

# Improving the Dissolution Rate of Folic Acid via the Antisolvent Vapour Precipitation

J. Y. Tan, L. C. Lum, M. G. Lee, S. Mansouri, K. Hapgood, X. D. Chen, M. W. Woo

**Abstract**—Folic acid (FA) is known to be an important supplement to prevent neural tube defect (NTD) in pregnant women. Similar to some commercial formulations, sodium bicarbonate solution is used as a solvent for FA. This work uses the antisolvent vapour precipitation (AVP), incorporating ethanol vapour as the convective drying medium in place of air to produce branch-like micro-structure FA particles. Interestingly, the dissolution rate of the resultant particle is 2-3 times better than the particle produce from conventional air drying due to the higher surface area of particles produced. The higher dissolution rate could possibly improve the delivery and absorption of FA in human body. This application could potentially be extended to other commercial products, particularly in less soluble drugs to improve its solubility.

**Keywords**—Absorption, antisolvent vapour precipitation, dissolution rate, folic acid.

## I. INTRODUCTION

FOLIC acid (FA), also known as Vitamin B-9, is a synthesize form of folate found in vitamin supplements. In the pharmaceutical industry, FA has received vast attention due to its benefit in preventing diseases such as colon cancer [1], anemia [2] and stroke [3]. In the recent years, governments across the world have been emphasizing about the importance of folate uptake in combating neural tube defect (NTD) for healthy fetal development in pregnant women [4]. Despite the implementation folate fortification [5], pregnant ladies are not attaining optimal folate intake against NTD due to the fact that folate is less effective compared to its synthetic form, FA and commercially available FA supplements are too costly [6]. It was also reported that four out of seven United States Pharmacopeia (USP) standard FA were unable to meet the dissolution standard [7].

Recently, a novel antisolvent vapour precipitation (AVP) has been developed, incorporating ethanol vapour as the convective drying medium in place of air [8]. This approach has been shown to produce large amount of sugar (lactose) [9] and protein (whey-protein) [10] amorphous microparticles within a single droplet. Under atmospheric conditions, the absorption of ethanol vapour into the aqueous droplet reduces

the solubility of the solute and induces rapid precipitation of smaller particles. Smaller particles have larger surface area which allows higher contact area with the solvent, resulting in higher dissolution rate [11]. Improving the dissolution rate is an effective approach to enhance the oral absorption and bioavailability of poorly soluble materials [12].

In view of this idea, the AVP technique is used to dry FA particles and the dissolution rate of the resultant dried particles is measured. Furthermore, it is also of interest to investigate AVP applicability on vitamin-based material. FA is used as the model vitamin supplement due to its poor solubility in water and wide range of pharmaceutical applications. Within the range of some commercial formulation, FA was firstly dissolved in sodium bicarbonate solution in a ratio of 1:4 [13], [14]. Using the single droplet drying experiment coupled with in-situ video monitoring, the drying of FA under conventional air drying method and AVP was observed and subsequently, the dissolution rate of both approaches were compared. Further SEM analysis was also conducted on the resultant particle morphology of FA. The results from this work could be extended to other commercial applications, particularly in the delivery of poorly soluble drugs.

## II. PROCEDURE

### A. Materials

Folic acid,  $\geq 97\%$  (F7876, Sigma-Aldrich) solutions were prepared by dissolving folic acid powder in sodium carbonate solution with weight ratio of 1:0.67, 1:4 and 1:8. Sodium bicarbonate,  $\geq 99.5\%$ , crystalline (S8875, Sigma-Aldrich) solutions was prepared by dissolving sodium bicarbonate tablet in Milli-Q water at a concentration of 0.1M.

### B. Single Droplet Drying under AVP

In this work, the single droplet drying experiment explained in Chen and Lin [15] and further modified by Mansouri et al. [8] to incorporate the AVP process was used. Dry nitrogen gas was bubbled through two conical flask filled with liquid ethanol connected in series. It is noteworthy that the use of nitrogen gas is an appropriate representation of air due to the high proportion of nitrogen in air. The volume of liquid ethanol in each conical flask was adjusted to control the ethanol humidity. The nitrogen-ethanol vapour mixture was then pre-heated through a water bath up to 35°C and flow through the drying chamber. A standard 3  $\mu\text{L}$  solution droplet was generated using a 5  $\mu\text{L}$  micro-syringe and the droplet was suspended onto a glass filament in the drying chamber. During the droplet transferring process, a bypass barrier was used to impede the flow nitrogen-ethanol vapour. This was to ensure

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no droplet drying process occur prior to the intended drying run. The droplet was allowed to dry for approximately 30 minutes and the entire drying process for each run was monitored and recorded using a Sony handycam (Model: HDR-CX350). The fully dried sample was collected for SEM imaging analysis using a Phenom benchtop SEM unit (FEI Company, Melbourne, Australia). Due to the sensitivity of FA to light, the exposure of light on the samples was minimized throughout the experiment.

