

## Scale Up of Fluid Bed Coating from Prototype to Production, Case Histories

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### **Introduction:**

Many people and companies today perform coating of particles using fluid bed (Wurster) coating techniques. Usually the early work is done using smaller scale equipment, and must be scaled into larger equipment when a suitable prototype has been developed. Although it is common to further refine processes and products with experience, a more immediate concern is simply to scale the process from the prototype to a manufacturing scale. This discussion is intended to shed some light on various scale up issues by use of real life examples.

### **Discussion:**

There can be several definitions of "manufacturing" scale. In real life it ranges from a few thousand "pieces" to many thousands of kilograms. Regardless of ones definition, it is usually necessary at some point to make a bigger batch of a product that one has made previously as a "test" batch. It is usually desired that the larger batch will have characteristics similar to the prototype in question. Even though improvements may be possible, or even necessary, at a certain point the issue is to simply scale up the process with few changes. In order to do this one must have an understanding of the equipment one is using and what the critical factors are.

A comment heard too frequently goes something like "We scaled up to a larger piece of equipment and had to re-invent the process." or "When we scaled up to larger batches the process took much longer." If one is truly scaling up a fluid bed coating process neither of these comments should apply, if it does then something else is also happening and one needs to determine what that something else is.

The most critical issues in scale up are a) maintaining a balance between coating application rate and drying capacity of the process and b) scaling up the atomization of the coating. There are of course many other significant factors, but these are key. It is usually best to approach scale-up in a systematic manner. A method that has worked well is to first select the plate pattern to replicate that used in smaller equipment, then define our working load size and establish good fluidization of the product.

A good first step is to establish a working batch size by filling the coating chamber based on visual observation. Then close the unit and fluidize the material. Observe the product flow and adjust air volume to achieve good fluidization. There is some legitimate disagreement over what constitutes "optimal" fluidization, but keep in mind that we are really talking about reproducing something you already did. If you had lots of "bubbling" at smaller scale you might reasonably expect the same at larger scale. That doesn't mean that it is good or bad, just similar. If bubbling is excessive or if product is not flowing properly you may need to change the plate to one having a different pattern. The whole pattern of the plate is simply means of controlling air distribution within the coating chamber, other methods also work but may be more complicated.

When performing scale up of a coating process, one is typically approximating the load size one will ultimately use in manufacturing, but sometimes materials limitations force one to work with less than the desired load size. Working with "manufacturing quantities" may result in a coating chamber that is relatively full compared to experimental batches where one often tries to minimize the amount of materials consumed. For example, if one is scaling from a 9" unit operated about half full, to an 18" unit fully loaded the candidate factors might be as follows:

	<u>9"</u> <u>Unit</u>	<u>18"</u> <u>Unit</u>
Plate diameter	9"	18"
Plate area (sq in)	63.6	254.5
Plate Factor		4X
Load in Kg	3 Kg.	42 Kg.
Load Factor		14X
Air flow (scfm)	76	

x plate factor = 304 scfm  
x load factor = 890 scfm

A key question is; "what air flow should I be using?" The product characteristics may have a significant influence in answering this question. While some materials are free flowing, uniformly sized, spherical beads... many are not. Some materials that are not very free flowing may behave better in larger equipment where greater mass flow dislodges material that may temporarily stop moving. An example of this would be a fine powder that tends to cling to the coating chamber walls. When working with small quantities one may have 20% or more of the material clinging to the walls, effectively removed from the process. When processing much larger quantities some material will still cling to the walls, but the mass flow will tend to dislodge accumulated material returning it to the process.

Other materials may behave better in smaller equipment where the available airflow is able to overwhelm tendencies to cake and adhere. One such material is a soft granular product that tends to cake into a hard mass. It can be processed fairly easily in small batches, but when one places 60 Kg into coating chamber it tends to pack down and stop fluidizing. In smaller batches the weight of material simply is not there, and one has a relatively large excess blower capacity to overpower any caking tendencies.

It is important to keep in mind that, while there are many compounding factors involved in working with larger quantities of material, there are really only a few important variables that influence the coating process itself. Somewhat oversimplified, these are airflow and spray rate. If one holds temperature constant during scale up, then drying capacity is determined by process air volume.

This relationship can be expressed as follows:

$$(\text{Fluidizing air volume})(\text{temperature}) = \text{drying capacity} ] \text{ spray rate}$$

$$\text{Fluidizing air volume} = (\text{linear air flow velocity})(\text{area})$$

$$(\text{Linear air flow velocity})(\text{area})(\text{temperature}) = \text{drying capacity} ] \text{ spray rate}$$

Particle size and shape determine the linear airflow velocity required to fluidize the particles. Terminal velocity of particles in air is a function of particle size (not density). Very small particles may remain suspended in still air for a very long time while large particles literally “fall like rocks”.

