Summary Report: Use of Medsaway® Activated Carbon adsorption technologies as a means to render drugs unavailable, unusable, and, subsequently no longer available for diversion
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Background:

According to a recent report, as many as 50% of Americans take at least one prescription drug in any given month [reference 1: Gu Q, Burt VL NCHS data brief no 42. Hyatsville MD, National Center for Health Statistics 2010]. Of 4 billion prescriptions written yearly, it is estimated that some 40% go unused [reference 2: PARADE July 4, 2010 p 15]. To address the disposal of unused medications, voluntary drug take-back programs have been successful in recovering "tons" of these unwanted drugs. However, a recent study has shown that these drug take back programs only account for about 2% of the total amount of unused medications [reference 3: Wisconsin Household Pharmaceutical Waste Collection- Challenges and Opportunities, report prepared for the Wisconsin Department of Natural Resources October 15, 2012].

For the home setting, this has an undesired consequence for accumulation of medications in medicine cabinets, representing safety, abuse, and environmental contamination hazards. In the case of opioids, a recent survey has found that 72% of patients that were prescribed opioids reported having leftover amounts, and 71% of those having leftover medication reported that they kept them [reference 4: Morbidity and Mortality Weekly report Vol 59, No. 6, Center for Disease Control and Prevention Feb 19, 2010]. These accumulations may be a contributing factor to the recent high incidence of opioid related poisonings, as over 530,000 emergency department visits are made each year for opioid–related poisonings [reference 5: Inocencio I., The Economic Burden of Opioid Related Poisonings in the United States; Pain Medicine, Jul 10, 2013].

In the institutional settings at present, many hospitals and clinics continue to dispose of narcotics into the sink, often in direct conflict with environmental regulations. The costs associated with environmentally responsible disposal of narcotics is prohibitive, and according to a recent article may be as high as $25,000 to properly dispose of a 50 gallon quantity [reference 6: USA Today 9/14/08].

There is a need to find a practical and safe way to destroy scheduled drugs 'at-source', so as to provide an economical means for users in both home and institutional settings to dispose of them in a safe and environmentally responsible way. We believe this need is consistent with DEA intentions stated in proposed rules: "This standard is intended to allow public and private entities to develop a variety of destruction methods that are

secure, convenient, and responsible, consistent with preventing the diversion of such substances" [reference 7: Dec, 21, 2012 Proposed Rules page 75803].

About Verde:

Verde is a privately held innovative organization, with Manufacturing and Operations based in Minnesota. Verde products include Medsaway® systems (SP, Home, Professional, and XL) and Medsaway® ContraPatch™ for safe inactivation of unused oral pills, liquids, and transdermal patches. Verde has recently been awarded a Phase 1 SBIR (Small Business Innovation Research) contract by the National Institute on Drug Abuse (NIDA), a branch of the National Institutes of Health (NIH) for the development of an inexpensive at-home deactivation system for unwanted abusable psychoactive drugs [reference 8]. The contract specifies the development of a system that would provide a simple way to safely inactivate and contain unwanted prescription drugs, thereby minimizing the potential for diversion or accidental exposure, and providing a safe and environmentally responsible way to properly dispose of pharmaceuticals.

Supporting Information

We propose use of activated carbon as a chemical means to inactivate drug substances. The binding mechanism that best describes the connection between pharmaceutical molecules and activated carbon is adsorption. With adsorption, an extremely thin layer of molecules (as of gases, solutes, or liquids) is adhered to the surfaces of the carbon with a mechanism arising from Van der Waals molecular forces. In some cases, adsorbed species can react with the surface and be held in place by bonds similar in strength to those in chemical compounds, a process known as chemisorption [reference 9: Chemistry, A Conceptual Approach; Charles E. Mortimer 1979]. Adsorption is contrasted to absorption, which is where compounds are simply taken in without adhesion to the surface (as with a household sponge).

With Medsaway, we use a significant amount of activated carbon surface area to insure sufficient adsorption and retention properties. Our Medsaway XL (with a capacity of approximately 450 pills), has a total carbon surface area equal to several football fields. As an option, the deactivation chemistries of activated carbon can also be supplemented with alkalinity agents (to facilitate chemical breakdown by hydrolysis) and/or anti-abuse agents (such as Bitrex or similar compound) that can be released with attempted misuse.

Historical Use of Activated Carbon

In a recent literature search using PubMed (U.S. National library of Medicine/NIH) and the keywords of "activated" and "carbon", over 21,000 publications were cited. Amongst numerous applications, activated carbon is used for removal of pharmaceutical impurities in water treatment processes, and in emergency treatments for deactivation of ingested drugs and other poisons. In emergency medical treatments, administration

of activated carbon is recommended for treating any chemical poisonings except those related to heavy metal (iron, lead, mercury), volatile, or corrosive agents [reference 10: Thakore S, Emergency Medical Journal, 2002, 19, 63-65].

