing trial and all three manufacturing principle trials all displayed the intended *in vitro* dissolution profile (**Figure 2A**), which was typical of an ER matrix obeying the Higuchi square-root-time law.

In vitro dissolution of Oxy-PSH is quite similar for all dose strengths, but with a small increase in release profile with increasing dose (**Figure 3A**). *In vitro* dissolution curves of Oxy-PEO tablets of the larger size (325 – 360 mg, 10-mm diameter) were lower than the dissolution curves of the respective dose-equivalent Oxy-PSH tablets, whereas the *in vitro* dissolution of the smaller Oxy-PEO tablets (215 mg, 9-mm diameter) closely approximated that of the respective dose-equivalent Oxy-PSH tablets Oxy-PSH (**Figure 3B**).

The *in vitro* dissolution profiles of all final formulations (**Figure 3C**) were bracketed by the 5- and 40-mg dose strengths with the brackets themselves fulfilling dissolution similarity requirements yielding an f_2-value of 68.5 for the biobatches tested. Stability of all dose strengths has been tested according to the requirements of the ICH stability guidelines [20-24].

3.1.3 *Long-term stability*

The assay of active ingredient, tramadol HCl, in tablets produced by the third manufacturing principle manufacturing trial remained unchanged and fluctuated only around the initial value. No degradation products could be detected. The *in vitro* dissolution rate (**Figure 2B**) increased to a small extent (≤ 7%) during storage time, indicating that the formulation was already quite stable but should be further improved for future commercial products.

Assays of Oxy-PEO tablets after 24 months of storage at 25°C/60% RH and after 6 months at accelerated conditions of 40°C/75% RH revealed no decrease in oxymorphone content and no increase in degradation products. The *in vitro* dissolution remained stable with a negligible increase of about 3% in maximum. Dissolution of the 40-mg Oxy-PEO tablet biobatch is presented as a representative example (**Figure 3D**). No tablets from the stability study could be crushed by the breaking force tester generating a force of about 1000 N. This demonstrated that the hardness properties remained stable over the intended shelf life of the product.

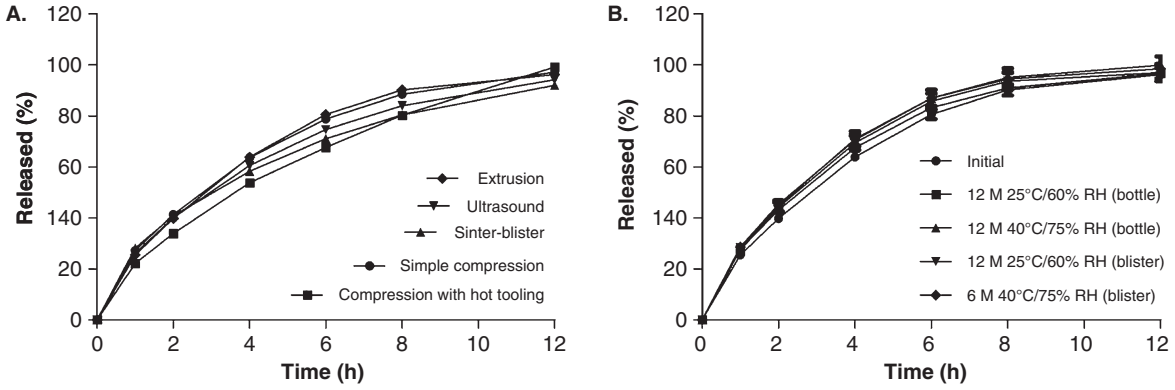

Figure 2. *In vitro* dissolution of experimental tramadol extended-release tablets: (A) tablets produced by different manufacturing processes; (B) formulation manufactured by hot-melt extrusion, stored in capped bottles or blister packages at 25°C/60% relative humidity for 12 months and at 40°C/75% relative humidity for 6 months.

