*Drug Development and Industrial Pharmacy*, 32:727–746, 2006

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040500529093

Taylor & Francis

# Development and Preliminary Experience with an Ease of Extractability Rating System for Prescription Opioids

**N. P. Katz**
Inflexxion, Inc., Newton, MA and Tufts University School of Medicine, Boston, MA

**D. C. Buse**
Harvard Medical School, Boston, MA

**S. H. Budman**
Inflexxion, Inc., Newton, MA and Harvard Medical School, Boston, MA

**S. Wing Venuti, K. C. Fernandez and C. Benoit**
Inflexxion, Inc., Newton, MA

**R. Bianchi**
Prescription Drug Research Center, Fairfax, VA

**D. Cooper**
Signature Consulting, Rockville, MD

**D. R. Jasinski**
Johns Hopkins Bayview Medical Center, Baltimore, MD

**D. E. Smith**
Haight Ashbury Free Clinics, San Francisco, CA

**S. F. Butler**
Inflexxion, Inc., Newton, MA

Address correspondence to K. C. Fernandez, Inflexxion, Inc., 320 Needham St, Suite 100, Newton, MA 02464. E-mail: kfernandez@inflexxion.com

**ABSTRACT** One important factor in the abuse potential of an opioid product is the ease with which active drug can be extracted. There are currently no standards for testing or reporting extractability. This article describes the development of an Extractability Rating System for use by the pharmaceutical industry and regulators. Despite several limitations, this effort serves as a call for standardized testing and reporting so that products can be accurately rated, and should help establish goals for drug developers who wish to develop "abuse-resistant" opioid products.

**KEYWORDS** Extractability, Substance abuse, Opioid, Narcotic, Controlled Substances Act

## INTRODUCTION

Prescription opioid abuse is a major, rapidly growing problem in the United States, having surpassed cocaine and heroin as drugs of abuse in both population-based surveys such as the National Survey of Drug Use and Health (SAMHSA, 2004) and emergency department-based surveys (DAWN, 2002). One regulatory approach to controlling the availability of prescription opioids is the drug scheduling process mandated in the Controlled Substances Act (1970) in which drugs with abuse potential are assigned to a progressively higher schedule as the perceived abuse liability increases. One of the factors considered in evaluating the abuse potential of a prescription drug, and therefore its schedule, is the ease with which active quantities of drug can be extracted from the drug product ("extractability").

Despite the acknowledged importance of extractability, and the effort expended on studying it, there has been no consensus on exactly how extractability should be defined, tested, or rated. There is no standard set of tests to which a product is subjected in order to judge its extractability, and this varies from sponsor to sponsor, lab to lab, and chemist to chemist. Were a dataset on chemical extractability tests for a specific product to become available, there is no agreement on how this information should be summarized or synthesized to generate a concise rating of extractability. Developing standards for the testing and reporting of extractability requires several different steps. First,

the scope and content of the concept of extractability must be defined. Second, a connection must be developed between various laboratory extraction procedures and the difficulty that would be experienced by "street users" in implementing such procedures; the concept of ease of extractability has no meaning unless referenced to the end user of interest. Third, standard methods need to be developed for conducting extraction procedures; the degree of active drug extracted from a product by dissolution in alcohol, for example, will depend on such factors as the volume of diluent, temperature, and time in solution. Thus, a "standard extractability battery" is needed. Fourth, once the tests are done, a method for objectively interpreting the results, and arriving at an overall extractability rating, is needed. The present paper describes our efforts to build these components of a rating system for the extractability of prescription opioid products.

## METHODS

This project was divided into five stages (Fig. 1):

Stage 1: Qualitative Phase (Pre-Concept Mapping)
Stage 2: Concept Mapping
Stage 3: Development of the Extractability Rating System: Expert Consensus Meetings
Stage 4: Refinement of Extractability Rating System
Stage 5: Expert Ratings of Extractability

## OVERALL APPROACH

The first step was to operationally define the concept of extractability and its components based on expert input, including the perspectives of individuals who have been involved in extraction activities at illicit laboratories ("street chemists") and prescription drug abusers. A process called Concept Mapping (CM) was used to generate a comprehensive list of extraction techniques used by prescription opioid abusers and the perceived difficulty of these techniques. CM was then used to re-examine a known categorization system of ease of extractability. A series of expert consensus meetings took place to develop an Extractability Rating System (ERS), including a formal definition of extractability and its components, a standard battery of extractability tests to be performed on every product, and a method for synthesizing these data into a summary extractability rating. Experts then used this ERS to evaluate the extractability of five prescription opioids, extrapolating from best available data. Finally, experts provided global ratings of the overall extractability of five selected opioids. Each stage will be described next.

### Stage 1: Qualitative phase (Pre-Concept Mapping)

The pre-Concept Mapping phase was a qualitative process of gaining expert input. The first step involved open-ended interviews with an initial group of experts. Participants included professionals in the field of substance abuse as well as individuals who have abused opioid medications. Substance-abusing participants were recruited from substance abuse centers, Internet-based resources, and electronic classifieds. They were compensated with $100 gift certificates for their participation. Experts included former DEA chemists, experts in addiction and pain management, and substance abuse counselors. Data collected during these interviews were used to structure the CM process (see Stage 2). Content analysis of individual interview data was conducted to (1) identify similarities and differences between users who chew and/or swallow opioid medications and others who prepare opioids for snorting or intravenous use; (2) define the components of extractability; and (3) define the scope and boundaries of the ERS. In this phase we explored approaches to validating a method for categorizing ease of extractability of prescription opioid products, beginning with a review of the DEA's working approach.

### Stage 2: Concept Mapping

Concept Mapping (Trochim, 1989) approaches were used to gain empiric support for a categorization scheme for ease of extractability. Concept Mapping is a qualitative and quantitative method for organizing and providing a quantitative framework for qualitative data. Since the initial phases of instrument development typically involve capturing qualitative data (e.g., lists of statements about a disease, condition, or process) and organizing it into conceptually similar groups (e.g., dimensions or domains), CM has been increasingly used to provide greater structure and efficiency to this process (Bigne et al., 2002; Butler et al., 2004; Jackson & Trochim, 2002; Tracey et al., 2003; West

