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REGULAR ARTICLE

The advent of a new pseudoephedrine product to combat methamphetamine abuse

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Abstract

Background: The personal and societal effects of methamphetamine abuse are well documented. The ease of accessibility to methamphetamine and the quality of the "high" it produces makes the drug highly desired by its abusers. Over time, many methamphetamine users will also become methamphetamine cooks, where pseudoephedrine in over-the-counter cold products is converted to methamphetamine through a simple, albeit extremely dangerous, process. New laws limiting access to these products have had limited success. No existing commercial pseudoephedrine products offer significant impediments to slow or limit the extraction and conversion of pseudoephedrine in clandestine methamphetamine laboratories. *Objective and Methods*: A new pseudoephedrine 30 mg tablet product using Impede technology (Nexafed®) to deter methamphetamine production has recently been introduced into the marketplace. Using methods designed to mimic clandestine laboratory processes, the ability of this product to disrupt extraction and conversion of pseudoephedrine to methamphetamine yet provide therapeutic effectiveness was evaluated. *Results*: Impede™ technology tablets limited the extraction and/or conversion of pseudoephedrine to methamphetamine when compared to a commercially marketed pseudoephedrine product (Sudafed®). Nexafed® tablets were also shown to be bioequivalent to the same control product, thus ensuring therapeutic equivalence. *Conclusions*: With the advent of new pseudoephedrine products in the marketplace with features to limit the extraction and conversion of pseudoephedrine to methamphetamine, new tools are now available to minimize the clandestine manufacture of the drug and potentially limit its social impact.

Keywords

Clandestine laboratories, extraction, Impede technology, methamphetamine abuse, Nexafed, pseudoephedrine

History

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Introduction

Methamphetamine is a powerful stimulant occasionally used to treat attention deficit/hyperactivity disorder (1). However, methamphetamine is also a frequently abused, highly addictive drug that can be manufactured from ''over-the-counter'' (OTC) cold/allergy medicines. The National Survey on Drug Use and Health estimates that 353 000 people in USA ages 12 years or older abuse methamphetamine annually (2). The cost of methamphetamine abuse in USA was estimated at $23.4 billion in 2005 including costs for health care, incarceration and parole supervision, clandestine laboratory site cleanups, property damage, drug arrests, hospital costs, custodial care for children, lost productivity, lower quality of life and premature death (3). There were an estimated 6 million crimes committed by methamphetamine abusers in 2004 (4). In 2011, more than 10 000 illicit methamphetamine laboratories were found in USA (5). Each laboratory creates environmental hazards that necessitate expensive and timely cleanup. From 1998 to 2012, a Missouri program processed 16 000 methamphetamine laboratory incidents accounting for 280 tons of hazardous waste (6). In 2011, the Tennessee Meth Initiative for Child Advocacy Centers supported 369 endangered children rescued from methamphetamine sites (7).

Methamphetamine cooks (methamphetamine producers) are typically users for an average of 5 years before their first production attempt. Most methamphetamine cooks are taught the process by relatives or friends and produce for personal use. Many are successful on their first attempt and consider the process relatively easy. However, laboratory fires were reported by 24% of the methamphetamine cooks in the survey (8).

Methamphetamine's highly addictive nature and the ease of acquisition through production has resulted in an epidemic growth of methamphetamine abuse in USA. Pseudoephedrine and methamphetamine molecules are chemically different by a single oxygen atom. Two popular chemical reduction reactions are used to remove this oxygen atom (Table 1).

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Table 1. Three common methods for converting pseudoephedrine to meth.

