



## Encapsulation of Curcumin by Milk and Whey Powders Using Spray Drying

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### Abstract

Curcumin, a natural, yellow, food coloring agent, has been used for thousands of years in Indian and Chinese medicine. More recently, it has been found to provide health benefits to humans such as preventing colon cancer and combatting heart disease. When ingested orally, the bioavailability is low due to the metabolism of the compound through the gastrointestinal tract. Encapsulation allows the required dosage of curcuminoids to be delivered to the colon, where it can be absorbed. Spray drying was used as an inexpensive and reliable method of encapsulation. The single effect pilot scale spray dryer used resulted in varied, low yields (30-70%), which would have to be increased to make the process viable on a large scale. A novel method for analyzing the release of bioactive capsules was used to create capsule release curves. Whole milk powder was the most effective shell material with complete dissolution of curcumin occurring between 10 and 30 minutes. Meanwhile, skim milk powder provided comparable encapsulation efficiency, but the technique affected the performance of the equipment by blocking the nozzle. Whey protein isolate provided no protection to the curcumin core, resulting in immediate capsule release. The encapsulation of curcumin in milk powders showed promising results, however further optimization of the process is necessary before commercial use.

**Keywords:** Capsule; Curcumin; Encapsulation; Milk; Release; Shell; Spray drying; Powder

### Introduction

Bioactive compounds, such as curcumin, are examples of functional foods. Functional foods provide health benefits in addition to intrinsic macro- and micro-nutrients needed daily. It has been shown that consumers are willing to pay more for foods which provide health benefits [1], with the worldwide market for such foods reaching a record revenue of 300 billion US dollars in 2017 [1]. The high obesity rates in the western world has sparked a search to find so-called 'superfoods' to help tackle this rising issue, which has produced a valuable industry constantly developing new products with health beneficial claims. The history of adding curcumin to food for medicinal purposes dates back thousands of years in both China and India [3, 4]. Only in the last 50 years

however, has it been extracted to obtain higher purities and used as a health supplement. Turmeric powder is known to contain only small amounts of curcumin, <5 wt % [5]. Therefore, doses provided from the normal addition of turmeric powder to foods are not sufficient to provide optimal health benefits.

Curcumin is approved for use in food by the European Food Safety Authority (under code E100). Curcumin is yellow-orange and gives dishes, such as curries, a distinctive color. Curcumin is the major component of the curcuminoid group, obtained from the root of *Curcuma longa* (turmeric) via solid-liquid or ultrasound extraction. Curcumin has the highest antioxidant capacity of the curcuminoid group compounds, curcumin > demethoxycurcumin > bisdemethoxycurcumin [6]. Curcumin is one of the most powerful natural chemo preventive and anticancer agents [7]. *In vivo* studies of Curcumin have proven health benefits such as the ability to block colon tumor initiation [8], suppressing symptoms of

Crohn's disease [9] and even combatting baldness [10].

The major issue in the addition of curcumin to foodstuffs as a supplement is its low bioavailability: which is a common issue with bioactive compounds [11]. The low bioavailability is due to curcumin's rapid metabolism and poor absorption in the body [12]. As of yet, no double-blinded, placebo controlled clinical trial of curcumin has been successful because of this fact [13]. Encapsulation is a viable solution to overcome this issue when targeting the compound for use in the mass food market. Spray drying is the most commonly used encapsulation method [14]. The low cost, scale up potential and worldwide availability of this process has led to its widespread use in recent decades. A successful encapsulation process should produce a powder containing high levels of encapsulated curcumin, with a small particle size allowing the powder to be added to foodstuffs without altering the texture or taste.

Higher efficiency processes have led to the spray drying of more expensive products with larger profit margins. Spray drying is a process which has been refined in the dairy industry over decades and is now used to dry a number of foods such as avocado [15,16], watermelon [17] and pomegranate [18]. In order for the spray drying of curcumin to be used in the food industry, high product yields are necessary. A fluidized bed dryer or additional filters in series with the spray dryer are suggestions to increase the yield of curcumin encapsulated powders. GEA Group AG (Düsseldorf, Germany), CEE Engineering Pvt. Ltd. (Pune, India) and SiccaDania are examples of companies which manufacture Multi Stage Spray Dryers (MSSD). SiccaDania (Kolding, Denmark) released their latest MSSD in 2015, designed for careful control over the product powder in small scale production.

