Recovery of Active Pharmaceutical Ingredients from Unused Solid Dosage-Form Drugs

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ABSTRACT: The concept of drug recycle by recovering active pharmaceutical ingredients (APIs) from unused tablets and capsules was demonstrated using acetaminophen, tetracycline HCl, and (R,S)-(±)-ibuprofen as case examples. The recovery process comprised three core unit operations: solid–liquid extraction, filtration, and crystallization. Recovery yields of 58.7 wt %, 73.1 wt %, and 67.6 wt % for acetaminophen, tetracycline HCl, and (R,S)-(±)-ibuprofen were achieved, respectively. More importantly, all of the APIs were of high purity based on high-performance liquid chromatography assay. The crystal forms of the recovered APIs were in conformity with the standards.

INTRODUCTION

The current raise of living standard leads to the demand for more intricate and numerous consumer products, which in turn generates more wastes over time. Circular economy has gained traction recently as the answer to this challenge. Waste materials or part of them are recycled back as the raw materials to make the same or different products, forming a closed-loop system. A term of urban mining was coined, which refers to the huge amount of waste in the cities containing a lot of unseen valuable substances ready to be mined. Usually, this concept refers to the scrap metals in daily utensils, rare earth metals in electronics, plastics, papers, glass, and many more.

One of the probably forgotten waste is the unused, unwanted, or expired drugs. They often end up being disposed as household trash, flushed down the toilet, or thrown out into an incinerator. Pharmaceutical pollution has already occurred in the surface, ground, and drinking water, among which some of these problems may be attributed to the improper disposal practices. Even worse, resistant bacteria may also emerge because of the presence of antibiotics in waste water.

There were several attempts to overcome the waste drug problem. For the unexpired drugs, some drug collecting and reusing programs have already been initiated in several places. However, no known attempt has been put forth to recycle expired medications. It has been reported that many drugs still retain their potency years after their expiration dates. Despite that, almost all of the expired drugs ended up being destroyed in reality. The US Food and Drug Administration (FDA) recommends the proper disposal of expired drugs because of the concern of health concern risks and drug abuse.

Apparent that the best way to deal with drug waste is by isolating the active pharmaceutical ingredient (API) from the excipients in unused drug products such as drug tablets and capsules. The API is the most valuable component in a drug product and often causes greater environmental impact than the excipients do. Recycling the unused drugs will recover the APIs in their pure forms, which can later be reformulated into new drug products. In addition, recovering APIs is economically more attractive than synthesizing APIs from scratch because of the former having less-tedious and less-expensive chemical steps.

A previous study in drug recycling was conducted by recovering an undisclosed API from tablets with known excipient contents and compositions by solid–liquid extraction, membrane separation, and antisolvent crystallization. The process outlined in this study could give high recovery yield (>91%) and purity (>99%). Unfortunately, the feasibility of using this process to recover other types of APIs was not being explored.

In other research work, (R,S)-(±)-ibuprofen was recovered from commercial tablets with known excipient contents but unknown compositions by solid–liquid extraction using ionic liquid and citrate buffer followed by antisolvent crystallization. A very good extraction performance was achieved owing to the use of an ionic liquid–water–citrate buffer mixture, resulting in a remarkably high recovery value (~98%). Unfortunately, this process suffered from low purity (70–80%).

These aforementioned research studies either dealt with the drugs with known excipient compositions or the drugs of only one brand. In reality, almost all of the medications sold in the market are often manufactured by different manufacturers and formulated under different brands and each brand comes with

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different excipient contents and compositions. Usually, the label in the drug product mentions the API content and its dose, but the information about its excipients is often obscure. Sometimes, manufacturers only mention the name of the excipients in the label without their compositions being mentioned, but in some cases, no excipients were listed at all. These inconsistencies among manufacturers have made API recovery from drug products challenging. Therefore, the aim of our study is to establish a protocol for recovering APIs from unused tablets and capsules irrespective of their excipient contents and compositions. The developed process was mainly based on solid-liquid extraction, filtration, and crystallization. Because of the importance of product safety, all of the solvents used for the API recovery belong to the class 3 (solvents with low toxicity) and class 2 (solvents for limited use) solvents according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) classification.20

Three model drugs were selected: (1) acetaminophen, an analgesic and fever reducer; (2) tetracycline HCl, an antibiotic; (3) (R,S)-(+) -ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID). The molecular structures of the APIs are depicted in Figure 1. All of the experiments used mixtures of two or more brands at once. All the drug products we used had clear labels. If not, the recovery yield will be impossible to determine.