1. The ''Birch method'' is a chemical reduction reaction to convert pseudoephedrine in base form into methamphetamine. Although the method was developed by Authur John Birch in 1944, the method has become more popularly known as the Nazi method. Contrary to popular belief that the method was used extensively by the Nazis during World War II, the name is more likely to have come from an early methamphetamine cook having Nazi symbols on the recipe letterhead (16). The method is prevalent throughout the Midwest because of the ease of access to a raw material often used by farmers as fertilizer. The method is capable of producing multiple grams to kilogram quantities of methamphetamine, provided a methamphetamine maker has access to a sufficient supply of pseudoephedrine which can be obtained through mass buying of cold/allergy products containing pseudoephedrine HCl.
2. The ''Red Phosphorous method'' is a chemical reduction reaction utilizing red phosphorus/hydriodic acid chemistry to convert pseudoephedrine to methamphetamine. The method is less prevalent in USA because of the need for specialized processing equipment and certain regulated chemicals. However, the Red Phosphorous method is the primary method used by Mexican ''super laboratories'' to make multiple kilogram/ton quantities of highly potent methamphetamine. On the street, this methamphetamine is known as ''Mexican ice''.
3. The ''one-pot method'', also known as ''shake-and-bake'', is a simplified variation of a Birch reduction method used to convert pseudoephedrine HCl tablets into methamphetamine. The method uses readily obtainable reactants and pseudoephedrine cold/allergy products to produce small quantities of low quality methamphetamine. All the ingredients are added to small, sealable vessels, such as 2-L soda bottles, and multiple simultaneous chemical reactions convert the pseudoephedrine HCl in the drug tablets into methamphetamine using little expertise or training.

The Red Phosphorous method utilizes red phosphorous and hydriodic acid. The Birch method, or more commonly referred to as the Nazi method, utilizes anhydrous ammonia and a reactive metal. The ingredients needed for each reaction can easily be obtained from local stores (9).

Early US and Mexican methamphetamine ''super laboratories'' produced large quantities of methamphetamine from pure pseudoephedrine powder imported from pharmaceutical industry suppliers. The 1996 Comprehensive Methamphetamine Control Act gave the US Drug Enforcement Administration authority to regulate pseudoephedrine imports inside and outside USA (10). Domestic methamphetamine laboratories adapted to the law by extracting pseudoephedrine from pharmaceuticals legally obtained from retailers. These laboratories, manufacturing in kilogram quantities, typically use extraction processing to first isolate and purify the pseudoephedrine prior to methamphetamine conversion to improve batch sizes, yield and purity. A variety of solvents are used to separate, dissolve and filter the pseudoephedrine including tap water (11).

Pseudoephedrine products were further regulated to curb methamphetamine production with the 2005 Combat Methamphetamine Epidemic Act (CMEA) which enforces monthly consumer purchase restriction and behind the counter safe-keeping (12). An immediate decrease in laboratory seizures was seen from 2005 to 2007; however, a rebound in laboratory seizures has been noted from 2008 to 2011 (5). The larger, for-profit laboratories adopted ''smurfing'', a network of multiple purchasers with multiple identifications, to illegally circumvent purchasing restrictions and obtain needed batch quantities of over 30 g of pseudoephedrine. The DEA also acknowledged the advent of small capacity laboratories, referred to as ''shake-and-bake'' or ''one-pot'', allowing for personal quantity production using legal quantities of purchased pseudoephedrine tablets. One-pot employs a Birch reduction reaction on crushed tablets where the extraction and conversion are completed in a vessel, typically a soda bottle, in a single process. The increase in laboratory seizures from 2008 has primarily been a result of growing popularity for the one-pot process (13).

Recently, immediate release pseudoephedrine HCl 30 mg tablets presenting barriers to converting pseudoephedrine to methamphetamine have been introduced (Table 2). Nexafed® (Acura Pharmaceuticals Inc, Palatine, IL) uses Impede™ Technology, a mixture of polymers to incorporate methamphetamine resistance to the formulation, as measured by a substantial reduction in the extraction and conversion of pseudoephedrine to methamphetamine from the product. This report explores the bioavailability of the active ingredient in Nexafed® as well as its tamper resistant properties.

Table 2. Percentage of pseudoephedrine HCl extracted from various solvents.

	Deionized water	Methanol	0.1 N HCL
Impede® 30 mg tablets	NR	NR	NR
Sudafed® 30 mg tablets	97	89	NT

NR = none recovered, a thick gel formed with Impede tablets when volumes up to 7.5 mL/tablet were added. Pseudoephedrine from these gels was not extractable. Higher volumes of solvent were not tested. NT = not tested.

Method

The methamphetamine resistance of Impede™ technology was evaluated using a comparative extraction study and one-pot conversion study. It is important to note that there are multiple variations used by methamphetamine laboratories, but the primary constituents and related chemistries remain constant. An independent laboratory (Madison, WI) completed the extraction and one-pot testing. The impact of the Impede™ technology on the pharmacokinetic profile of pseudoephedrine following administration was evaluated in a study in normal subjects by Worldwide Clinical Trials (San Antonio, TX).