Shell material selection and poor formulation of the spray dryer feed solution can lead to low encapsulation efficiencies. Decisions on the shell material to use should be based on several factors [19]: the ability to produce a stable emulsion when mixed with the core; the ability to create a structure around the core; the ability to release the core in the desired location; a suitably low viscosity at high solid concentrations; cost-effective and legally permitted for use for use in foods. There are several groups of long chain molecules which fit these criteria such as starches, gums, waxes and fatty acids. However, their ability to dissolve curcumin is of importance due to its low solubility in many materials. Curcumin is readily soluble in media with higher fat content, therefore these are more suitable for use as a shell material [20]. In this study, SMP, WMP, WPI, WPC and GA were investigated as encapsulating materials for curcumin.

## Materials and Methods

### Materials

**Core Material - Curcumin:** *Curcuma longa* (curcumin) extract (Sami Labs Ltd, Bangalore, India) was used. The orange-yellow powder originated from the Indian turmeric and extracted using ethyl acetate (Sami Labs Ltd, Bangalore, India). The content of total curcuminoids, determined by HPLC, was not less than 95.0% (w/w) with the curcumin accounting for more than 75.0% but not more than 81.0%.

**Shell Materials:** Anchor™ trim skim milk powder (SMP, 0.62% fat) and Blue™ whole milk powder (WMP, 27.69% fat) were purchased from Pak and Save Ltd supermarket (Auckland, NZ). Whey protein isolate 895 (WPI, 0.2% fat) was supplied by Fonterra (Auckland, New Zealand (NZ)). Whey Protein Concentrate (WPC 510, 0.2% fat) was provided by Fonterra (Auckland, NZ). Gum Arabic (GA) manufactured by Caldic (Auckland, NZ) was purchased online (nzchemicalsuppliers.co.nz).

**Chemicals:** All chemicals used in the study were of analytical grade or higher. Acetic Acid, Methanol and Acetonitrile used in the HPLC process were purchased from Thermofisher Scientific (Auckland, NZ).