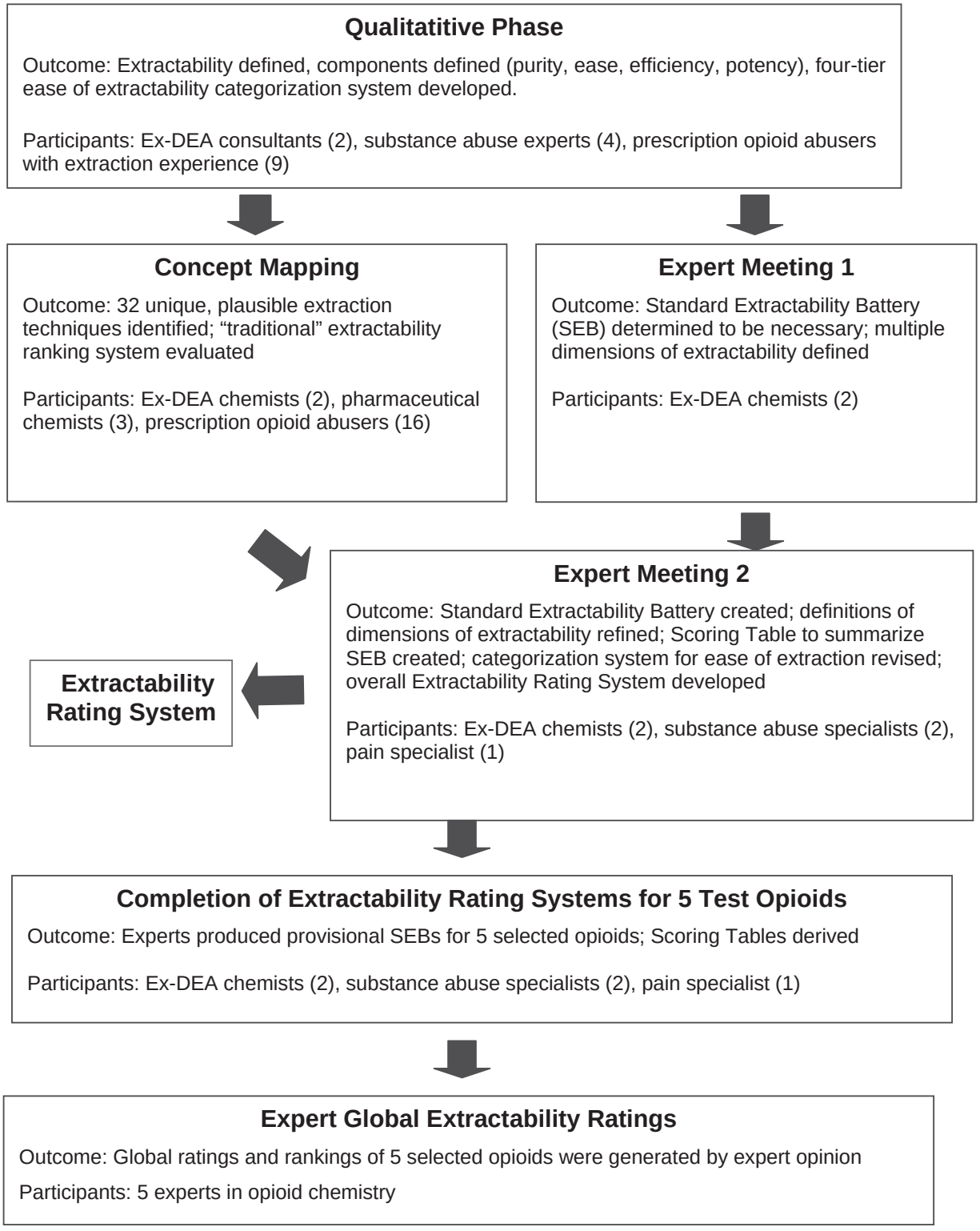


**FIGURE 1** **Overview of Development of The Extractability Rating System (See Text for Details).**

et al., 2002). Concept Mapping includes a sequence of structured activities linked to a series of multivariate statistical analyses that process the group input and generate maps. These maps depict an aggregate representation of the content in the form of thematic clusters as generated by respondents. The process typically involves participants brainstorming a large set of statements relevant to the topic of interest and then in individually

sorting these statements into piles based on conceptual similarity (Weller & Romney, 1988). Analysis includes a two-dimensional, multidimensional scaling (MDS) of the sort data and a hierarchical cluster analysis of the MDS coordinates. The resulting maps represent a "structured conceptualization" or a multidimensional graphic representation of the group's set of ideas. Each idea is represented as a point, with ideas that are more similar (as determined by the multivariate analysis of the participants' input) located closer to each other. Ideas (i.e., points on the map) are clustered statistically into larger categories that are overlaid on the base maps. The proximity of the clusters represents how similar the statements in each cluster were to each other.

The goal of this phase was to generate a comprehensive list of unique and plausible extraction techniques used by substance abusers. This part of the process is called "item generation" or "brainstorming." The initial list of items was reviewed by two ex-DEA chemists to eliminate any redundant or implausible items, resulting in a final, reduced list. This list of extraction techniques, empirically generated by a variety of stakeholders, including substance abusers, was later adapted to create the comprehensive list of extraction techniques contained in the Standard Extractability Battery.

An additional goal was to use the second stage of the concept mapping procedure ("sorting and rating") to assess the validity of the DEA's working system for categorizing ease of extraction procedures, as conveyed by our consultants. This step required raters to take each extraction technique and sort it into one of four categories in that system representing relative ease of extractability: (1) No equipment or special knowledge needed; (2) Readily available equipment but no special knowledge needed; (3) Readily available equipment and special knowledge needed; and (4) Difficult to obtain equipment (i.e., a lab) and special knowledge needed. Raters were not given any more elaborate definitions of these terms.

Finally, the rating technique from concept mapping was used to have subjects rate the extent to which the difficulty of each extraction technique constituted a barrier to their potential recreational use of an opioid. The purpose of this step was to provide additional information validating (or invalidating) our categorization scheme for ease of extractability, as well as to later provide benchmarks for understanding the "clinical significance" of differences in extractability ratings. Subjects were asked to provide three ratings to assist in interpretability for each of the extraction techniques: (1) to what extent this technique was a barrier or obstacle to using opioid pain medication to get high; (2) how likely they would be to perform or attempt each technique to get high; and (3) how likely they would be to get a better high if they used this technique.

## Stage 3: Development of the Extractability Rating System: Expert Consensus Meetings

Two expert meetings were held with the purpose of developing an alpha version of the ERS and a scoring algorithm. This process proceeded in parallel with the CM procedures. The goals of the meetings were: (1) Review the overall architecture of the proposed Extractability Rating System; (2) Review and reach consensus on the components/dimensions of extractability; (3) Determine how to operationalize the measurement of these components of extractability, to refine the previously generated extraction techniques into a Standard Extractability Battery; and (4) Attempt provisional extractability ratings for selected prescription opioid products for the purpose of testing and refining the rating system.

## Stage 4: Refinement of Extractability Rating System

The next step was to refine the ERS based on information accumulated to date, and to complete usability testing of the SEB and ERS. An expert was asked to complete a Standardized Extractability Battery for two opioid products (OxyContin 80 mg and Duragesic 100 mcg) as well as provide ratings based on the easiest extraction technique that could be used to generate a usable quantity for each route of administration, the purity of the extract, the percent extracted, and the estimated number of doses produced. This task was followed up by a cognitive debriefing session with the expert, in order to revise the ERS and create a beta version.

## Stage 5: Expert Ratings of Extractability

The final step in this project was to have experts make preliminary ratings of extractability using the ERS. The number of prescription opioid products to

**TABLE 1** Scoring Table

| | Ease | Purity | Efficiency | Potency |
|---|---|---|---|---|
| IV | | | | |
| PO | | | | |
| SL | | | | |
| Smoking | | | | |
| Nasal | | | | |

be rated, and the specific products to be rated were determined in the expert meetings. Each expert was sent a rating sheet, where they were first asked to provide a global rating of extractability for each medication, from "extremely difficult to extract" to "not at all difficult to extract," prior to using the formal ERS. The purpose of this overall rating was to establish a quasi-gold standard of overall extractability. Each expert received a Standardized Extractability Battery as well as a Scoring Table (Table 1) to complete, based on best available information, for each of the five products. Experts were instructed to record their individual ratings, then meet in two small teams, attempt to come to consensus on the ratings, and provide the groups' consensus ratings. The output of this session was to be the consensus of the two teams on the overall extractability rating for each of the five drugs.

# RESULTS

## Stage 1: Qualitative phase (Pre-Concept Mapping)

### *Participants*

Nine prescription opioid abusers with a range of extraction experience and six experts participated in this stage. Among the opioid abusers, four were female and five male, age ranged from 26 to 48 years (mean 37), eight were white and one was African-American, and seven had completed at least the twelveth grade. Eight characterized their environment as urban and one rural. Six experts were interviewed at this stage, including two former DEA chemists, one addiction specialist, one abuse liability expert, and two substance abuse counselors.

### *Definitions and Scope of "Extractability"*

The goal of this phase was to propose an initial description of the concept of extractability, to be submitted to a consensus process. Experts defined extraction as "the manipulation of a product to remove, concentrate, and/or purify the active ingredient." Extractability is the extent to which extraction procedures performed on a drug product result in quantities of active ingredient relevant to substance abuse. The fundamental issue in extractability is the *ease/difficulty* of the extraction procedures required to liberate usable quantities of active drug. However, a unidimensional concept of extractability based on ease alone (i.e., a drug can or cannot be extracted using a specific technique) was revealed to be overly simplistic; other proposed dimensions of extractability included *efficiency, purity, and potency* of the extract. A plan to develop a scale to measure extractability as a subjective phenomenon (like depression or pain) was rejected in favor of an objective concept of extractability (assessed by laboratory tests, the results of which are synthesized).

