ADAIR: An Abuse Deterrent Oral Formulation of Immediate Release Dextro-Amphetamine Sulfate (d-amphetamine)

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DISCLOSURE INFORMATION

Vallon Pharmaceuticals provided funding for this study.
David Siner is a full-time employee of Vallon Pharmaceuticals.
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BACKGROUND

- Amphetamine, a central nervous system stimulant, is commonly used for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).[1] Immediate release (IR) stimulants are the most commonly prescribed ADHD medications in adolescents and adults, are abused more frequently than extended release stimulants, and are frequently diverted.[2,3] Furthermore, intranasal (IN) administration of stimulants is seen in 40% of college students who abuse stimulants.[5]
- In a study of stimulant abuse by adults admitted for abuse treatment, 38% used the IN route, and 10% injected stimulants by the intravenous (IV) route.[3]
- Intranasal abuse often involves the physical manipulation of a drug to reduce the product particle size. The Food and Drug Administration (FDA) has previously determined that one clinically meaningful measure of abuse deterrence is the percent mass of particles (<500 µm) available for insufflation.[7]
- To facilitate IV injection, the drug needs to be solubilized into a liquid that can be aspirated into a syringe at sufficient yields. For a drug abuser, the attractiveness of the solubilized drug is largely influenced by the viscosity of the liquid, affecting the force needed to push the plunger of the syringe, which enables the delivery of the solubilized drug through a needle gauge into the vein. This activity often includes the use of a commonly found filter (such as a cigarette filter) to ensure the removal of any dangerous particles from the injected material.
- The current study sought to explore the physical properties, related to both intranasal (IN) and intravenous (IV) abuse deterrence characteristics, of an Abuse Deterrent Formulation of immediate release dextroamphetamine (ADAIR), in comparison with the physical properties of a commercially available IR dextroamphetamine tablet.

METHODS

In order to explore the relative resistance to physical manipulation of ADAIR and IR dextroamphetamine, aiming to reduce the particle size for insufflation purposes, several procedures were performed. Since early findings indicated that the ADAIR product was not susceptible to any manipulation without thermal pre-treatment, the reported experiments all included thermal pre-treatment (i.e., freezing the capsules in the freezer or using dry ice, heating them using a microwave or an oven, cooling the grinder compartment of the coffee grinder in the freezer prior to grinding) followed by grinding, crushing, grating or cutting and grinding, alone or in the presence of flux enhancers. The physically manipulated products were then transferred to a sieve array ranging from 0.106 mm to 1 mm sieves, and the mass retained on each sieve was quantified.

Physical manipulation to assess potential for insufflation.

A) Milling with a coffee grinder

The shells of five whole dosage units (each dosage unit consisted of a 10 mg capsule of ADAIR, which had been frozen for 24 hours or IR dextroamphetamine, which did not require pre-treatment) were removed and the capsule contents transferred into a vial and weighed. The capsule contents were placed into an electric coffee grinder and ground for one minute. The coffee grinder containing the capsule contents was weighed and then the contents transferred to a 1 mm mesh size sieve at the top of a sieve array. The grinder was re-weighed to confirm the amount of capsule contents that had been transferred to the sieve array. The particle size distribution was determined using 1, 0.5, 0.25 and 0.106 mm mesh size sieves after shaking (5 min @ 1000 rpm). The weight of material retained on each sieve was weighed. The amount of material retained on each sieve was additionally analyzed by high performance liquid chromatograph (HPLC), to determine dextroamphetamine content.

B) Crushing using mortar and pestle and flow enhancers

Following ADAIR thermal pre-treatment, the product (IR dextroamphetamine or pre-treated ADAIR) was crushed using a mortar and pestle. Flow enhancers were used in an attempt to generate smaller particle sizes. The shells of five whole dosage units (ADAIR, which had been frozen for 24 hours, or IR dextroamphetamine, which was not pre-treated) were removed. The capsule contents were placed into a mortar and pestle and 0.2g of a flow enhancer (Talc or Sodium Chloride) was added, and then immediately ground for five minutes. The particle size distribution was determined using 1, 0.5, 0.25 and 0.106 mm mesh size sieves.

C) Heating the capsules prior to grinding

In order to assess whether heating (as an alternative thermal pre-treatment) would be effective in increasing the yield of smaller particles, ADAIR samples were heated, either in an oven at 105°C for 24 hours, or in a microwave at full power (700-800 Watt) for 4 min. The samples (IR dextroamphetamine or pre-treated ADAIR) were then ground with a coffee grinder and the particle size distribution was determined using the same array of sieves.