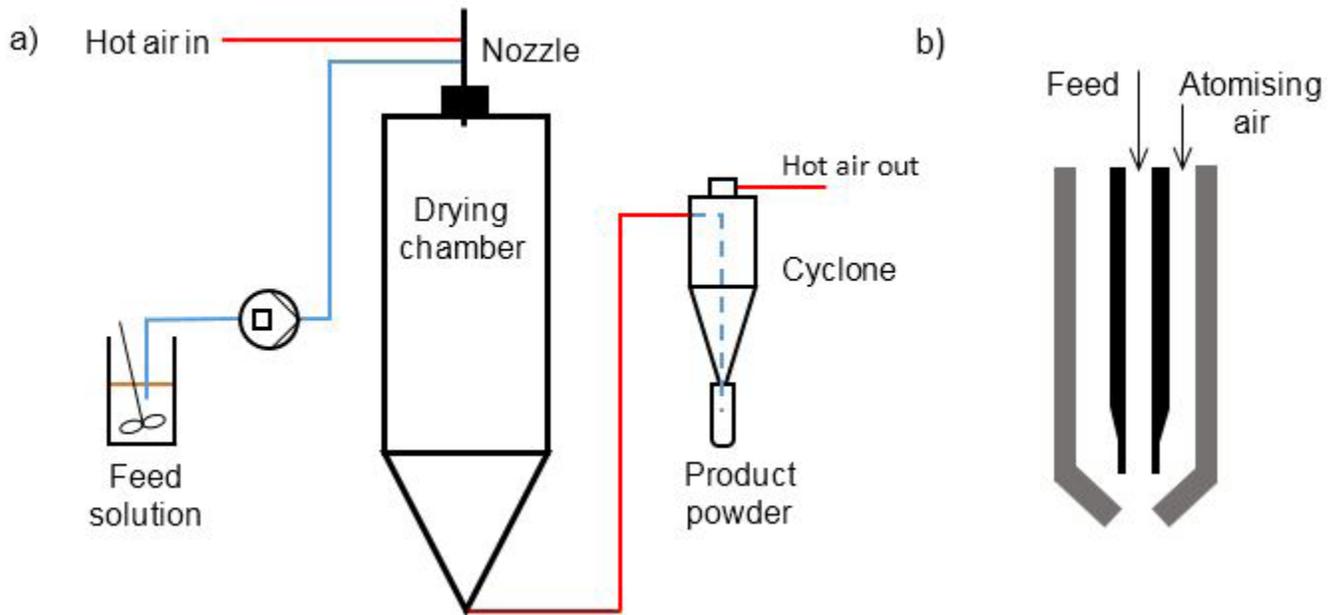
### Spray Dryer Feed Formulation

The shell materials were dissolved in distilled water to the correct concentration (10-30% w/w) at room temperature (20°C) and mixed for 10 minutes at 300 rpm with a magnetic stirrer (Variomag, USA). Curcumin was added to the solution in the correct ratio and mixed for 10 min before being loading into the spray dryer. For the controls, the original mixture was mixed for 20 minutes. The core:shell ratios of 1:4, 1:3, 1:2 were chosen based on previous studies of spray-drying encapsulation [21,22], with adjustments to facilitate the solubility of curcumin.

### Spray Drying Process

The encapsulation process was carried out using a pilot-scale, single effect, spray dryer (Saurin SL-10 Pilot Spray Dryer, Saurin Enterprises Pty. Ltd., Australia) with a water removal capacity of 1.0kg/hr. The unit was equipped with a twin fluid pneumatic atomiser nozzle (Figure 1) with a liquid outlet diameter of 0.8 mm. The drying chamber measured 1400 mm x 800 mm. Operating parameters (flow rate and temperatures) were set based on preliminary results that gave the highest yield of sprayed powder

based on one of the carrier material (whole milk powder without curcumin) and the inlet temperature of 160°C and an outlet temperature of 80°C was used. This is further discussed in section 3.4.4.



**Figure 1(a, b):** (a) Schematic diagram of a single effect spray dryer (b) Cross-section of a pneumatic (twin fluid) nozzle. Based on the Saurin SL-10 Operating manual (Saurin, Australia)

The solution (500 g) to be dried was pumped into the nozzle using a peristaltic pump (RS Components, NZ). The average flow rate across all experiments was 10.1 ml/min. The nozzle cross section (Figure 1b) shows flow of direction of the two streams. The evaporation is rapid such that the entrapment of the core material occurs quasi-instantaneously [21]. The dried powder was blown down the chamber and up a pipe to remove any possible water droplets and into the cyclone. In the cyclone the heavy particles were collected into a collection vessel.

### Microscopic Analysis

The average particle size was measured using an Axiostar Plus microscope (Zeiss, Oberkochen, Germany) at 100x and 400x magnification. Photos of the particles were taken with the Zeiss Axiocam MRc microscope camera. The diameter of 40 particles from each sample was measured using the Axiocam computer software. Since the particles had both regular and irregular shapes, the diameter measured was the largest length of each particle, to maintain consistencies in measurements between powders. The results were repeated in triplicate with a geometric mean of each set being found and the final stated particle size being an average of the geometric means.

### HPLC Analysis

**Feed Solutions:** The release profiles of curcumin from the capsules formed in the spray drying process were analysed by HPLC. The three powders analyzed all used a core:shell ratio of 1:4. The shell materials used were SMP (10 wt%), WMP (10 wt%) and WPI (10 wt%). The powders were prepared using the same spray drying parameters described in Section 2.4.

Equal amounts of powder (0.0152 g) were dissolved in 20 ml of 96% ethanol (ThermoFisher, Auckland, NZ) to give 0.5mM of curcumin with constant stirring. Upon the addition of the ethanol, a 1 ml sample was immediately taken and at the following time intervals (min): 0.5, 1, 2, 5, 10, 30, 60, 120. Each sample was syringe filtered (45 µm) prior to HPLC to determine the curcumin concentration in the ethanol (Figure 2). The shell materials are insoluble in ethanol; thus no interference was present. A curcumin standard stock solution (1 mM) was prepared in 96% ethanol and further diluted to create solutions of 0.5, 0.25, 0.125, 0.0625 and 0.03125 mM. A standard curve of concentration against peak area was produced. The concentrations of the encapsulated material solutions were determined by interpolation from the standard curve (Figure 3).