### *Classification of "Ease of Extractability"*

According to our ex-DEA chemists, the current working classification system for ease of extractability used by regulators could be summarized as follows:

Category 1. No special equipment or special knowledge required
Category 2. Commonly available equipment needed but no special knowledge
Category 3. Commonly available equipment and special knowledge needed
Category 4. Special equipment and special knowledge needed

### *Phenomenology of Extractability*

Information was gathered from opioid abusers regarding the actual phenomenology of extractability. The majority of users preferred oral intake (45.4%) to injection (36.4%) or smoking/inhalation (0%) in this small group. Extractions are performed mostly by individual opioid abusers (as opposed to "street chemists") and extraction procedures in common use do not require special equipment or knowledge in chemistry. Individuals may use more elaborate methods of extraction as they become more experienced with the drug and build up tolerance, which is associated with evolution of the route of administration from oral to nasal or intravenous. Extraction techniques are shared

by word of mouth or through the Internet. Thus the concept of "special knowledge" as a factor that separates relatively simpler from more difficult extraction techniques did not appear to apply to prescription opioids. The "clandestine chemist," defined as an individual who engages in large-scale extraction procedures for the purpose of selling to a group of customers, does not appear to exist in the world of prescription opioid abuse (in contradistinction, for example, to methamphetamine abuse). In fact the preferences of the prescription opioid user, in contrast to other drug abusers, is to purchase a product that has not been tampered with, and retains the pharmaceutical company's "seal of quality."

## Stage 2: Concept Mapping

The goals of this stage were to generate a comprehensive list of real-world extraction techniques; rate their difficulty from the perspective of the end user; and assess the working classification system of ease of extractability described previously.

### *Participants*

Eleven prescription opioid abusers participated. The mean age was 41 (range 22 to 53); eight were male and three female, five were white, three African-American, and three Hispanic; eight had completed less than twelveth grade education; all resided in urban areas. Subjects were categorized based on preferred route of administration: the oral route was preferred by five, nasal by one, intravenous by four, and one preferred multiple routes. Six had a history of substance abuse treatment. In addition, two former DEA chemists and three scientists from a pharmaceutical company specializing in opioid delivery systems participated.

### *Listing Extraction Techniques*

The participants generated an initial list of 111 extraction techniques. After removal of any items that were duplicative (same techniques, just different wording) and items that were nonsensical (i.e., "cup to drink"), 79 items remained. Two ex-DEA chemists reviewed these items to remove techniques that were implausible (e.g., would not yield an ingestible compound or would not result in extraction). The final list of extraction techniques included 32 unique techniques (see Table 2). These were later reduced on conceptual grounds to 19 techniques in three categories (see the next section).

### *Evaluating the Classification System*

Eleven substance abuse clients with varying degrees of extraction expertise and different preferences for route of administration sorted and rated the 32 extraction techniques into the four categories of ease of extractability described above. The research team examined a variety of Concept Mapping solutions for the results of the sorting activity, focusing on the four-cluster solution suggested by the original classification schema, as well as a three-cluster solution (Fig. 2). In the four-cluster solution (not shown), Categories 2 and 3 were found to be conceptually indistinct; inspection of the items sorted into these two categories revealed that there was little agreement on which extraction techniques fell into Category 2 (Uses readily available equipment but requires no special knowledge) versus Category 3 (Uses readily available equipment but requires special knowledge). Both clusters contained a mix of techniques requiring special knowledge and not requiring such knowledge. The statements were then redistributed, based on the sorting data, into a three-cluster solution, which as expected combined the two middle clusters into one. Stakeholders thus appeared to divide techniques into three distinguishable technique categories, not four. These results suggested that the original concept of "special knowledge" distinguishing the two middle categories was flawed. As will be described next, the concept of "special knowledge" was also rejected in the expert consensus process.

### *Barriers to Extraction*

Figure 2 shows the three-cluster solution with mean rating for each cluster as to whether the specific extraction techniques within that category would be a barrier to a substance abuser. The "barrier ratings" indicated that increasing difficulty of extractability was perceived by substance abusers as posing an increasing barrier to use/abuse of that product and providing validation of the utility of a classification system for ease of extractability. Despite this, *currently used techniques in even the highest category of difficulty were not rated on average as*

**TABLE 2** List of Extraction Techniques*

1. To get opioid crystals from a liquid, slowly add drops of NaOH solution until the water reaches pH 9. At pH 9, crystals should develop forming a cloud in the water. Put the glass in the freezer for about 10 min, and then filter out the crystals. Dissolve the crystals in anhydrous (99%) alcohol, add 1ml of HCl and shake, let the alcohol evaporate (do not boil).
2. Wipe off the coating with alcohol swab and crush the tablet into fine powder. Let the powder sit in sterile water for 4 or 5 min, stirring occasionally. Draw through cotton into a syringe, then attach 0.08 micron filter and expel into a clean glass.
3. Apply heat to increase the therapeutic effect (use hot tubs, electric blankets, heating pads, hot baths, hot showers, hot towels, etc.).
4. Bite and chew the whole pill.
5. Boil the patch (90 C for 60 min) to extract the active ingredient for IV preparation.
6. Break open a capsule and smoke, snort, or inhale the drug.
7. Crush the pill, cook it and then shoot it through a needle.
8. Crush the pill and smoke, snort or inhale it.
9. Cut open the reservoir of a patch with a knife. Then squeeze out the gel into a glass. Dissolve the gel in ethanol, vinegar, and a little saline.
10. Cut open the reservoir of a patch with scissors, put a glob of gel (the size of a match head) in an oil pipe and then evaporate/vaporize with a lighter.
11. Cut open an unused patch and dilute it so it can be injected.
12. Cut open an unused patch and snort the gel.
13. Cut open an unused patch and suck out the contents.
14. Cut open an unused patch, heat with a flame, and inhale the fumes.
15. Dissolve in water.
16. Drop the pill in a drink.
17. Place the unfolded patches contents in vodka (85C for 2 h).
18. Place the unfolded patches in vinegar.
19. Dissolve the drug in solvents such as freon, methylene chloride, or acetone.
20. Freeze patch. Cut into small pieces and then ingest.
21. Mix the drug with a little baking soda and abut a drop of water on a piece of tin foil. Use a lighter to heat the tin foil until it becomes a liquid. The liquid can be ingested/injected.
22. Dissolve the lozenge (or lollipop) in sterile water or saline.
23. Stick a syringe needle into a patch reservoir and draw out the gel for injection or ingestion.
24. Cut open the patch to IV.
25. Cut open an unused patch and apply the contents to the skin.
26. Cut open an unused patch and inject the gel.
27. Put tablets in ethanol in a pot over a flame. Boil until almost dry and then place the liquid into a syringe for injection.
28. Cut the patch into smaller pieces and soak the pieces in a jar in a small amount for 70%– 99% anhydrous isopropyl alcohol. Leave in the jar for about 12 h (or up to several weeks if multiple patches are added). Then filter the alcohol and express the filter so as much as possible of the substance will fall in a glass dish. Place some basil leaves or some other smokeable herb in the alcohol, allow the alcohol to evaporate, smear the herb in remaining contents of the glass (can use a razor to scrape up any residue to place on the herb) and smoke the herb.
29. Scrape the coating off the pill with a razor and then crush it up and snort it.
30. Put the drug on a spoon and heat it with a lighter or other flame, put a piece of cotton in the spoon and draw the solution up in the needle (A.K.A. "Slam").
31. Transdermal or oral dosage forms can be soaked in solution to extract the opioid for ingestion or injection.
32. Transdermal patches can be cut up into smaller pieces and sucked on directly to extract the drug.

*This list contains the 32 unique and plausible techniques derived from the initial raw list of 111 techniques supplied by substance abusers and experts. This list was further reduced on conceptual grounds to create the 19 items of the Standard Extractability Battery (see text for details).

*being a significant barrier to abuse* (2.62 on a 1–5 scale). This conclusion reinforced our experts' opinion that all currently marketed prescription opioids can be extracted using the relatively simple techniques on the reduced list of extraction techniques (Table 2). As will be seen next, experts felt that an additional category of difficulty of extractability should be added to the three-category system suggested by the Concept Mapping, in order to accommodate future abuse-resistant formulations.