Overview of the API Recovery Process. The API recovery process comprised three core unit operations: solid–liquid extraction, filtration, and crystallization, with comminution and rinsing as additional unit operations that could be employed if necessary, depending on the nature of the drug waste. The schematic diagram of the API recovery from solid dosage forms is shown in Figure 2.

In the first unit operation, the drug tablets or capsules were charged into a solvent capable of dissolving the APIs but not for most of the excipients. To find out the best solvent, initial solvent screening has to be performed first, as has been explained in the previous section. The ideal solvent used for the solid–liquid extraction should act as a “good solvent” for the API and as a “bad solvent” for as many excipients as possible.

Once the solid–liquid extraction is finished, the next step is to separate the solution phase from the undissolved excipients. Both filtration and centrifugation are capable of separating the suspended particles from the mother liquor, but filtration is more scalable than centrifugation. For filtration, successive filtration from larger to lower filter pore sizes may be necessary to minimize early clogging.

The last important step is crystallization by antisolvent addition, that is, addition of another solvent in which the API substance has a poor solubility. This second solvent can be selected among the “bad solvents” from the initial solvent screening. It is introduced slowly into the extract solution. Upon the addition of the antisolvent, the API crystals will precipitate until the antisolvent has reached a certain volume in which no more crystals will precipitate out. It should be noted that the extract solution may contain some amounts of dissolved excipients, especially when the solvent used for extraction was also a “good solvent” for the excipients. Nevertheless, in almost all of the cases, the proportion of the API in a tablet or capsule is far greater than the amount of any individual excipient, and the volume of the solvent used in the solid–liquid extraction step is near the saturation of the API but at the undersaturation of any individual excipient. Therefore, antisolvent addition will only precipitate the API but not the excipients. As illustrated in Figure 3, upon the addition of the antisolvent, the API reached the saturation point (point 1 $\rightarrow$ 2), and continual antisolvent addition led to the precipitation of API crystals (point 2 $\rightarrow$ 3). On the other hand, the excipient started in an unsaturated concentration; as more antisolvent was added, the excipient concentration would become more dilute and never reach the saturation point (point 1’ $\rightarrow$ 2’).

In addition to these three core unit operations, other unit operations may also be added if necessary. For example, comminution may be performed prior to the solid–liquid extraction, either by grinding or cutting. This step may be omitted in the case of tablets because in the solid–liquid extraction process, the tablets are readily disintegrated, but for capsules, it may be important to dislodge the drug granules from the capsule matrix and expose them to the extractant. Rinsing the API crystals with cold water right after the antisolvent crystallization step is capable of removing the residual solvents and some common water-soluble excipients. Rinsing should be

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**Figure 1.** Molecular structure of the APIs recovered in this study: (a) acetaminophen, (b) tetracycline HCl, and (c) (R,S)-(++)-ibuprofen.

**Figure 2.** Flowchart of the API recovery process from solid dosage forms drugs (gray: core unit operations, red: optional unit operations).
done with caution as it may lead to the lowering of recovery yield or, worse, the decomposition of the API.

■ RESULTS AND DISCUSSION

Initial Solvent Screening. To map the suitable solvent(s) for performing the API recovery, all the solubility values of the APIs and excipients were examined under the 23 selected common solvents at 25°C and 1 atm. The sheer number of excipients and the variations in the contents and compositions among manufacturers made the solubility measurements of excipients immensely tedious. Therefore, only some of the common excipients were chosen as the representatives: α-lactose monohydrate, α-cellulose, and starch were diluents/fillers;21–25 α-cellulose and starch were disintegrants;21–23,25 stearch and magnesium stearate were tablet lubricants;27 starch and hydroxypropyl cellulose were powder binders;25,27 hydroxypropyl cellulose was a coating material;27 ascorbic acid, butylated hydroxyanisole, and citric acid were antioxidants;21,28,29 and anhydrous citric acid was an acidifying agent.21

Following the criteria of Lee et al.,30 a solvent was regarded as a “good solvent” of a material if it is capable to dissolve the material with the minimum solubility value of 5 mg/mL; otherwise, it was regarded as a “bad solvent”. The results for the APIs and the selected excipients were summarized in the form space (Table 1) and the detailed values are listed in Table S1. It should be noted that the initial measurement was made by sight and the values were inexact.30

