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# SOLVENT FILM COATING: AQUEOUS VS. ORGANIC

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When I was invited to give a presentation on this subject, I told them that while I thought we had some experiences and technology to share, I also explained that my expertise, if you will, is based on coating with Air Suspension Process—well known in the industry as the Wurster Process. So if they could accept my prejudice for a certain coating process, I felt that with some updated information from my former colleagues I would accept their kind invitation. While most of the thoughts we will discuss are applicable to any coating system, in my mind there is no other system that performs the one function that is so important to solvent film coating (namely, that of drying) better than the Wurster Process.

We will explore some of the present thinking about aqueous versus organic solvents and discuss some guidelines that might be useful for selecting an appropriate solvent system as well as cite some industrial situations where these choices have been made.

In the recent past, aqueous sugar coating was the procedure of choice for the pharmaceutical industry. During the 50's and early 60's, organic solvent film coating was shellac/alcohol but later other synthetic film materials were introduced, along with more sophisticated organic solvent systems. Today a mixture of organic and aqueous film coating solvents may be found in many companies. However, what might the future hold for solvent film coating? How about other pressures of the times and how do we resolve these situations?

There is no question about it; many companies are evaluating aqueous film coating in a big way. Some of us might say "So what! We are known for a long time that water is a good solvent for our films, but we are satisfied with the organic systems. Besides, no one is telling us we have to change…" But suppose you were to consider making a change from your present organic system to an aqueous system. What might you be up against?

1. Your department head may tell you not to rock the boat.

2. Regulatory people will say that all products will have to be resubmitted for FDA approval.

3. Quality control people will say that product stability and efficacy will be affected.

4. Production will say we can't make enough product now and if you change, you are inviting problems; We'll have to have more equipment and space.

5. Safety people might say "go ahead" as we would like to get rid of that solvent—it's dangerous, it smells, and it's not good to breathe.

6. Environmentalists might say "right on." No more organic solvent down the drains or evaporated into the atmosphere.

These are just a few of the arguments that you might hear and, depending upon who has the soapbox and shouts the loudest at the moment, they can legitimately influence the others.

This brings me to what I meant to convey in the abstract as the philosophy regarding film coating. Film coating is dominated by organic solvent systems. We live with it—it's comfortable—but someone says there might be a better way. The philosophical attitude must be—What is the "best" way? —regardless of what way we are now using. After this question is answered, we can still nod our heads and say that's fine, but a very natural, human response is to continue following our established procedures. This is where management and managers must be wiling to stand up to their philosophical principles and at this point "cool" heads must prevail. One doesn't act hastily or irrationally unless he is looking for employment elsewhere…a commitment to the objective is necessary. We begin to look for facts and/or other credible evidence on which we can weigh the advantages and disadvantages. Perhaps we find that the disadvantages outweigh the advantages but we must keep in mind the directives and commitment that management has for the program. As a self-protective measure, we might change a disadvantage into a potential advantage if it is preceded with an "if", a "we believe," or "others have said."

Persuasion couched in these terms doesn't carry much weight in the real world unless there is a pot of gold at the end of this rainbow and, for management, the word is profit. If profit is somewhere in the picture, then the investment (either large or small) is usually available. I would like to summarize this philosophical attitude by paraphrasing from article that appeared in the February 1978 issue of Food Engineering Magazine:

> Falls Dairy in Jim Falls, Wisconsin (population 250) now sports in the nation's first six effect evaporator for whey. In the U.S.A., it is the first such six effect system, period. And this flies directly in the face of conventional evaporation technology in this country.
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> In 1976, management sat down and determined that energy costs were going to continue to rise and that they must lay out a program of conservation. They resolved then to reduce energy consumption at Falls Dairy 50% by 1981. Management discovered it was easier to make a resolution to save energy than it was to find more energy-efficient system.
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> They were told this system would be too costly and would be virtually impossible to operate. Now they expect to pay back the cost of the machine through energy and labor savings in two years. With the installation of this system alone, they have already cut energy demand by 40 percent.

Discussions about the pros and cons of aqueous coating versus organic solvent-based film coating usually center on the problems involved with the emission of organic solvents. In most states the amount of organic solvent, which one can emit into the air, is monitored and controlled by one or more government agencies. If today a coating system is contemplated, one must:

1. obtain a permit to emit the solvent;

2. prevent the emission of solvent into the atmosphere; or

3. use an innocuous solvent

If all things were equal, an innocuous solvent such as water would be an easy choice for film coating since it is readily available and can be emitted directly into the atmosphere. However, all things are not equal. Many factors must be considered before one can decide which type of solvent is best for your particular situation.