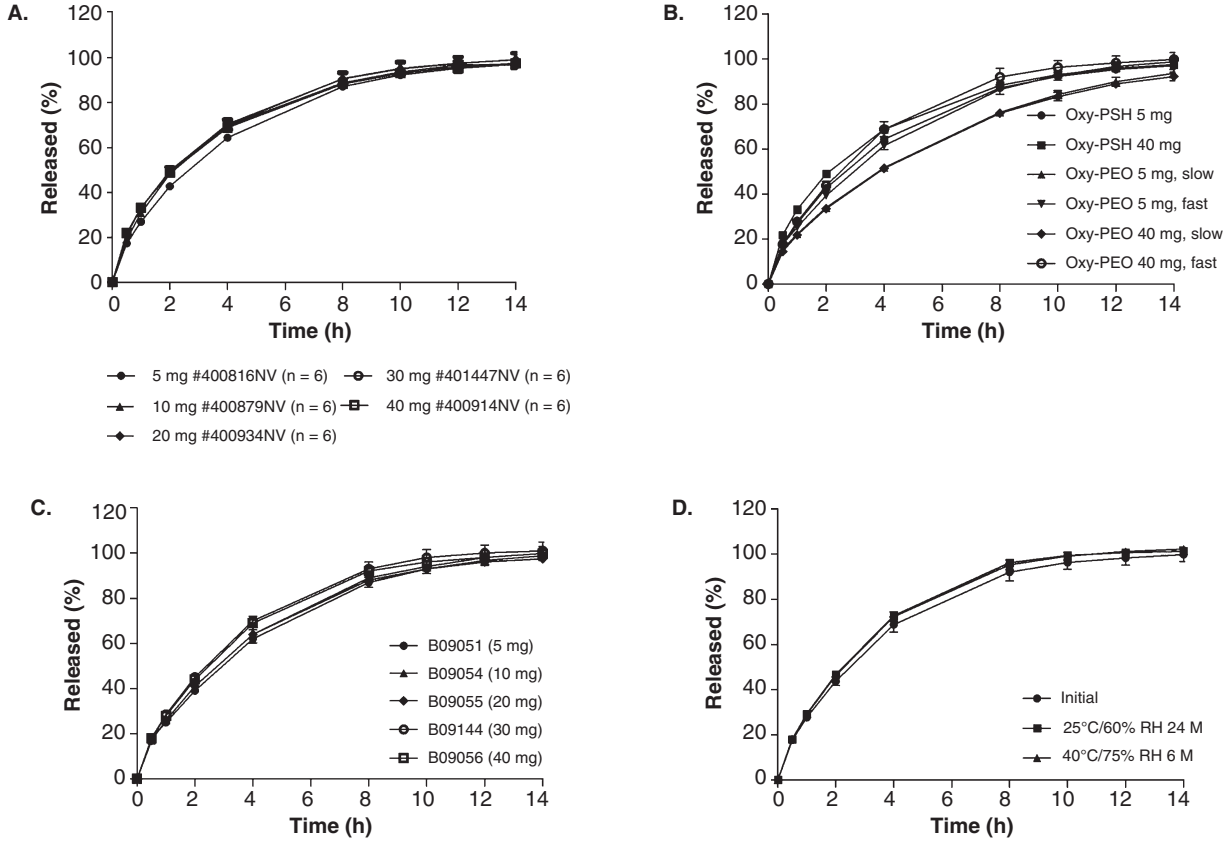

Figure 3. *In vitro* dissolution of oxymorphone extended-release tablets (A) of traditional extended-release oxymorphone of different strengths without tamper resistance (Oxy-PSH); (B) 5- and 40-mg tablets of commercial oxymorphone extended release (Oxy-PSH), experimental oxymorphone extended release (Oxy-PEO, 9 mm; Oxy-PEO, 10 mm); (C) comparison of finally selected Oxy-PEO tablets across all dose strengths; (D) 40-mg Oxy-PEO tablets at initiation of stability testing, after 6-month storage at accelerated conditions (40°C/75% relative humidity) and after 24-month storage at 25°C/60% relative humidity.

