Disposal of leftover and expired drugs by sequestration in cross-linking polymers

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Introduction:

Many medicaments, such as pharmaceutical drugs that are psychoactive or analgesic, have significant ability to cause euphoria or pleasurable effects, and are thereby at risk for abuse. In many instances such drugs are crushed, melted, dissolved or altered, and are then inhaled, snorted, injected or swallowed in a manner or dosage that is inconsistent with their intended or safe usage. Extraction of immediate release, or extended release formulations in particular, will rapidly deliver a bolus dose and produce a variety of serious and life threatening side effects, including respiratory depression and failure, sedation, cardiovascular collapse, coma, and death. It is important to dispose of such unused medications properly to prevent addiction, overdose and contamination of landfills and water supplies.

The types of pharmaceutical drugs that are particularly targeted for abuse are those listed on Drug Enforcement Agency's Schedule II list, such as opioids, phenylephrine, stimulants like amphetamines and methylphenidate, benzodiazepines such as lorazepam (Alivan®) and alprnzolam (Xanax®) and other types of drugs of abuse, which can be extracted from their dosage form in a variety of ways. For example, the dosage form can be mixed with a suitable solvent (e.g., water or alcohol), and then the drug can be filtered and/or extracted from the mixture for intravenous injection. Extended release dosage forms can be dissolved in water, alcohol or another "recreational solvent" to hasten the release of the drug, and then ingested orally; this provides high peak plasma concentrations of the drug and maximum euphoria effects. There is an enormous need to dispose of these drugs, especially opioids, safely since leftover opioids contribute to the steady increase of opioid abuse, overdoses and death.

To address the opioid epidemic, a major safety campaign is currently underway in the United States to dispose of drugs at risk for abuse in a manner that will prevent their misuse, either by accidental administration or by illicit use. The United States Food and Drug Administration (FDA), the Drug Enforcement Agency (DEA), and Environmental Protection Agency (EPA) offer guidance for unused pharmaceutical product disposal, which includes directions to flush drugs down the toilet or to mix drugs with coffee grounds to throw away, and encouragement to participate in "take-back" programs. This guidance, however, is dependent on consumer compliance, contributes to environmental exposure and may lead to diversion.

This study was designed to assess the chemical properties of DisposeRx cross-linking polymers and to test the ability to extract opioids (e.g. Oxycontin®) once they are physically and

chemically sequestered. An additional goal was to evaluate the safety and biodegradability over time of drugs captured in the DisposeRx matrix.

Materials and Methods

Disposal Composition Material

The disposal composition is comprised of polymer with reactive functional groups and a chemical cross-linker, such that the material forms a mass after mixing with water over a suitable period of time. This mass deters, slows and prevents the extraction of the active agent by aqueous or alcoholic means or by vaporization.

Disposal Composition Agent	**Function**
Sequestering Polymer(s) / Viscosity Increasing Agent	Encapsulating and immobilizing drug(s) to limit physical and functional access
Cross-linking Agent	Chemically (ionic or covalent) link or bind polymer(s) into a viscous gel network
pH Modifier	Adjust pH to optimize conditions for cross-linking
Diluents / Additives	Aid dispersion, provide color/opacity

We are unable to reveal the specific ingredients since they are the subject of our pending patent, however they include Generally Recognized as Safe (GRAS) ingredients such as polyvinyl alcohols, carrageenans, alginates and chitosan as well as a non-toxic polymerization catalyst. Many of these reagents are used as components in Elmer's glue, for example.

Screening Disposal Composition Agents

Pharmaceutical excipients were screened for their ability to increase the viscosity of aqueous/alcoholic solutions and their potential use in disposal compositions. Viscosity increasing agents (VIAs) were categorized based on their polymer class (various grades within a class were also screened). Table 3 lists samples of VIAs tested with or without additional excipients, and qualitative results of these agents on solution viscosity.

The screening was performed using an extraction/filtration test. Briefly, 0.5 grams of powder were transferred into a container and 10 ml of water (tapped water at a temperature between 26 and 28° C) was added. The mixtures were vigorously shaken until they were homogeneous and aided by a spatula when necessary to complete homogenization. The resulting suspensions were immediately filtered through a standard coffee filter (GK Connaisseur). Viscosity increase was evaluated by visual inspection, while filtration rate was evaluated by comparing the amount of liquid added to the filter to the amount of liquid recovered in the filtrate after 10 minutes of filtration.

Table 3: Disposal Composition Agents Screening Study.