Pseudoephedrine extraction

Historically, large scale manufacture of methamphetamine from pseudoephedrine tablets using the Birch or Red Phosphorous reduction reaction starts with an initial extraction and separation of pseudoephedrine HCl from inactive tablet ingredients. Bulk quantities of pseudoephedrine HCl

tablets are crushed, dissolved, filtered and dried to obtain purified pseudoephedrine HCl for use in the reduction chemistry. Using pure pseudoephedrine in large or small scale processing (i.e. one-pot) is preferred as yields are improved by removing other tablet ingredients, which to some extent interfere with the reaction. In this study, a method was developed and optimized to assess the percent of pseudoephedrine extracted from pseudoephedrine tablets (Supplement 1). In this method, 100 tablets were crushed, dissolved in either aqueous or organic polar solvent (in which pseudoephedrine is highly soluble), and filtered. The resultant filtrate (if obtained) was assayed for pseudoephedrine HCl content using high-performance liquid chromatography (HPLC).

One-pot methamphetamine conversion

A ''one-pot'' process was developed and optimized to test the conversion of various pseudoephedrine formulations to methamphetamine. The ''one-pot'' chemistry performs a biphasic separation of the pseudoephedrine HCl from the crushed tablets by adding chemicals to convert the pseudoephedrine salt to its free base which then partitions into a non-polar organic solvent. The simplicity of one-pot is that all chemicals and solvents are added at once, creating simultaneous reactions resulting in the production of free base methamphetamine. The resultant methamphetamine containing solvent is separated from the unwanted reactants and converted to methamphetamine HCl for final use.

The one-pot process developed in the current study used 100 conventional pseudoephedrine HCl 30 mg tablets obtained from a pharmacy. This process was optimized to maximize methamphetamine yield by testing varying levels of strong base (Step 5), total reduction reaction time and additional processing in the acidic gasification process (Step 11). The qualitative one-pot process and methods used in this evaluation are summarized in Supplement 2. [For ethical reasons, the exact reaction parameters are not included in this article.] The yield of pseudoephedrine HCl and methamphetamine HCl present in the final non-polar solvent was quantified using gas chromatography. These results were compared to a theoretical 2.7 g yield of methamphetamine HCl that represents a 100% conversion of 3 g (100 pseudoephedrine HCl 30 mg tablets) based on molar equivalents.

The one-pot process was executed using three non-polar solvents commonly used in one-pot methods: petroleum distillates (camper fuel), heptane/ether mix (automotive starter fluid) and hexanes.

Pharmacokinetic evaluation

An open-label, randomized crossover study was conducted in 30 healthy adult subjects dosed with two separate single-dose administrations of two pseudoephedrine HCl 30 mg tablets (60 mg dose) following an overnight fast. There was a minimum washout period of 7 days between treatments. The two treatments were Sudafed® (McNeil Laboratories, Fort Washington, PA) and Nexafed® Tablets (Acura Pharmaceuticals Inc., Palatine, IL) which uses the Impede™ technology. Nexafed® tablets used in the pharmacokinetic study were manufactured in a full-scale commercial batch, whereas Impede™ technology tablets used in the aforementioned extraction and one-pot evaluations were manufactured on smaller scale R&D equipment.

Blood samples were collected at time 0 (pre–dose) and at 18 time-points over the ensuing 24 h post-dose with the first sample taken at 15 min. Plasma samples were assayed for pseudoephedrine using a validated liquid chromatography–tandem mass spectroscopy procedure. The method was validated for a range between 2.00 and 500 ng/mL of pseudoephedrine in the pharmacokinetic analysis. Concentrations below the limit of quantitation (BLQ) were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as ''missing''. Full precision concentration data and actual sampling times were used for all pharmacokinetic and statistical analyses. The following pharmacokinetic parameters were determined: peak concentration in plasma (C_{max}), time-to-peak concentration (T_{max}), elimination rate constant (λ_z), terminal half-life ($T_{1/2}$), area under the concentration-time curve from time-zero to the time of the last quantifiable concentration (AUC_{last}) and area under the plasma concentration time curve from time-zero extrapolated to infinity (AUC_{inf}). The comparisons of the log-transformed pharmacokinetic parameters C_{max}, AUC_{last} and AUC_{inf} for pseudoephedrine across treatments, Nexafed® (test) versus Sudafed® (reference/control) was performed using an analysis of variance (ANOVA) model and the Schuirmann's two one–sided *t*-test procedures at the 5% significance level. The geometric mean ratios (test/reference) and the 90% confidence intervals about the ratios were reported.