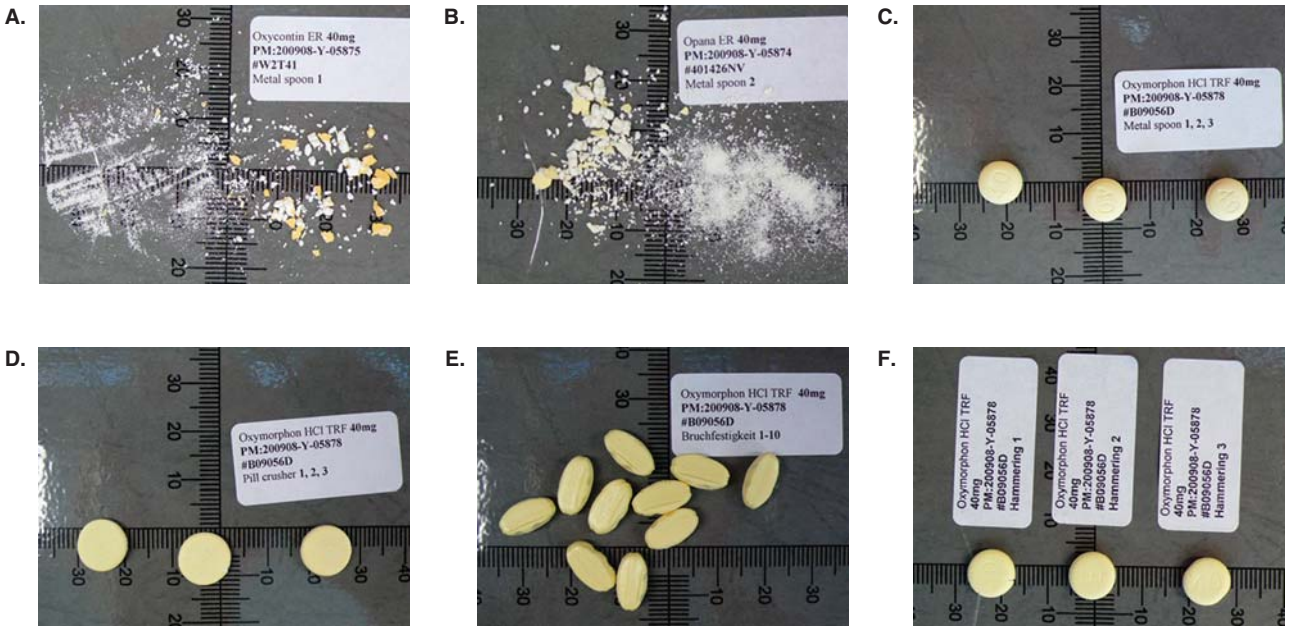

Figure 4. Effect of compression with two spoons on (A) traditional controlled-release oxycodone without tamper resistance, (B) traditional extended-release oxymorphone without tamper resistance and (C) crush-resistant oxymorphone extended-release tablets. Effect on crush-resistant oxymorphone extended-release tablets of compression by (D) professional pill crusher, (E) pharmacopeial breaking strength tester, (F) standardized hammer apparatus.

3.2 *In vitro* tampering

3.2.1 *Crush resistance*

Unlike traditional tablets without tamper-resistant features (**Figure 4A and B**), the new formulation could not be crushed between two spoons (**Figure 4C**) or by a mortar and pestle. Use of pill crushers was also unsuccessful. While simple plastic pill crushers for home use broke when pressing hard on the new tablets, professional die-cast metal pill crushers just flattened the tablets to a minor degree (**Figure 4D**). When tested in a pharmacopeial breaking force tester, no breaking but only plastic deformation of the tablets was observed with forces up to 1000 N (**Figure 4E**).

The highest mechanical forces in the test series were generated by pounding the tablets with a 500-g hammer. It was determined that a precise hit on a tablet by a hammer generated a force of 5 – 10 kN. For comparative testing of pounding on a tablet with a hammer, it was necessary to standardize the testing procedure and avoid variability of manual pounding by different people performing the test. From an analysis of videotape, the velocity of the hammer before hitting the tablet was determined to be about 4.5 m/s, with a kinetic energy of about 5 J. The same energy could be generated by a weight of 500 g with a squared bluff body of 25-mm edge length falling accelerated by gravity from a height of about 1 m onto the tablet. The testing was conducted using a Coesfeld Dart-Tester. The new tablet formulation could not be crushed by the hammer apparatus (**Figure 4F**) and was only flattened to the same extent as seen with the professional pill crusher.