Sample No.	Viscosity Increasing Agents (% w/w on dry basis)		Other Excipients (% w/w on dry basis)	Initial Appearance	Filtration After 10 minutes
001	Category 1-A	100	0	Highly viscous solution/gel	Unfilterable
002	Category 1-A	83	17	Highly viscous solution/gel	Unfilterable
003	Category 1-A	5	95	Highly viscous suspension	Unfilterable
004	Category 1-A	5	95*	Highly viscous suspension	Unfilterable
005	Category 2-A	100	0	Slightly viscous solution	Filterable
006	Category 3	100	0	Slightly viscous solution	Filterable
007	Category 4	100	0	Highly viscous suspension	Unfilterable
008	Category 5	100	0	Slightly viscous solution	Filterable
009	Category 1-A	20	80	Very viscous suspension	Unfilterable
010	Category 1-B	20	80	Very viscous suspension	Unfilterable
011	Category 1-C	20	80	Viscous suspension	Unfilterable
012	Category 4	20	80	Slightly viscous solution	Filterable
013	Category 6	20	80	Highly viscous suspension	Unfilterable
014	Category 7	20	80	Slightly viscous suspension	Filtration rate decreased
015	Category 8	20	80	Non-viscous suspension	Filterable
016	Category 9	20	80	Non-viscous suspension	Filterable
017	Category 10	20	80	Slightly viscous suspension	Filterable
018	Category 11	20	80	Non-viscous suspension	Filterable
019	Category 12-A	100	0	Viscosity increases with time	Filtration rate decreased with the time
020	Category 12-B	100	0	Viscosity increases with time	Filtration rate decreased with the time
021	Category 2-B	100	0	Non-viscous suspension	Filterable
022	Category 2-C	100	0	Non-viscous suspension	Filterable
023	Category 12-C	100	0	Non-viscous stable suspension	Solid materials passed through the filter

Sample No.	Viscosity Increasing Agents (% w/w on dry basis)		Other Excipients (% w/w on dry basis)	Initial Appearance	Filtration After 10 minutes
024	Category 13-A	100	0	Slightly viscous stable suspension	Filtration rate decreased
025	Category 13-B	100	0	Slightly viscous stable suspension	Filterable
026	Category 14-A	100	0	Viscous cloudy liquid	Filterable/ cloudy liquid
027	Category 14-B	100	0	Highly viscous cloudy liquid	Unfilterable
028	Category 14- C	20	80	Viscous cloudy liquid	Filtration rate decreased
029	Category 14-D	18	82	Viscous cloudy liquid	Filtration rate decreased
030	Category 1-A	10	90	Highly viscous suspension	Unfilterable

* Tablets were produced from the powder blend of Sample No. 003 using a hydraulic press (Model C, Carver Inc.) with an 8 mm diameter standard concave tooling and a compression force 1750 lbf (14-15 kp).

Additional polymers were screened for their ability to increase the viscosity of aqueous solutions with the aid of a cross-linking agent. Table 4 lists samples of disposal composition agents tested with available cross-linkers along with qualitative results of these agents on solution viscosity. The screening was performed using the same extraction/filtration test discussed above.

Table 4

Sample number	Disposal Agent[1]	Cross-linker composition	Initial Appearance	Filtration
		(% w/w on dry basis)	(0.05 g / mL)	(after 10 min)
1	XVIA-1-A	1.5	Stiff gel -no flow	Unfilterable
2	XVIA-1-A	1.5	Stiff gel -no flow	Unfilterable
3	XVIA-1-B	1.5	Stiff gel -no flow	Unfilterable
4	XVIA-1-B	1.5	Stiff gel -no flow	Unfilterable
5	XVIA-2-A	1.5	Gel -slow flow	Unfilterable
6	XVIA-2-B	1.5	Gel -slow flow	Unfilterable
7	XVIA-2-C	1.5	Stiff gel -no flow	Unfilterable
8	XVIA-3-A	5	Spongy stiff gel -no flow	Unfilterable
9	XVIA-3-A	10	Spongy stiff gel -no flow	Unfilterable
10	XVIA-3-B	5	Spongy stiff gel -no flow	Unfilterable
11	XVIA-3-B	10	Spongy stiff gel -no flow	Unfilterable
12	XVIA-3-C	5	Spongy stiff gel -no flow	Unfilterable
13	XVIA-3-C	10	Spongy stiff gel -no flow	Unfilterable
14	XVIA-3-A	5	Spongy stiff gel -no flow	Unfilterable
15	XVIA-3-A	5	Spongy stiff gel -no flow	Unfilterable

16	XVIA-4-A	10	Stiff gel -no flow	Unfilterable
17	XVIA-4-B	7.5	Stiff gel -no flow	Unfilterable
18	XVIA-4-B	10	Stiff gel -no flow	Unfilterable
19	XVIA-4-C	5	Stiff gel -no flow	Unfilterable
20	XVIA-4-C	7.5	Stiff gel -no flow	Unfilterable

[1] Cross-linking viscosity increasing agents were categorized based on polymer type. The viscosity is affected by different characteristics of the materials, most importantly the molecular weights of the polymers. The concentration of the polymer in water can be adjusted to increase or decrease viscosity.

