New Abuse-Deterrent Pseudoephedrine Product To Hinder One-Pot Conversion To Methamphetamine
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Purpose
Abuse of consumer pseudoephedrine (PSE) products is a known issue as currently-available formulations do not adequately impede extraction and one-pot conversion (OPC) to methamphetamine (MA). This study introduces a new abuse-deterrent formulation (ADF) for PSE tablets based on Grünenthal’s INTAC® technology. ADF properties of new formulations were characterized at NMS Labs and were compared with existing marketed products (Sudafed®, Nexafed®, Zephrex-D®).

Methods
6 different new tablet formulations (120 mg PSE, extended release) and two comparators: non-ADF C1 (Sudafed® 120mg PSE, extended release), ADF C2 (Nexafed®, 30mg PSE, immediate release, IMPEDE® abuse-deterrent technology) were manipulated (mechanically and chemically) and extracted into different media under various conditions. Eight different tools (pliers, hammer, coffee grinder, mortar and pestle, knife, Ped Egg™, razor blade, spoons) were used to identify the most effective manipulation techniques for particle size reduction. Solubility and extraction studies were conducted with different solvents in order to identify the most suitable conditions for solubilizing the test materials and for further conversion experiments. Aqueous and organic solvents were used under different conditions (Set A: water and 40% ethanol at room temperature and elevated temperature, agitated and non-agitated, pulverized and intact; set B: methylene chloride, ethyl acetate, diethyl ether, pulverized tablets at various pH conditions, with and without the addition of sodium chloride to enhance solubility).

PSE was converted to MA by applying different methods: (a) lab OPC (ground tablets) (b) optimized OPC (ground tablets) (c) indirect OPC (PSE extraction from ground tablets with subsequent conversion). Modifications were made to method (a) including the proportions and addition times of chemical reactants throughout the time course of the experiments to identify a more-optimized method (b). Samples were analyzed via LC-MS/MS to measure PSE extraction efficiency and MA yields. Physical manipulation with a coffee grinder and method (a) were also applied to a second ADF comparator C3 (Zephrex-D® softgels, 30mg PSE, immediate release, Tarex® abuse-deterrent technology) in order to compare the drug product performance with one of the test INTAC® ADF products.

Results
Both comparators C1 and C2 were very easily crushed within 5 to 10s in a coffee grinder and exhibit 86-100% PSE release within 15min during solubility testing (stirred, at room temperature and elevated temperatures). Physical manipulation of INTAC® products was more difficult and time consuming and the resulting material was more coarse compared with particles from manipulation of comparators. For INTAC® products, the most significant particle size reduction was achieved using a Ped Egg™, and manipulation took 15min on average. Conversion of PSE from comparator products using method (a) resulted in 64% of the theoretical yield of MA for product C1 and 62% for C2. When applying similar conditions to all 6 INTAC® tablets, a negligible amount of MA was created (less than 1%). Subsequent optimization of OPC for each product (method (b)) led to maximum yields of 82-100% (C1) and 64-90% (C2). One of the INTAC® formulations yielded 18-54% MA (mean of 39% MA) applying this optimized method (b). Additionally, preliminary extraction (method (c)) did not lead to higher MA yields for INTAC® tablets (at the most 8.5%). For C1, up to 100% MA was produced using method (c) depending on number of tablets and volume of solvent used. Since ADF comparator C3 is a softgel capsule with a waxy interior, physical manipulation was performed using a coffee grinder. Contrary to the claims on the packaging of Zephrex-D®, “Tamper Resistant, Meth-Blocking Technology”, Methamphetamine was produced using method (a) and the maximum conversion amounts ranged from 47-51%.

Conclusion
Formulations to deter misuse of PSE including conversion into MA were developed, characterized by an independent testing laboratory and compared to marketed PSE products. Laboratory experiments were conducted in a manner to simulate clandestine drug synthesis operations. Using non-optimized method (a), a MA yield of 64% (non-ADF product), an insignificantly lesser yield of 62% (marketed ADF product), and yields ranging from 47-51% (second marketed ADF product) were achieved. Conversion using INTAC® formulations led to negligible conversion to MA applying this OPC method. This method was optimized, requiring knowledge of the synthetic process and appropriate measures to take in order to enhance yield. Applying the more-optimized OPC method (b), up to 100% MA yield was achieved for marketed products and a mean of 39% MA was produced for the best INTAC® formulation.