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Active Pharmaceutical Ingredients from Unused Solid Drugs

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ABSTRACT

The increased use of pharmaceuticals globally over the past two decades has contributed to an increase in unused pharmaceuticals and a corresponding surge in pharmaceutical waste. Thus, there is an impetus for the development of processes for the recovery of the active pharmaceutical ingredients (APIs) from these unused drugs. This study introduces a decision framework for solvent selection to enable the recovery of APIs using a general separation train where cooling crystallization is the final step. The framework is designed to base solvent selection not just on the solubilities of the formulation contents but also considers the overall recovery that can be achieved in the process. In addition, the environmental sustainability of the framework is analyzed using the process mass intensity metric (PMI). The effectiveness of this framework is demonstrated by using paracetamol (PA) as a model API in a formulation consisting of five of the excipients commonly found in PA formulations. The results show that selecting a solvent based on the dissolution of pharmaceutical tablets may not be the best possible approach, whereas choosing a solvent that maximizes the theoretical recovery is preferred.

Keywords: API recovery, Solvent Selection, Sustainability, Process Design

INTRODUCTION

The rapid population growth and escalating use of medicines to treat human diseases have caused a concurrent rise in pharmaceutical waste, necessitating proper management strategies to address this challenge effectively. Unused pharmaceutical products are often disposed of as household trash or flushed down the toilet. Incineration and land disposal are the two common ways to get rid of unused drugs collected as trash, resulting in an inherent environmental impact [1]. Even though incineration (involving heating at temperatures over 1000°C) is effective, it is highly energy-intensive and releases harmful gases such as CO_2, SO_2, NO_x, etc. Drugs that are disposed of in landfills or flushed down the toilets eventually appear in the water system, causing harm to the flora and fauna, if not people. Another source of waste drugs is batches that fail final quality control during manufacturing, which are then incinerated. Expired drugs which are discarded at any point in the supply chain are another source of unused drugs.

Research has shown that many expired drugs retain a substantial portion of their potency[2] and thus, whether in landfill or wastewater, constitutes a hazard. One of the effective ways to treat the disposal of expired drugs is to have an infrastructure that facilitates their return at collection centers and recovery of the active pharmaceutical ingredient (API) from the unused drug formulation. The API is the most valuable component of a drug product; recovering it in its pure form enables its reformulation and conversion into new drug products. Among various drug administration methods, oral administration via tablets and capsules is the primary route for delivering APIs to patients [3]. When recycling APIs, it is crucial to ensure that the recovered APIs possess the desired critical quality attributes (CQAs), such as purity, drug shelf life, and bioavailability, while adhering to strict FDA regulations.

Crystallization is the process of converting a chemical from a liquid or solution into a solid crystalline state, where the atoms or molecules are arranged in a definite geometric pattern or lattice. Crystallization serves both

as a separation process and a particle control strategy to target specific CQAs such as yield, polymorph selection, and crystal size distribution (CSD). Over 90 % of active pharmaceutical ingredients (APIs) are synthesized as crystalline products. Proof-of-concept studies demonstrating API recovery have been carried out in the past [4]. However, these processes suffer from low overall recovery and lack sufficient solvent selection guidelines for the final separation stage via crystallization.

To address these gaps, this study aims to develop a solvent selection framework to enable a higher overall recovery of the API present in the unused formulation. The remainder of the paper is organized as follows: first, the solvent selection framework for optimal solvent selection is presented. Subsequently, the devised framework is applied in a case study consisting of a formulation of paracetamol with five of the common excipients, and preferred solvents are narrowed down from an existing ten solvents commonly used in cooling crystallization.

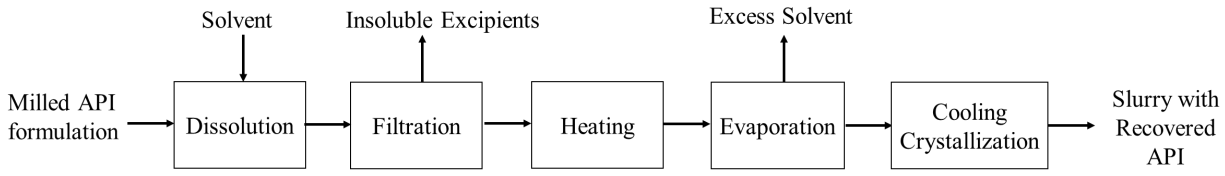

Figure 1: Generic separation train considered for the API recovery process.