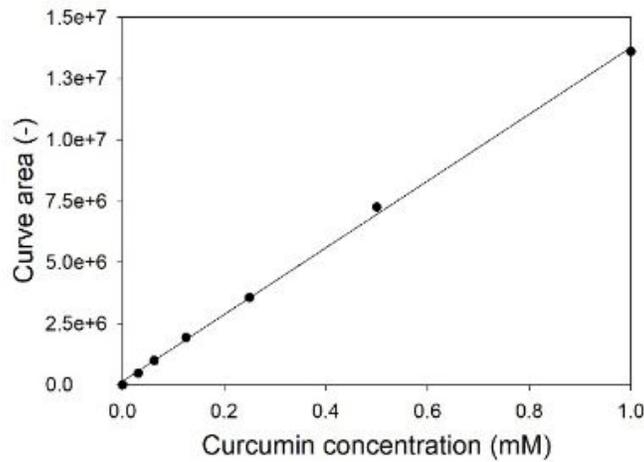


Figure 2: Graph of curcumin standard solution 2.5.2.

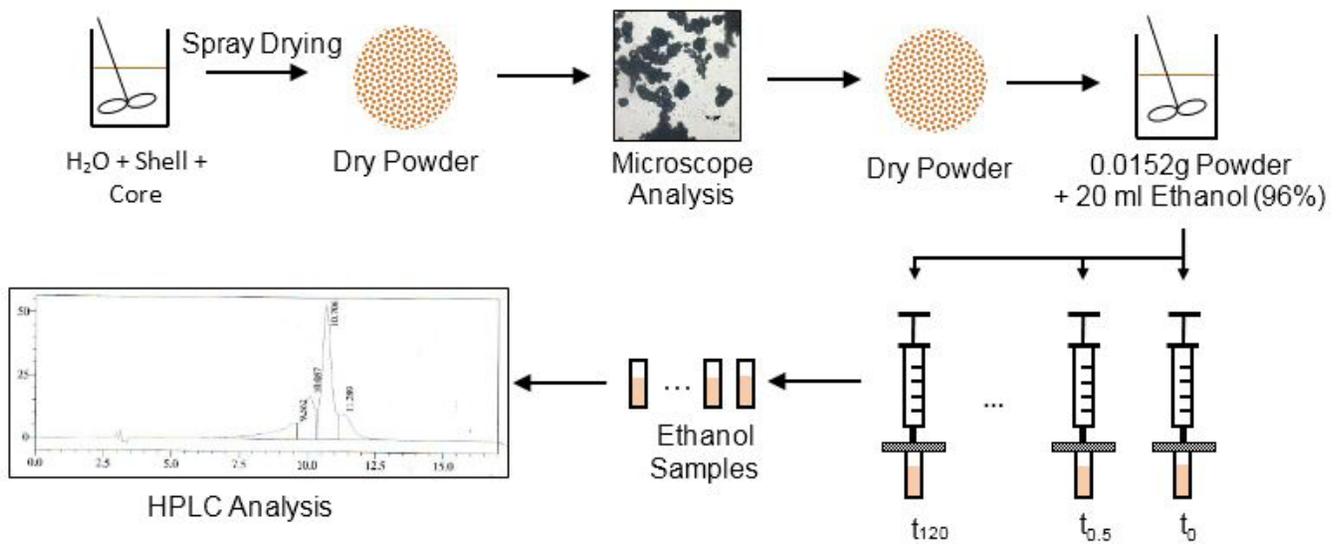


Figure 3: Overview of encapsulation and analysis. Notes: t=time (minutes).