From the regulatory point of view one must be concerned not only with the various federal and state agencies concerning emissions, but also with the FDA regarding product safety and efficacy. As various organic solvents come under fire for a variety of reasons, it will become necessary to remove those materials from formulations or to demonstrate that residues are essentially nonexistent. I believe we can anticipate the day when it will be necessary to include residual solvent statements with new drug applications and residual solvent tolerances will be established.

For example, several years ago the WARF Coating Laboratory developed a solvent-based coating for an encapsulated vitamin that was intended for sue in the food industry. The product was successful and was published in the Federal Register. For all intentions and purposes, it could have been commercialized; however, the company felt uneasy about the fact that it contained a few parts per million of residual solvent. So, it was back to the laboratory to develop another coating that did not have the solvent objection. You can guess that the new coating formulation almost had to contain either an alcohol, water, or combination of both. The challenge was met, but it was the commitment of management to eliminate any potentially questionable solvents in their products that enable the technical people to pursue another, and obviously costly, development program.

It is imperative that film coated products be able to demonstrate efficacy. This implies drug stability and bioavailability. Stability and bioavailability. Stability and bioavailability are greatly influenced by the selection of coating and the solvent system from which it is applied. Many drugs react in the presence of water; thus, residual moisture in the film coated product may present more of a problem than residual organic solvents. Although moisture can be eliminated by heat, some products are unstable at higher temperatures or the combination of heat and moisture (humidity).

The coating itself becomes important. Materials such as cellulose acetate phthalate and shellac can themselves be altered by the presence of moisture during extended storage. Similarly, gelatin and starch films can retrograde and change dissolution characteristics. Obtaining the desired release characteristics is not only a function of the coating material, but the coating is influenced by the presence of residual solvent. It is imperative to have specifications on residual solvent tolerances for wax containing coatings applied from solvents. A wax coating with high solvent residues will not provide the barrier properties inherent of the wax alone.

There are many costs, which go into a coated product. Foremost is the cost of the coating materials themselves. If the same coating material is used, whether applied from organic or aqueous solvent, its costs will not change. Frequently, however, we find that the material choice and solvent choice go hand-in-hand and cannot be separated. For example,

ethylcellulose is not water soluble nor, as commercially prepared, readily emulsified. It must be applied from organic solvents, although some are now available in latex form. Similarly, starches and gelatin are not soluble in organic solvents and are normally applied from water.

As already stated, water is readily available at modest cost compared to organic solvents. While water is less expensive, it is not free. In many areas water contains significant quantities of minerals as well as a wide range of trace elements and other possible contaminants. The cost of softening, de-ionizing, distilling, or otherwise treating the water supply must be added to analytical and distribution costs in arriving at a realistic cost for water.

While aqueous coatings are in many ways less expensive than organic solvent coatings, we find that more energy is consumed in applying them. The removal of water from water soluble films such as hydroxypropylmethyl cellulose, methylcellulose, gelatin, or starch requires the use of higher drying temperatures than does the removal of methanol from a film. This is not surprising when one considers their heats of evaporation. This analogy is not directly applicable when applied to latex based coatings since the polymer film does not tend to retain water. Because these films dry very rapidly, they can be processed at lower temperatures than water soluble films and, consequently, require less energy.

For many of the reasons already pointed out, organic solvents are the solvents of choice. When this situation exits, management, irrespective of outside influences, must consider newly available technology for solvent recovery and recycling. A commitment to meet the challenge of increasing solvent costs together with energy and timesavings can be a viable alternative to eliminating organic solvents from consideration.

Another critical element in any comparison between aqueous and organic film coating systems has to relate to time. The processing time for any film coating application is extremely important to meet production goals. Often we tend to think of aqueous coatings are requiring longer processing times than organic solvent systems. We base this on the relative differences in evaporation rates and do not take into account the drying efficiency of the processing equipment, the temperature limitations of the product, and the solids content of coating solution. These statements are equally true in comparing one organic solvent system to another. It is necessary to consider what the minimum cycle time will be when considering the various solvent systems. It is necessary to include any secondary drying time in the total time estimate.