Proposed Methodology

A general separation train for recovering API, as depicted in Figure 1, comprises a few general processing steps: (i) dissolution, (ii) filtration, (iii) heating, (iv) evaporation, and (v) crystallization. Initially, the tablets are milled, and the resulting powder is dissolved in the selected solvent at a specified temperature. After dissolution, the mixture is filtered, separating the insoluble excipients. A 5% solvent loss is considered to account for filtration losses. After filtration, the solution is heated to saturation to evaporate excess solvent, a critical step to facilitate nucleation when the temperature is subsequently lowered. Each step involves operating decisions that impact the performance of the given flowsheet. The entire process is conducted in a batch mode. In the process, the operating temperatures for each operation are important to ensure minimal energy consumption while ensuring a high yield in the batch crystallization.

The solvent selection framework is based on three important considerations. The first is selecting the solvent right at the dissolution stage, which was adopted in an earlier study [4], in a preliminary form, where a solvent was classified as a 'good solvent' if it dissolved the API in more than a specified quantity However, our approach seeks to maximize the relative difference between the API (m_{API}^{d}) and the excipients (m_{Ei}^{d}) dissolved at a given dissolution temperature T_D.

$$\begin{aligned} &\max_{\boldsymbol{x},\boldsymbol{y}} f \\ &s.t.\ g_i(\boldsymbol{x}) \le 0\ \forall\, i \in I, \\ &h_j(\boldsymbol{y}) \le 0\ \forall\, j \in I \\ &\boldsymbol{x_{lb}} \le \boldsymbol{x} \le \boldsymbol{x_{ub}} \\ &\boldsymbol{y} \in \{0,1\} \end{aligned} \tag{1}$$

Equation 1 shows that the mathematical formulation of the solvent selection framework can be posed as an optimization problem in which an objective function is maximized given a set of constraints and variable bounds. The objective function selected depends on the criteria for solvent selection. The second metric consists of selecting a solvent based on the overall recovery of the process, thus giving a more comprehensive picture. The third metric consists of selecting a more sustainable solvent, i.e., a minimal requirement for solvent for API recovery.

Solvent Selection Criteria

Table 1 shows the two different methods for solvent selection. In the dissolution-based approach, the solvent that dissolves the API selectively but not the excipients is considered a good solvent.

Table 1: Description of the dissolution and recovery-based solvent selection methodologies.

Description	Dissolution Based	Recovery Based
Objective Function	$S_j\left(m_{API}^{d} - \sum_{i=1}^{n} m_{Ei}^{d}\right)$	$S_j\left(\frac{100}{1-X_2}\left(1-\frac{X_2}{X_1}\right)\right)$
Decision Variable(s)	T_D, S_j	T_1, T_2
Constraint(s)	$\sum_{j=1}^{m} S_j = 1$	$X_{solids} \le 0.2$ $\sum_{j=1}^{m} S_j = 1$
Variable bounds	$T_{LB} \le T_D \le T_{UB}$ $S_j \in \{0,1\}$	$T_{LB} \le T_1 \le T_{UB}$ $T_{LB} \le T_2 \le T_{UB}$

This approach can provide the optimal solvent for the given objective and determine the optimal dissolution temperature that facilitates selective API dissolution.

Multiplying this relative difference with a binary variable (S_j) that indicates if a solvent is selected results in an MINLP formulation. On the other hand, the recovery-based approach focuses on increasing the yield obtained during the final stage, i.e., crystallization.

The objective, given in Table 1 for this approach consists of the percentage recovery under cooling crystallization [5] where X_1 and X_2 are the API's initial and final mass fractions before and after cooling at temperatures T_1 and T_2. It is important to note that while in cooling crystallization, as the solids begin to crystallize, there is an increasing possibility of fouling in the transfer line. Thus, a constraint to restrict the amount of solids crystallized is imposed. Finally, the bounds on the dissolution temperature are imposed. The initial and final temperatures vary from the maximal of the freezing point of a solvent and the lowest possible temperature that may be achieved by the heat exchanger and the smaller of the API degradation temperature and the boiling point of the solvent for the upper bound.