The selected solvent for the solid—liquid extraction should be a “good solvent”, represented by a blue grid, for the API but a “bad solvent”, represented by a red grid, for as many excipients as possible. The selected antisolvent for the API crystallization should be “bad” represented by a red grid for the API. Other important consideration was the safety of the solvent, which could be determined based on its classification according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for residual solvents.20 Ideally, all of the solvents and antisolvents used should be class 3 solvents (i.e., solvents with no hazard for human consumption at levels normally accepted) or, if it was not possible, class 2 solvents (i.e., solvents to be limited in pharmaceutical products because of their inherent toxicity) could be considered. Class 1 solvents should be avoided at all costs.

Table 1. Form Space of Acetaminophen, Tetracycline HCl, (R,S)-(−)-Ibuprofen, and the Representative Excipients, Showing the Solubility of Each Compound in 23 Common Solventsa

| SOLVENT | API | EXCIPENTS |
|---------|-----|-----------|
|         | Acetaminophen | Tetracycline HCl | (R,S)-(−)-Ibuprofen | α-lactose monohydrate | α-cellulose | Starch | Hydroxypropyl cellulose | Ascorbic acid | Butylated hydroxyanisole | Citric acid | Magnesium stearate |
| Class 1 | Benzene | Xylene | Toluene | Chloroform | Tetrachloroethane | 1,4-Dioxane | Acetonitrile | N,N-dimethylformamide | Methanol | Blue: good solvent (solubility ≥ 5 mg/mL at 25°C) | |
| Class 2 | n-Heptane | Ethyl acetate | Methyl tert-butyl ether | Methyl ethyl ketone | Acetone | n-Butyl alcohol | Isopropyl alcohol | Ethanol | Dimethyl sulfoxide | n-xylene | Red: bad solvent (solubility < 5 mg/mL at 25°C) | |
| Class 3 | Other | 2-Methoxyethanol | N,N-dimethylformamide | Nitrobenzene | Benzyl alcohol | Water |

Solvent Classification According to ICH Guideline for Residual Solvents (Q2C)

Class 1: Solvents to be avoided, known human carcinogens, strongly suspected human carcinogens, and environmental hazards
Class 2: Solvents to be limited, non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity, suspected of other significant but reversible toxicities
Class 3: Solvents with low toxic potential to man; no health-based exposure limit is needed
Other: Solvents that did not fall into any classifications in ICH Guideline for Residual Solvents (Q2C)

*aBlue denotes a good solvent having a solubility value of ≥5 mg/mL at 25 °C, while red denotes a bad solvent with a solubility value of <5 mg/mL at 25 °C. The exact solubility values are summarized in Table S1.
For acetaminophen, there were 15 good solvents and eight bad solvents. Being the safest solvent, water was considered to be an excellent candidate as a good solvent, but it is also known to dissolve some polymeric binders commonly used in tablets, such as hydroxypropyl cellulose, as can be seen in Table 1. IPA was eventually chosen as the good solvent despite its ability to dissolve some excipients (i.e., butylated hydroxyanisole and citric acid anhydrous). These excipients were antioxidants, which only existed in trace amounts, and could be removed during the crystallization step, as illustrated in Figure 3. The selected antisolvent for crystallization was n-heptane. From the solubility curve in Figure S1, the inflection was hardly distinguished. A concentration of 80% (v/v) n-heptane in IPA was decided to be the best ratio for inducing acetaminophen crystallization on one hand, without taking up too much vessel volume by the antisolvent on the other.

There are five “good solvents” for tetracycline HCl: DMF, methanol, DMSO, benzyl alcohol, and water. Water was omitted because it could dissolve capsule shells and create problems in filtration and crystallization. DMF, DMSO, and benzyl alcohol all have a high boiling point and low volatility, making them difficult to remove by drying. Therefore, methanol was the only viable choice, and despite being a class 2 solvent, it is easy to remove by drying. For the antisolvent for crystallization, seven relatively safe “bad solvents” were considered: ethyl acetate, MTBE, acetone, MEK, IPA, acetonitrile, and THF. From preliminary tests, none of these antisolvents could precipitate tetracycline HCl from its methanolic solution in a reasonable proportion except for MTBE. Although the solubility of tetracycline HCl in the methanol–MTBE cosolvent with a volume ratio of 40:60 was already low (Figure S2), the amount of tetracycline HCl precipitated was quite less. The methanol-to-MTBE volume ratio which gave the highest crystallization yield was 17:83 (Figure S2). Because of the lack of choices, this solvent–antisolvent combination of 17:83 was used.