Supporting Data

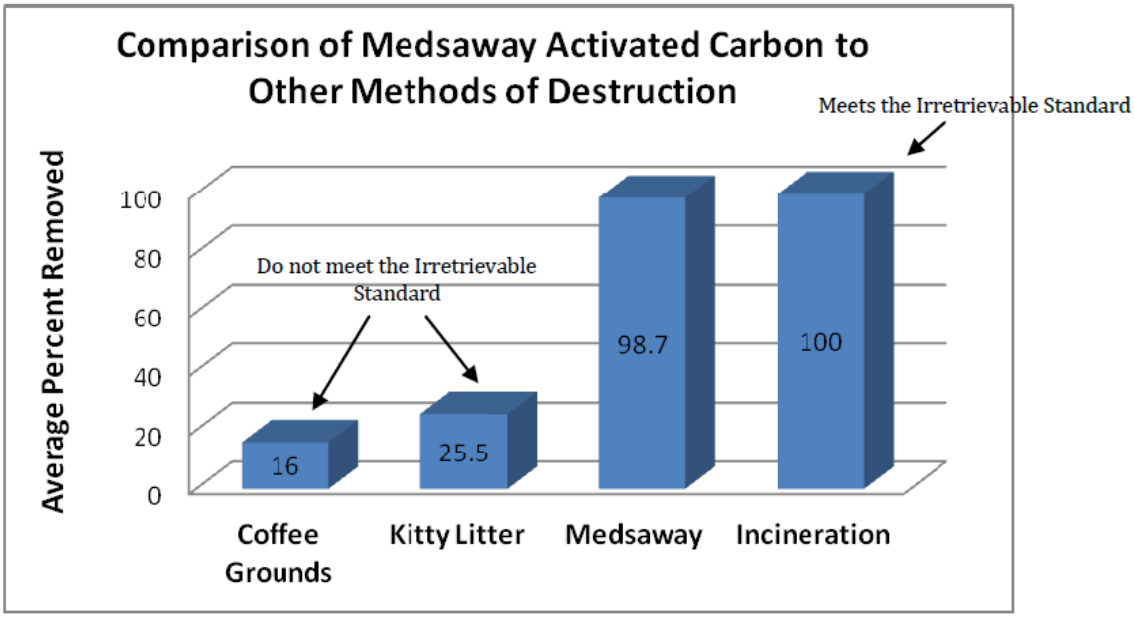
Verde has tested a number of model pharmaceutical compounds with different chemical structures, water solubility, formulation, and potency. In a first study, we directly compared the effectiveness of Medsaway activated carbon to the deactivation effectiveness of cat litter, sawdust and coffee grounds. The full report is attached, and includes our test procedures [reference 11]. This study was furnished as part of our contract application to NIDA/NIH for development of an at-home deactivation system for unwanted psychoactive drugs, which was subsequently awarded to Verde. A summary table of results is provided below:

Procedure Outline:

1) Deactivate the drugs using Medsaway® Activated Carbon
2) After a 7 day period, expose the inner reacted contents to a bolus of water in a washout test.
3) Determine the percentage of drug deactivated (not releasable in the washout)

Comparison Test for Percent of Drug Deactivated				
	Medsaway	Coffee Grounds	Cat Litter	Sawdust
Generic Vicodin, 10/325	99.6	0	0	0
Generic Percocet, 5/325	100	5.3	0	0
Naproxen, 220 mg	99.4	0.9	0	0
Ibuprofen, 200 mg	94.3	0	0	0
Diphenhydramine, 25 mg	99.8	49.2	83.6	67.7
Dexamethasone, 4 mg	99.2	3.5	34.8	67.5
Amoxicillin, 250 mg	97.5	10.8	0	7.9
Effexor XR, 75 mg	98.9	38.8	87.4	59.3
Ketoprofen, 75 mg	99.9	35.6	23.6	47.2
Average	98.7	16.0	25.5	27.7
Standard Deviation	1.8	19.5	36.3	31.7

The DEA in proposed rulings cited above specifically describes an incineration process as being sufficient for destruction, while mixing with Cat Litter and Coffee Grounds as being an insufficient method. The graph below illustrates our results in comparison to those methods (assuming 100% efficiency for incineration).

