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# Statistical optimization for production of mefenamic acid–nicotinamide cocrystals using gas anti-solvent (GAS) process

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ABSTRACT

This study aims to produce mefenamic acid–nicotinamide (MEF–NIC) cocrystal using gas anti-solvent (GAS) process in order to improve dissolution rate of MEF. Box–Behnken design was used to investigate the effects of three operating parameters: operating temperature, coformer-to-drug molar ratio and % drug saturation in the starting solution in the ranges of 25–45 °C, 3–5 and 70–90%, respectively. The analysis of experimental design showed that coformer-to-drug molar ratio and %drug saturation are significant parameters affecting the dissolution rate of the cocrystals. At a temperature of 45 °C, a coformer-to-drug ratio of 5 and a %drug saturation of 70% were found to be the optimal conditions for achieving the fastest dissolution time. Additionally, the sieved MEF–NIC cocrystal obtained from the optimal GAS conditions showed an enhanced dissolution rate 38 times greater than that of pure MEF and 1.6 times greater than cocrystal from a traditional slow evaporation method.


## Introduction

It has been estimated that more than 40–60% of commercially available active pharmaceutical ingredients (APIs) are poorly water soluble drugs [1]. For these drugs, poor aqueous solubility and poor dissolution correlates with low bioavailability after oral administration [2–4]. Therefore, an improvement of physicochemical properties of poorly water soluble drugs has become essential in drug development. Various techniques have been developed to improve drug solubility, such as nanocrystallization, salt formation, solid dispersion, complexation, nano-suspension and self-emulsifying drug delivery systems [5,6].

Pharmaceutical cocrystallization is a potential method to improve physicochemical properties of a drug, such as solubility, dissolution rate and subsequent bioavailability of poorly water-soluble drugs, without changing the chemical composition of the drug. Pharmaceutical cocrystals are crystalline materials formed from an active pharmaceutical ingredient (API) and a coformer (i.e., crystal former) or another API in a definite stoichiometric ratio. The components in a cocrystal lattice are held together with non-covalent interactions such as hydrogen bonding and van der Waals attractive forces [7–11]. Cocrystals can be prepared by various methods––for example, solvent evaporation, grinding, solvent-drop grinding and melt crystallization [12,13]. The use of $CO_2$ is also a technique to form pharmaceutical cocrystals but less than twenty drug–coformer systems have been studied [14]. Some of them, such as sulfamethoxazole–L-malic acid cocrystals [15], naproxen–nicotinamide cocrystals [16], itraconazole–succinic acid cocrystals [17], itraconazole–L-malic acid cocrystals [18], indomethacin–saccharin cocrystals [19] and ketoconazole–4-aminobenzoic acid cocrystals [20], were prepared by the gas anti-solvent (GAS) process. For the preparation of cocrystals from the GAS process, the species are first dissolved in an organic solvent, and the addition of compressed $CO_2$ into a solution under high pressure chamber results in reduction of solute solubility and solute precipitation [16,17]. Compared to traditional cocrystallization methods, GAS cocrystallization offers some advantages. It offers a rapid single-step process, provides an opportunity to control the particle size and morphology in a more efficient manner, reduces the thermal and mechanical stress acting on API compared to grinding processes, reduces organic solvent use and reduces residual solvent in cocrystal powder compared to a traditional solution-based method [18,21,22].

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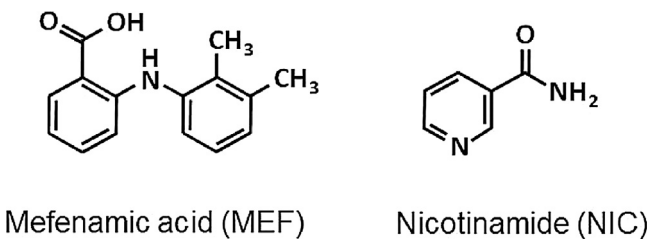


**Fig. 1.** Structural formulas of mefenamic acid (MEF) and nicotinamide (NIC).

Mefenamic acid (MEF, Fig. 1) is a non-steroidal anti-inflammatory drug (NSAID). It is widely used to treat pain, including headache, dental pain, menstrual pain and osteoarthritis [23]. Mefenamic acid belongs to the biopharmaceutical classification system (BCS) class II, having low water solubility but high permeability. Therefore, its oral bioavailability is determined by its dissolution rate in the gastrointestinal fluid [24]. Several techniques have been used to increase the solubility of MEF, such as solid dispersion [23,24], freeze drying [25] and cyclodextrin complexation [26]. Charoenchaitrakool et al. [27] employed the gas anti-solvent (GAS) process to co-precipitate MEF–PEG for improving the dissolution rate of MEF. It was found that the composites of MEF–PEG by GAS provided a higher dissolution rate than the precipitated MEF by GAS and could dissolve completely within 3 h, while the unprocessed MEF could only dissolve 82% within 4 h. Fábián et al. [28] reported that the MEF–NIC cocrystals could be produced by liquid-assisted grinding and solution crystallization methods. The complete formation of cocrystals of were found at 1:1 molar ratio of MEF and NIC, while using the 1:2 molar ratio of MEF and NIC always resulted in the observation of residual nicotinamide present. Utami et al. [29] reported that a 1:2 molar ratio of MEF–NIC cocrystal was synthesized successfully by using melt crystallization method. The solubility of cocrystal was 57.97% higher than MEF solubility. To date, however, the production of MEF–NIC using the GAS process has not been reported.