For the third metric of process sustainability, the process mass intensity (PMI) is used in this study. This metric was chosen over the E-factor metric as it is the ratio of the total mass in the process and the amount of API recovered, thus providing a fuller picture of the process's inputs and not just the waste. Equation 2 shows how PMI is calculated.

$$PMI = \frac{Total\ Mass\ [kg]}{API\ recovered\ [kg]} \quad (2)$$

FRAMEWORK APPLICATION

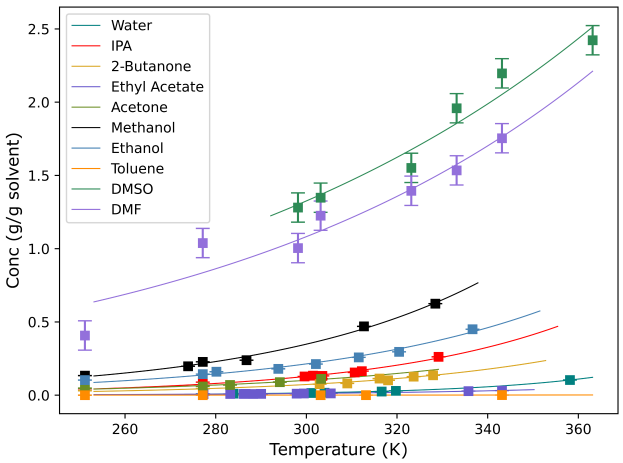

Figure 2: Solubility of API in all the chosen solvents.

The above-described solvent selection approach is applied to a formulation of paracetamol. The formulations for any specific API differ slightly from manufacturer to manufacturer; however, the set of excipients employed does not vary significantly. Hence, with this API, five common excipients are chosen to constitute a representative formulation. The details of this formulation can be seen in Table 2. The developed solvent selection framework applies to selecting solvents from an existing set. Hence, a list of ten common solvents for crystallization is proposed for selecting the appropriate solvents, as shown in Table 3, is proposed from which the most appropriate solvent will be selected. Most of the solvents belong to class 3, which are solvents of low toxicity, and two of them belong to class 2, which are solvents of limited use according to the guidelines of the International Council of Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) [6].

Table 2: Selected paracetamol formulation adapted from [7].

Label	Name	Quantity (mg/tablet)
API	Paracetamol	500.00
E1	Starch	44.00
E2	Microcrystalline Cellulose (MCC)	30.00
E3	PVP-K-30	18.00
E4	Magnesium Stearate	2.00
E5	Silica	2.00

Table 3: Common solvents used in crystallization studies.

Label	Solvent Name	Solvent Class
S1	Water	3
S2	Methanol	3
S3	Ethanol	3
S4	Toluene	2
S5	2-Propanol (IPA)	3
S6	Dimethylformamide (DMF)	2
S7	Acetone	3
S8	Ethyl acetate	3
S9	2-Butanone	3
S10	Dimethyl sulfoxide (DMSO)	3

Having selected the candidate solvents, the solubility of the API is determined experimentally using the Technobis Crystalline equipment apparatus [8], which measures the transmissivity of solutions during heating and cooling cycles. The clear point of a sample is defined as the temperature at which transmissivity reaches 100% during heating, indicating full transparency. In contrast, the cloud point is the temperature at which transmissivity drops to zero during cooling, indicating turbidity. For measurements, solutions of the API with known

Table 4: Summary of excipients solubilities in chosen solvents; Y: soluble, N: insoluble.

Solvent Names	MCC	MgSt	PVP-K-30	Silica	Starch
Water	N	N	Y	N	N
Methanol	N	N	Y	N	N
Ethanol	N	N	Y	N	N
Toluene	N	N	N	N	N
2-propanol	N	N	Y	N	N
N,N-Dimethylformamide	N	N	Y	N	N
Acetone	N	N	Y	N	N
Ethylacetate	N	N	N	Y	N
2-butanone	N	N	Y	Y	N
Dimethyl sulfoxide	N	N	Y	Y	N

concentrations were prepared in 5 ml vials for the selected solvents. The obtained experimental data is then fitted to a two-parameter modified Apelblat equation (Equation 3), where C is the concentration of API in g/g-solvent at temperature T, and the constants A and B are obtained.

$$\ln C = A + BT \tag{3}$$

The solubilities of the excipients were determined using the gravimetric method. The reason is that most excipients are sparingly soluble in the candidate solvents, making the transmissivity measurements difficult.