**HPLC equipment:** The HPLC method used had previously been optimised for the analysis of samples containing curcumin, based on the studies by [23,24]. A C18 Grace Smart column (250 x 4.6 mm, particle size 5  $\mu$ m, Grace Davison Discovery Sciences, USA) equipped with reverse phase HPLC system (Prominence UFLC, Shimadzu Corporation, Japan) was used to separate the curcuminoids (curcumin, demethoxycurcumin and bisdemethoxycurcumin). The HPLC system consisted of a CBM-20A system controller, LC-20-AD solvent delivery unit, DGU-20A3 online degasser, rack changer, SIL-20AHT auto-sampler, CTO-20A column oven, SPD-M20A photodiode array detector and an RF-20A XS fluorescence detector. Mobile phase A comprised of 2% acetic acid (v/v, Thermofisher, Auckland, NZ), 4% methanol (v/v, Thermofisher, Auckland, NZ), 25% acetonitrile (v/v, Thermofisher, Auckland, NZ) in water. Mobile phase B was comprised of 2% acetic acid (v/v), 10% methanol (v/v) in acetonitrile (v/v). A constant ramp gradient program was run from 0% to 35% B over 17 min. The oven temperature was maintained at 40°C with a mobile phase flowrate of 1ml/min. The injection volume was 10  $\mu$ l. Analysis was carried out using LC Solutions software with Postrun analysis (Shimadzu, Japan). The total areas under the peaks of the absorbance graph at a wavelength of 425nm were considered. The integration bounds were kept constant throughout.

## Results and Discussion

### Particle Size Analysis

Generally, the process of spray drying significantly increases the particle size of the powder (Table 1). Photographs of the dried powders Figure 4 show large aggregates of powder which varied in size. The measurement of the largest diameter of each powder led to a large size range in each sample. The shell materials were each spray dried at an initial solution concentration of 10% with no curcumin and the particles sizes were compared to the raw powder. Each of the three shell materials, SMP, WMP and WPI increased in size by factors of 3.3, 4.1 and 12.1 respectively. The increase in size seen is due to a combination of factors including the properties of the raw material as well as the physical properties of the spray-dried powder. High levels of protein aggregation through covalent bonding and/or non-covalent interactions could be the reason for the large increase in size when spray drying WPI [25].

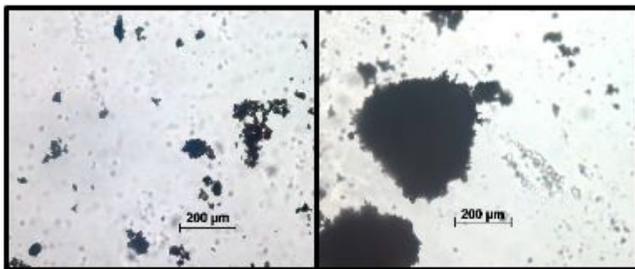


Figure 4(a, b): Microscopic photographs (a) Curcumin sample (b) Spray dried WPI and Curcumin (1:4). Images at 100x magnification

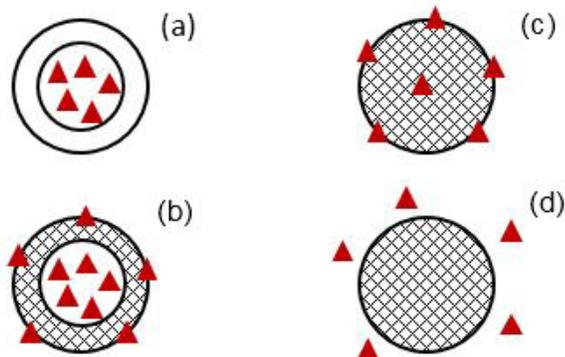
The microscope images of the spray dried WPI and curcumin powder (1:4) show small particles on and around the larger aggregates (Figure 4b). These are comparable in size and shape to the curcumin seen before spray drying (Figure 4a). The visible “Free” curcumin suggests that there were low levels of interaction between the shell and core. Free curcumin is defined as curcumin which did not interact or had little interaction with the shell material during spray drying. The images suggest the spray dried powder is in the form of Figure 5d. If this is the case, it is predicted that the curcumin will dissolve immediately upon ethanol addition. The curcumin has not formed capsules with the shell material. SMP was dissolved at three concentrations (10, 20 and 30% w/w) and spray dried in order to see any change in particle size due to concentration differences (Table 1). As the feed concentration increased from 10 to 20 wt%, the particle size increased (332 to 440 µm), with the largest increase seen from 10 to 15 wt% (332 to 421 µm). A decrease in particle size was seen at an initial SMP concentration of 30 wt%. Although the exact reason for this is unknown, it is possible that the limit of solubility in the initial solution was being reached, leading to some milk powder being dispersed rather than dissolved.