All of the solvents acted as good solvents for (R,S)-(±)-ibuprofen, except water. Among all of the class 3 solvents, n-heptane, ethyl acetate, and MTBE seemed to be good choices, as they dissolved less amounts of excipients. However, they could not be used because of their immiscibility with the only antisolvent for (R,S)-(±)-ibuprofen, water. Acetone was eventually selected because it was a common class 3 solvent, miscible with water, and easy to remove by drying. The optimal acetone-to-water volume ratio giving a high crystallization yield was about 45:55 (Figure S3).

In general, the use of water as an extractant may lead to some problems. Most of the polymeric excipients, such as binders and capsule shells, dissolve and/or get swollen in water. This type of behavior will make the extract impure and viscous. Solution thickening is problematic for liquid–solid separation. Even though some polymeric excipients can be precipitated out by raising the temperature of the aqueous solution above their cloud points (e.g. hydroxypropyl cellulose has a cloud point of 45 °C), in the case of a batch operation consisting of a mixture of drug products with many unknown excipients, the cloud points are difficult to be determined. Furthermore, some polymeric excipients, such as methylcellulose and hydroxypropyl methylcellulose, undergo gelation upon heating. More importantly, heating can sometimes decompose heat-sensitive APIs, such as tetracycline. Ultrafiltration was reported to remove the dissolved known polymeric excipient in water, but in our case, the overall process would have been much simpler if the problems associated with the dissolution of many types of unknown polymeric excipients in water can be avoided from the beginning. Consequently, the use of an organic solvent at ambient temperature is preferred in our case when the excipient contents and compositions are unknown. Detailed information including the yield and purity with the use of water for the API solid–liquid extraction and crystallization is enclosed in the Supporting Information.

Only eight excipients are evaluated in Table 1, even though the number of excipients is many more in reality. These eight excipients have adequately represented the other commonly used excipients. In general, there are two types of excipients in our processes: (1) insoluble in the extractant and (2) soluble in the extractant. The extractant-insoluble excipients are separated as solids during filtration, whereas the extractant-soluble ones are removed upon the crystallization of the API because of the relatively low concentrations of excipients as opposed to the high concentration of the API, as outlined in the concept in Figure 3. Additionally, traces of impurities which may be present on the API crystal surfaces (e.g., colorants) can be adequately removed by rinsing (see Figure 2). These excipient removal measures should be sufficient enough to produce the recycled API with a high purity.

Recovery of Acetaminophen from Unused Tablets. Acetaminophen was recovered from tablets from three different brands containing 19 different excipients. The recovery process was quite straightforward, with the operating conditions outlined in Table 2 and the photoimages given in Figure 4. First, the tablets were charged into a vessel, followed by the introduction of IPA. Under stirring at 300 rpm, the tablets slowly disintegrated. After that, filtration must be performed in a successive manner: coarse undissolved matter was removed using a 25 µm wire mesh; finer undissolved matter was filtered with a 2 and 1 µm cellulose filter paper, and lastly, ultrafine matter which could be seen floating in the solution was removed using a 0.22 µm PTFE filter membrane. Afterward, n-heptane was added to the filtrate to crystallize out the dissolved acetaminophen. Although water was a “good solvent” at 25 °C, water rinsing had to be done on the recovered acetaminophen crystals to remove impurities from the crystal surface, especially tartrazine that gave some tablets a faint yellow color. To minimize the loss of acetaminophen crystals due to dissolution, cold water at 5 °C was used under 300 rpm for 1 h. The final amount of acetaminophen crystals recovered was 58.7 wt %, using the labeled amount of acetaminophen in the tablets as the basis. The high-performance liquid chromatography (HPLC) assay was 99.1%, which fell within the US Pharmacopeia standard of 98.0–102.0%. The representative HPLC chromatograms are given in Figure S4. Moreover, the recovered acetaminophen was in pure form I, which was the commercial polymorph as determined by powder X-ray diffraction (PXRD), as shown in Figure 5.