Disposal characteristics and use

Disposal composition formulations were submitted to extraction attempts with water and alcoholic beverage. Vodka is the solvent of choice for street addicts attempting to inject opioids. For each sample, placebo capsules were placed in a vial along with the disposal composition and activated by adding water and agitating per normal instructions. The extraction was carried out under different extraction conditions such as agitation (by shaking or using a spoon), heating or cooling and using different extraction solvent volumes as explained below. The resulting mixtures were immediately filtered through a standard coffee filter. Filtration rate was evaluated by comparing amount of filtered liquid phase recovery after at least 10 minutes compared to the initial volume used for extraction attempt.

Method #1: Solvent at RT: Activated composition was immersed into the solvent and the mixture was homogenized by hand mixing.

Method #2: Activated composition was immersed into the solvent and the mixture was heated to boiling using a Microwave (about 30 sec). Mixture was homogenized by hand mixing.

Method #3: Activated composition was immersed into the solvent recently removed from the refrigerator (T=5-10°C) and the mixture was homogenized by hand mixing

Method Number	**Solid phase (g)**	**Liquid phase (mL)**	**Solvent / Extraction Conditions**	**Extraction Solvent Volume**	**Filtrate (g)**
1	2.0	30	Water at RT	30	0
	2.0	30	Vodka at RT	30	0
1	2.0	30	Water at RT	60	0
	2.0	30	Vodka at RT	60	0
2	2.0	30	Heated water	30	~10

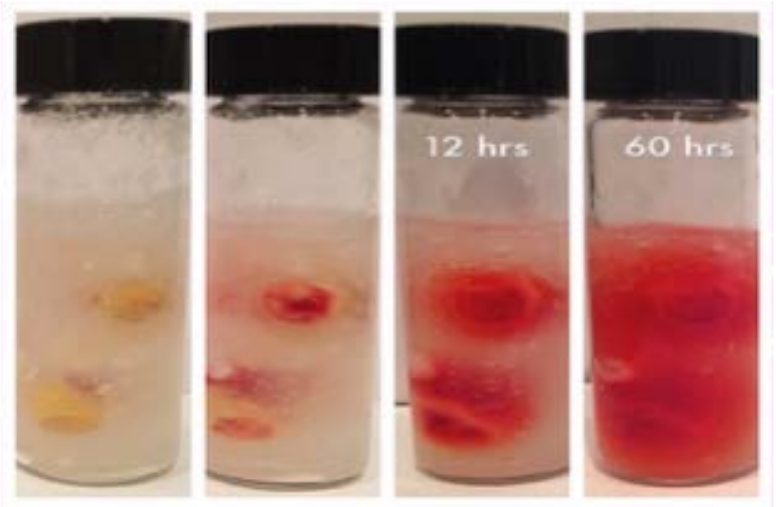
Method Number	Solid phase (g)	Liquid phase (mL)	Solvent / Extraction Conditions	Extraction Solvent Volume	Filtrate (g)
	2.0	30	Heated Vodka	30	~10
3	2.0	30	Cooled water	30	0
	2.0	30	Cooled Vodka	30	0

The results demonstrate that the cross-linked polymers can absorb additional solvent without separating. The additional capacity within the matrix will prevent efficient extraction up to at least three times the activating volume. Additions of heated solvents do lower the viscosity of the system to the point where liquid can be collected from the filter. However, as observed with room temperature solvents there is no phase separation such that the small quantity of filtrate quickly solidifies back to a stiff gel once cooled.

Studies have also been performed using prototypes of DisposeRx's materials incorporated as an abuse deterrent compared to Purdue® Pharma's "New" (also with an abuse deterrent technology) and "Old" (no abuse deterrent technology) formulations of Oxycontin®. In order to address the chemical inactivation of Oxycontin in various formulations where the deterrent was incorporated in the Oxycontin pills, solvent extractions were performed following physical challenges aimed at defeating the controlled release matrix of the products such as crushing/grinding, freezing or extreme heating. The two most common liquids (water and alcohol-vodka) available to potential abusers were used. Neither water nor vodka were able to extract the oxycodone from the gel matrix.

The disposal composition material, when combined with a solvent and the medicament, forms a gel or mass, i.e., a substance of high viscosity so that it is not easily pourable, transferable, or mixable, and generally remains in the container in which it is formed, such that the medicament is no longer useable for administration as directed in the use information, cannot be misused or accidentally used, subject to abuse or leach into landfills.