<u>Particle Diam</u>	<u>Settling Rate (1)</u>
1000 μ	≈500 cm/sec
100	≈45
10	≈0.6

Therefore, if particle size and shape are reproduced between small scale and larger scale, the required linear air velocity will remain unchanged. If process air temperature is also kept the same, then only area of the plate (chamber diameter), which correlates with fluidizing air volume, remains as a significant scale up factor.

**Example:** Scale from 4/6" to 18" to 46" Unit (Code TTAF)

### IMPROVED STABILITY OF PRODUCT

Common Conditions:

Coating Material: Solvent based, 20% solids  
 Core: Fine Powder Active  
 Inlet Temperature: 115°F (46°C)

Unit	<u>4/6"</u>	<u>18"</u>	<u>46"</u>	<b>Factors</b>	<u>+2 years</u>
Load	1.0 Kg	35.0 Kg	250 Kg	<b>35x 7.1x</b>	250 Kg
Fluidizing Air	19 scfm	600 scfm	4600 scfm	<b>31x 7.7x</b>	3200 scfm
Partition Gap	3/8"	7/8"	7/8"		
Pump Rate (Active)	8.8 g/min	255 g/min	1.80 Kg/min (257 g/min/nozzle)	<b>29x 7.1x</b>	1.80 Kg/min
Nozzle	1 @ 15 psi	1 @ 80 psi	7 @ 80 psi	<b>7.0x</b>	

Comments:

1. Pump rate is approximately in proportion to airflow and also load size. Airflow in 46" unit was reduced after initial scale up.
2. Partition raised in 18" unit in response to observed marginal flow of material.
3. 46" unit is made up of 7 modules, each comparable to one 18" unit. Each nozzle is functionally identical to the nozzle used in an 18" unit and is delivering the same quantity of liquid as in the 18" unit. For this reason, there is no scaling up of the nozzle function in going from 18" to 46" coating unit.

Of course life cannot be that simple. A variety of other factors influence scale up of the coating process. One of these factors, often beyond your control, is batch size. In the early stages of product development one is frequently asked to conserve materials, and perhaps time as well. If materials are expensive, or have a 3-week lead-time, you may be required to work with less than optimal quantities. This puts you in the position of working with a unit that is operating below its capacity. Limited availability of materials may also force you to be overly conservative in selecting process conditions.

Either of these can result in low coating efficiency, which may change when scaling up and more material is available.

Friability of the core material may also be an issue. If one is trying to coat large crystals, then any attrition of the crystals introduces fines, which have dramatically more surface area. Since release curves are skewed by presence of fines, this is certainly an issue to be dealt with. In one case, work at small scale gave very nice results, but when scaled to larger equipment the release profile was too fast. This was ultimately determined to be related to attrition of the crystals. In the larger scale equipment greater physical forces were at work, with the most significant factor being the nozzle itself. In smaller equipment (1- 3 Kg batches) it was only necessary to use 12 - 15 psi atomizing air pressure, which had little effect on the crystals during the short time before they became significantly coated.

Upon scale up, the anticipated spray rates were much greater ( $\approx 350$  g/min) and it was anticipated that much greater nozzle pressures and volumes would be required. It turned out that the high pressure (80 psi) was sufficient to abrade the crystals very quickly, creating fines and adversely affecting the release profile. It was determined that this was best controlled by using much lower atomizing air pressures and applying the coating as quickly as possible. The following example describes the changes required.

### **EXTENDED RELEASE OF PHARMACEUTICAL**

**Common Conditions:**

Coating Material:	Solvent based, 5% solids
Core:	Large Single Crystals, $\approx 800\mu$
Bed Temperature:	130°F (55°C)
Load:	70 Kg

	<u>1<sup>st</sup> Batch</u>	<u>Good Batch</u>	<u>Changes</u>
Scale Up Load	60 Kg	70 Kg	Increased to maximum
Airflow	500 scfm	700 scfm	Greater fluidization
Pump Rate (Active)	320 g/min	750 $\rightarrow$ 300	Much faster at start, rate reduced to sustainable rate after short time
Atomizing Air	80 psi	45 $\rightarrow$ 80 psi	Pressure reduced until crystal stabilized
Fines Content	12-15%	Max 2%	Fines minimized
Release Rate	2x target	At target	Fast releasing fines avoided

**Conclusions:**

It is hoped that as a result of this talk, "scale up" will be demystified to some extent, and that those who are given the sometimes daunting task of taking a laboratory, or pilot, operation to larger scale, and eventually to manufacturing, will be given some reassurance that it can be accomplished without use of human sacrifice or relying on dumb luck.