Recovery of Tetracycline HCl from Unused Capsules. The capsules used in tetracycline HCl recovery did not provide any information about the excipient content. The vessels used for the recovery process had to be wrapped with an aluminum foil to keep the whole apparatus in the dark because of the light-sensitive nature of tetracycline HCl. The capsules had to be opened first to expose the granules to methanol during solid–liquid extraction. The extract solution was not too viscous and did not contain much undissolved matter. One-time filtration using a 0.22 µm PVDF filter membrane was sufficient to separate the undissolved matter from the extract. After that, tetracycline HCl could be precipitated out from the extract solution by the
addition of the MTBE antisolvent. Based on our small scale preliminary studies, aging the tetracycline HCl solids after antisolvent crystallization in the methanol:MTBE system was necessary to improve the crystallinity of the final crystals. As illustrated in Figure 6, short 30 min aging produced intense yellow powders, while 1 h of aging or more produced faint-yellow powders. The PXRD patterns in Figure 7 revealed that the intense-yellow powders were actually amorphous, while the faint-yellow powders were crystalline, meaning that a minimum of 1 h of aging was necessary to generate crystalline tetracycline HCl. For making sure that crystalline tetracycline HCl was formed, 2 h of aging was implemented instead. Vigorous agitation of 900 rpm during the antisolvent addition and subsequent aging was necessary to ensure the production of crystalline tetracycline HCl with a faint-yellow color (Figure 8), as evidenced by the PXRD pattern in Figure 10. However, a slower agitation rate would produce intense-yellow amorphous powders (Figures 8 and 10). Normally, the system would be cooled down after antisolvent addition to increase the yield, but this would not work in our case. When the temperature was cooled from 25 to 5 °C, amorphous solids with an intense-yellow color were produced (Figure 8). If the temperature was maintained at 25 °C, faint-yellow crystalline powders could be harvested instead.

This shift from the amorphous to crystalline phase was always accompanied with the color change from intense to faint yellow. It was speculated that the molecular alteration of tetracycline HCl had played an important role. Because the tertiary ammonium group (R_3NH^+) on the tetracycline molecule has a pK_a value of 9.7[35] and methanol (MeOH) has a pK_a value of 15.5,[36] the H^+ and Cl^- ions originally associated with the tetracycline molecule would now interact more with the MeOH molecules when tetracycline HCl was dissolved in methanol. The sudden addition of the MTBE antisolvent with a pK_a value of -2.0[37] would further dissociate the H^+ and Cl^- ions from the tertiary ammonium group (R_3NH^+), turn it into a tertiary amine group (R_3N), and crash out the tetracycline as amorphous free base solids. Upon vigorous mixing and aging, MTBE would start to associate with MeOH and liberate H^+ and Cl^- ions, which would associate themselves with the tetracycline free base again to form tetracycline HCl through salt formation in the slurry by mass transfer and long enough time. The fast agitation (Figure 8) enhanced the mass transfer rate, thereby shortening the aging time. Aging at 5 °C did not induce the base–acid conversion at all because of the slow kinetic rate, as compared with the one at 25 °C (Figure 8).

The proposed mechanism was verified by several solid-state characterizations conducted on the amorphous and crystalline powders. The IR spectra in Figure 9 revealed that there were differences in the 3700–3100 cm^-1 region, indicating the change in the stretching of the amine functional groups between the amorphous and crystalline sample. Unlike the crystalline sample, the amorphous free base sample showed no absorbance in the region of 2800–2300 cm^-1, indicating that the stretching vibration of the tertiary ammonium salt[39,40] was absent on the tetracycline molecule (Figure 1b).

From all of these observations, the best operating conditions for recovering tetracycline HCl are outlined in Table 2. Using those operating conditions, about 73.1 wt % of crystalline tetracycline HCl was recovered based on the labeled tetracycline HCl content in the capsule, with the HPLC assay of 99.2% (Figure S5).

### Table 2. Operating Parameters of the Recovery of Acetaminophen, Tetracycline HCl, and (R,S)-(+)-Ibuprofen from Unused Drug Products

| Parameter | Unit | Value |
|-----------|------|-------|
| API no. of tablets or capsules recycled | | |
| Solid−liquid extraction | | |
| Filter | | |
| agitation | rpm | 300 |
| time | h | 1 |
| Antisolvent addition | | |
| temperature | °C | 285 |
| speed | rpm | 300 |
| time | h | 1 |
| Filtration | | |
| agitation | rpm | 300 |
| time | h | 1 |
| Antisolvent addition | | |
| temperature | °C | 285 |
| speed | rpm | 300 |
| time | h | 1 |
| Crystallization | | |
| Antisolvent addition | | |
| temperature | °C | 285 |
| speed | rpm | 300 |
| time | h | 1 |
| Antisolvent addition | | |
| temperature | °C | 285 |
| speed | rpm | 300 |
| time | h | 1 |
Recovery of (R,S)-(±)-Ibuprofen from Unused Tablets.

