

## SCALE UP OF FILM COATING OPERATIONS Aqueous and Non-Aqueous

by

R. E. Pondell  
Coating Place, Inc.  
Verona, WI 53593

In dealing with scale up parameters in film coating, one needs to take into consideration all of the factors involved. Each can cause a failure in a potentially successful product. Therefore, we need to break down all of the variables available and realize that there are no factors which can be assumed to scale up without any problems. I have attempted to list the major factors with which we are normally concerned. In doing development work, we many times deal with quantities of material from suppliers which are greater in a single shipment than we could ever need in development or have time to use. In-house manufactured products may be made in a quantity sufficient only for the development stage. We therefore find many projects developed using a very small number of different samples of raw materials. What if all the materials were samples? Could they be the best of the material produced? Will what you receive when you start to purchase this material vary more than all the samples you tested? Is the sampling and testing procedure developed capable of eliminating material scale up problems?

All raw materials used in a product, from core to coating to carrier, must be categorized. An example of this problem has more than once become obvious to us. Resins vary over a large range from the same supplier, and may vary even more drastically between different suppliers. You may test every known characteristic of a material only to find that blending the material with other components can cause a reaction or variation which can only be seen by a test of the mixture. All components of a multi-component system must be considered even when one is dealing with only one of them. What are some of these changes? Viscosity, solubility, permeability, and age stability quickly come to mind. All of these may have a drastic affect on the product. What are other scale up problems? What is the weighing accuracy? Does the production mixer use the same amount of sheer force in making a solution that was used in development? The fiver shape after mixing can change more than just the viscosity. Nothing may show up until permeability studies or solubility studies are done. Will the solution be mixed and used in the same time frame and will there be more or less hydration, complexing with age, degradation or microbial contamination?

In film coating pharmaceuticals, there are basically two types of equipment, pan coating and fluid bed coating. Within the category of pans, are a wide variety of conventional pans with shape, size or material of construction being the most significant difference. These may or may not have air handling equipment, controlled application of coating independent of operator technique, and sensing equipment. There are also vented pans, in which the differences are loading/unloading, direction of air flow, volume of air flow, and location, shape and size of venting. Again, they may vary from highly monitored, to limited or no controls.

Fluid bed coating covers more than one type of equipment. There is random uncontrolled flow or very controlled, cyclic flow. Again, these units may be used with few or no controls and monitors, or be very well monitored and easily automated.

Now that the equipment is defined, what are the problems with which we must deal? The most obvious is the increase in material which we must deal? The most obvious is the increase in material which must be handled. In many research and development projects, we have dealt with small quantities usually transferred by hand, and therefore handled more gently. Now, we are involved with bulk material handling equipment which may destroy our product before or after coating.

Pan coating systems may have limitations with automatic handling of particles. Larger batches will cause particle size restrictions to become an important factor. The density of a particle must be considered along with the bed depth and force that can be exerted on the lower particles. As the pan gets larger, these forces will increase and cannot be duplicated in a small research pan.

Physical changes will occur which can drastically affect the scale up performance. The distance of the nozzle from the particles will be increased, the type and/or size of nozzle changed, the angle may be varied, and the addition rate per nozzle and the number of nozzles may be drastically increased.

If nozzles are too close to the bed, an area in the bed center can be easily over-wetted. Nozzles too far away yield a grainy finish with low efficiency (spray drying) and a dirty pan. Nozzles located too far apart can lead to low efficiency and a dirty pan (over spray). The angle of the spray can cause turbulence, coating build-up and tablets sticking to the pan bottom.

Hydraulic nozzles may be used instead of air atomizing. Hydraulic guns are commonly used on larger coating units. Because no atomizing air volume has to be dealt with, the bounce of the spray will be different. Normally, hydraulic droplets are larger than air atomized droplets and are much more sensitive to rate. A hydraulic gun cannot be used efficiently below 700 grams/minute; will clog up with latexes and, like air atomizing, is viscosity sensitive. Hot melt coatings, which are highly cost effective, are difficult to work with in research processes because of the great heat loss involved with such a small quantity of material.