| Material | Particle size (µm) | Feed concentration (wt %) | Spray dried particle size (µm) |           |             |           |
|----------|--------------------|---------------------------|--------------------------------|-----------|-------------|-----------|
|          |                    |                           | w/o curcumin                   | Yield (%) | w/ curcumin | Yield (%) |
| SM P     | 101.44             | 10                        | 331.82                         | 55.0      | 280.70      | n/a       |
|          |                    | 15                        | 420.82                         | 76.1      |             |           |
|          |                    | 20                        | 439.04                         | 62.6      |             |           |
|          |                    | 30                        | 387.77                         | 52.0      |             |           |
| WM P     | 58.35              | 10                        | 241.28                         | 38.7      | 252.88      | 33.8      |
| WPI      | 31.77              | 10                        | 383.80                         | 60.3      | 384.35      | 66.4      |
| Cur      | 19.99              | -                         | -                              | -         | -           | -         |

Table 1: Summary of mean particle sizes (µm) and product yields.

### Predicted Capsules

The type of capsule or matrix formed will depend on the physicochemical properties of the core and shell material used, as well as the encapsulation method used [21]. Figure 5 shows 4 predicted capsule models: a) a simple core surrounded by a shell; b) a matrix on the surface of the capsule with curcumin embedded; c) a combination of a core of material and an outer matrix; d) no interaction between the core material and the shell.



**Figure 5(a-d):** Predicted capsules formed during spray drying. Adapted from [26].

The principal steps involved in the release of the active agent from a matrix system depend on whether the active agent is dissolved or dispersed in the matrix [26]. Curcumin was dissolved in the SMP and WMP solutions but was only dispersed in the WPI solution. Therefore, it was expected that curcumin was more efficiently incorporated into the matrix in the WMP and SMP which would result in a slower release than WPI shell matrix. The result of this would be a slower increase in curcumin concentration after ethanol addition to the powder.

### Curcumin Release

Encapsulation is defined as the packing of solid, liquid or gaseous material into capsules which release their contents at controlled rates [27]. The release of the core material is highly important. In the pharmaceutical industry, capsules can be designed to release their load slowly over the course of days or weeks [28,29]. Encapsulated curcumin should ideally be released in a manner which overcomes rapid metabolism in the stomach and poor absorption in the [12]. This is achieved through delivery to the colon. While not quantified in this report, it is believed that the slow release of curcumin past the stomach will result in a significantly higher bioavailability. Graphs are plotted as the means  $\pm$  standard deviation for error bars. The curves are exponential increases of curcumin concentrations with initial offsets.

### Release Profiles

To determine the release profiles of the encapsulated materials, the concentration of curcumin in ethanol was evaluated at nine time intervals following ethanol addition. The shape of the curcumin release graphs provide insight into the matrix produced from the different shell materials, and also indicates if high levels of free curcumin. An ideal shell material will keep the amount of free curcumin to a minimum. Further, an ideal shell material should allow the curcumin to be released over time. The aim of the encapsulation process is to protect the curcumin from being metabolized

in the body before it reaches the colon. It is possible that the novel method described in this study (section 2.5.1) could lead to further studies on the release of encapsulated bioactive material.

Qualitatively, the most effective encapsulation shell material was WMP. WMP which is inexpensive and readily available, provided sufficient protection to the core material to delay its release. The shape of the release profile shows that initially, large amounts of curcumin were dissolved by the ethanol. The initial steep slope of the curve (Figure 6a) suggests that some free curcumin was present, this rate slowed until the regression curve plateaued between the 10 and 30-minute sample. It is believed that the matrix formed is similar to Figure 5c with certain levels of curcumin on the outside of the molecule and further curcumin fully encased in shell material. The shell material was able to create a stable matrix. The fully encapsulated curcumin diffused through the shell material slowly, with material still being dissolved after 10 minutes. There was an offset at the maximum concentration from the other shell materials. The maximum concentrations of curcumin obtained for WMP, SMP and WPI were 0.30, 0.30 and 0.32 mM, respectively.