Recovery of (R,S)-(±)-ibuprofen was conducted in tablets from four different brands, containing 28 different excipients in total, with the photoimages given in Figure 11. Comminution was not required for (R,S)-(±)-ibuprofen tablets, as the tablets were easily disintegrated during solid–liquid extraction under 300 rpm. The process was straightforward without any major difficulties. Successive filtration was required to remove the undissolved matter from the extract solution, minimizing clogging problems. Some of the tablets had erythrosine E127 and tartrazine as the colorants. Rinsing with cold water for the removal of colorants was essential. Discoloration of the final (R,S)-(±)-ibuprofen crystals was not observed. About 67.6 wt % yield was recovered based on the labeled (R,S)-(±)-ibuprofen content in the tablets. The crystal form obtained was form I (R,S)-(±)-ibuprofen crystals was not observed. About 67.6 wt % yield was recovered based on the labeled (R,S)-(±)-ibuprofen content in the tablets. The crystal form obtained was form I (R,S)-(±)-ibuprofen, as indicated in Figure 12, which is the common form of (R,S)-(±)-ibuprofen crystals. The recovered (R,S)-(±)-ibuprofen has an HPLC assay of 99.7% (Figure S6), well within the US Pharmacopeia standard of 97.0−103.0%. The chiral resolution of (R,S)-(±)-ibuprofen by diastereomeric salt formation through common resolving agents such as α-methylbenzylamine (MBA) and (S)-lysine or cocristallization through a coformer such as levetiracetam is a well-known technique. Chiral resolving agents are known to be recyclable. Applying these methods to the API recovered from tablets should be straightforward. Although (R)-(−)-ibuprofen is therapeutically less-active than (S)-(+) ibuprofen, it is nontoxic. Therefore, any ee % above 0% is acceptable.

■ CONCLUSIONS

The concept of drug recycle by recovering APIs from unused drug products has been successfully studied. Acetaminophen was recovered from tablets obtained from three different brands containing 28 different excipients, with recovery yield of 58.7 wt % based on the labeled amount, HPLC assay of 99.1%, and in the stable form I crystals. Tetracycline HCl was successfully recovered from capsules from two different brands with unknown excipient contents, with a recovered amount of 73.1 wt % based on the labeled amount, HPLC assay of 99.2%, and in

Figure 4. Photoimages of the acetaminophen recovery process.

Figure 5. PXRD patterns of acetaminophen form I: (a) recovered from tablets and (b) reference obtained from Cambridge Crystallographic Data Centre (CCDC) (CCDC refcode: HXACAN01).

Figure 6. Colors of tetracycline HCl powders aged for different times: (a) 0.5, (b) 1, (c) 1.5, and (d) 2 h.

Figure 7. PXRD patterns of tetracycline HCl: (a) purchased and recrystallized in the methanol−MTBE system with mixing for different aging times: (b) 0.5, (c) 1, (d) 1.5, and (e) 2 h.
the crystal form in conformity with the tetracycline HCl standard. (R,S)-(±)-ibuprofen could also be recovered from the unused tablets from four different brands containing a total of 28 different excipients with the recovery yield of 67.6 wt % based on the labeled amount, HPLC assay of 99.7%, and in the stable Form I crystals. In the near future, recovery of APIs from unused drugs is a sustainable act, which could help in saving our environment because APIs such as acetaminophen, tetracycline HCl, and (R,S)-(±)-ibuprofen are known to pollute water bodies.3–8 Moreover, recovering APIs domestically from unused drugs would reduce our reliance on drug importation from other nations. This could be vital, especially during wartimes. Drug price may also be relieved because of the possibility of skipping the many costly synthetic steps.

Figure 8. Photoimages of tetracycline HCl recovered under different conditions for 2 h aging.

Figure 9. Solid-state FTIR spectra of tetracycline HCl powder recrystallized in the methanol–MTBE system with different aging times: (a) 0.5 and (b) 2 h. The gray region indicates the region of change in spectra between (a,b).