Results

Pseudoephedrine extraction

The extraction procedure (Supplement 1) was conducted separately with 100 Sudafed® tablets (control) and 100 tablets containing the Impede™ technology (test). All tablets contained 30 mg pseudoephedrine HCl. Individual trials were conducted using deionized water to represent an aqueous solvent and methanol to represent a polar organic solvent.

The crushed control tablets readily dispersed and dissolved in both solvents and the resultant liquid easily passed through filter paper providing a clear liquid, slightly pink from the coating dye. The pseudoephedrine HCl in the filtrate was assayed by HPLC indicating 97 and 89% of the pseudoephedrine HCl was extracted in water and methanol, respectively (Table 2).

When the solvents were added to crushed Impede™ technology tablets, a thick gelatinous single-phase mass was rapidly produced. Approximately 200 mL of this mass was transferred to a filter. However, after 2 h, no extraction liquid had passed through the filter with the pseudoephedrine remaining bound in the polymer matrix. Therefore, the samples in both aqueous and polar organic solvents could not be assayed by HPLC and no pseudoephedrine HCl was extracted.

To further evaluate the effect of low pH on Impede™ technology tablets, an additional extraction evaluation was performed using 0.1 N HCl (pH 1.1) as the solvent. As observed for the aqueous and polar organic solvents, a viscous

gel resulted when aqueous 0.1 N HCL was mixed with the crushed tablets and the extraction attempt resulted in no recoverable pseudoephedrine HCl. From these data, Impede™ technology tablets represent a significant impediment to extracting pure pseudoephedrine when compared to control. Pure pseudoephedrine is required as a starting material for Birch and Red Phosphorous methods.

One-pot methamphetamine conversion

Trials were conducted using the one-pot procedure (Supplement 2) on Sudafed® tablets (control) and Impede™ technology tablets (test). Three different primary non-polar solvents were tested. Heptane/ether mix (automotive starter fluid), and hexanes were evaluated as a single trial for each whereas petroleum distillates (camper fuel) was performed as duplicate trials. Each trial used 100 crushed tablets containing 30 mg of pseudoephedrine HCl. Initially, a consistent amount of non-polar solvent was present on top of the insoluble drug products and added reactants. Once the reaction commenced (Step 7), the control and test articles progressed differently. The texture of the control reaction solids remained granular with the non-polar layer remaining visibly unchanged in volume. The Impede™ technology tablet polymer matrix became coarse and ultimately swelled to subsume a large amount of the non-polar layer. This mixture also entrapped gas bubbles throughout the reaction and gas pockets could be seen throughout the solids at the completion of the reaction. Subsequently, less than half of the solvent was recovered after filtering the reaction mixture.

The results of all trials for the control and Impede™ technology tablets are shown in Table 3. The one-pot reaction experiments for the control resulted in a mean methamphetamine HCl yield of 1.81 g/reaction for a mean yield of 67% relative to the 2.7 g theoretical 100% yield. The range of methamphetamine recovery for control was 1.44–2.10 g. The Impede reaction experiments resulted in a mean methamphetamine HCl yield of 1.02 g/reaction for a mean yield of 38%. The range of methamphetamine HCl recovery for Impede was 0.77–1.33 g. In all reactions, Impede resulted in a lower yield than control regardless of the solvent type used. Overall, Impede™ technology tablets are 44% lower in mean total methamphetamine recovery relative to the control. In general the methamphetamine recovery results were fairly consistent for the three solvents tested with a relative standard deviation for all four trials at 15.1 and 22.4% for control and Impede, respectively.

Several *post hoc* attempts to improve methamphetamine recovery from Impede™ technology tablets were made. Rinsing the reaction solids resulted in 12 and 1.3% additional methamphetamine and pseudoephedrine recovered, respectively. Thus a full recovery of methamphetamine could not be achieved with additional solvent extraction. In another *post hoc* trial using Impede™ tablets, reagents and reactants were added more frequently such that the reactants were spent in about one-third the optimized method time. The expedited reaction time for this trial is estimated to be in line with a normal clandestine one-pot reaction time. Using petroleum distillates (camper fuel) as the non-polar solvent, this experiment yielded just 18% total methamphetamine HCl recovered compared to 29 and 49% recovery from the optimized reactions and a 54% reduction in methamphetamine recovery for the more rapid reaction time. Additionally, there was nearly a 6-fold increase (458 versus 79 mg) in the amount of pseudoephedrine recovered from the expedited reaction when compared to optimal process.