### C. Dissolution Test

Dissolution test was conducted on the dried particle sample. This was done by suspending a 3  $\mu$ L water droplet onto the dried sample. Video monitoring and recording were conducted throughout the entire dissolution process. The duration at which the dried sample fully dissolved was recorded.

## III. RESULTS

The droplet precipitation process with AVP and  $N_2$  were illustrated in Fig. 1. For AVP drying, the suspended droplet initially expanded due to the higher rate of ethanol vapour absorption into the droplet compared to the evaporation of water, induced by higher concentration of ethanol between the droplet and its surroundings. The droplet gradually turned opaque due to particles precipitation during the drying run. Over time, the ethanol concentration gradient diminishes and the droplet began to shrink, as the rate of evaporation of water became higher. The droplet continuously shrunk until the final fully dried precipitated particles were obtained. On the other hand, for the  $N_2$  drying run, the droplet gradually shrunk from the beginning due to the evaporation of water. It turned opaque much later in the drying process and eventually dried until the final precipitated particles were obtained.

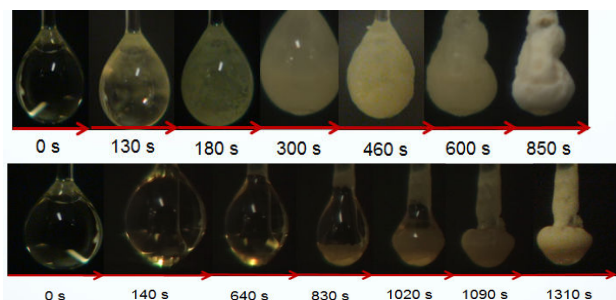


Fig. 1 Video monitoring of FA + sodium bicarbonate drying process: AVP (top); nitrogen only (bottom)

Post-analysis SEM imaging was conducted for fully dried sodium bicarbonate (white) and mixture of FA and sodium bicarbonate (orange) particles for both AVP and conventional air drying method (i.e. nitrogen gas only). The SEM images for all the dried samples are shown in Fig. 2. For the nitrogen drying, an organized feather-like structure and a solid structure were observed for sodium bicarbonate and mixture of FA and sodium bicarbonate particles respectively. The introduction of ethanol vapour resulted in a more disorganized needle-like particle structure for sodium bicarbonate. Interestingly, a

branch-like structure was observed for mixture of FA and sodium bicarbonate particles dried under AVP.

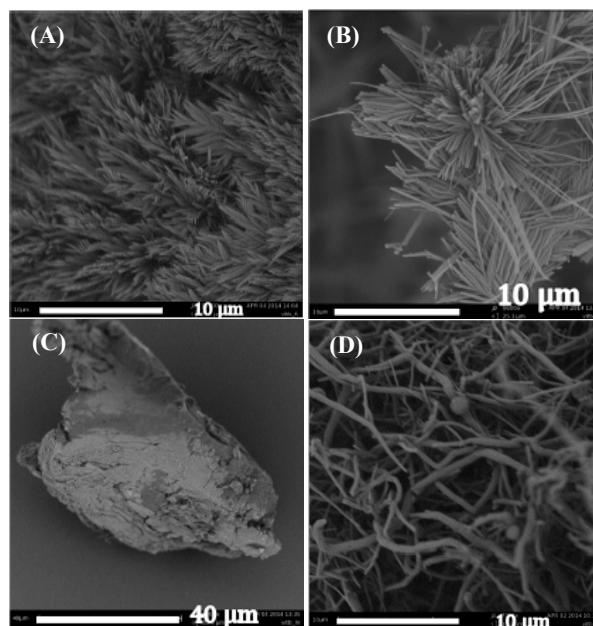


Fig. 2 SEM images of dried particles: (A) sodium bicarbonate (nitrogen only); (B) sodium bicarbonate (AVP); (C) FA + sodium bicarbonate (nitrogen only); (D) FA + sodium bicarbonate (AVP)

Dissolution test was conducted on the fully dried FA + sodium bicarbonate particles for both drying approaches at FA to sodium bicarbonate weight ratios of 0.67:1, 1:4 and 2:8. Remarkably, for all three weight ratios the time taken for particle dissolution is 2-3 times faster for particles dried under AVP compared to the nitrogen only drying. Fig. 3 shows the dissolution process of the dried solid sample for both drying approaches. The solids dried by the AVP process dissolved almost instantaneously when the water droplet was added to it, with only small amount of solid deposited at the bottom of the droplet. It takes a total of 2 minutes for the droplet to turn clear (i.e. solid fully dissolved). As for the nitrogen gas dried sample, only small amount of solid was dissolved when the water droplet was added. A large portion of the solid accumulated at the bottom of the droplet and it took a further 5 minutes for the droplet to turn clear.