Figure 10. PXRD patterns of tetracycline HCl: (a) purchased and recovered from mixed capsules in a 500 mL reactor tank aged for 2 h at 25 °C under different agitation rates: (b) 650 and (c) 900 rpm.
Three different acetaminophen tablet brands were used, with the given API content per tablet listed as follows: Panadol film-coated caplets (500 mg/tablet) were produced by GlaxoSmithKline Dungarvan Ltd. (Waterford, Ireland); Acetaminophen “C.A.” tablets (500 mg/tablet) were produced by Chanan Chemical Industry Co. Ltd. (Changhua, Taiwan R.O.C.); Fucole Paran tablets (500 mg/tablet) were produced by Yung Shin Pharmaceutical Industrial Co. Ltd. (Taichung, Taiwan R.O.C.).

Two different tetracycline HCl capsule brands were used, with the given API content per tablet listed as follows: NOVA-BIOTIC tetracycline capsules (500 mg/capsule) were produced by PT. Novapharmin Pharmaceutical Industries (Gresik, Indonesia); KINGDOM tetracycline hydrochloride capsules (250 mg/capsule) were produced by Synpac-Kingdom Pharmaceutical Co. Ltd. (Taipei, Taiwan R.O.C.).

Four different racemic (R,S)-(±)-ibuprofen tablet brands were used, with the given API content per tablet listed as follows: Perofen 400 tablets (400 mg/tablet) were produced by Remedica Ltd. (Limassol, Cyprus); Setonlin tablets (600 mg/tablet) were produced by Yuanchou Chemical & Pharmaceutical Co. Ltd. (Nantou, Taiwan R.O.C.); Ibunon Extra F.C. tablets “Daiyu” (400 mg/tablet) were produced by Weidar Chemical & Pharmaceutical Co. Ltd. (Taichung, Taiwan R.O.C.); Ibucon Extra F.C. tablets (600 mg/tablet) were produced by Chinn Teng International Pharmaceutical Manufacture Corp. (Taichung, Taiwan R.O.C.).

**Solvents.** A total of 23 solvents were used in this study: n-heptane (99.0% purity), toluene (100.0% purity), chloroform (99.99% purity), tetrahydrofuran (THF) (99.0% purity), ethanol (99.5% purity), and dimethyl sulfoxide (DMSO) (99.8% purity) were purchased from Echo Chemical Co. Ltd. (Taiwan R.O.C.). Xylene (98.5% purity) and 1,4-dioxane (98.0% purity) were purchased from Avantor Performance Materials Co. Ltd. (PA, USA). p-Xylene (99.0% purity), ethyl acetate (99.5% purity), methyl tert-butyl ether (MTBE) (99.9% purity), benzene (99.0% purity), methyl ethyl ketone (MEK) (99.6% purity), acetone (99.5% purity), n-butyl alcohol (99.4% purity), isopropyl alcohol (IPA) (99.8% purity), benzyl alcohol (99.8% purity), acetonitrile (99.96% purity), dimethylformamide (DMF) (99.8% purity), and methanol (99.9% purity) were purchased from TEDIA (USA). N,N-dimethylaniline (DMA) (99.0% purity) and nitrobenzene (99.0% purity) were purchased from Acros Organics (NJ, USA). Water was clarified by reverse osmosis (RO) through a water purification system (model Milli-RO Plus) bought from Millipore (Billerca, MA, USA).

**Initial Solvent Screening and Form Space of the APIs and Eight Representative Excipients.** Following the initial solvent screening method by Lee et al., the gravimetric titration method was applied by carefully titrating 10 mg of sample powders against one of the 23 common solvents. The total volume of the solvent needed to dissolve the powders was recorded through naked eyes. If the tested sample powders were dissolved in the organic solvent, giving a solubility value of 5 mg/mL or more, the solvent would be regarded as a “good solvent” for that sample material or else a “bad solvent” for that particular sample material. The results are summarized and depicted in a form space in Table 1.

**Recovery of Acetaminophen, Tetracycline HCl, and (R,S)-(±)-Ibuprofen from Unused Drug Products.** All of the recovery processes by the three core unit operations with the details of the operating parameters are listed in Table 2. Comminution was not required for acetaminophen and (R,S)-(±)-ibuprofen cases, as the tablets were readily disintegrated upon contact with the solvent during the solid–liquid extraction step. However, for tetracycline HCl, comminution in the form of capsule opening was necessary to dislodge the drug granules from the capsule matrix. Water rinsing was performed on the recovered acetaminophen and (R,S)-(±)-ibuprofen crystals as an additional step for the removal of impurities, especially for the colorants, but the same protocol could not be implemented on the recovered tetracycline HCl crystals because of their high water-soluble nature.