Pharmacokinetic evaluation

Per the FDA Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products-General Considerations (14), systemic exposure measures such as C_{max} and AUC may be used to demonstrate comparable rate and extent of drug absorption from two products (e.g. a test formulation and a reference or control product), which in turn achieves the underlying statutory and regulatory objective of ensuring comparable therapeutic effects across products. The test formulation is bioequivalent to the reference product if there is no significant difference in

Table 3. Methamphetamine recovery of control (Sudafed®) tablets and Impede tablets using various one-pot solvents.

	Solvent	Solids isolated (mg)	Total PSE HCl[a] (mg)	Total meth HCl[a] (mg)	Methamphetamine yield (%)[b]
Methamphetamine recovery of control (Sudafed®) tablets using various one-pot solvents					
Control RX1	Coleman fuel	2910	82	1813	67
Control RX2	Coleman fuel	2768	55	2104	78
Control RX3	7:3 heptane:ether	3527[c]	176	1446	53
Control RX4	Hexanes	2445	49	1883	69
Mean	–	–	–	1811	67
RSD	–	–	–	15.1%	–
Methamphetamine recovery of Impede tablets using various one-pot solvents					
Impede RX1	Coleman fuel	1121	157	773	29
Impede RX2	Coleman fuel	1949	0	1325	49
Impede RX3	7:3 heptane:ether	1593	239	988	37
Impede RX4	Hexanes	1612	65	984	36
Mean	–	–	–	1017	38
RSD	–	–	–	22.4%	–

[a]The weight of either methamphetamine HCl or PSE HCl contained in the solids isolated based on GC analysis of the isolate. [b]The theoretical methamphetamine HCl yield from 3 g PSE HCl = 2.709 g. All of the % yield values are based on this number rather than 3 g PSE starting material. [c]The high amount of isolated solids in the control 7:3 heptane:ether reaction is unexplained as the Impede® 7:3 heptane:ether reaction ran normally. It is expected that if the control 7:3 heptane:ether reaction was repeated that the amount of isolated solids would return to trend with the other control reactions.

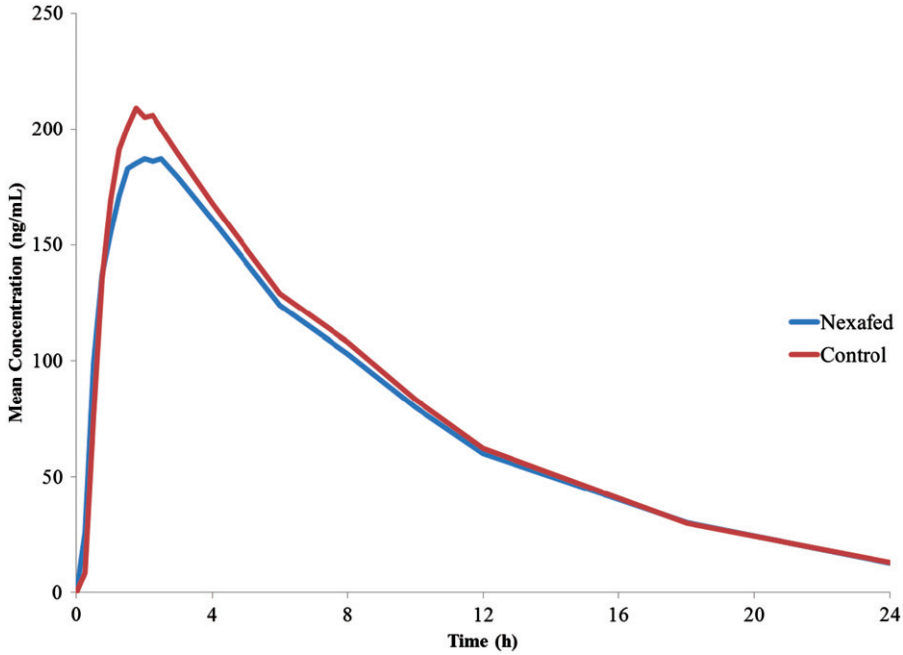


Figure 1. Mean Pseudoephedrine Concentration-Time Profiles after Administration of Nexafed® Tablets and Control Tablets.