SMP proved to be an almost equally efficient shell material as WMP (Figure 6b), which was unexpected due to the difficulties in spray drying the curcumin and SMP solution (core:shell ratio 1:4). Curcumin has significantly lower solubility in SMP than WMP, possibly due to SMP's lower fat content. When spray drying the mixture containing SMP, there were issues with the nozzle becoming blocked and only small amounts of powder were formed. Although enough powder was created for further analysis, it was insufficient to be a commercially viable process. This led us to believe that the encapsulation had not been a success. However, the curcumin release results were similar to that of the WMP shell solution which indicates the difficulties in the spray drying had no apparent effect on the ability of SMP to encapsulate curcumin. The fat content of SMP and WMP powders were 0.66% and 27.69% respectively. This difference in fat content was expected to have a large impact in the mixtures ability to form a protective capsule, however, this was not the case. The fat percentages impacted on the ability of the mixtures to be spray dried but had no impact on the release profiles of curcumin from the capsules.

Having analyzed photographs of the WPI and curcumin spray-dried powder, it was expected that the encapsulation process was not successful. The WPI did not protect the curcumin sufficiently to prevent large amounts of curcumin immediately dissolving into the ethanol. We believe that the matrix formed would be like that of Figure 5d with some potential interactions, depicted by b). The curcumin was able to dissolve in the ethanol from an early stage with complete dissolution achieved by 2 minutes. When the solution of WPI and curcumin to be spray-dried was formulated, the curcumin did not dissolve as readily when compared to the other shell materials used. Rather than the curcumin dissolving in the WPI, a dispersion was formed. Results show that WPI does not

meet the requirements of an effective shell material as it does not form a structure around the core [19]. The chemical composition and physicochemical properties of the WPI led to few interactions with the core material during spray-drying. Thus, large amounts of free curcumin are present in the dried powder. Horcajada et al. [29] reported similar findings in the release profile of drug delivery, with some materials not creating sufficient interactions to protect the core material and thus the core was immediately released into the surrounding fluid resulting in similar profiles to that of Figure 6. This indicates that studies conducted in the medical industry on capsule release can be applied to the release of food grade capsules.

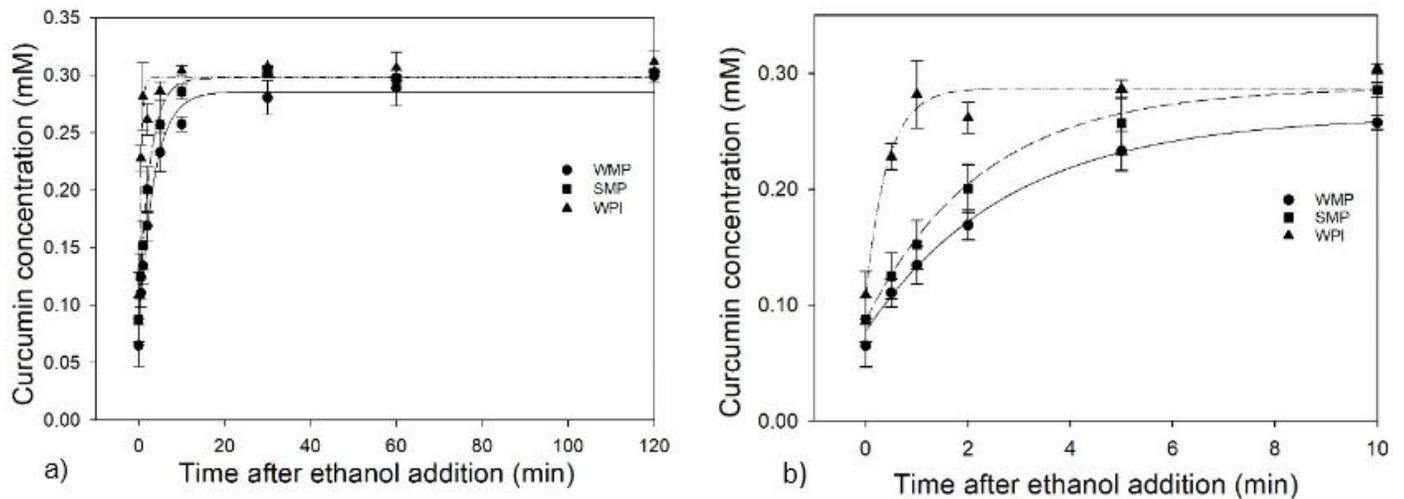


Figure 6(a, b): (a) Concentration of curcumin over a 2-hour period; (b) Concentration of curcumin over the first 10 minutes.