D) Using household tools in an attempt to reduce particle size

In order to assess whether using a domestic kitchen grater or scalpel (as an alternative grinding method) would be effective in increasing the yield of smaller particles, an attempt was made to use a domestic kitchen grater and grate ADAIR capsule contents. An attempt to fine-cut the capsule content with a scalpel was made as well.

E) Extended grinding time

The standard grinding time in a coffee grinder initially applied was 1 minute. In order to assess the effectiveness of increasing the grinding time on further reducing the particle size, the grinding time was increased to 5 minutes.

F) Grinding with dry ice or cooling the coffee grinder.

Assessment of the effect of grinding the material in the presence of dry ice (to keep the fill mass at low temperature) in an attempt to reduce the particle size was also performed. In addition, the coffee grinder was placed in the freezer for 1 hour prior to the manipulation in order to try and grind the material in a lower temperature environment.

Methods to assess potential for injection.

Syringeability assessment studies of ADAIR compared to the IR dextroamphetamine comparator were based on the April 2015 FDA draft guidance for Abuse Deterrence of Generic Solid Oral Opioid Drug Products and included single capsule/tablet extraction in ambient and hot water in different volumes (5 and 10 mL), utilizing a range of successively larger needle gauges (26, 23, 20 and 18), and assessments, including the use of cigarette filters.

A) Syringeability using a 26-gauge needle following extraction in 5 mL and 10 mL water (Ambient and Hot):

Syringeability assessments were performed using 26 gauge needles, which are commonly used by abusers. A single ADAIR capsule was crushed and then ground with 5 mL or 10 mL of water at ambient temperature for up to 30 min until homogenous. The solution was drawn up into a syringe via a 26-gauge needle and the approximated amount of liquid drawn up was recorded. In cases where 1 ml or more was drawn up and was feasible to be expelled through the needle, the syringe content was dispensed into a suitable volumetric flask and prepared for HPLC analysis. Samples that passed pre-specified test criteria (<5% yield) utilizing ambient water were assessed again using water heated to 90-95°C. The IR dextroamphetamine tablet was also tested for syringeability in parallel as a reference to the ADAIR capsule.

B) Syringeability using 18 gauge needle following extraction in 5 mL and 10 mL water (Ambient and Hot):

The effect of different needle gauges as well as attempts to draw the solution through a cigarette filter were performed. In the first set of tests, 18-gauge needles were used with the same method as described above for the 26-gauge needle. Samples that passed the test criteria at room temperature (<5% yield) were assessed again using water heated to 90-95°C.

A cigarette filter was placed into the mortar and allowed to absorb any remaining liquid. The needle was then placed into the cigarette filter and the absorbed solution was drawn into the syringe. In cases when 1 mL or greater volume was drawn up and, the syringe contents were dispensed into suitably sized vessel and the filtering process was repeated two times or until the fluid was translucent. When a translucent solution was produced, the solution was prepared for HPLC analysis using the standard assay method diluent. Where a translucent solution was not produced following multiple filtering rounds, the sample was not analyzed (n/a).

C) Syringeability using a texture analyzer for assessing viscosity:

A preliminary qualitative assessment of the force needed to be applied in order to expel manipulated capsule contents from a syringe fitted with 26 gauge needle was made using a Texture Analyser (TA-XTPlus). For IR dextroamphetamine, three full tablets were ground with 10 mL of potable water until homogenous. The resultant material was filtered through a 0.45 µm PVDF syringe filter to mimic preparation for injection. For ADAIR, bulk mix formulation (equivalent to fill material of six 10 mg ADAIR capsules) was ground with 20 mL of potable water until homogenous.

Texture analysis was carried out using a Texture Analyser TA-XTPlus (Stable Microsystems) equipped with a Universal Syringe Rig. For the tests performed, 5 mL Leur-lok syringes and 26 Gauge needles were employed. For each test, the syringe was loaded with material to be tested, air bubbles were removed and the plunger was set to the 3 mL mark. The testing was run in compression mode, with a test speed of 0.5 mm/s. The force profile obtained from compressing the plunger a distance of 9 mm (to expel ~ 1 mL of material through the needle) was recorded.

D) Syringeability of the melted product:

As ADAIR is a liquid-filled formulation, syringeability of the melted product was also assessed. The crushed ADAIR capsule or IR dextroamphetamine contents were placed on a watch glass and heated until melted; the temperature of melting was recorded. Any product drawn by a syringe via 18- or 26-gauge needles were quantified.