Replicate solutions in sets of three to minimize error containing excess excipient were prepared in 20 ml scintillation vials, which were stirred for 24 hours. The temperature was kept within ± 0.1°C of the desired temperature and was checked with a Pt-100 resistance thermometer. After equilibration, the excess excipient was allowed to settle for 24 hours without agitation. A sample of clear saturated solution (approximately 10 ml) was transferred into a previously weighed petri dish (m_d) after filtering with the filter of pore size 0.2 µm and weighed again (m_s). Subsequently, the filtered samples were left in the oven at 45°C for the solvent to evaporate for 3 days. The dishes were weighed each day to account for changes in mass. After the mass of dishes did not change by more than 5 mg, the mass of dry residue (m_r) was recorded. The solubility was calculated as shown in Equation 4.

$$C = \left(\frac{m_r - m_d}{m_s - m_r}\right)\frac{g\ solute}{g\ solvent} \tag{4}$$

The excipients were then simply classified as soluble or not in a specific solvent, as summarized in Table 4. Consequently, the solvent required to dissolve the API completely becomes crucial. Also, post-filtration, the solution is saturated with the active ingredient by evaporating the excess solvent. Since paracetamol is sparingly soluble in toluene, the most solvent is required if toluene is used. By contrast, DMF and DMSO are required in lesser quantities due to their high solubility of the API. The next step involved applying the solvent selection framework for a formulation of PA (Table 5) to execute the flowsheet described in Section 2. A basis of 1000 g (1 kg) of API was chosen for evaluating the associated process flowsheet. The optimal solvent for dissolution

Table 5: Summary of preferred solvents for each method and the process parameters required to achieve the desired recovery.

Metric	Preferred Solvents	Process Parameters				Recovery
		T_D (K)	T_1 (K)	T_2 (K)	Solvent Required (kg)	(%)
Recovery	Water	298.2	353.2	273.2	75.7	94.7
	2-Butanone	298.2	253.2	352.8	17.7	92.0
	Ethyl Acetate	298.2	350.3	253.2	105.0	90.5
Sustainability	DMF	353.2	353.2	253.2	0.6	30.7
	DMSO	353.2	353.2	292.2	0.6	30.9
	Methanol	337.9	337.9	253.2	1.3	47.0
Solubility	Ethyl Acetate	298.2	350.3	253.2	105.5	92.0
	Toluene	298.2	353.2	253.2	2942.2	83.3

depends on the solution of the solubility metric described in Table 1.

An enumeration-based approach was used to solve the problem formulated in Equation 1 for both dissolution and recovery-based methods. Thus, the objective functions for both approaches were evaluated for all the solvents at the respective temperature bound of the solvent.

Interestingly, for the chosen formulation, four out of the five excipients were insoluble in the solvents initially considered for screening. This meant that the relative difference in the amount of API and the excipient dissolved reduced to the difference in the quantity of PA and PVP-K-30 dissolved. Solvents ethyl acetate and toluene are preferable when selecting a solvent based on dissolution, as none of the excipients are soluble in them. All the remaining solvents are equally favorable as the difference in the API and excipients dissolved is constant.

For the recovery-based solvent selection, Figure 3 shows the maximum possible recoveries that can be obtained using the ten solvents. Water has the highest recovery, followed by 2-butanone and ethyl acetate. Due to the constraint on the solids fraction in the crystallization stage not being more than 20%, the actual recovery is lower than the predicted theoretical recovery, limiting the extent to which the feed can be cooled. Hence, the recoveries for solvents DMF and DMSO are significantly lower, even though PA is highly soluble in these solvents.

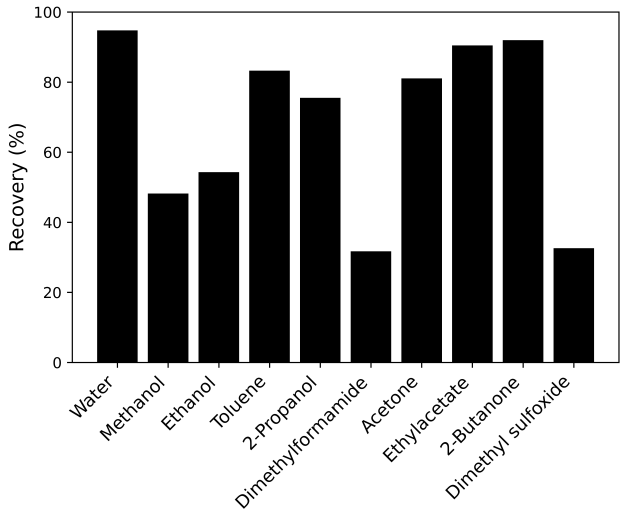

Figure 3: Recovery of PA from the chosen formulation for the chosen solvents.