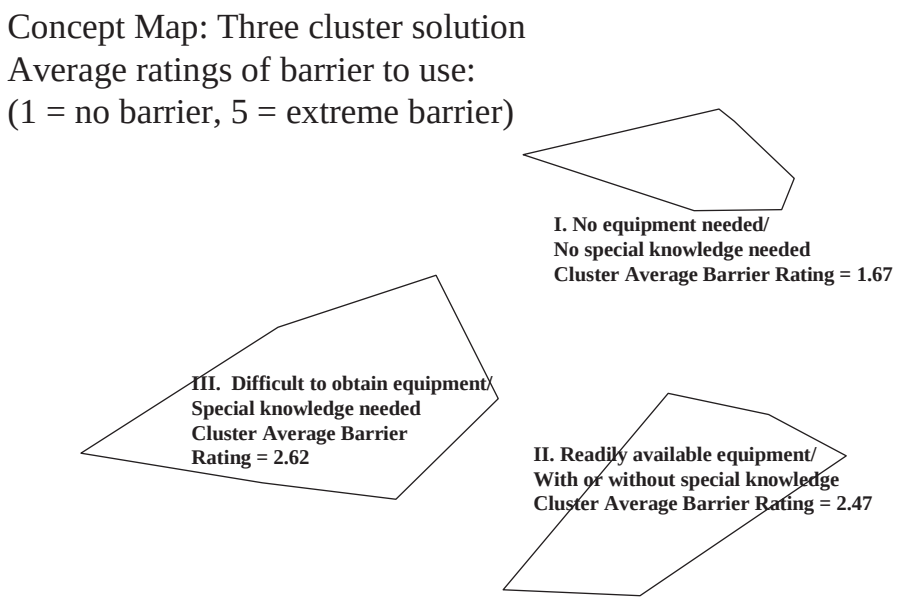


**FIGURE 2** **Results of Concept Mapping: Three Cluster Solution**

**A four-cluster solution, suggested by the current working system for classifying ease of extractability, resulted in two conceptually indistinct middle categories; this three cluster solution combining these two middle categories proved more appropriate.

## Stage 3: Development of the Extractability Rating System: Expert Consensus Meetings

Two expert meetings were held (see Appendix A for participants), during which consensus was sought and achieved on the following issues, resulting in the development of an Extractability Rating System.

### *Refined Definition of Extractability*

Recognizing that the conceptual definition of extractability arrived at earlier in the project required further clarification in order to be implemented, the group achieved consensus on the following definition of the dimensions of extractability:

- *Ease of extractability*: The category of difficulty associated with the simplest technique required to extract a product (see revised classification below)
- *Purity of the extract*: The weight of the active ingredient in the extract divided by the weight of the entire extract (actives plus inactives). For example, if an extract weighing 100 mg contained 10 mg of active, the purity would be 10%.
- *Efficiency of extraction* (or percent extracted): The weight of active ingredient in the extract divided by the weight of active ingredient in the starting material. For example, if the starting material (e.g., tablet) contained 100 mg of active, and the extract contained 50 mg, the efficiency would be 50%.
- *Potency of the extract*: The number of doses sufficient to produce a mind-altering effect contained in the extract. Given limited data in this area, the experts agreed that the most appropriate surrogate for the active mind-altering dose is the starting analgesic dose for opioid-naïve individuals. For example, if the starting analgesic dose of an active drug is 10 mg, and a particular extract contained 60 mg, then the potency would be 6 in our schema.

### *Standard Extractability Battery*

The group agreed that standardization of ratings of extractability would require that the ratings be based on the results of laboratory tests (rather than opinions or estimates of likely results). Furthermore, the group agreed that the laboratory tests performed in order to generate these ratings must be standardized, in order to ensure that different rated drug products had been subjected to the same battery of tests performed in the same manner. The group further felt that even in cases in which a drug could be extracted using a simple

technique, the results of more complicated extraction techniques would also be of interest, even if unlikely to be implemented on the street. The group therefore developed a "Standard Extractability Battery (SEB)," which is a proposed core set of tests to be performed on any prescription opioid product in order to produce an extractability rating. The SEB was derived by the group by reducing the list of 32 extraction techniques derived from experts and substance abusers, on conceptual grounds, into the 19 fundamental approaches represented by those methods. The SEB consists of three categories of manipulations, corresponding to the three categories of difficulty of extractability derived earlier, described next.

### *Revised Classification of Ease of Extractability*

The group determined that on conceptual grounds, the list of 32 currently used extraction techniques could be reduced to three groups of techniques (see SEB): (1) Simple Physical Manipulations; (2) Single-Step Chemical Extractions; (3) Multi-Step Chemical Extractions; and (4) Complex Laboratory Extractions. The fourth category, not containing any currently used techniques, was added to accommodate future abuse-resistant products. Approaches in higher categories may first require steps in lower categories, e.g., crushing (Simple Physical Manipulation) followed by dissolution in water (Single-Step Chemical Extraction). It was recognized that all existing prescription opioid products could be effectively extracted using techniques in categories 1–3, and most using techniques in Category 1. It was also recognized that even products requiring level three extractions (Multi-Step Chemical Extraction) do not pose a high barrier for many users. This revised classification system was developed and accepted on conceptual grounds and was not subjected to re-validation.

### *Scoring Approaches*

While the team's recommendation was for each product to be fully described in a completed SEB, the team recognized the need to reduce the elaborate SEB results into a more concise summary of the drug product's extractability. Two approaches were developed by expert consensus and subsequently tested. The first approach was based on the principle that the simplest extractability technique that yielded at least one active dose of product would be the technique used on the street, and therefore was the most relevant indicator of the real-world extractability of the drug. However, the team recognized that extracting a drug for intravenous administration, for example, may require a different complexity of extraction technique than if the intended route were oral. Thus it became clear that a comprehensive rating of extractability of a prescription opioid product would require separate ratings for each intended route of administration. A *Scoring Table* (Table 1) was developed to capture the key elements from the completed Standard Extractability Battery (Appendix B) required to profile the extractability of a drug. The desirability of having a single *Composite Score* of overall extractability was recognized by the team, to facilitate interpretation by clinicians, industry, and regulators. The results of efforts to produce a single composite score are described below (but did not lead to a valid composite scoring approach).

### *Extractability Rating System*

Using the building blocks developed above, an Extractability Rating System (ERS) (alpha version) was developed, which allows the rater(s) to synthesize the results from the Standard Extractability Battery into a scoring profile for each drug and potential route of administration. The process envisioned for implementation of the ERS is illustrated in Fig. 3. Based on the Standard Extractability Battery laboratory extractability tests would be conducted and the results recorded on the Standard Extractability Form. Using a Scoring Algorithm (Appendix B), the Standard Extractability results would be reduced to a Scoring Table, which would be the form in which overall drug extractability would be evaluated.

During the Expert Meeting it was agreed that the following drugs should be rated during the subsequent rating stage of the project: OxyContin 80 mg; Percocet 5/325 mg; Fentanyl Matrix Patch 10.2 mg, Talwin-NX 50 mg; and Duragesic Patch 10 mg; The reasons for choosing these specific prescription opioids were as follows: both prescription opioid products of primary interest (the Duragesic fentanyl reservoir patch and the fentanyl matrix patch) were included; a product perceived to be of very high "extractability" (OxyContin 80 mg) was included; researchers hypothesized that the extractability ratings of Percocet would be essentially identical to those for hydrocodone compounds

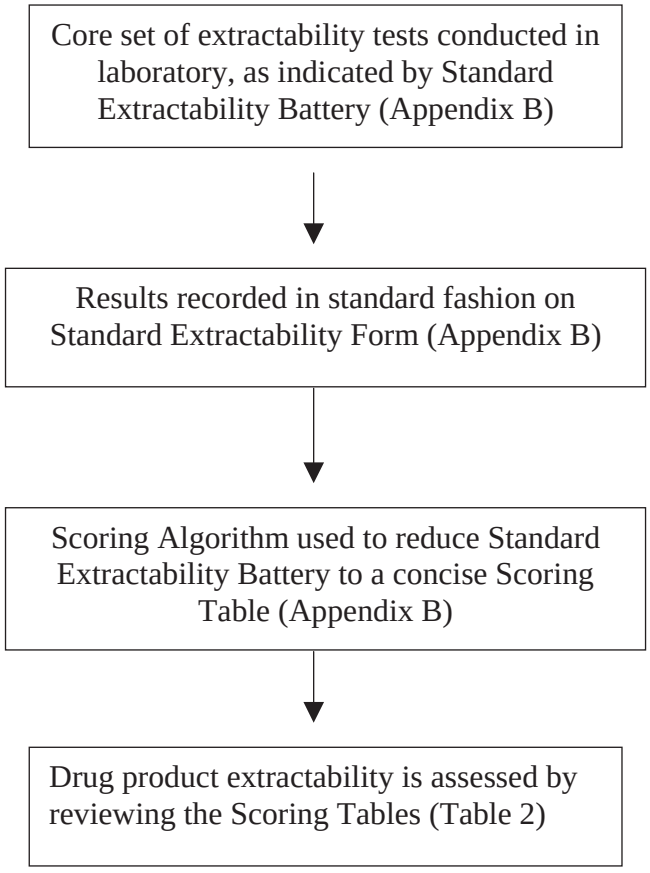


**FIGURE 3** **Proposed Implementation of the Extractability Rating System.**

(e.g., Vicodin); therefore Percocet would reasonably represent the most widely abused group of opioids in the United States (oxycodone and hydrocodone compounds); and Talwin-NX represents a drug with a specific extraction-resistant feature (the presence of an antagonist) that would allow the ERS to rate such a product.