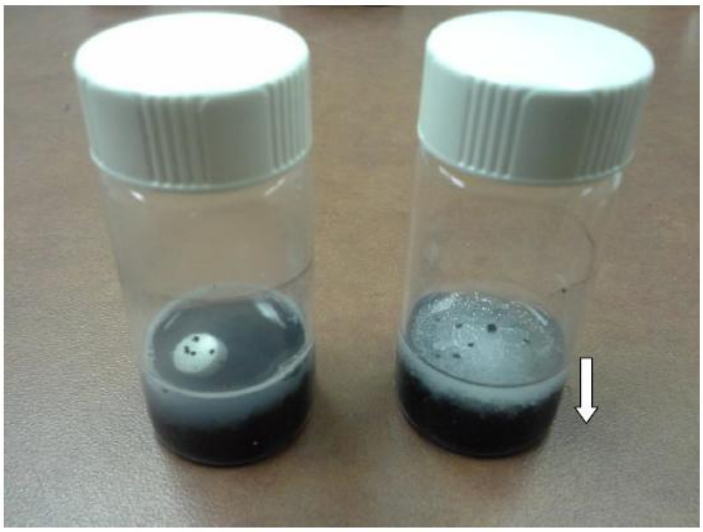


In order for substances to react with carbon, they must be in a dissolved, liquid state. For liquids, drugs are already in pre-dissolved form. For solids, drugs must be first dissolved before reaction takes place. Consequently, the carbon used for deactivation of pills is in an aqueous slurry. This aqueous slurry will cause pills to first break apart and release drug into dissolved form, followed by a molecular reaction with carbon. The following pictures illustrate the effect of the initial break-up using generic Percocet 5/325 (Mallinckrodt) as an example:

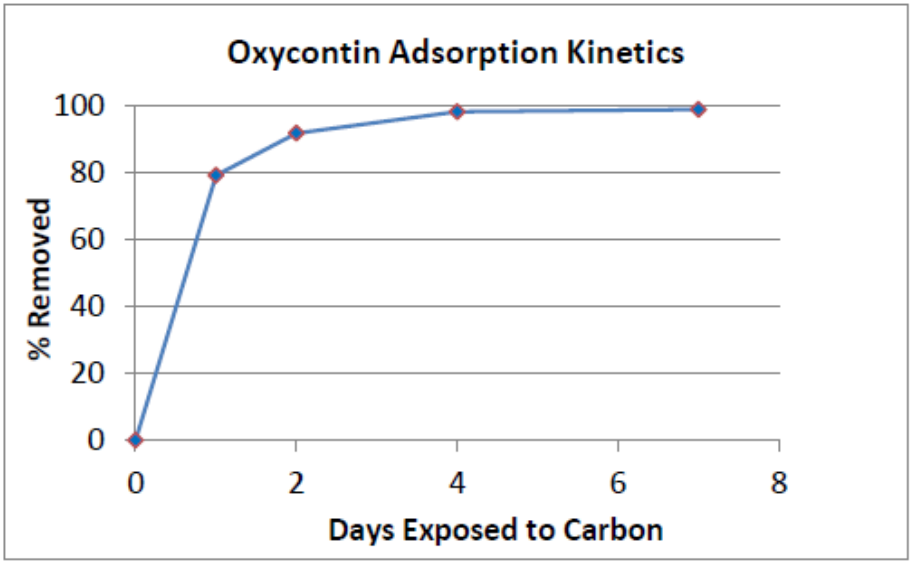
Untreated Generic Percocet is shown on the above left picture. After one hour in the aqueous carbon slurry, the pills are no longer recognizable and are finely co-mingled with the carbon granules. Ingesting the carbon with any as-yet un-reacted components at this stage would have a neutralizing effect. Over time, the drugs will adsorb and bind into the carbon pores, depicted as the arrow.

The kinetics of pill dissolution and deactivation via carbon adsorption were also investigated using Oxycontin as an example [reference 12: Fowler: “Medsaway System

Deactivation of Drugs in Abuse Deterrent Formulations; An Investigation using Oxycontin as a Model Compound"]. The tablets were found to absorb water, creating a hydrogel mass as pictured below (an initial time-point on the left, a 24 hour time-point on the right). Drug deactivation would occur through diffusion of the dissolved drug into the carbon layer (depicted by the arrow on the right):



Our results indicate that oxycodone HCl freely diffuses from the gel mass into the carbon layer, where it becomes insoluble and deactivated via an adsorption process. Approximately 80% of the drug was deactivated after 24 hours, and 99% was deactivated by 4 days. The rate of deactivation over the 7-day test period is depicted below:



Validation using an Independent Laboratory Setting

As part of Medsaway development, we have partnered with Mercer University with the intent of validating Medsaway performance using an independent laboratory setting. At Mercer, the Principle Investigator we are working with is Dr. Ajay Banga, who is a Professor and Chairman of the Department of Pharmaceutical Sciences. Dr. Banga has over 106 peer reviewed scientific publications, has served as principle investigator of 70 grant-funded research projects, and is currently serving on the Editorial Advisory Board of 10 scientific journals. All Mercer study results have been submitted, accepted, and presented at annual conference meetings for the American Association of Pharmaceutical Scientists, and those presentations are attached.