E) Syringeability in additional needle gauges:

Similar to the tests conducted using 18 and 26 gauge needles, intermediate (20 and 23 gauge) needles were tested in 5 and 10 mL ambient and boiling water, as well as with and without a cigarette filter.

RESULTS

Potential for insufflation.

A) Milling with a coffee grinder

The results are summarized in Table 1 for IR dextroamphetamine, and Table 2 for ADAIR. Figure 1 includes representative images from the experiments demonstrating that ground ADAIR capsule contents clumped together, forming a sticky and waxy substance that cannot pass through the first 1mm sieve. Similar results were obtained when the capsules were frozen in dry ice prior to grinding, and when the grinding chamber was also cooled prior to use.

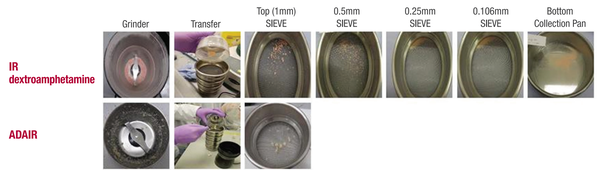
Table 1 - Particle Size Assessment Results of IR dextroamphetamine Samples

IR dextroamphetamine SAMPLE 1			IR dextroamphetamine SAMPLE 2		
Sieve level	Weight present (mg)	% of recovered weight	Sieve level	Weight present (mg)	% of recovered weight
1 mm	490.7	35.8	1 mm	555.3	43.2
0.5 mm	227.4	16.6	0.5 mm	185.7	14.4
0.25 mm	226.0	16.5	0.25 mm	199.9	15.6
0.106 mm	223.3	16.3	0.106 mm	211.7	16.5
base	203.4	14.8	base	133.2	10.4

Table 2 - Particle Size Assessment Results of ADAIR Samples

ADAIR SAMPLE 1			ADAIR SAMPLE 2		
Sieve level	Weight present (mg)	% of recovered weight	Sieve level	Weight present (mg)	% of recovered weight
1 mm	788.1	99.1	1 mm	832.1	100
0.5 mm	0.7	0.1	0.5 mm	-0.5	nd
0.25 mm	2.4	0.3	0.25 mm	-2.8	nd
0.106 mm	1.2	0.2	0.106 mm	-3.7	nd
base	2.6	0.3	base	-2.8	nd

Figure 1 - Sample Images of IR dextroamphetamine and ADAIR Products Following Grinding and Sieving



B) Crushing using mortar and pestle and flow enhancers

Following grinding of ADAIR, samples became a sticky off-white paste and the capsule contents were retained on the top 1 mm sieve.

C) Heating the capsules prior to grinding

Heating of ADAIR capsules in either an oven or a microwave followed by grinding resulted in a waxy material, which was fully retained on the top sieve, and therefore no further analysis was performed.

D) Using household tools in an attempt to reduce particle size

In attempting to reduce particle size by grating or by cutting with a scalpel, the manipulation resulted in solid, pasty mass which was retained on the top sieve.

E) Extended grinding time

The ADAIR sample did not grind in a coffee grinder after 1 minute or 5 minutes, and remained as a solid mass on the top sieve after both grinding times.

F) Grinding with dry ice or cooling the coffee grinder

After grinding with dry ice or cooling the coffee grinder, ADAIR did not grind under either condition, and was retained as a solid mass on the top sieve for both conditions.

Potential for injection.

A) Syringeability using a 26-gauge needle following extraction in 5 mL water (Ambient and Hot)

While IR dextroamphetamine was easily syringed, with a dextroamphetamine recovery of 60-70%, syringeability tests of ADAIR often required increased force for drawing up and, when applicable, expelling the manipulated material, generally resulting in a dextroamphetamine recovery of <10% (recoveries were generated by assay analysis using HPLC). The results were similar for both ambient and boiling water. Analysis with 10 mL was repeated using a cigarette filter in order to demonstrate a likely, representative abuse practice given the appearance of the material.

Tables 3 and 4 below detail the syringeability results of IR dextroamphetamine and ADAIR utilizing ambient and boiling water using 26-gauge needle in 5 mL of water. Figure 2 contains a representative image of the resultant solution of manipulated ADAIR.