## Stage 4: Refinement of Extractability Rating System

The alpha version of the Extractability Rating System was tested by having a single rater (retired DEA chemist with over 20 years of experience, including working for the FDA Division of Forensic Sciences), utilize the system to rate two prescription opioid products, OxyContin 80 mg and Duragesic 10 mg, based on best available data, followed by review of the results and a cognitive debriefing session. The rater felt the tasks were straightforward and that he felt the results, even while not based on lab work, should be fairly reproducible among expert chemists. He did point out several ambiguities about the task, which the team clarified by creating standards for the duration of extraction (30 min) and the amount of fluid used for extraction (10 mL). In addition, it was noted that calculation of purity requires knowing the weights of prescription opioid products, which is unpublished proprietary information. While this could be obtained simply by obtaining and weighing each product, for the purpose of this conceptual exercise, "best guess" weights were assigned to the rated products. A problem was discovered with the assessment of "potency" (the number of active doses in an extract). Experts were estimating the weight of active ingredient in an extract and dividing by their best guess as to the minimum active dose, which was inconsistent across raters. Given the lack of data on minimum euphorigenic doses, and the consensus of the research team that the euphorigenic doses were approximately equivalent to starting analgesic doses, the team chose to change potency to a derived variable, using starting analgesic doses for opioid naïve individuals from a commonly used reference (American Pain Society, 2004) as a proxy for the minimum active euphorigenic dose.

## Stage 5: Expert Ratings of Extractability

### *Participants and Tasks*

There were five participants in this stage: two former DEA chemists, one former DEA and FDA chemist, one expert on transdermal drug delivery, and one pharmaceutical chemist. The original plan to have two teams of raters provide individual ratings, then consensus ratings of each team, was modified based on limited availability of experts, and observations of difficulties in achieving consensus. Based on "best available information" participants rated five opioid products: OxyContin 80 mg, Percocet 5/325 mg, Fentanyl matrix patch 10.2 mg, Talwin-NX 50 mg, and Duragesic Fentanyl reservoir patch 10 mg. The ratings provided included a Global Rating of Extractability (five-point anchored scale from "1" or "Extremely Difficult to Extract" to "5" or "Not at all Difficult to Extract"), a Global Ranking of Extractability, and a completed Standard Extractability Battery and Scoring Table for each drug.

**TABLE 3** ICCs for Expert Ratings Across All Drugs by Route of Administration

| | N of raters | Ease of extraction | Purity | Percent extracted | Potency | Likelihood of abuse of extracted product | Mean (median) ICC per Route of administration |
|---|---|---|---|---|---|---|---|
| PO | 5 | .29 | .70 | .53 | .83 | –.36 | .40 (.53) |
| Nasal | 3 | –.73 | .99 | .42 | .95 | .07 | .34 (.42) |
| IV | 5 | .60 | .79 | .93 | .66 | .67 | .73 (.67) |
| Smoking | 3 | –.40 | .86 | –.26 | –.46 | –.40 | –.13 (–.40) |
| SL/Buccal | 3 | –.22 | .68 | –.28 | .79 | .49 | .29 (.49) |
| Mean (median) ICC per dimension of extractability | | –.09 (–.22) | .80 (.79) | .38 (.42) | .55 (.79) | .09 (.07) | |

*Note: ICCs range from + 1 (reflecting perfect agreement) to –1 (reflecting perfect disagreement).

## Scoring Tables: Inter-Rater Reliability

Table 3 presents the Intraclass correlations for the experts' ratings of the extractability dimensions across all drugs for each route of administration. Also presented are the column and row averages, representing the average ICCs for each extractability dimension across all routes of administration (columns) and the average ICCs for each route of administration across all dimensions (rows). Traditionally, interpretations of the magnitude of ICCs assume that values greater than .80 represent perfect agreement, .61 to .80 is substantial, .41 to .60 is moderate, and .21 to .40 is fair reliability (Landis & Koch, 1977). As can be seen, there was very good agreement for purity ratings across routes of administration (Mean ICC = .80) and for IV ratings across the components (Mean ICC = .73). Moderate agreement was obtained for potency ratings across routes of administration (.55) (ratings obtained prior to converting potency to a derived variable). Otherwise, the agreement was fair to poor. These data suggest that overall, the expert raters were able to agree much more often on the more mathematical/chemical components of extractability (i.e., purity, percent extracted, and potency) than those components requiring greater judgment, knowledge of clinical pharmacology, or experience with substance abusing populations. These data suggest that intensive efforts to achieve standardization and/or consensus on the components requiring more judgment would be required in future work with the extractability system, should ratings based on "best available information" (as opposed to actual laboratory data) be desired. One should note in the column "N of Raters" the fact that for PO and IV, all five experts rated all drugs, whereas for the nasal, smoking, and sublingual routes of administration, two of the raters did not provide ratings. This is consistent with the absence of much data on these routes of administration from which the raters could make judgments, and may (both fewer raters and fewer data) have contributed to the lower agreement seen with these routes of administration. Selected extractability profiles, derived from the Scoring Tables, are shown for illustration purposes in Fig. 4. For the purpose of illustration, all components of extractability were transformed into a 0–100 scale.

## Scoring Tables: Findings

As a result of the general lack of reliability of the ratings, the actual ratings must be interpreted very cautiously. However, several findings were of interest. In the case of OxyContin (Fig. 4), the ERS showed that extracts could be easily produced across multiple routes of administration, the extracts had high abuse liability, and a moderate number of doses could be produced. Talwin-NX was distinguished by its ease of extractability only for oral use (no extraction required), but its quite difficult extractability for use by any other route (due to the presence of antagonist). By any extraction technique, few doses were produced from Talwin-NX. The Duragesic fentanyl reservoir patch and the fentanyl matrix patch were rated as relatively easy to extract, and the number of doses produced by extracting from either transdermal product was quite high due to the potency of fentanyl. These ratings do not account for any differences between these products of the abuse liability of the extracts. In separate ratings (data not shown), experts rated the abuse liability of extracts from Duragesic as lower than extracts from the fentanyl matrix patch, likely due to the difficulty in metering the amount of fentanyl in extracts from Duragesic, with potentially fatal consequences.