In a small unit we have equipment that is many times oversized for the work being performed. In contrast, when we scale up, we many times try to exceed the rated capacity of pumps, nozzles, and other equipment. Large equipment is more efficient until you exceed its capacity. We try to compensate for this by using additional equipment, which may cause variations in flow, spray patterns, and particle wetting. Multiple equipment also increases the variation that can be caused by a multicomponent system. Nozzle overlap is critical. The rate of solution through each nozzle vs. the overall rate of addition, and the maximum capacity of each nozzle will determine the wetting of the particles. To use some aqueous numbers which have been generated, a 60" Accela-cota using 2000 SCFM of air, may have an application rate of 400-500 grams/minute. To handle this amount of fluid efficiently, 4 guns will be needed at an application rate of 100 to 125 grams/minute per nozzle. Other examples are a 48" Accela-Cota - 3 nozzles; a 30" angular pan - 1 nozzle; a 40" angular pan - 2 nozzles; a 38" oval pan - 2 nozzles; and a HCF-130 Hi Coater - 4 nozzles. Using 3 nozzles instead of 2 can cut the application time. With the increased addition rate, the removal of this solvent will be more critical. Only if we have even distribution of spray will we have edge to edge uniformity. Many particles are very sensitive, and it is important not to run too wet or dry. Because of this, monitoring is important, and the number and location of these monitored points is critical. Residuals that can be tested for after removing the product are a must.

With open pans, the spray and dust that does not remain in the pan could cause some health concerns within the process area. One big problem with pans is their particle size restriction. As we increase the drying air and the nozzle air, we start to blow away beads and powders. So, even if small particles could be handled in a small pan, we can't successfully scale up to larger pans.

Fluid bed systems are much better at handling the wide range of particles with which we now deal, but even in fluid bed systems, particle size restrictions have to be considered.

What then are fluid bed scale up problems? With increases in bed depth, channeling or erratic flow can be a problem, especially in the random flow units. This problem can be compounded in units which have limited visibility. In many units, we recommend acrylic chambers for ease in viewing new products.

Temperature profiles will vary more in smaller equipment. Heat transfer and loss may affect projections.

Controlled cycle fluid beds can limit considerably the amount of channeling. Of all units evaluated, this unit allows for the greatest variation in both raw materials handled, and coated products desired. Mass and depth can be scientifically calculated for flow characteristics and the unit modified to handle those conditions. Complete automation and monitoring has been successfully done to this equipment with extremely high reliability.

As in pan coating, the performance of nozzles, pumps, and other support equipment may become a limiting factor in scale up. We have spent considerable time evaluating both pumps and nozzles to find those which give us the best performance in comparison to the smaller test units. If we weren't able to duplicate performance, multi-component units were preferred to use of a single component, less efficient unit. When one considers multi-nozzle coating occurring in a single batch, how does the failure of one or more of these nozzles affect the product? We have done this development work on scale up from an 18" fluid bed coating unit to a 46" fluid bed coating unit. We did uniformity studies on product produced when different numbers of nozzles were taken out of use. The results were very good. One nozzle removed from service gave us a 2% variation over the standard variation of a single nozzle.

As nozzles were removed from service, the pumping rate to the remaining nozzles was kept constant. Therefore, the run time was longer to achieve the same amount of coating.

This assumes that one is capable of determining that there is a problem with the spraying system. This can be accomplished with the proper monitoring equipment. Again, we mention monitoring equipment! All coating systems can be formidable if one cannot monitor all of the important and variable parameters involved.

This is absolutely necessary in the smooth transfer of information from research staff to production personnel. At a minimum, airflow, temperatures, nozzle performance and pump performance must be monitored accurately. This will eliminate much of the trial and error which can ruin a good product.

After we have determined that the product is feasible, that it can be scaled up, we have the issue of regulations to deal with. Emissions regulations are possibly one of the most difficult

items to deal with. It is almost impossible to eliminate all emissions to the atmosphere. Most states have a volume per period of time allowance. Aqueous systems are generally considered to be free of this government regulation.  $\text{MeCl}_2$  has been granted similar status in some states.

Solvent recovery systems have become a necessary part of many production facilities. Much of this equipment has now been successfully adapted to all forms of ducted equipment. They must be a minimum of 85% efficient. I highly recommend that you do a cost analysis between systems based on efficiency, cost of recovery, effectiveness, and safety. Check with others who have installed systems.

But, even if you are exempt from solvent recovery, this doesn't mean you've no problem. Will there be any odor problems, health problems, or internal safety problems?

Worker exposure to solvent vapors can be controlled. The fluid bed systems produced recently are vacuum systems. This means that even with leaks, no solvent fumes will be forced into the area where the operator would come in contact with the fumes. Vented and hooded pans can also limit the exposure if properly run.

Residual solvent levels may increase as one adds more solvent. Monitoring is important to make sure that the heat transfer is as efficient as in the smaller unit.

Explosion protection can be a concern, depending on the product. In fluid beds, vents can be installed and safety features added to the unit to eliminate hazards to the operators. Pans are more difficult to do, but proper care and design of any equipment and product can greatly reduce the risks involved.

I have covered the most obvious problems which can be encountered in scale up. Each project and its reaction with components of manufacturing will have its own variations. Hopefully, we can begin to project these and understand the results for future scale ups.