Freezing the tablets at -20°C or in liquid nitrogen is a method employed by abusers to increase brittleness of formulations. However, even after freezing, the tablets could not be crushed. Crushing by two spoons led to fast release of the drug from traditional tablets without tamper-resistant features (**Figure 5A** and **B**), but the spoons had virtually no impact on the release of drug from the crush-resistant tablets (**Figure 5C**). Attempts at crushing tablets with a pill crusher or hammer resulted in small (< 10%) increases in drug release (**Figure 5C**), which was attributed to minor increases in the tablets' surface area when they were flattened slightly during mechanical stress. Thus, the tablets were able to withstand high crushing forces and preserve their ER dissolution profiles.

3.2.2 *Resistance to chemical extraction*

Results of the extraction tests after 15 min are presented in the upper part of **Table 4**. For comparison, the intended release of the drug from intact tablets derived from standard *in vitro* dissolution testing is presented as well as the dissolution of 'pill-crushed' tablets. *In vitro* dissolution testing of the oxymorphone tablets in 40% ethanol compared with 0.1 N HCl revealed a decrease in drug release in the alcoholic environment (**Figure 5D**).

In simulated beverages, the extraction was identical to the *in vitro* dissolution of the tablets as intended for compliant use. In alcoholic beverages, the extraction rate was even lower. In follow-up dissolution testing, ER of the drug from