Another way in which water and organic solvents differ is in their support facilities. Because of their volatile and toxic nature, organic solvent must be handled and stored in areas designed for this purpose. This entrails the construction of fairly expensive areas of limited utility and also the ventilation of these areas. The ventilation adds a substantial cost to the solvent designated area since in many instances the air must be filtered, conditioned, and exhausted with potentially large energy losses. The use of water as a solvent presents minimal problems in this regard since the air can be recirculated through filters where materials are mixed. Because water is non-toxic and non-flammable, specially designed storage facilities are not required.

In passing, we have mentioned some specific film materials. In appraising film coating today, it is now possible to include materials not previously considered; for example, various gelatins and starches in combination with water, synthetic polymers, and other soluble materials. Various combinations may exhibit improved pharmacological properties as well as reducing

materials cost. Some of these combinations are already finding their way into "modified" sugar coatings. Having a choice of solvents broadens the choice of coating materials.

We might also point out that enteric coatings are not readily adaptable to aqueous systems, except for some hydroxypropylmethyl cellulose phthalate systems that can be used with alcohol/water mixtures and the Eudragit 30 acrylic emulsion. The door is open for coating systems that are based on water and/or emulsion technology. This is especially true for the enteric and water insoluble (ethylcellulose) materials.

We have already discussed some of the relative advantages of handling aqueous versus organic solutions, but additional advantages can be realized if other polymers could be manufactured through emulsion technology. For Example:

1. Emulsion or latex systems offer low viscosity with high solids content. Twenty-five to 50% emulsion solids are readily spray-applied.

2. Emulsion systems are easily formulated because they can be diluted with water.

3. Water is evaporated more rapidly from emulsion systems than from solution systems because the emulsified particles coalesce and release the water more readily.

4. Temperature stability of emulsified systems during shipping and storage requires special, but not unusual, handling procedures.

Coating materials that lend themselves for aqueous systems seem to be readily available. In fact, the more recent introduction of low viscosity cellulose polymers has enabled some companies to take aqueous film coating seriously. It seems to me that suppliers to the pharmaceutical industry are interested in seeing that this segment of the market is well supplied. However, new polymers and/or latex emulsions of new and existing coating systems will still require FDA approvals. Several companies are already working with the suppliers who have established master files for newer coating compositions with the expected hope of obtaining the necessary approvals. Right now this is a rather slow process but, hopefully, as more interest and data are established, new applications can be processed more rapidly.

After this discussion of the advantages and disadvantages of aqueous vs. solvent film coating, it would seem prudent to hear how industry is evaluating these differences.

Before discussing some industrial experiences, I should like to point out that five years ago the then WARF Coating Laboratory did aqueous coating of pharmaceutical tablets and presented the information at the August ACS meeting. This work was eventually published in Microencapsulation: Processes and Applications, under the title, "Air Suspension Encapsulation of Moisture Sensitive Particles Using Aqueous Systems."

I remember we went into this program with full confidence that aqueous systems had a place in film coating pharmaceutical tablets. This confidence stemmed from the fact that the WARF Coating Laboratory had been encapsulating a wide variety of agricultural seeds such as ornamental flower, vegetable, and field crop seeds with aqueous systems for a number of years. Moisture and critical processing temperature conditions were extremely important in coating these products as they directly related to seed viability and storage. So, prior to encapsulating pharmaceutical tablets, we had already conducted several projects and had gained a great deal of expertise in aqueous film coating.

We first had to demonstrate that tablets with different moisture contents could be coated without changing their moisture content. This was done and the following chart shows data obtained under normal drying conditions and indicates that under those conditions little or no moisture was added to the product. When drying conditions are inadequate, the moisture content of the product does increase.

| Tablets | Percent Moisture | | |
|---|---|---|---|
| Uncoated | 3.2 | 2.5 | 1.0 |
| Coated, HPC | 3.1 | 1.4 | 1.0 |
| Coated, PVDC | 2.9 | 1.6 | 1.1 |

This data demonstrates that water applied as part of the coating system could be removed by the Wurster Process, but did not tell us whether damage to the core material might have occurred. Another series of experiments was conducted to determine the effect of aqueous coating systems on materials known to be sensitive to water. Ascorbic acid and acetylsalicylic acid tablets were selected because both are water-sensitive and both have degradation products readily determined by standard analytical methods.