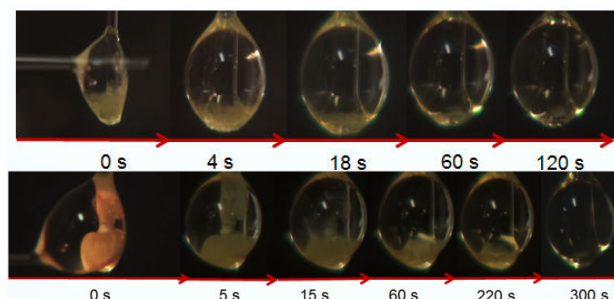


Fig. 3 Video Monitoring of FA + sodium bicarbonate dissolution test dried: AVP (top); nitrogen only (bottom)

The results for the dissolution time for both the drying approaches at varying FA and sodium bicarbonate weight ratio are tabulated in Table I. Higher FA + sodium bicarbonate weight ratio required longer dissolution time due to the higher amount of solute to be dissolved.

TABLE I  
DISSOLUTION TIME OF FOLIC ACID SOLUTION FOR BOTH DRYING  
APPROACHES AT VARYING WEIGHT RATIO

Weight ratio of FA to sodium bicarbonate (% w/w)	Dissolution time for particle dried with AVP (s)	Dissolution time for particle dried with N <sub>2</sub> (s)
1:0.67	30	90
1:4	120	300
2:8	110	280

#### IV. DISCUSSION

One of the interesting observations is the formation of branch-like particle structure when a mixture of FA and sodium bicarbonate was dried using AVP. Contrary to the solid chunk structure obtained from drying with nitrogen gas, the absorption of ethanol vapour during the drying process seemed to have induced a different precipitation mechanism. For the nitrogen gas only drying run, the solute underwent the supersaturation mechanism as water was being evaporated. Upon supersaturation, the particles 'crashed out' and formed a solid chunk when it was fully dried. On the other hand, the formation of the branch-like particles from the AVP drying indicated that there was an additional mechanism driving this precipitation process. This fact has previously been established by Mansouri et al. [8] and subsequent work by the research group revealed a 'pinched off' mechanism [9] which may not be applicable to this work based on the final particle structure obtained. Therefore, it is theorized that apart from supersaturation, there may be two different precipitation mechanisms route under the AVP drying dependent on the type of materials, possibly due to its crystallinity properties. The sodium bicarbonate only drying runs were conducted to distinguish the particle structure with the presence of FA. The orange colour of the fully dried mixture of FA and sodium bicarbonate particles and the difference in particle structure for sodium bicarbonate and mixture of FA and sodium bicarbonate indicates the presence of FA within the dried particles of interest. However, further analysis is required to determine the exact locality of FA within the particles.

Three different weight ratio of FA to sodium bicarbonate were dried under AVP and conventional air drying (nitrogen gas only). The initial weight ratio of 1:0.67 was used to test the applicability of AVP on FA solution. In view of the positive dissolution results and particle structure obtained, the weight ratio of 1:4 was used to mimic the FA and sodium bicarbonate weight ratio range from available patents [13], [14]. Lastly, the weight ratio of 2:8 was used to show the scaling up potential for this application. All three weight ratios formed the same branch-like structure and showed 2-3 times improvement of dissolution time taken for AVP compared to the nitrogen only gas drying. The increase in dissolution rate is due to the higher surface area of the branch-like particle

structure. There are more gaps and exposed surface area within the particles. This allows more particle contact area with the solvent and enables higher solute-solvent interactions.

In view of the improved dissolution rate, it is proposed that the AVP drying application can be extended to other pharmaceutical materials, particularly for less water soluble drugs. Based on the same principles, it is possible that the drying of these products via AVP could result in the formation of micro-structured particles with improved dissolution. Nevertheless, it is important to ensure that the products are not sensitive to ethanol to avoid degradation or undesired reactions. Besides that, it is also reported that the improve dissolution helps enhance the absorption in human body [12]. The apparent absorption of folic acid in the human body is merely 79% [16]. By improving the absorption efficiency, the cost and product effectiveness of commercial FA could be enhanced. It is noteworthy that the absorption mechanism of FA within the human body is not studied in this work. Future work is required to verify the direct relationship between the dissolution rate and absorption of FA in the human body.

#### V. CONCLUSION

Precipitation of mixture of FA and sodium bicarbonate via the AVP process resulted in branch-like particle structure. Such particle has a higher surface area and more contact area with the solvent. As a result, the dissolution rate of FA dissolved in sodium bicarbonate increased by 2-3 times compared to drying through conventional air drying. The increase in dissolution rate could enhance the absorption of FA in the human body. This work could possibly be extended to other application, particularly for poor water soluble drugs.

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