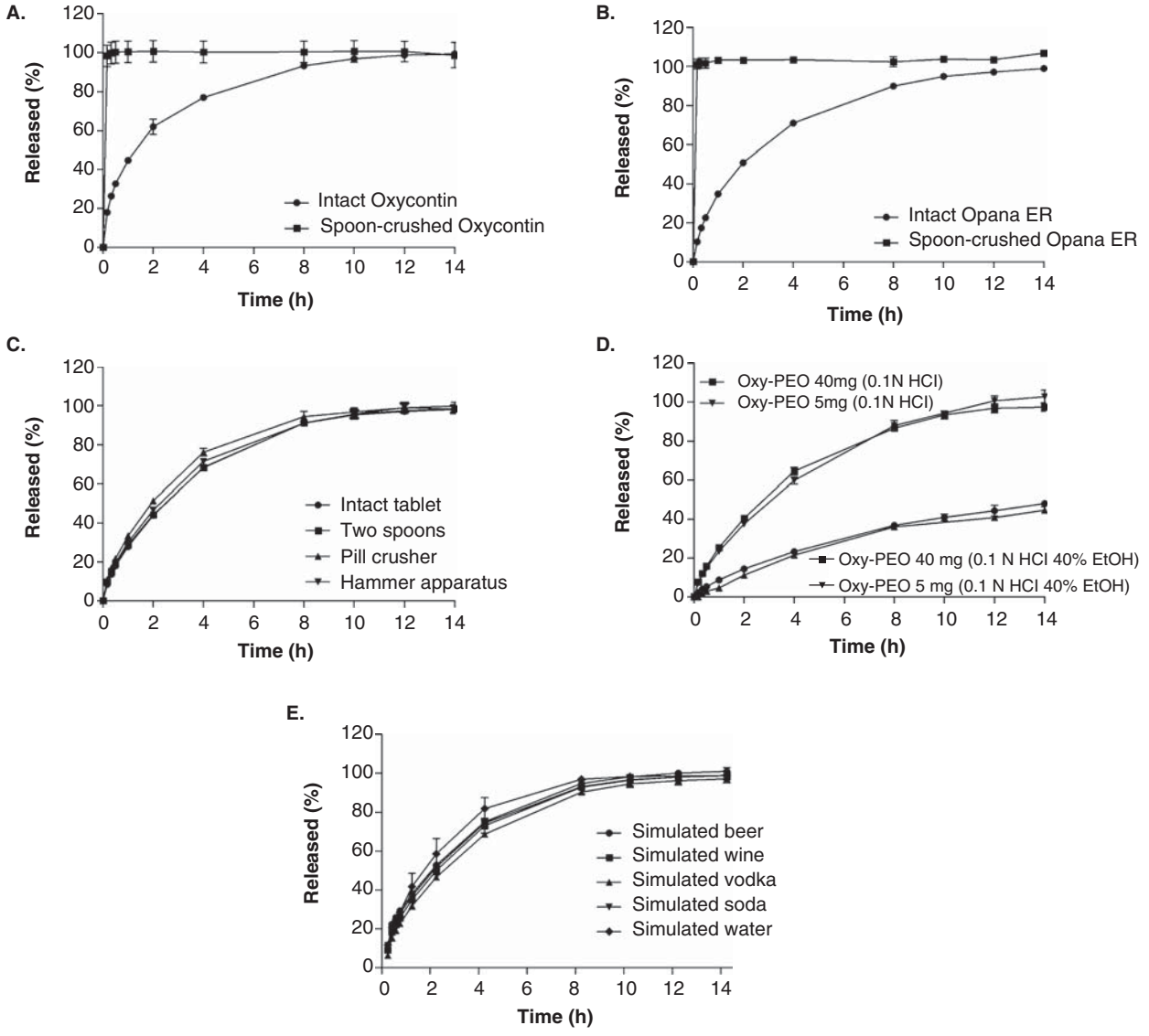

Figure 5. *In vitro* dissolution of (A) traditional controlled-release oxycodone without tamper resistance after mechanical manipulation, (B) traditional extended-release oxymorphone without tamper resistance after mechanical manipulation and crush-resistant oxymorphone extended-release 40-mg tablets (C) after mechanical manipulation; (D) with and without 40% ethanol; (E) after 15-min vigorous shaking in simulated beverages.

the tablet was maintained, proving that the ER matrix had remained intact (Figure 5E).

The results of efforts to extract oxymorphone from the Oxy-PEO tablets using acidic and alkaline media and organic solvents are shown in the bottom part of Table 4. Apolar solvents and solvents of low polarity did not extract any oxymorphone from the tablets, whereas solvents with greater polarity did extract oxymorphone to some extent. Pure ethanol and 0.1 N sodium hydroxide were of medium extraction power compared with 0.1 N hydrochloric acid, water, or methanol. However, in none of these media was the extraction higher at any time point than the intended release of the active ingredient seen in the *in vitro* dissolution testing at the same time points. Thus, solvents did not increase extraction from the Oxy-PEO formulation. For comparison, *in vitro* dissolution of the tablets after the same release times is included in the table.

4. Discussion

A manufacturing process that combined an active drug (oxymorphone HCl) with a PEO of high molecular weight above the PEO melting point and simultaneously applied force on the heated mass yielded Oxy-PEO, an ER oxymorphone tablet with physical properties resistant to benchtop crushing and subsequent steps typically involved in the

Table 4. Oxymorphone extracted with different simulated beverages or solvents from intact and pill-crushed tablets.

	5-mg Intact tablet	40-mg Intact tablet	5-mg Pill-crushed tablet	40-mg Pill-crushed tablet
Release (%) after 15 min of standard *in vitro* dissolution testing	9	11	12	14
Release (%) after 60 min of standard *in vitro* dissolution testing	-	28	-	33
Simulated beverages, quantity extracted after 15 min of intensive shaking, %				
360 ml water, simulating a glass of water	10	12	14	16
360 ml 0.001 N HCl, simulating a glass of carbonated soft drink	9	12	12	17
360 ml 5% ethanol in water, simulating a glass of beer	9	9	12	12
150 ml 12% ethanol in water, simulating a glass of wine	8	9	10	12
30 ml 40% ethanol in water, simulating a glass of distilled beverage (e.g., vodka)	7	6	10	9
Solvents, 30 ml each, quantity extracted after 15 min/60 min of intensive shaking, %				
Water		9/21		11/23
0.1 N HCL		9/20		8/22
0.1 N NaOH		3/6		5/7
0.1 N 40% ethanol		7/14		8/16
0.1 N 96% ethanol		1/4		4/10
0.1 N methanol		8/18		15/30
0.1 N isopropanol		0/0		0/0.3
0.1 N acetone		0/0		1/2
0.1 N ethylacetate		0/0		0/0
0.1 N organic food corn oil		0/0		0/0

preparation of opioid tablets for purposes of abuse and misuse. The commercial-scale manufacturing process uses hot melt extrusion coupled with a newly designed downstream process of cutting and forming the extruded strands. Long-term stability testing demonstrated that the Oxy-PEO formulation should have a shelf life of at least 24 months, and tests under accelerated conditions suggest allowing for extrapolation to a shelf life of as long as 36 months according to the International Conference on Harmonisation Guidance on Evaluation of Stability Data Q1E [24], when developed and manufactured on a commercial scale.