The chart showing the data on acetylsalicylic acid tablets is included but the same type of experiment was done on ascorbic acid. Aspirin tablets containing 325 mg. (5 grains) of unstablilzed acetylsalicylic acid were analyzed for the decomposition product, salicylic acid. In this test a more distinct pattern is observed which reflects the effect of varying the coating conditions.

Decomposition of Aspirin
(% salicylic acid)

| Tablets | Process air Temperature | 10-14 Days | Accelerated Storage |
|---|---|---|---|
| Uncoated | | 0.09% | 0.23% |
| Coated, A | 130°F | 0.14% | 0.48% |
| Coated, B | 115°F | 0.12% | 0.18% |
| Coated, C | 110°F | 0.12% | 0.84% |

While all of the above samples surpass the U.S.P. standards for salicylic acid content in aspirin tablets, the differences between samples A, B, and C correlate with process temperatures during encapsulation. These tests indicate that either excessive heat as demonstrated in sample A, or inadequate drying as demonstrated in sample C, are undesirable and contribute to instability of the product.

It is observed in sample B that under properly controlled conditions it is possible to apply aqueous coating systems with a minimum of hydrolysis to the product.

After demonstrating that aqueous film coating was feasible, we did an evaluation of the energy and solvent costs associated with organic vs. aqueous film coating.

Energy and Solvent Cost

| Conversion Factors | Organic System | Aqueous System | |
|---|---|---|---|
| ) T (air 22°C @ 50% RH) | 38°C | 63°C @ 15% RH | 63°C @ 65% RH |
| 1000 CFM air, kcal/min. | 309 | 513 | 513 |
| Coating Time, Minutes | 40 | 105 | 58 |
| Approx. cu. ft. of Gas | 49.4 | 215.5 | 119.0 |
| ) CU. FT., Gas | 0 | 166.1 | 69.6 |
| Gas @ $0.0024/CU. FT. | $0 | $0.40 | $0.17 |
| Solvents (77 lbs.) @ $0.21/LB | $16.17 | --- | --- |
| Coating Rate, mls/min. | 875 | 330 | 600 |

Solutions: 35L 5% w/v Methocel A-15
(1:1 Methylene chloride: alcohol)
35L 5% w/v Methocel A-15, water
2.5% coating solids applied to 70 kg tablets

It was in 1974 that we became aware of some early work that Merck-Frosst was doing in Montreal with aqueous film coating and during the summer of 1975 we learned that Leo Pharmaceutical Products in Denmark was actively pursuing aqueous systems. More recently we were all made aware of aqueous coating systems being used by Merck Sharp & Dohme and Shaklee Corporation's coating of vitamins and minerals. Individuals from Leo, Merck, and Shaklee were kind enough to relate to me some of their thoughts about aqueous systems and their economic benefits in order that I might share these with you.

Leo Pharmaceutical Products is presently film coating with both aqueous/alcohol and aqueous systems. They are manufacturing five products and have now finished two-year stability tests with an acetylsalicylic acid tablet with good results. Presumably this product will be on the market soon.

FILM COATED TABLETS

Aqueous/Alcohol System:

Slow Release K CL
Multivitamin
Antibiotic

Aqueous System:

Antibiotic; Two
Acetylsalicylic Acid

The following charts show some comparative costs of film coating in the 18-inch Wurster Column, as supplied by Leo.

COMPARATIVE COSTS

| Pigmented Coating | Organic | Aqueous-Alcohol 1:1 |
|---|---|---|
| ) T (air 22°C @ 50% RH) | 38°C | 53°C |
| 1000 CFM, k cal/min | 309 | 432 |
| Coating Time, min. | 75 | 75 |
| Heat energy, k cal | 23,200 | 32,400 |
| ) Energy, k cal | 0 | 9,200 |
| ) Energy, KWH | 0 | 10.7 |
| Energy @ 0.30 d.k.r./kwh | 0 | 3 20 D.KR. |
| Solvents | 248 D.KR. | 74 D.KR. |
| Cost Differential | 171 D.KR. | - |

Organic vs. Aqueous- Alcohol Pigmented Coating Systems:

80L 3% w/v HPMC 50 cps (1:1 methylene chloride: ethanol)
55L 5% w/v HPMC 15 cps (1:1 ethanol: water)
Coating solution applied to approximately 70 kg. tablets.