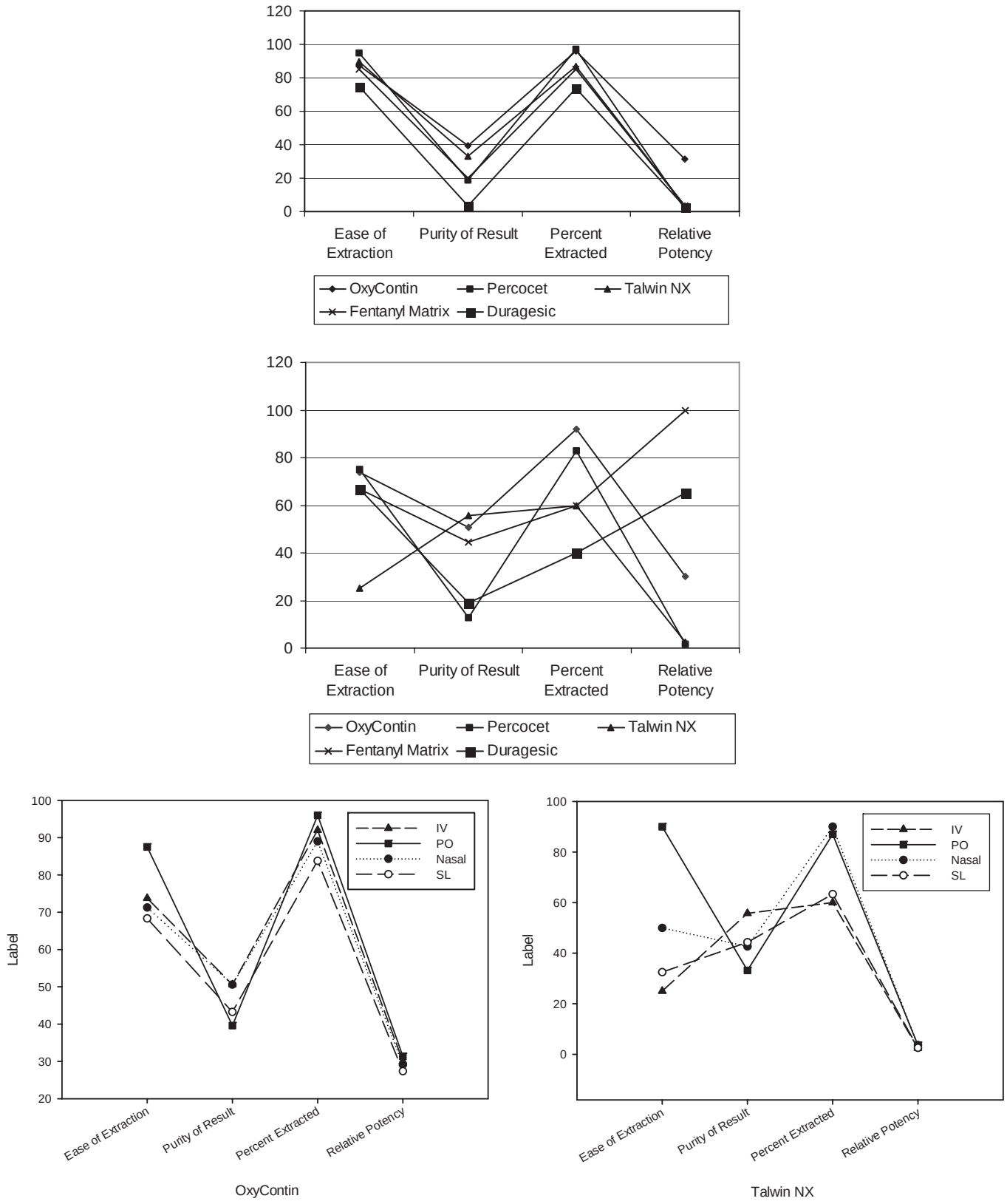


**FIGURE 4** **Selected Extractability Profiles *a. By Route of Administration*: Here all drugs are displayed together illustrating relative extractabilities for the oral, then for the intravenous routes of administration. Similar figures for other routes of administration are not shown. b. *By drug: Here extractability profiles are illustrated for two medications, OxyContin and Talwin NX. Similar profiles generated for the Duragesic reservoir patch, the fentanyl matrix patch, and Percocet are not shown*.**

### Global Ratings and Rankings

The results for experts' global ratings and rankings of overall extractability are illustrated in Fig. 5. Experts' global ratings indicated that OxyContin and the Fentanyl Matrix patch were rated as easiest to extract and Talwin-NX and the Duragesic fentanyl reservoir patch as most difficult. The Kendall's W for ordering of agreement based on the ratings was .39 ($df = 4$, $p = .184$), which was not significant. In a separate task, the experts also ranked each drug from "least extractable" to "most extractable." The ranking of the drugs from most to least extractable yielded results consistent with the results of the rating task. In their rankings, the experts achieved a Kendall's W of .34, df = 4, p = .142 (NS). High or significant values of Kendall's W may be interpreted as meaning that the raters are applying essentially the same standard in ranking the objects under study (Siegel, 1956). Note that "high" values are comparable to Pearson r's, in the sense that significance implies that the statistic is significantly different from zero or no relationship, and that whether a particular value of r (or W) is significant depends in part on the number of observations. Thus, other things being equal, a W of .30 reflects a reasonable relationship while the higher the value, the stronger the observed relationship. The low N in the present study certainly compromised any ability to achieve statistical significance of the reported relationship, although other sources of variability may also have contributed. In summary, the actual ratings must be interpreted cautiously given the small sample of raters and poor reliability. However, both exercises, ratings and rankings, suggested that OxyContin and the fentanyl matrix patch tend to be rated as highly extractable, whereas the Duragesic fentanyl reservoir patch and Talwin-NX tended to be rated at the bottom in terms of extractability (Fig. 4).

### Efforts to Produce a Single Composite Extractability Score

However a number of obstacles to calculating a valid composite score were discovered: the different components of extractability were expressed in different units; the relative impact on overall extractability of these different components was unknown; there was no clear conceptual approach to combining extractability for various routes of administration; and it was not clear that the components of extractability would correlate with each other (a general requirement for creating a composite score). For example, if a product could be extracted for oral ingestion by chewing (Category 1), but one could produce a product for intravenous administration by a multi-step chemical extraction (Category 3), there was no obvious composite extractability score. However, based on expert consensus the team generated a provisional approach to creating a composite score that was tested in a subsequent stage of the project. This method consisted of transforming each component of extractability (ease, purity, efficiency, and potency) into a 0–100 scale (note

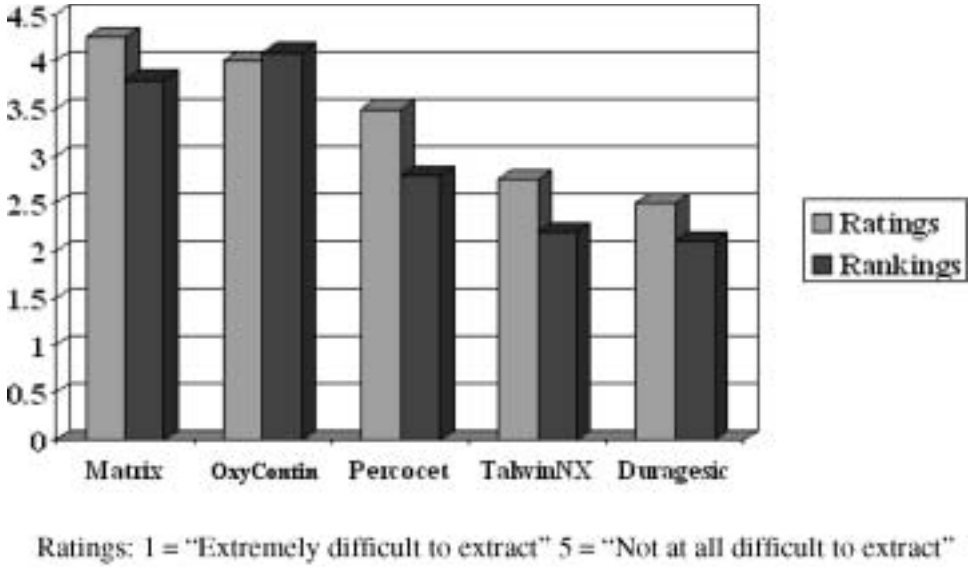


**FIGURE 5** **Mean Global Ratings and Rankings.**

that purity and efficiency were already presented as 0–100 percent scores and required no transformation), and mathematically combining these components in various ways. A number of approaches were explored to generate a single composite rating of extractability from the data in the Scoring Tables. Correlation matrices of each rater response within medication and across the dimensions of the extractability rating system were produced. Even considering that correlations based on five cases will be very unstable, these correlation matrices yielded very inconsistent results, ranging from 1.00 to –0.999. Line graphs of the individual variable ratings revealed, for example, that quite often purity and efficiency are inversely related. This suggests that the variables are not reflecting an underlying dimension that can be captured by a composite score, such as summing items or taking their mean. Thus these procedures were not done.

Other approaches to develop a composite score included developing simple conceptual models of overall extractability based on the Scoring Tables. For example, one approach was based on assigning the first priority to drugs that could be extracted with the simplest possible extraction techniques, which were then stratified based on the number of active doses produced. After exploring a variety of approaches, we were unable to find a composite scoring method that seemed to resonate in a satisfactory manner with conventional wisdom or the global ratings made by the experts. This may be due to the fact that the statistical performance of some variables may be an artifact of the experts attempting to estimate some of the results of the core laboratory tests of the SEB, without actual laboratory data upon which to rely. It may reflect our low sample sizes of expert raters, which were constrained by time, recruitment, and scheduling issues. Finally, it may be due to the need to further explore the concept of extractability, to better understand what exactly about extractability is most relevant to the problem of prescription opioid abuse.