Table 4. Pharmacokinetic parameters of pseudoephedrine.

	Test product (Nexafed)			Reference product (Sudafed)		
Parameter	*n*	Mean (SD)	CV%	*n*	Mean (SD)	CV%
T_{max} (h)	30	2.10 (0.85)	40.59	30	1.93 (0.75)	38.91
C_{max} (ng/mL)	30	206 (51.6)	24.97	30	223 (53.9)	24.15
AUC_{last} (h ng/mL)	30	1852 (426.2)	23.01	30	1931 (450.3)	23.32
AUC_{inf} (h ng/mL)	30	1963 (476.9)	24.29	30	2040 (496.1)	24.32
AUC_{Extrap} (%)	30	5.36 (3.48)	64.94	30	5.05 (3.43)	67.91
λ_z (h^{-1})	30	0.1337 (0.0259)	19.38	30	0.1375 (0.0267)	19.43
$T_{1/2}$ (h)	30	5.40 (1.19)	21.97	30	5.25 (1.19)	22.60
T_{last} (h)	30	24.01 (0.01)	0.05	30	24.00 (0.00)	0.02
C_{last} (ng/mL)	30	12.9 (7.27)	56.13	30	13.1 (7.22)	55.33

Full precision data used in pharmacokinetic analysis.

Table 5. Statistical analysis of the log-transformed systemic exposure parameters of pseudoephedrine.

Dependent variable	Geometric mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/ref)	Lower	Upper		CV%
$\ln(C_{max})$	200.0541	216.5413	92.39	89.56	95.30	1.0000	7.09
$\ln(AUC_{last})$	1807.6140	1882.4256	96.03	93.31	98.82	1.0000	6.54
$\ln(AUC_{inf})$	1911.3434	1983.8007	96.35	93.33	99.47	1.0000	7.26

[a]Geometric mean for the ''test formulation (test)'' and ''reference product (ref)'' based on least squares mean of log-transformed parameter values.
[b]Ratio(%) = geometric mean (test)/geometric mean (ref).
[c]90% confidence interval (CI).

the rate and extent of drug absorption. Statistically, to demonstrate bioequivalence the 90% confidence intervals about the geometric ratios (test/reference) of the log-transformed values of C_{max}, AUC_{last} and AUC_{inf} must be within the accepted limits of 80–125%. In this study, Sudafed® served as the reference and Nexafed® with Impede™ technology was the test formulation.

The mean concentration-time profile is shown in Figure 1 and the mean pharmacokinetic parameters are shown in Table 4. Pharmacokinetic parameters of T_{max}, C_{max} and AUC show Impede™ tablets (test) to be similar to control (reference), reflecting that therapeutic levels of pseudoephedrine would be comparable for the two products. From the log-transformed systemic exposure parameters (Table 5), the three critical pharmacokinetic exposure parameters meet the FDA criteria for bioequivalence. The 90% confidence interval for $\ln(C_{max})$, $\ln(AUC_{last})$ and $\ln(AUC_{inf})$ are 90–95%, 93–98% and 93–99%, respectively. Therefore, Nexafed® tablets with Impede™ technology are bioequivalent to the control product.

Discussion

Conventional pseudoephedrine containing products on the US market do not present significant impediments to methamphetamine conversion. Attempts to curb the diversion and misuse of these products to date have been mixed (13). The Government Accountability Office has recently reported that electronic tracking systems primarily implemented from CMEA have helped enforce pseudoephedrine sales limits, but have had little effect in reducing methamphetamine laboratory incidents. Law enforcement agents in Indiana and Tennessee have reported that since the system blocks individuals from purchasing larger amounts of pseudoephedrine, pseudoephedrine diversions are not as readily identified. Furthermore, smurfing operations with recruits such as elderly, homeless, gang members and college students, coupled with fake identifications to purchase above the legal limits, are compromising the effectiveness of electronic tracking to identify and reduce pseudoephedrine diversion. Because of the limited success of CMEA to reduce the number of methamphetamine laboratory incidents, the incidence of medical and fire emergencies, arrests and incarcerations, child foster care and environmental clean-up related to methamphetamine cooks and their clandestine laboratories has remained prevalent. In states where prescription only laws have been implemented, clandestine laboratory seizures have shown significant reductions as well as reductions in medical, legal and environmental impact caused by methamphetamine cooking. However, prescription only pseudoephedrine products are less accessible and more costly to the consumer than in non-prescription states.