## Technical Considerations

**Single Effect Spray Dryers and Product Yield:** The product yield of a spray dryer is defined as the mass of powder produced as a percentage of the mass of powder in the feed solution. During the operation of the single effect spray dryer (Figure 1a), fine particles were observed in the air outlet pipe of the cyclone. This occurred during each experiment and is potentially the largest contributor to the low yields obtained. A number of these fine particles were also detected in the air outlet pipe, when the pipe was flushed during the cleaning process. Pilot scale spray dryer used in this study inevitably carries the danger of lower yield as the surface area to bulk ratio is low therefore it is recommended to use larger scale spray dryer to overcome these issues and increase the yield. On a smaller scale, this issue has been addressed in recent years with the addition of further processing, known as multi-effect or Multi-Stage Spray Drying (MSSD). Initially, the idea of MSSD was introduced to reduce the amount of agglomerates in the product [30]. This has progressed to increasing product quality and reducing cost of production. It is possible that the use of MSSD may result in high yields making the production of encapsulated curcumin viable on a large scale. This study has shown that encapsulation is possible with readily available materials. However, further research into how to increase the product yield is required.

**Powder Collection:** The powder collection vessel of the cyclone

collected most of the powder however some became stuck on the cyclone wall and in the pipe leading to the cyclone. Removing the powder from these two locations was difficult and some powder was not able to be collected, contributing to the low yields. However, the same methods for powder collection were used for each experiment, making a comparison between yields possible.

**Nozzle Blockage:** A core:shell ratio of 1:2 was determined as being too high for the materials being used. If more expensive materials or non-food approved materials were to be used, it may be possible to use larger ratios. If the solutions were not well mixed, it is highly likely that high levels of undissolved solids would cause the dryer nozzle to become blocked. The nozzle used has inner diameter 0.8 mm and is a pneumatic (twin fluid) nozzle (Figure 1b). Such small orifice requires fine suspension of curcumin particles and preliminary studies on best candidates for carrier materials (not reported here) revealed that curcumin dissolution was best with reported materials at given concentrations. The feed solution had to be constantly agitated for all experiments to maintain this suspension; however higher concentrations of curcumin resulted in aggregates formation in investigated solutions. These aggregates resulted in a blockage in the nozzle which prevented any further inner fluid flow and causing a build-up in pressure as the pump continued operation. A blocked nozzle would be disastrous were it to happen on a larger scale with higher operating flow rates. In large scale production a blocked nozzle would stop production

and be inefficient hence certain shell materials and high Curcumin concentrations can be discounted immediately due to their propensity to cause blockages.

**Inlet Air Temperature:** The inlet air temperature is a parameter which has a profound effect on the outcome of the spray drying operation. The low yields obtained when using WMP as a shell material were thought to be influenced by the air inlet temperature. Three inlet air temperatures were tested 140, 160 and 180°C which resulted in powders with mean particle sizes of 290, 253 and 219 µm respectively. The respective yields were 34.4, 33.8 and 33.0%. The mean particle size was reduced as the inlet temperature increased. This is due to a slower evaporation process upon stream contacting in the dryer and was the expected result. An insignificant decrease in yields was observed as the inlet temperature increased although possibly attributable to the decreased mean particle size. As the particle size decreases, a smaller proportion of the powder was being caught in the cyclone. It was hoped that a much larger yield would be seen when operating at a lower air inlet temperature. Due to a larger mean particle size leading to increase capture rate in the cyclone. However, this was not the case which suggests that the properties of raw WMP are the reason the yields are low.

## Conclusions

The encapsulation process presented unlocks the ability of bioactive compounds to provide health benefits, by overcoming the issue of bioavailability. Advantages - inexpensive materials and readily available equipment - and disadvantages - low yields - to the curcumin encapsulation process were found. This study has shown promising results for using spray drying with a SMP or WMP shell to encapsulate curcumin. The curcumin release profiles indicated that spray drying with SMP or WMP shell can encapsulate curcumin, but spray drying with WPI did not have the same effect. The low yields may be attributed to losses through the cyclone. It is suggested that the use of an MSSD may provide more efficient drying while delivering the same encapsulation process.

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