In a first series of experiments, we worked with Mercer to identify chemical agents that could be used to inactivate pharmaceuticals. Agents investigated included chemical oxidizing agents (percarbonates), hydrolysis agents (alkalis), sequestration agents (zeolites), and binding agents (activated carbons). The results of these studies are provided were presented at scientific conferences [References 13, 14: AAPS conference presentations]. Activated carbon was considered clearly superior amongst the agents tested.

A second series of experiments was used to validate the effectiveness of activated carbon using model pharmaceutical compounds and a procedure replicating that used internally at Verde. The result of this study was presented at a scientific conference [reference 15: AAPS conference presentation], and results are presented graphically below.

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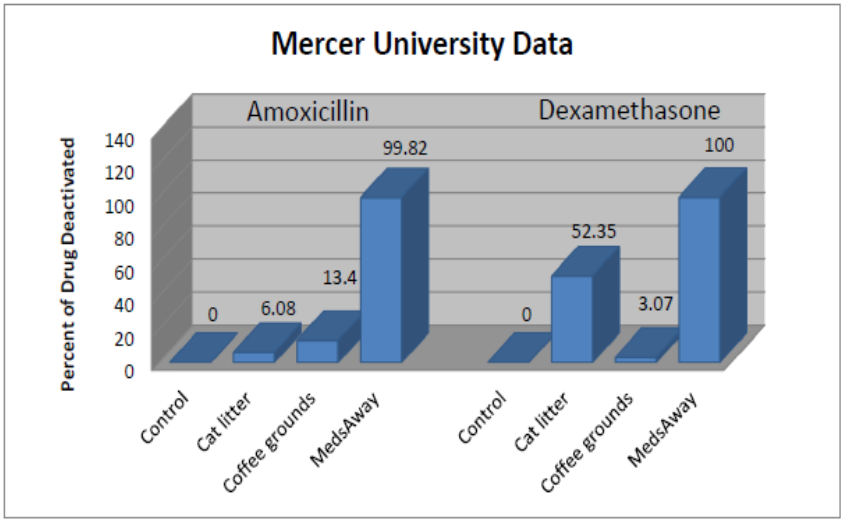


The Inactive And Unusable Nature Of Drugs Adsorbed Onto Activated Carbon:

The effectiveness of activated carbons use for inactivating/deactivating toxic chemicals was first demonstrated by a French pharmacist in 1831 when he ingested a lethal dosage of strychnine along with 30 grams of activated carbon without ill effect (reference 16: Albertson T, Olson K, Fisher C., "The use of activated charcoal in cases of poisonings and drug overdose", *Epitomes-Emergency Medicine* 1985, 142, pp 385-6, attached). The authors of this publication recommend use of activated carbon for treatment of any toxic compound overdose with the exceptions of iron and alcohols, (and possibly acetaminophen when administration of the antidote, N-acetylcysteine, is contemplated).

Activated carbon adsorbs a poison in the gastrointestinal tract and therefore reduces its absorption into the systemic blood circulation [reference 17: Derlot RW, Albertson TE, "Activated Charcoal- Past, Present and Future" West J Med 1986 Oct; 145: 493-496]. The use of activated carbon as a method of treating poisoned patients is supported in the Positions Statement of the American Academy of Clinical Toxicology, European Association of Poisons Centers, and clinical toxicologists [reference 18: Chyka PA Position Statement: single dose activated charcoal. J.Toxicol. Clin. Toxicol. 1997; 35: 721-741]. The Thakore article (reference 10 noted previously) also suggests that adsorption of toxins onto activated carbon will inhibit the absorption of those toxins into systemic blood circulation, and further notes that the mean bioavailability of the drug/toxin can be reduced by 88.6% if activated carbon is administered in a timely manner following an overdose (within 30 minutes). The Thakore article also recommends activated carbon as being universally effective with few exceptions (heavy metals, corrosives and volatile agents as noted earlier).

