Recovery of Active Pharmaceutical Ingredients from Expired Medicines and Thermodynamic Modeling

Hamedan University of Technology

Dec 2022

Fatemeh Zarei, Jaber Yousefi Seyf

Department of Chemical Engineering, Hamedan University of Technology, Hamedan,65155, Iran.

(jaber.yousofi@yahoo.com)

National Research & Technology week

Abstract

Pharmaceuticals are formulated as a combination of active pharmaceutical ingredients and excipients (to obtain optimal properties such as flowability, viscosity and absorption) and are marketed in different dosage forms. This study aims to recover the active pharmaceutical ingredient from the finished product (FPPs) with acceptable purity. Eight pharmaceuticals including Acetaminophen, Ibuprofen, Carbamazepine, Lamotrigine, Phenobarbital, Phenytoin and Primidone were chosen for the process. In addition, the primary solvent of the leaching and anti-solvent of the crystallization steps are selected from 62 approved solvents by FDA in the pharmaceutical industry. Analyses such as TLC, melting point and UV were performed to ensure the relative purity. Finally, the purity of the recovered APIs were checked by FTIR and HPLC techniques.

Keywords : Recovery, Purity, Active Pharmaceutical Ingredients, Solid-Liquid equilibrium, Crystallization, Thermodynamic models

Introduction

One of the probably forgotten waste is unused or expired pharmaceuticals. They often end up being disposed of as household trash. Pharmaceutical pollution has already occurred in the surface, ground and drinking water among which some of these problems may be attributed to improper disposal practices. Several papers describe effects of API on environmental. Excessive use of diclofenac was forwarded as the cause in the decline of a vulture population in Pakistan. It has been reported that many pharmaceuticals still retain their potency years after their expiration dates. In addition, the production of API requires an investment of both time and financial resources, often costing several thousand dollars per kilogram of API. The objective of this study is to provide a separation process to recover APIs from FPPs.

Materials and method

Separation process composed from three main steps including solid-liquid extraction, filtration and crystallization (Fig.1). First, screening of the solvent and anti-solvent was carried out by the NRTL-SAC or UNIFAC-DMD models. Other important consideration is the safety of the solvent and anti-solvent. Then, undissolved solids were separated by filtration. Finally, the crystallization step was done to APIs precipitation. Operational conditions of each FPPs are shown in Table 1.

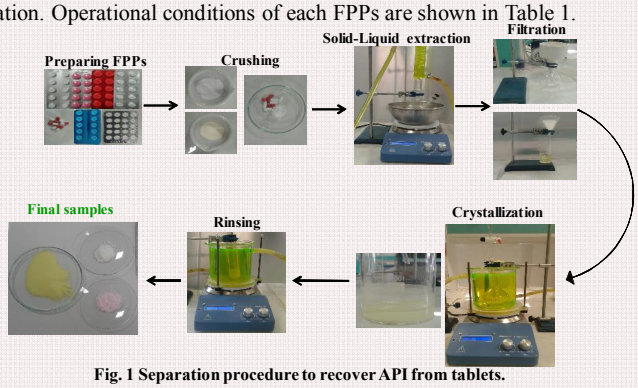

Fig. 1 Separation procedure to recover API from tablets.

Table 2. Operating conditions for recovery of pharmaceuticals

pharmaceuticals	Initial API value (gr)	Solid-liquid extraction (solvent)	Filtration	Crystallization method (anti-solvent)	Model used
Acetaminophen	1	30 ml aceton	cellulose filter paper	n-hexan as a anti-solvent	NRTL-SAC
Ibuprofen	0.8512	20 ml ethanol	cellulose filter paper	Cold water as a anti-solvent	NRTL-SAC
Lamotrigine	1	160 ml ethyl acetate	Buchner funnel and pump	Cooling and evaporation	NRTL-SAC
Phenobaebital	0.6	80 ml toluene	cellulose filter paper	Cooling and evaporation	NRTL-SAC
Phenytoin	0.5	40 ml ethanol in room temperatue	cellulose filter paper	Cold acetone as a anti-solvent	NRTL-SAC
Primidone	1	70 ml ethanol	Buchner funnel and pump	Cooling and evaporation	NRTL-SAC
Carbamazepine	1.2	50 ml methanol	cellulose filter paper	Cold water as a anti-solvent	NRTL-SAC