In this work, GAS technique was used to produce the cocrystals of mefenamic acid with nicotinamide in order to improve dissolution rate. Nicotinamide, commonly used as a coformer (NIC, Fig. 1), is a form of vitamin B3 and classified as generally recognized as safe (GRAS). It has effective functional groups such as an amide group and a pyridine ring to form the intermolecular hydrogen bonds required for cocrystal formation [30,31]. The GAS process was performed using acetone as a solvent and carbon dioxide as an anti-solvent. Box–Behnken experimental design with response surface methodology was used to study the influence of process parameters––namely, operating temperature, coformer-to-drug molar ratio and %drug saturation––on the time required to dissolve 63.2% of the drug ($t_{63.2}$), and the process conditions were also optimized to achieve the fastest dissolution time. The dissolution performance and solid-state characterization were investigated and compared with the cocrystals produced by a conventional method such as slow evaporation.

## Materials and methods

### *Materials*

Commercial mefenamic acid (MEF) (Sigma, 98% purity) and nicotinamide (NIC) (Acros Organics, 99% purity) were used as received. Acetone (Quality Reagent Chemical, 99.5% purity) was used as an organic solvent. Carbon dioxide (high purity grade, TIG) was used as an anti-solvent. Potassium phosphate monobasic (Calro Erba Reagents, 99% purity) and sodium hydroxide (Calro Erba Reagents, 98% purity) were used to prepare the phosphate buffer solution pH 7.6 for dissolution studies.

### *Cocrystallization by GAS process*

The schematic diagram of the GAS process for particle precipitation can be found elsewhere [15,32]. Solutions of MEF and NIC in acetone at predetermined concentrations and molar ratios were prepared. The saturated solubility data of MEF at different temperatures were obtained from a previous report [33]. In each experiment, 5 mL of solution was charged into the precipitation chamber (Jerguson sight gauge series no. 32) which was immersed in a temperature-controlled water bath. The system was set to a desired operating temperature (25–45 °C) and maintained at a constant temperature, to within 0.1 °C, using a recirculation heater (Thermoline Unistat 130). Liquid $CO_2$ was fed to a syringe pump (ISCO model 260D) and delivered through a preheating coil. The initial pressure prior to feeding $CO_2$ to the system was set to be 63 bar for each experiment. The system was pressurized by delivering $CO_2$ at a constant flow rate of 10 mL/min through a 0.5 μm filter from the bottom. When the solution is pressurized with $CO_2$, the solvating power of acetone is reduced, causing precipitation of MEF–NIC cocrystals. Precipitated products were collected on the filter at the bottom of the chamber. Carbon dioxide was fed to the system until the system reached 90 bar in order to ensure a complete precipitation. For the washing step, the residual solvent in precipitated product was removed by flushing with approximately 80 mL of $CO_2$. After washing, the vessel was depressurized through the exit line, and products were collected for analyses.

### *Cocrystallization by slow evaporation method*

MEF and NIC at predetermined concentrations and molar ratios were dissolved in 5 mL of acetone. The solution was then sonicated at 40 °C for 10 min. The clear solution obtained was left in a petri dish to evaporate at room temperature for 48 h. The dried solid was collected for further analyses.

### *Experimental design for the GAS cocrystallization*

Box–Behnken design is an experimental design for Response Surface Methodology (RSM). It is a useful statistical tool for identifying the relationship between controllable input parameters and the response variable and also for optimizing the process parameters [34]. In this work, a three-factor-three-level Box–Behnken design was used to investigate the effects of different parameters on the dissolution time. The operating temperature (25–45 °C), the coformer-to-drug molar ratio (3–5) and the %drug saturation (70–90%) were selected as input variables, and the time required to dissolve 63.2% of the drug ($t_{63.2}$) was selected as a response (output variable). The $t_{63.2}$ (i.e., mean dissolution time or MDT), commonly used to compare dissolution profiles [35], is a characteristic parameter of the Weibull function, which is often used to describe an *in vitro* dissolution curve [36,37]. The range and levels used in the experiments are shown in Table 1.

**Table 1**
Factors and their levels in the GAS crystallization.

| Factors | Symbols | Uncoded levels | | |
|---|---|---|---|---|
| | | Low | Medium | High |
| Temperature (°C) | *T* | 25 | 35 | 45 |
| Coformer-to-drug ratio | *C* | 3:1 | 4:1 | 5:1 |
| Drug saturation (%) | *S* | 70 | 80 | 90 |