# DISCUSSION

## Rationale for Project

Prescription opioid abuse is a significant and rapidly growing issue. Despite much media attention, and development of "abuse-resistant" formulations, there has been little systematic work in identifying what aspects of prescription opioid products confer enhanced or reduced abuse liability. Federal regulatory agencies, including the DEA and FDA, have for decades considered ease of extraction to be a critical component of risk assessment, and have informally, and without standards, assessed extractability in making scheduling and other risk-related decisions. Pharmaceutical companies are beginning to develop abuse-resistant formulations, which in many cases means "extraction-resistant," without any clear research on which to base their approaches, or methods for measuring the extractability of these products. The purpose of this project was to begin the process of creating standards for assessing the extractability of prescription opioid analgesics.

### *Results*

Several important goals were accomplished in this project. Significant foundational work was required before developing a measure of extractability could be considered. Definitions of extractability, agreement on its dimensions, and definitions of these dimensions were developed. Obstacles in implementing the calculation of these dimensions were identified and overcome. The traditional classification system for ease of extractability was examined, found wanting (in this setting of prescription opioid abuse), and revised. A comprehensive inventory of extraction techniques employed by actual substance abusers, as well as proposed by experts, was created, and fueled the development of the Standard Extractability Battery. The Standard Extractability Battery functions as (1) a comprehensive inventory of extraction techniques, (2) a minimum dataset of laboratory tests that must be done to assess extractability, and (3) a standardized documentation tool for such studies. A Scoring Table has been produced that distills the SEB into a concise and readable summary of the extractability tests for a specific drug–an "extractability profile." Global ratings and rankings of overall extractability of five selected prescription opioids were generated. While inter-rater agreement was low, and the results therefore cannot be viewed as definitive, results suggested that OxyContin and Fentanyl matrix patch were most extractable, and Talwin-NX and Duragesic least, with Percocet in the middle.

The qualitative phases were extremely informative and shaped our understanding of the prescription opioid abuse problem as it relates to the extractability of prescription

opioids, as well as caused a shift in our thinking about how a tool could be the most clinically and socially meaningful. Our definitions and dimensions of extractability, with empiric support from Concept Mapping, have withstood several iterations of testing and appear robust. We have introduced a new vocabulary to this field to support its future development. The Standard Extractability Battery alone will be an addition to the forensic chemistry literature, and in our vision will assist regulatory agencies and pharmaceutical companies to begin to create standards for extractability testing, and rating of compounds.

### Limitations

This project is a first step and was characterized by a number of important limitations that we hope will be addressed in future work, by others and ourselves. The qualitative underpinnings of the concepts of extractability were developed with small, albeit diverse "stakeholders," and should be confirmed with larger groups of subjects. The Extractability Rating System we developed appears conceptually solid, but requires further work to improve standardization and reliability in some of its aspects. Further usability testing and refinement of the ERS will help improve its reliability. Ultimately the "expert opinion" approach, implemented in this study primarily for the purpose of testing and refining the ERS, will need to be replaced with actual laboratory data, and in that sense our ERS is a call for the conduct of the research studies that will inform and allow accurate extractability ratings. The search for a single, interpretable, composite score remains an important but elusive goal; further research to better understand the concept of extractability, and its relationship to abuse liability, and investigations with larger samples, will no doubt lead to a robust composite measure.

There were a number of other specific limitations. Implementing the Extractability Rating System with actual laboratory data could not be done due to the lack of availability of such data. Therefore an interim approach of completing the rating materials based on expert opinion was embarked upon. This led to low reliability and will require more extensive refinement and rater training to improve inter-rater reliability. In this study, drugs were compared in two ways: visual inspection of the Scoring Tables and review of global rankings/ratings. Although these approaches reveal interesting aspects of extractability, neither can be considered a valid or reliable measure of "overall extractability." Finally, our revised classification system for ease of extractability, based on the first empirical examination of the validity of this classification system, appears to be an improvement over the previous system. Nevertheless, our system was found to have its own limitations and can be improved with further refinement. Despite these limitations, investigators can begin to use the Extractability Rating System as a guide to assessing extractability, and report their own experiences with and refinements of the system.

### Expert Opinion versus Laboratory Data

Although assessing extractability using the ERS based on "expert opinion" was not the optimal approach to implementing the ERS in the opinion of the team, and did not yield high inter-rater reliability the use of the ERS with "expert opinion" data could be made much more robust and reliable through further standardization of approaches, such as: providing the weights of the drug products; providing standard starting doses of opioids; clarifying which fields needed to be provided and which would be derived; and providing raters basic information (e.g., manuals of opioid solubility, data from the Internet on extraction procedures). Also, rater training would be a requirement for producing reliable results. A rating system based on expert opinion, although not as satisfying as a system based on laboratory data, could have a tremendously important role in rating compounds for which data will not be forthcoming.

### Relevance of Extractability Ratings

One may legitimately ask whether the ERS is relevant to prescription opioid abuse, since we indicated that most extraction procedures currently performed on prescription opioids require relatively simple techniques (Categories 1 and 2) and are performed by end users for their own use, rather than by "clandestine chemists" for redistribution. Clearly, as long as prescription opioid mediations that can be abused by chewing and swallowing are widely available, the fact that one can also engage in a Category 3 or 4 procedure to extract that opioid for abuse is of little practical relevance. However, even with currently available products, nuances of their extractability may explain important differences in their abuse rates, for example, the relatively low abuse rate of MSContin compared with OxyContin. Also, deliberate changes in the

extractability of currently available products, to make an "extraction-resistant opioid," have been used to decrease abuse rates (e.g., Talwin to Talwin-NX). Finally, in view of the hundreds of patents filed in the last several years for abuse-resistant products based mainly on raising extractability barriers, methods for rating extractability must accommodate products in the pipeline.

### *Interpretation of Extractability Ratings*

The extractability ratings produced in this study must be interpreted with caution, due to the small number of raters and modest inter-rater reliability. However, global ratings of the five products studied herein place the Fentanyl matrix patch and OxyContin at the top of the extractability scale and the Duragesic Fentanyl reservoir patch and Talwin-NX at the bottom. Further work with the scoring tables is required before they can generate comparative rankings. However, interesting patterns reflective of real-life experience and concerns have emerged, including the potential for sublingual abuse of the Fentanyl matrix patch (based upon the assumptions of the experts, without human sublingual absorption data). Extractability in the end is a judgment of how the disparate objective aspects of extraction add up to a concept that is relevant to "street" use of a drug. Further work is needed to determine exactly how the current working dimensions of extractability (purity, potency, efficiency, ease) relate to the likelihood of street abuse. For example, what exactly is it about purity that is relevant to a potential user's decision to extract an opioid? Does it matter whether it is 40 or 70% pure, or is the issue whether or not there are impurities that can cause significant harm or not? This will require assessing substance abusers, which could be done with concept mapping or other approaches, but is essentially qualitative. Once a more refined list of dimensions of extractability, closely related to abuse liability, were developed, then pursuing a "scale" to measure overall extractability from the perspective of the substance abuser, building upon the foundation laid in this study, could be pursued, using traditional scale development approaches.

## CONCLUSION

We have developed an Extractability Rating System with multiple important components that will set provisional standards for the industry and regulators in the assessment of the extractability of prescription opioid products. Ratings of five products suggest that the ERS can detect clinically relevant features of extractability that are relevant to abuse liability. "Extractability Profiles" for these medications point out potential avenues of abuse, and also illustrate the barriers created by abuse deterrent formulations, such as the low extractability ratings for IV use of Talwin-NX. At a minimum, our study will function as a call for much-needed laboratory testing so that products can be accurately rated. Moreover, the categorization system of ease of extractability will set forth goals for drug developers who wish to develop "abuse-resistant" ("extraction-resistant") opioid analgesic products.

## ACKNOWLEDGEMENTS

We gratefully acknowledge funding support of Janssen Pharmaceutical Incorporated. In addition we would like to acknowledge Wilmer Kiser, BA, Audra Stinchcomb, Ph.D., and Surya Vangapandu, Ph.D., for their participation in the usability testing of our rating tools.

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## APPENDIX A. EXPERT PARTICIPANTS

Stage 1: Qualitative Phase: Two former DEA personnel, one addiction specialist, one opioid abuse expert, and two substance abuse counselors were interviewed.

Stage 2: Concept Mapping: Two former DEA chemists and three scientists from a pharmaceutical company specializing in opioid delivery systems participated.

Stage 3: Development of the Extractability Rating System: Expert Meetings: Two former DEA chemists, one abuse liability specialist, one addiction specialist, and one pain specialist participated.