**Instruments.** High-Performance Liquid Chromatography. HPLC measurement was performed using a Shimadzu Prominence-i LC-2030C 3D Plus equipped with a photodiode array detector for determining the assay of the recovered APIs by peak area percent calculation against the purchased standard API, as given by eq 1

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\text{assay by area percent (\%)} = \frac{A_{\text{SP}} \times W_{\text{STD}}}{A_{\text{STD}} \times W_{\text{SP}}} \times 100
\]
where $A_{SP}$ = the average peak area of the substance in the test solution, $A_{STD}$ = the average peak area of the substance in the standard solution, $W_{SP}$ = the weight of the substance to be examined (mg), and $W_{STD}$ = the weight of the standard substance (mg).

HPLC analysis of acetaminophen followed the procedure of Merck-Millipore in acetaminophen, aspirin, and caffeine (USP)—Excedrin tablet dissolution,46 using a Shimadzu Shim-pack GIST C18 5 μm, 100 × 4.6 mm HPLC column. The mobile phase was water:methanol:glacial acetic acid with a volume ratio of 69:28:3. The sample solution was prepared in 0.1 mg/mL concentration using methanol:glacial acetic acid with a volume ratio of 95:5 as the solvent. A 10 μL sample was injected into the column with the mobile phase pumped in an isocratic flow at 2.0 mL/min with the column temperature at 45 °C. The sample was detected by its UV absorbance at 275 nm.

HPLC analysis of tetracycline HCl was performed by following the United States Pharmacopeia—National Formulary (USP35-NF30).47 The column used was the Phenomenex Luna C8 5 μm, 4.6 mm × 250 mm column. The mobile phase was 0.1 M ammonium oxalate:DMF:0.2 M dibasic ammonium phosphate with a volume ratio of 68:27:5 at pH 7.6–7.7, adjusted by 3 N ammonium hydroxide or 3 N phosphoric acid. The concentration of the sample solution was 0.5 mg/mL in 0.1 M ammonium oxalate:DMF with a volume ratio of 68:27 as the solvent. The sample injection volume was 20 μL, with the mobile phase pumped in an isocratic flow at 2.0 mL/min, with the column temperature set at 30 °C. The sample was detected by its UV absorbance at 280 nm.

HPLC analysis of (R,S)-(±)-ibuprofen followed the USP35-NF30 procedure41 with modifications. The column used was the Shimadzu Shim-pack GIST C18 5 μm, 100 × 4.6 mm HPLC column. The mobile phase was prepared by dissolving 4 g of chloroacetic acid in 400 mL of DI water, and then, 600 mL of acetonitrile was added to the acidic aqueous solution to make up acetonitrile:DI water with a volume ratio of 600:400 at pH 3. The sample solution was prepared in 12 mg/mL concentration with 0.35 mg/mL valerophenone as the internal standard, using the mobile phase solution as the solvent. A 5 μL of sample was injected into the column with the mobile phase pumped in an isocratic flow at 1.0 mL/min with the column temperature kept at 30 °C. The sample was detected by its UV absorbance at 254 nm at 30 °C.

**Powder X-ray Diffraction.** The PXRD pattern was collected using a Bruker AXS D8 ADVANCE PXRD (Karlsruhe, Germany). X-ray radiation Cu Kα1 ($λ = 1.5405$ Å) was set at 40 kV and 25 mA passing through a nickel filter. Samples were subjected to PXRD analysis with a sampling width of 0.01° in a continuous mode with the scanning rate of 2°/min over an angular range 2θ of 5° to up to 50°.

**Fourier-Transform Infrared Spectroscopy.** The Fourier-transform infrared (FTIR) spectrometer used was the PerkinElmer Spectrum One (Norwalk, CT, USA). About 1 mg of sample powders was gently ground with dry potassium bromide (KBr) powders with a weight ratio of about 1–100 in an agate mortar. A manual press was used to compress the powders into a pellet. The pellet was scanned in the region of 4000–400 cm⁻¹ with a resolution of 2 cm⁻¹.

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**ASSOCIATED CONTENT**

*Supporting Information*

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