New tamper resistant pseudoephedrine products, such as Nexafed® tablets with Impede™ technology, have recently been introduced in the US marketplace. Importantly, Nexafed® is bioequivalent to a similar national brand product providing assurance to physicians, pharmacists and consumers of a comparable level of decongestant effectiveness. However, the Impede™ technology polymer matrix provides impediments to disrupt the extraction and conversion of pseudoephedrine into methamphetamine. Extraction and purification of pseudoephedrine from Nexafed® tablets as a starting material for methamphetamine production has been shown to be significantly hampered in common extraction solvents when compared to a control product. Extraction of control resulted in high-yield pseudoephedrine extractions, however; Nexafed resulted in the formation of a single-phase, gelatinous mass which was not filterable and no pseudoephedrine was extracted. Additionally, the mean methamphetamine recovered from Nexafed® tablets in the one-pot methamphetamine conversion method averaged 38% which represents a 44% reduction compared to control tablets in an optimized process. With federal pseudoephedrine purchase limits in place from CMEA, a reduction in methamphetamine yield will directly lower the amount of methamphetamine available in the community as additional raw materials cannot be legally purchased to run additional batches. Thus methamphetamine cooks and their surrogate smurfs are highly likely to avoid purchasing tamper resistant pseudoephedrine products.

The advent of tamper resistant pseudoephedrine products into the marketplace presents a significant tool to aid legitimate customers, pharmacists and law enforcement. For the cold and sinus sufferer, tamper resistant products such as Nexafed® provide an effective pseudoephedrine product to treat nasal decongestion; however, the stigma associated with purchasing a conventional pseudoephedrine product would be eliminated. Although the customer would still be required to show identification to pharmacy personnel and entered into the electronic tracking system, they would be assured of purchasing a product which is not favored by methamphetamine cooks and smurfs. Additionally, states with prescription only pseudoephedrine laws have provisions to exclude tamper resistant products from the prescription only requirement. Customers in these states would have greater accessibility to pseudoephedrine products than they have currently. Pharmacists and pharmacy personnel would be able to use tamper resistant pseudoephedrine products as ''discriminators'' to conventional products. Since CMEA requires pseudoephedrine products to be held ''behind the counter'', the pharmacist could offer the tamper resistant product to a customer with whom he is unfamiliar or uncertain of their intentions. Pharmacies selling tamper resistant products are also less likely to be targeted for theft and break-ins (15). With data collected from the pharmacies for the sale of tamper resistant versus conventional pseudoephedrine products, electronic tracking could be more effective to law enforcement agents in identifying diversion of pseudoephedrine.

Given the recent introduction of tamper resistant pseudoephedrine products to the marketplace, it is still too early to assess what impact they will have on domestic clandestine methamphetamine production. If these products are equally available for sale with conventional pseudoephedrine products as in the current marketplace, the impact of tamper resistant products will be minimized as methamphetamine cooks and smurfs will continue to purchase conventional products. However, if the pseudoephedrine efficacy and resistance to extraction and conversion to methamphetamine for tamper resistant products, as has been shown for Nexafed® in this article, can be substantiated in the marketplace, then the benefits will become more apparent as pharmacy, law enforcement and perhaps even legislative policy may change to favor the sale of only tamper resistant pseudoephedrine products in the future.

Declaration of interest

Dr. Brzeczko and Mr. Leech are employees of Acura Pharmaceutical Technologies Inc., a subsidiary of Acura Pharmaceuticals Inc. which markets Nexafed®tablets. As a part of their compensation, Dr. Brzeczko and Mr. Leech are eligible to incentive programs which may grant stock options and both are currently holders of Acura stock. All research presented was sponsored by Acura Pharmaceutical Technologies Inc. Dr. Stark is an employee of Worldwide Clinical Trials Inc., a company which was contracted by Acura Pharmaceutical Technologies to complete the bioequivalence study presented in this article.

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Supplemental content

Supplement 1: Pseudoephedrine HCl Extraction Procedure and Analytical Method
Supplement 2: Qualitative One Pot Methamphetamine Conversion Procedure and Analytical Method for Methamphetamine and Pseudoephedrine Determination

Supplements 1 and 2 are available for download at informahealthcare.com/ada