Despite the hardness of the Oxy-PEO tablet, its *in vitro* release of oxymorphone was virtually identical to that of marketed Oxy-PSH tablets, which are known to be suitable for a 12-h dosing interval. In follow-up to our *in vitro* studies, a series of pharmacokinetic trials in humans revealed full bioequivalence of Oxy-PEO and Oxy-PSH 5-mg tablets in fasted subjects and 40-mg tablets in fed and fasted subjects [25]. Thus, the prerequisites of gaining marketing authorization based on bioequivalence to an existing commercial product were achieved and Oxy-PEO was approved by the US Food and Drug Administration as a replacement for Oxy-PSH on December 9, 2011 [9].

Like other opioid analgesics, oxymorphone has significant abuse potential. Research among drug abusers has identified many factors that make a drug more or less attractive for abuse, among which is drug formulation [26]. Modifying opioid formulations to present obstacles to tampering may make these products less attractive to potential abusers. However, even if every effort is made to create such obstacles, no currently available method – including the one described here – can prevent an abuser from taking intact tablets in an effort to cope with withdrawal symptoms or try to achieve higher opioid blood concentrations by taking multiple doses.

In benchtop testing, Oxy-PEO tablets resisted crushing with professional pill crushers and a hammer. Only a small increase was found in dissolution from tampered tablets compared with intact tablets. Tests with simulated nonalcoholic and alcoholic beverages minimally increased extraction compared with dissolution in water or buffer.

In follow-up to our *in vitro* studies, studies in healthy volunteers found that coingestion of single intact tablets of Oxy-PEO 40 mg and Oxy-PSH 40 mg with 240 ml of 20 and 40% ethanol did not cause dose dumping of oxymorphone from either formulation. The bioavailability of oxymorphone as measured by area under the curve remained within 0.80 and 1.25 of the values for coadministration with water and increases in peak plasma concentration ranged from 14 to 80% [25].

A limitation of our study is that *in vitro* testing executed by trained laboratory staff working according to standard operating procedures probably differs from how abusers

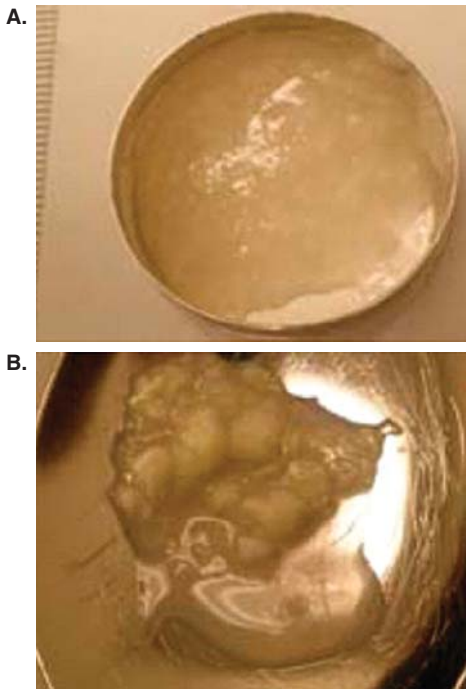

Figure 6. Gel resulting from attempt to prepare (A) a traditional extended-release oxymorphone tablet without tamper resistance and (B) crush-resistant oxymorphone extended-release tablet for intravenous abuse.

might work on tablets they want to abuse. It is possible that abusers might employ methods and implements not considered in our methodology to compromise the ER mechanism of an opioid tablet. However, two recent studies with experienced abusers were performed to check whether the design and *in vitro* tested properties of the Oxy-PEO matrix transformed into hurdles for real abusers. Forty experienced, nondependent, recreational abusers of long-acting prescription opioids were allowed to tamper with oxycodone controlled-release (CR) tablets (the previous formulation, which had no tamper-resistant properties) and a placebo tablet (PBO-PEO) made from the same matrix used to formulate Oxy-PEO. Participants were allowed to employ tools of their choice but were not allowed to consume either tablet [27]. After attempted tampering, subjects were asked which tablet they preferred and the price they would be willing to pay for each, presuming the oxycodone CR and PBO-PEO tablets contained equal amounts of oxycodone. About 90% of the experienced abusers preferred the oxycodone CR tablet over the PBO-PEO tablet. In addition, 35% were willing to pay nothing and another 42.5% were willing to pay less for PBO-PEO compared with oxycodone CR.