The Non-retrievability Of Drugs Adsorbed Onto Activated Carbon:

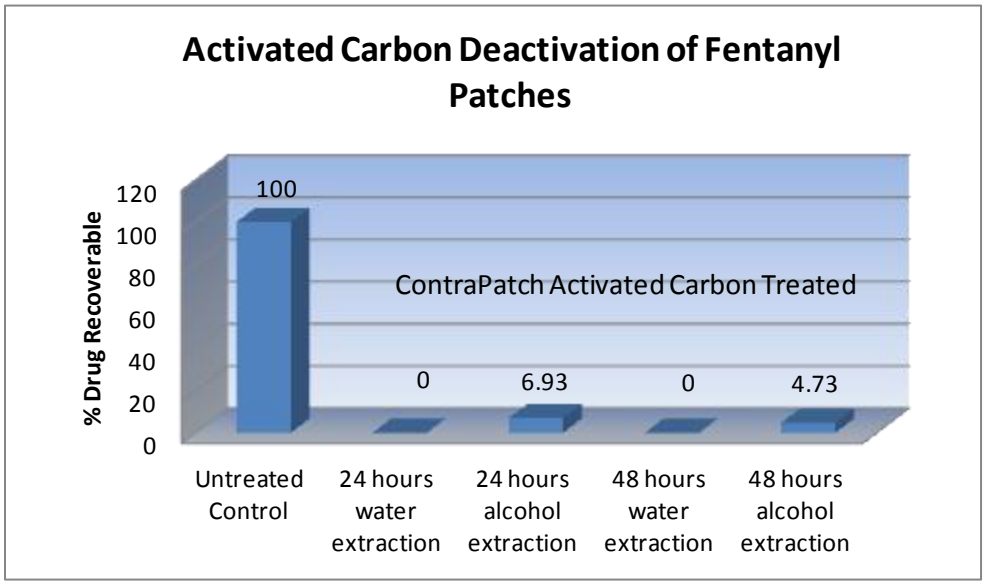
A. Resistance to Leaching By Water (Aqueous Extraction)

We have tested activated carbon for its ability to render drugs non-retrievable. In a first evaluation, we completely exposed the carbon deactivated drug (e.g. the inner contents with no protective bag), to a fresh water solution (250 mls water for each 10 tablets deactivated) in an environmental "washout" test for a number of model drug compounds [reference 11 noted previously]. We found an average of 98.7% of the drug was protected from aqueous washout/release.

B. Resistance to Alcohol Extraction

We also investigated the abuse deterrence aspect of activated carbon, hypothesizing that abusers may attempt to back extract the fentanyl off the activated carbon using water or water/alcohol mixtures (ex. vodka). Like in other Medsaway investigations, we partnered with Mercer University to demonstrate that our products can be shown to be

effective in independent laboratory evaluations, not just our own. The results found in Mercer testing are depicted graphically below and showed that after attempting extraction in water or alcohol solutions for 24 and 48 hours, little of the original drug content was recovered from activated carbon (in our ContraPatch product form). These results were presented at the 2012 annual meeting of the Association of Pharmaceutical Scientists held last November in Chicago [reference 19].



This study was also furnished as part of our contract application to NIDA/NIH for development of an at-home deactivation system for unwanted psychoactive drugs, which was subsequently awarded to Verde. Our experimental results showing the non-retrievable nature of activated carbon was also provided to the United States Patent Office as part of Medsaway patent applications. Patents were officially granted from the USPTO with claim language noting that "said binding agent includes an amount of activated charcoal that prevents later independent extraction of said medication" (U.S. patents 8,475,837 and 8,535,711).

C. Resistance to Extraction by Heat

Activated carbon avidly retains adsorbed organic species, and the carbon can be separated from the organics in a complex and energy intensive process that is required to reactivate "used" activated carbon [reference 20].

<u>Reactivation Process Described for Granular Activated Carbon (GAC):</u>
1. Drying: GAC de-watered at <100^{o} C to 50% of original weight
2. Desorption: 100-649^{o} C where volatile materials are driven off
3. Pyrolysis: 100-649 ^{o} C where heavy organics are burnt leaving residue
4. Gasification: 649-1038 ^{o} C where vapors and residue from previous stages are driven out of the carbon pores.

Temperatures between 100-649 ^{o}C are required to desorb and pyrolyze organics, and as high as 649-1038 ^{o}C are then necessary to drive off final residue from the carbon pores. Even with all of the higher temperature treatment, only about 70% of the carbon capacity can be reclaimed. The active ingredient in Medsaway is a very highly porous granular activated carbon.

References:

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13. Herdwaker A, Singh N., et. al. "Development of medication disposal kits to deactivate unused, residual, or expired medications". Presented at the American Association of Pharmaceutical Scientists (AAPS) Annual Meeting 2011, Washington DC.
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