COMPARATIVE COSTS – WURSTER 18-INCH

| Pigmented Coating | | Organic | Aqueous |
|---|---|---|---|
| ) T (air 22°C @ 50% RH) | | 38°C | 53°C |
| 1000 CFM, k cal/min | | 309 | 432 |
| Coating Time, min. | Small | 25 | 50 |
| | Large | 25 | 25 |
| Heat energy, k cal | Small | 7,730 | 21,600 |
| | Large | 7,730 | 10,800 |
| ) Energy, KWH | Small | 0 | 7.2 |
| | Large | 0 | 3.6 |
| Energy @ 0.30 d.kr. | Small | 0 | 2.20 D.KR. |
| | Large | 0 | 1.10 D.KR. |
| Solvents | Small | 156 D.KR. | 3.30 D.KR. |
| | Large | 78 D.KR. | 1.50 D.KR. |
| Cost Differential | Small | 151 D.KR. | |
| | Large | 75 D.KR. | |

Organic vs. Aqueous Clear Coating Systems:

Small tablets, 80-150 mg:

50L 3% w/v HPMC 50 cps (1:1 methylene chloride: ethanol)
20 L 8% w/v HPMC 6 cps, water

Large tablets, 400-700 mg:

25L 3% w/v HPMC 50 cps (1:1 methylene chloride: ethanol)
10L 8% w/v HPMC 6 cps, water

We have all heard about the new Merck facility in Elkton, Va., devoted to the production and aqueous film coating of Aldomet. In talking with Merck people in West Point, they made the following comments:

1. Merck has as a corporate commitment and goal to eliminate the use of chloroform in all film coating formulations. To this end, they are pursuing active programs relating to new formulations and coating techniques.
2. The pressures of state and federal regulating agencies toward solvent emissions and personnel safety have caused them to concentrate on aqueous coatings.
3. Some economics are realized as a result of coating with aqueous systems. These savings are in the range of 1¢ to 2¢ per 100 tablets.
4. They also stated that a disadvantage associated with aqueous coatings is their requirement for humidity control of the air system. This represents an expensive investment.

At this time Merck is applying aqueous film coating to Aldomet tablets. One other product is on the market and next month another product will be on the market. Their long range goal is to apply aqueous film coatings to all their film-coated products.

Merck has provided me with a few slides showing what goes on in the Elkton plant. In this facility they have four 24-inch Wurster units.

Another manufacturer converted to aqueous film coating is the Shaklee Corporation in Hayward, California. I have to say that the management of Shaklee deserves a big bouquet of roses for their commitment to convert from solvents to aqueous. They converted in "cold turkey" fashion. They were operating with 32 coating pans (42 inch) and 8 polishing pans on two shifts and replaced the solvent coating systems with two 46-inch Wurster Columns and aqueous film coating. If that doesn't show management commitment, I don't know what does—especially when we realize that the two 46-inch Wurster units are the first two manufactured for commercial use.

Shaklee personnel told me that the reason they felt so secure in converting to aqueous systems was because of the advantages they saw in the Wurster columns.

ADVANTAGES OF THE WURSTER COLUMNS

- Greater air volume provides increased drying capacity.
- Increased drying capacity results in:
    - Shorter cycle time
    - Greater flexibility in processing
    - Decision to go "aqueous" film coating
- Eliminated factors relating to solvent cost, handling, and emission control equipment.
- Scale-up 12-inch and 18-inch columns were valid for the larger units.

Six months ago they started applying aqueous film coating to three products. Some characteristics of these tablets and processing conditions are shown in the following table.

THREE FILM COATED PRODUCTS

7/16-inch diameter, compressed on deep cup punches

Hardness: Two, 14-16 Strong-cobb units
One, 6-8 Strong-cobb units

Processing Conditions:

8500 CFM processing air at 70°C
Exhaust air at 43°C
Air atomizing nozzles
400 kg per 45 minute cycle

Coated tablets evaluated statistically, rejection rate less than 1%.

The Wurster columns were manufactured by the Werner Glatt Company and supplied by Glatt Air Techniques, Inc. The slides of the installation and equipment were furnished through the cooperation of Glatt Air Techniques and the Shaklee Corporation.

Conclusion:

1. Changing existing products or converting established manufacturing procedures from solvent to aqueous film coating requires a sincere commitment on the part of management. In fact, I relate such dedication to a corporate philosophy that such changes are better for the corporation, it's employees, and the people it serves.
2. Several major companies have successfully marketed a variety of products from aqueous coating systems.
3. Each of the companies with aqueous coated products have indicated some tangible economic benefits associated with the change.