Within one minute after adding DisposeRx to the prescription vial containing drugs along with water, shaking for 15 seconds, the drugs dissolve and are sequestered into the polymer matrix. As a result, the gel/mass deters use of the medicament by an individual for whom the medicament was not intended and prevents an abuser from modifying the product to be used in a manner that is not consistent with the prescribing information or instructions for use. **The treated vial is then thrown into the trash.**



Over 60 hours, tablets or capsules become increasingly dissolved in the cross-linking polymers within which they are permanently physically and chemically sequestered. Over days to weeks, mold and bacteria grow in the sequestered drugs and polymers to start the process of biodegradation in landfills (right).

DisposeRx formulated its products to be compliant with evolving recommended governmental standards including DEA guidelines. According to the DEA (Dec. 21, 2012, 21 CFR Subpart C, 1317.90): *The method of destruction shall be consistent with the purpose of rendering all controlled substances to a non- retrievable state in order to prevent diversion of any such substance to illicit purposes and to protect the public health and safety.* DisposeRx complies with this DEA guideline.

Conclusions:

DisposeRx's solidifying substance of high viscosity gel sequesters drugs in a solid matrix from which they cannot be easily extracted or leach into the environment. Opioid drugs such as Oxycodone® are chemically sequestered in the polymer matrix. In order to measure drug inactivation, they must first be extracted. Attempts to extract the drugs from the DisposeRx polymer using water or alcohol demonstrated that the drugs could not be solubilized and assayed since they are both physically and chemically inactivated. The matrix components of the sequestering polymer are listed by the FDA as generally recognized as safe (GRAS), and in fact, they are often found in various prepared foods. The cross-linking activator is listed as non-toxic. Many of these ingredients are found in white glue. Accordingly, if the contents of the DisposeRx packet are accidentally ingested, there is no toxicity. If the contents of the DisposeRx plus pills (e.g. opioids) are ingested after inactivation, the drugs will not be absorbed and will be excreted in the feces. Even with the safety of DisposeRx products, packaging recommends no ingestion or inhaling and that this product is not meant for the use with sharps and to keep out of the reach of children and pets.

DisposeRx™ matrix permanently sequesters drugs in any form (powders, pills, tablets, capsules, liquids or patches) forming our patented* gel matrix, which is designed to prevent, extraction of active agent by aqueous, alcoholic means or vaporization. Furthermore, both the drugs, and the DisposeRx™ polymers into which they are sequestered, are biodegradable. In landfills, for example, microbes will consume this polymer-drug mixture and release carbon dioxide and methane as metabolite gasses over time.

About the Authors:

Marcus Schestopol (*co-founder, Exec. Vice President, Manufacturing*) is a pharmaceutical development chemical engineer with over 15 years of experience in pharmaceutical CMC product development, process scale-up, formulations and biodegradable polymer development. He has directed all phases of pharmaceutical development from laboratory feasibility studies of NCE development to commercialization of drug products. Marcus currently advises on CMC strategies to support FDA filings including IND, NDA, BLA and post approval supplements in establishing practical plans that incorporate current process designs along with future improvements to deliver data and process packages in accordance with current health authority thinking. During his career he was named on several patents ranging from novel chemical synthetic pathways to device design. Marcus received his Chemistry degree from Emory University and his Chemical Engineering degree from the Georgia Institute of Technology.

John W. Holaday, Ph.D. *(Chairman & Co-founder)* is a seasoned entrepreneur and pharmaceutical scientist with decades of experience in neuroscience, oncology and

immunology. John was the former CEO of QRxPharma Limited (QRX-ASX); co-founder of Medicis (MRX-NYSE); EntreMed (ENMD-NASDAQ) CEO. He is Co-founder and Executive Chairman of ExoCyte Therapeutics, and Director of Pixspan, CytImmune Sciences and Accelovance. Dr. Holaday obtained a BS and MS from the University of Alabama, and PhD with honors from the University of California, San Francisco School of Medicine. He is a Fellow in the American College of Neuropsycho-pharmacology (FACNP) and a Fellow in Critical Care Medicine (FCCM). He served at the Walter Reed Army Institute of Research as Captain, US Army, and Chair Neuropharmacology Branch. Dr. Holaday was Professor of Anesthesiology and Critical Care Medicine at the Johns Hopkins University School of Medicine, and remains as Adj. Professor of Psychiatry, Uniformed Services Univ. of Health Sciences. He raised over $500M for his companies with exits or market capitalizations of over $3 billion. Dr. Holaday was inducted into the E&Y Entrepreneur of the Year 2006 Hall of Fame and served on the advisory board for E&Y for several years. He has received numerous honors and awards, including the Algernon Sydney Sullivan Award as outstanding Alumnus, University of Alabama. John holds over 90 patents and has published over 230 scientific articles and five books.