Stage 4: Refinement of the Extractability Rating System: One former DEA and FDA chemist participated.

Stage 5: Expert Ratings of Extractability: Two former DEA chemists, one former DEA and FDA chemist, one expert on transdermal drug delivery, and one pharmaceutical chemist participated.

## APPENDIX B. EXTRACTABILITY RATING SYSTEM GUIDE

Step 1. Complete the Standard Extractability Battery on the next two pages.

**Instructions**: For each extraction procedure on the list, fill in the blanks for the **purity of the extract** that have resulted from the specific procedure and the **percent by weight extracted**. These terms are defined below. Under **Routes of Administration**, place an X in the box under any route of administration for which the following applies: the specific extraction procedure was able to generate a usable amount of active ingredient that could be ingested via that route. In the **Total Number of Routes of Administration column**, indicate the total number of routes of administration you placed an X in indicating that the extraction procedure would be successful.

**STANDARDIZED EXTRACTABILITY BATTERY:** _____

| Technique | Category of Difficulty | Purity* | Percent extracted* | Potency | Routes of Administration* | | | | | Total Number of Routes of Administration |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | IV | PO | SL/buccal | Smoking | Nasal | |
| **Simple Physical Methods**: | | | | | | | | | | |
| Crushing | I | | | | | | | | | |
| Cutting | I | | | | | | | | | |
| Peeling | I | | | | | | | | | |
| **SIMPLE CHEMICAL MANIPULATIONS*** | | | | | | | | | | |
| Cold Water | II | | | | | | | | | |
| Hot Water | II | | | | | | | | | |
| Ethanol | II | | | | | | | | | |
| Olive Oil | II | | | | | | | | | |
| IPA | II | | | | | | | | | |
| Acetic acid | II | | | | | | | | | |
| Acetone | II | | | | | | | | | |
| Gasoline | II | | | | | | | | | |
| Methanol | II | | | | | | | | | |
| Mineral Spirits | II | | | | | | | | | |
| Ether | II | | | | | | | | | |
| Ethyl acetate | II | | | | | | | | | |
| Coleman Fuel | II | | | | | | | | | |
| Methylene chloride | II | | | | | | | | | |
| Chloroform | II | | | | | | | | | |

**Simple Chemical Manipulations* are defined as a process of extraction following *or* not following a simple physical manipulation which includes one step solvent extractions, with *or* without filtration, and with *or* without evaporation and or reconstitutions.

**KEY**:

**Purity = Active ingredient (mg)/total weight of the product**

**Percent Extracted = mg. of active post-extract/mg. of active pre-extract**

**Routes of Administration** = If the extraction technique will yield a substance that is suitable for that route of administration, place an X in the corresponding box.

**STANDARDIZED EXTRACTABILITY BATTERY: _____**

| Technique | Category of Difficulty | Purity* | Percent extracted* | Potency | Routes of Administration* | | | | | Total Number of Routes of Administration |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | IV | PO | SL/buccal | Smoking | Nasal | |
| Multi-step extractions ***(For basic drugs)*** | | | | | | | | | | |
| Acid dissolution followed by: Methylene chloride, then separate methylenechloride, then discard it, add equal volume methylenechloride to aqueous phase, adjust pH to 9, shake, and let separate, separate methylene chloride, reduce it to dryness | III | | | | | | | | | |
| **Complex procedures requiring laboratory setup and specialized knowledge, that may require resynthesis**.** | IV | | | | | | | | | |

**KEY:**
**Purity = Active ingredient (mg)/total weight of the product**
**Percent Extracted = mg. of active post extract/mg. of active pre extract**
**Routes of Administration = If the extraction technique will yield a substance that is suitable for that route of administration, place an "X" in the corresponding box.**

## Step 2. Scoring: _____

Instructions: Please complete the Scoring Table below for the product you rated in Step 1. **For each route of administration**, select the extraction procedure from the Standard Extractability Battery that was in the **lowest category of difficulty** (i.e., the easiest procedure) that led to a usable quantity of active drug. Then transcribe the cells for purity, and efficiency from the Standard Extractability Battery from the row for that specific extraction technique. Next please indicate potency. Finally, given the various factors that are attributed to abuse liability (ability to meter a dose, the safety of the dose, the absence or presence of an opioid antagonist, etc.) please rate how likely, with 1 being extremely unlikely and 5 being extremely likely, the extracted product is to be abused.

| | Ease | Purity | Percent Extracted | Potency* | Likelihood of Abuse ** |
|---|---|---|---|---|---|
| PO | | | | | |
| Nasal | | | | | |
| IV | | | | | |
| Smoking | | | | | |
| SL/ Buccal | | | | | |

**This was an experimental item which was added for future evaluation. While this was not one of the core components of extractability as we defined it, this variable was added to gather information about potential abuse liability of extract.

**KEY:**
**Ease = Ease of extraction Technique (Categories I-IV)**
**Purity = Active ingredient (mg)/total weight of the product**
**Percent Extracted = mg. of active post extract/mg. of active pre extract**
**Potency = Number of doses extracted**

# APPENDIX C. ABBREVIATIONS AND DEFINITION OF TERMS

## Abbreviations

| | |
|---|---|
| CM | Concept Mapping |
| DEA | Drug Enforcement Administration |
| ERS | Extractability Rating System |
| FDA | Food and Drug Administration |
| ICC | Intra Class correlation |
| MDS | Multidimensional scaling |
| MROs | Modified Release Opioids |
| PASS | Power Analysis and Sample Size |
| PO | Orally |
| Pre-CM | Pre-Concept Mapping |
| RA | Research Assistant |
| SAP | Statistical Analysis Plan |
| SEB | Standardized Extractability Battery |
| SL | Sublingual |

## Definitions of Terms

CM: Concept Mapping–A qualitative and quantitative technique of capturing information from a group of respondents, and mapping the organization of the thinking of this group, using statistical techniques such as multidimensional scaling and hierarchical cluster analysis. Concept Mapping has two stages, an Item Generation or "Brainstorming Stage" and a "Sorting and Rating" stage.

ICC: Intra Class correlation–A correlation coefficient used as a measure of inter-rater reliability for continuous data that share a common metric and variance. The modern methods for calculating the ICC statistic use mean squares from an analysis of variance. The classic paper by McGraw and Wong (1996) notes that this means the model for the sample data must be specified. In this study, the model chosen was the two-way ANOVA model, with the rater factor treated as a fixed factor, resulting in a two way mixed model. In the mixed model, inferences are confined to the particular set of raters/judges used in the measurement process (McGraw & Wong, 1996). The output of this analysis is an F value with associated p values, reflecting the extent to which the ICC (rater agreement) is significant.

Kendall's W(Coefficient of Concordance)–A coefficient of agreement among two or more judges. As noted by Siegel (1956), in his classic text on nonparametric statistics, "A high or significant value of Kendall's W may be interpreted as meaning that the observers or judges are applying essentially the same standard in ranking the N objects under study. Often their pooled ordering may serve as a 'standard,' especially when there is no relevant external criterion for ordering the objects" (p. 237). Note that "high" values are comparable to Pearson r's, in the sense that significant implies that the statistic is significantly different from 0 or no relationship, and that whether a particular value of r (or W) is significant depends in part on the number of observations. Thus, other things being equal, a W of .30 reflects a reasonable relationship while the higher the value, the stronger the observed relationship.

MDS: Multidimensional scaling–An alternative to factor analysis. In general, the goal of the analysis is to detect meaningful underlying dimensions that allow the researcher to explain observed similarities or dissimilarities (distances) between the investigated objects. In factor analysis, the similarities between objects (e.g., variables) are expressed in the correlation matrix. With MDS one may analyze any kind of similar-

ity or dissimilarity matrix, in addition to correlation matrices.

MROs: Modified release opioids–Prescription opioid products in which the active ingredient is delivered in a modified form in order to alter the delivery kinetics.

PAI: Personality Assessment Inventory–A self-report instrument measuring personality factors (referred to in the Statistical Analysis Plan as comparison measure).

Pre-CM: Pre-Concept Mapping–The phase of a study involving Concept Mapping, which takes place prior to the actual Concept Mapping activities, and involves qualitative exploration of the content area, feedback from experts, and soon.

SEB: Standard Extractability Battery–A standardized set of the minimum recommended laboratory studies needed to describe the extractability of a prescription opioid. Implicit in the concept of the SEB is that specific drug products may require specific extractability tests not specified in the core set.