Figure 4 summarizes the amount of solvent required to achieve the recoveries described in Figure 3 and the respective PMI. Solvents with high solubility of API naturally are required in lesser quantities and, therefore, have a low PMI. On the contrary, despite a relatively high theoretical recovery, the PMI is the highest in the case of toluene due to its tendency to dissolve a very small quantity of PA. Thus, there is a trade-off when it comes to selecting a solvent with a high recovery and a sustainable solvent. Targeting high recovery while maintaining a relatively low PMI was observed in the cases of water and 2-butanone. These solvents were notable because the mass fraction of crystallized solids did not exceed the 20% threshold, ensuring that the flowability constraint was not violated. This allows the maximal recovery to be the same without considering the flowability constraint.

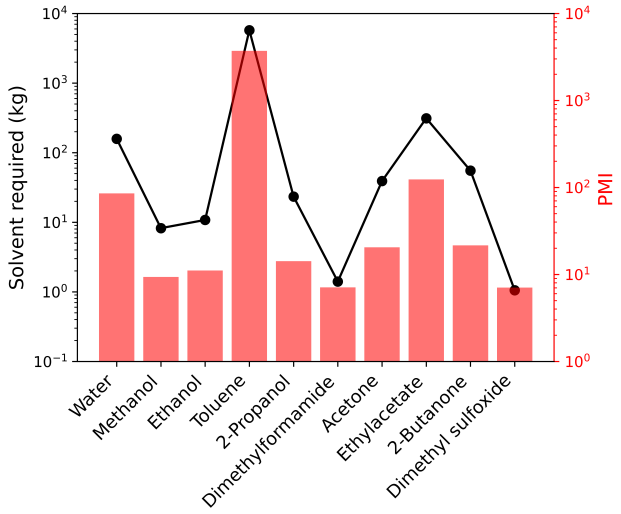

Figure 4: Amount of solvent required and the respective PMI for a basis of 1 kg of PA in the formulation.

The specific metrics of interest should guide the selection of solvents. Although 2-butanone and ethyl acetate exhibit a lower PMI than water, this is accompanied by a trade-off in recovery. Table 5 summarizes this solvent screening approach, which allows for the prioritization of specific metrics, facilitates informed decisions regarding solvent selection based on objectives, and enables subsequent process modeling. As can be seen, the values of the objective function of each metric (such as recovery and the amount of solids dissolved) change as the temperatures T_1, T_2, and T_d vary with changes in these temperatures (< 1°C). The sensitivity of this change is related to the solubility of the API and the excipients at those temperatures, which depend on the constants A and B obtained from experiments. However, with small changes in temperatures, the overall ranking of the solvents is not impacted significantly.

However, a formulation with excipients that show different behaviors, such as gel formation, will need more attention when applying this methodology. Either imposing different bounds on the process temperature or eliminating the solvents where these different behaviors are observed will be necessary. Overall, the developed solvent selection approach provides a systematic

framework for enabling API recovery with maximal recovery and ensuring the key process constraints are met.

CONCLUSION

In this study, a solvent selection framework was developed for a sustainable recovery of API. The framework was applied effectively in a case involving a paracetamol formulation, wherein solvents are selected according to each desired approach. It can be shown that this framework can be extended to different APIs that have variable solubility with temperature, thus enabling separation via cooling crystallization with a high recovery. Analyzing the solvents by ranking them provided valuable insights into the trade-offs of choosing a solvent with high recovery and a more sustainable solvent. This solvent selection framework constitutes an important step towards the development of a generalized framework for sustainable API recovery processes.

After obtaining the API from cooling crystallization by selecting the most appropriate solvent, further processing is necessary to recover the API. While this will depend on the API that is being recovered, a general trend involves washing and filtering the crystallized slurry and subsequently drying the mixture.

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