Table 3 - Syringeability in 5 mL Ambient Water with a 26 Gauge Needle and Assay of Syringed Samples

Formulation	Sample	Volume syringed/drawn (mL)	% Recovery	Average % Recovery
ADAIR	1	<1.0	0.5*	1.5
	2	<1.0	3.0*	
	3	<1.0	1.1*	
IR dextroamphetamine	1	2.0	37.0	19.5
	2	1.5	N/A**	
	3	1.0	21.6	

* Note: Samples <1 mL were analyzed by HPLC and reported for information only.
** 1.5mL drawn into syringe but could not be expelled

Table 4 - Syringeability in 5 mL Boiling Water with a 26 Gauge Needle and Assay of Syringed Samples

Formulation	Sample	Volume syringed/drawn (mL)	% Recovery	Average % Recovery
ADAIR	1	<1.0	2.1*	2.8
	2	<1.0	4.3*	
	3	<1.0	2.1*	
IR dextroamphetamine	1	4.0	87.6	50.7
	2	3.0	64.5	
	3	<1.0	0*	

* Note: Samples <1 mL were analyzed by HPLC and reported for information only.

Figure 2 - Images of ADAIR Product following Preparation for Injection

B) Syringeability using 18 gauge needle following extraction in 10 mL of water (Ambient and Hot)

Using ambient and hot water with an 18-gauge needle (Table 5), the assayed dextroamphetamine results for ADAIR capsules were lower than for IR dextroamphetamine. Furthermore, the utilization of cigarette filters significantly reduced the yield of the dextroamphetamine recovered. Results using 5 mL ambient water or 5 mL boiling water (not shown) also showed a smaller average percent recovery for ADAIR than for IR dextroamphetamine.

Table 5 Syringeability with an 18 gauge needle

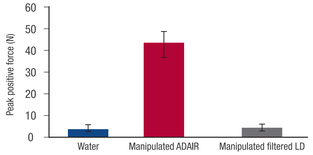
Formulation	Condition	Average Percent Recovery
ADAIR	10 mL ambient water, cigarette filter	6.6
IR dextroamphetamine	10 mL ambient water, cigarette filter	78.7
ADAIR	10 mL boiling water, cigarette filter	6.9
IR dextroamphetamine	10 mL boiling water, cigarette filter	70.3

C) Syringeability using a texture analyzer for assessing viscosity:

An attempt was made to pass ADAIR, ground with water, through a 0.45 µm syringe filter, but sufficient ADAIR material for the test could not be obtained due to rapid blocking of the filter. As the material could not be filtered, texture analysis was performed on an unfiltered sample.

From the data generated as summarized in the below figure (Figure 3), the force required to push the plunger with an ADAIR filled syringe is far greater than that with manipulated IR dextroamphetamine.

Figure 3 - Peak Positive Forces Recorded for Water, Manipulated ADAIR and Manipulated Filtered LD. Error Bars Represent Standard Deviation



D) Syringeability of the melted product

ADAIR was heated until it was fully melted to a temperature of 70°C. Following melting, ADAIR was drawn up using an 18-gauge needle, but it solidified before reaching the syringe compartment, demonstrating that ADAIR cannot be prepared for injection by melting the capsule contents.

Melted samples of ADAIR were impossible to draw up into a 26 gauge needle. When IR dextroamphetamine was crushed and heated to 200°C, it did not melt sufficiently to be syringed.

E) Syringeability in additional needle gauges

Similar to the tests conducted using 18 and 26 gauge needles, intermediate (20 and 23 gauge) needles were tested in 5 and 10 mL ambient and boiling water, as well as with and without a cigarette filter. The results (not shown) suggested a decrease in the amount of IR dextroamphetamine in ADAIR aspirated into the syringe compared to that of IR dextroamphetamine.

CONCLUSIONS

1. Physical manipulation of ADAIR, utilizing a variety of methods, including a coffee grinder, kitchen grater, scalpel, mortar and pestle, heating or cooling, all resulted in a preparation that could not appreciably pass through a 500 µm sieve, indicating a final particle size unsuitable for insufflation.
2. The syringeability study results demonstrate that the recovery of dextroamphetamine was consistently and meaningfully lower in ADAIR compared to IR dextroamphetamine. Attempts to prepare ADAIR for injection in hot or ambient water yielded a viscous, cloudy material which was usually impossible, and other times difficult, to syringe. Furthermore, the whitish, gummy (gel-like) appearance of the manipulated material is likely to represent an additional deterring factor for abusers through the IV route.
3. The force required to push the plunger with an ADAIR filled syringe is far greater than that with manipulated IR dextroamphetamine, suggesting that manipulated ADAIR is technically very difficult/impractical to syringe, and may in fact pose a danger if introduced intravenously.
4. Addressing IR stimulant abuse represents a major unmet need. If approved, ADAIR could present a deterrent to IN and IV abuse of IR d-amphetamine, a public health concern.[8,9]

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