Two subsequent studies compared Oxy-PEO 40-mg tablets (active tablets, not placebo) with Oxy-PSH 40 mg in 25 experienced intranasal abusers of prescription drugs and 25 experienced intravenous abusers of prescription drugs, respectively [28]. Using implements of their choice, all 25 intranasal abusers were able to crush Oxy-PSH (97.7% of particles smaller than 1.7 mm), whereas only 8 subjects were able to produce any particles by crushing Oxy-PEO tablets, and only 5.1% of these particles were < 1.7 mm. Twenty-four (96%) subjects stated that they would be willing to snort the particles from Oxy-PSH, compared with only two (8%) who would be willing to snort the particles from Oxy-PEO tablets. Asked about their willingness to pay for the tablets, 72% reported they would pay less and 28% that they would pay nothing for the Oxy-PEO tablets compared with Oxy-PSH. Collectively, these results suggest that impediments to tampering with Oxy-PEO may translate into reduced attractiveness to intranasal abusers, with a corresponding decrease in street value.

By contrast, all subjects had great difficulty trying to prepare either Oxy-PSH or Oxy-PEO tablets for intravenous abuse. The percentage yields of active drug extracted from the Oxy-PEO tablets versus Oxy-PSH were similar (1.95 vs 1.29%, respectively). Though easily crushed, Oxy-PSH contains a mixture of xanthan and locust bean gum that forms a highly viscous gel when immersed in water, making intravenous abuse difficult. Epidemiologic evidence has shown that Oxy-PSH is rarely abused intravenously but frequently abused intranasally [3]. Only six (24%) subjects could scrape off any material from the Oxy-PEO tablets; however, as with Oxy-PSH, the material obtained from Oxy-PEO tablets formed a highly viscous gel when immersed in water (**Figure 6**).

These investigations of Oxy-PEO suggest that the formulation has a high potential to increase hurdles against tampering; similarly, an unpublished study of Oxecta® summarized in the product label reported that experienced recreational drug users found it difficult to inhale crushed tablets because of nasopharyngeal discomfort, and many stated that they would not take the formulation again [7]. However, the potential effectiveness of these formulations in deterring abuse must ultimately be established by epidemiologic analysis of postmarketing data over a prolonged period.

The actual potential for a tamper-deterrence mechanism to prevent abuse can only be assessed epidemiologically after introduction of the products to market. Such an assessment was recently published following the reformulation of OxyContin® (Purdue Pharma, Stamford, Connecticut, USA) [12,29] into a tablet with high crush resistance marketed since August 2010. This study, utilizing data from the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO) sentinel surveillance network, reported that among individuals abusing any prescription opioid, the proportion of individuals abusing OxyContin by any administration route declined from 24% for the period before introduction of reformulated OxyContin to 12% for the 11-month period after its introduction. For the same period, the proportion of abuse via nonoral routes (e.g., injection, intranasal, smoking) declined from 18 to 5% in individuals abusing any prescription opioid, while oral abuse of OxyContin declined from 14 to 10%. Although these data reflect only a short time interval immediately after reformulation, they support the potential for crush-resistant

formulations to discourage abuse, particularly for the non-oral routes. Additional postmarketing data for available opioid formulations designed to resist crushing and extraction in fluids will be required before any label claim of abuse deterrence can be legitimately made.

5. Conclusions

The purely physicochemical approach to deterring tampering by imposing physical barriers to crushing addresses the shortcomings of TRFs that add non-therapeutic substances (e.g., antagonists or aversive agents) to prescription analgesics. These non-therapeutic substances may reduce the attractiveness of the formulation for abuse but may have the potential to compromise efficacy and tolerability in compliant patients without offering additional benefits. By contrast, a hardened matrix should have little or no effect on efficacy or tolerability, and might bring the added benefit of preventing accidental or misguided intentional crushing unrelated to abuse. Given its apparent resistance to crushing, the matrix used in formulating Oxy-PEO may be used to formulate any type of ER drug for which accidental or intentional crushing may produce adverse events [30].

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