Results and Discussion

The efficiency of the process was calculated according to initial mg of API labeled on the tablets. More than 50% efficiency with 100% purity was obtained for most of the samples. It should be noted that the efficiencies listed in Table 2 are after recrystallization. The recovered APIs were characterization by melting point, UV, FT-IR and HPLC. As reported in Table 2, all samples except phenytoin and primidone passed all analyses and have a good match with standard samples or reliable references. Although the two samples of primidone and phenytoin have low purity, by changing the recovery method, which includes changing the solvent and the crystallization method, acceptable purity can be obtained.

Table 2. Efficiency of recovery process

pharmaceuticals	Total efficiency (%)	UV	Melting point	FT-IR	Purity (HPLC method)
Acetaminophen	55.2	✓	✓	✓	100
Ibuprofen	80	✓	✓	✓	>100
Lamotrigine	81.1	✓	✓	✓	100
Lamotrigine (large scale)	78.5	✓	✓	✓	100
Phenobaebital	47.3	✓	✓	✓	100
Phenytoin	54	×	×	✓	38
Primidone	75	×	×	✓	70
Carbamazepine	68	✓	✓	✓	>100

Conclusions

Through the combination of multiple unit operations, an efficient recipe was proposed, and successfully tested for recovery of APIs from unused or expired finished products. Acceptable API purity was obtained, which shows that this valuable component can be recovered for reformulation before disposing of expired or unused drugs. In addition, The results of this study can be used by pharmaceutical companies to recover the rejected finished products. It also reduces pharmaceuticals pollution caused by improper disposal of pharmaceuticals, which is very valuable and beneficial.

References

1. Can We Create a Circular Pharmaceutical Supply Chain (CPSC) to Reduce Medicines Waste? Abdullah Alshemari,Liz Breen, Gemma Quinn and Uthayasankar Sivarajah
2. WHO. 8 Treatment and Disposal Technologies for Health-Care Waste. 1999.
3. Bujak, J. Thermal treatment of medical waste in a rotary kiln. *J. Environ. Manag.* **2015**
4. Askarany, D.; Franklin-Smith, A.W. Cost benefit analyses of organic waste composting systems through the lens of time driven activity-based costing. *J. Appl. Manag.*
5. Lopez, G.; Artetxe, M.; Amutio, M.; Bilbao, J.; Olazar, M. Thermochemical routes for the valorisation of waste polyolefinic plastics to produce fuels and chemicals. A review. *Renew. Sustain. Energy Rev.* **2017**
6. Disposal practices for unwanted residential medications in the United States/Susan T. Glassmeyer/2008
7. Pharmaceutical Occurrence in Groundwater and Surface Waters in Forests Land-Applied with Municipal Wastewater /Andrew D. McEachran /2016
8. Occurrence and concentrations of pharmaceutical compounds in groundwater used for public drinking-water supply in California / Miranda S. Fram a,Kenneth Belitz b /2011
9. Herbert Lieberman, Leon Lachman, Joseph B. Schwartz - PHARMACEUTICAL DOSAGE FORMS Tablets Volumes 3(1989, Informa Healthcare) - libgen.lc
10. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, 10th edition, 2013
11. Cantrell, L.; Suchard, J. R.; Wu, A.; Gerona, R. R. Stability of of active ingredients in long-expired prescription medications. Arch. Intern. Med. 2012, 172, 1685−1687.
12. Lyon, R. C.; Taylor, J. S.; Porter, D. A.; Prasanna, H. R.; Hussain, A. S. Stability profiles of drug products extended beyond labeled expiration dates. J. Pharm. Sci. 2006, 95, 1549-1560.

Approval: Dr. Jaber Yousefi Seyf