Radical Change in Research and Development:

The Shift from Conventional Methods to High Throughput Methods

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Paint and coating formulations are incredibly complex mixtures of a large number of ingredients. Even a simple clear coating or varnish formulation can consist of one or more resins and crosslinkers, solvents, curing catalysts, flow and leveling additives, gloss modifiers, stabilizers, and so on. Pigmented coatings require these same ingredients and, in addition, usually consist of several pigments and their dispersants and dispersion stabilizers.

Coatings must also meet a *combination* of performance requirements. All coatings have numerous requirements for appearance (color, gloss, texture), mechanical properties (hardness, flexibility, adhesion), durability (corrosion, weathering), and application (viscosity). The coating formulator is therefore challenged to use whatever information she can find to help her decide what ingredients to use, and also in what ratios to mix the ingredients in order to achieve the optimum in performance properties.

With all of the technical advances occurring in the world today, the process of formulating new coating products has largely remained unchanged. Some key improvements have been made in that the formulator now has access to computer software that can retrieve raw materials from a database and allow the formulator to experiment with various ratios of ingredients before committing to making and testing a formulation. Statistical experimental design, or design of experiments (DOE), has also become available in the past 20 years or so. However, statistical experimental design has not yet become standard practice for coatings formulators.

When it comes to making and testing coating formulations, essentially the same methods in use for over 100 years are typically used today. Recipes are developed, ingredients are weighed into a glass jar or can one at a time, mixed one at a time, coating test panels are prepared one at a time, cured, and properties measured one at a time. This process is repeated over and

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over until a formulation is identified that meets or is close to meeting the target requirements of the application. When the number of *possible* formulations is compared to the number of *actual* formulations prepared, a significant gap is readily apparent. Is there any way to close this gap and begin to approach the preparation and testing of the large number of potential formulations?

HIGH THROUGHPUT METHODS

Combinatorial and high throughput methods have been practiced in the field of drug discovery for over a decade. This approach began with the recognition that it was almost impossible to predict what specific chemical compound (i.e., a drug) would have a desired effect in treating a disease or condition. Synthesizing a series of compounds one at a time and testing them one at a time is an extremely inefficient use of resources, especially time and personnel. Thus, methods were developed to facilitate synthesis of multiple compounds simultaneously—in parallel—and then to also screen them for their activity, again in parallel. These techniques have evolved to the point that libraries of thousands of chemical compounds can be synthesized and screened in a single day.

With the recognition that the *throughput* of synthesis and testing of chemical compounds could be significantly accelerated, there has been growing interest in applying similar methodologies to the formulation of materials, including polymers and coatings.[1-7] Coating formulations are particularly suited to the application of high throughput methods due to their complexity. Coating formulations are *complex* due to the fact that the effect of each ingredient in a formulation, and especially the interaction of the ingredients in a formulation, cannot be completely predicted by fundamental theory. Thus, the only way to determine these effects and arrive at a satisfactory formulation is through experimentation.

Improving the throughput of experiments is expected to have several important consequences. First, acceleration of the experimental process means that a series of experiments that once took six to 12 months can now take one to two *weeks* to arrive at the same result. For a company that is in the business of selling coatings products, this acceleration means that the time from product conception to product introduction can be shortened considerably, increasing competitiveness and product value to the company.

Next, and equally important, since many more experiments can be carried out than is possible using conventional methods, significantly more compositional variations can be explored in a short period of time. Compositions that have a unique performance profile and are more highly optimized can result. More robust formulations can be identified as well. For example, it is well known that many additives used in coatings formulations must be carefully optimized since either too little or too much material can adversely affect the coating's performance. It is also known that additives can often interact with each other or other formulation ingredients in unexpected and, usually, undesirable ways. It is also often the case that a coating formulation may be "on the edge"—meaning that a very small change in composition may result in an unstable or unusable coating. Conducting experiments where the composition is systematically varied to map out the compositional space can identify those formulations that are on the verge of yielding undesirable or unstable results. Thus, these situations can be identified early before the product is introduced, resulting in a product that requires less maintenance after being introduced to the customer.

Third, being able to conduct large numbers of experiments and capture the results of the tests means that we can begin to approach understanding the effect of composition on performance in a way that was not possible before. Empirical and semi-empirical models can be constructed using data collected from large numbers of experiments that can be used to predict performance of coatings, further shortening development time.

THINKING THROUGH THE TRANSITION

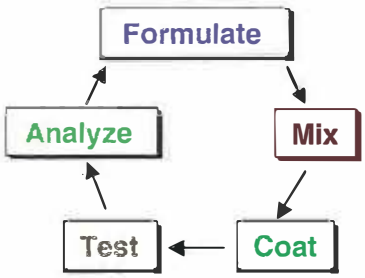
While a lot of emphasis has been placed on the design and implementation of complex and expensive automated systems, researchers can begin to use many of the concepts of high throughput experimentation now. There is a logical series of steps that can be undertaken in order to move from conventional experimental methods toward high throughput methods.

One of the first things that can be done is to *identify the workflow*. Everyone already practices a workflow, whether they are conscious of it or not. So, for example, a typical workflow for someone developing a coating formulation includes the steps of formulating; writing down the formula they will prepare; mixing the ingredients of the formulation; preparing a coating of the formulation; and testing the coating for key properties. Finally, the results of the experiment are analyzed and used to decide on the next formulation. This process is illustrated in *Figure* 1.

Once the workflow is identified, it can be further broken down into the individual steps. For example, formulation preparation involves dispensing various raw materials. What is their physical state: solid or liquid? What is the viscosity of the liquid raw materials?

How are these materials normally dispensed? Then, what are the slow steps in this process? These slow steps are also known as *bottlenecks*. Eliminating or improving the time it takes to solve these bottlenecks can have a large impact on the time it takes to conduct the entire workflow.

Figure 1—Typical workflow used for coating development.



Two main approaches can be taken to improve experimental throughput. The first is to reduce the time it takes to conduct an operation or task. Consider the time it takes to dispense low viscosity liquids. Gravimetric dispensing usually involves the user adding the liquid dropwise into a container while simultaneously watching the weight readout on the balance. The addition rate is slowed as the target weight gets closer. Volumetric dispensing can be carried out much more rapidly and accurately than gravimetric dispensing. Handheld pipettes are available that will reproducibly deliver microliter to multiple milliliter quantities of liquid reagents. These usually employ disposable pipette tips, so that after one reagent is dispensed, the tip is replaced with a fresh one and the next reagent can be quickly dispensed in sequence.

Next, begin examining the workflow and identifying areas where tasks can be conducted simultaneously—in *parallel*. Some hints of transitioning to a high throughput approach can already be seen in many laboratories. Many formulators are already in the habit of designing several formulations, then lining up jars or cans in a row and dispensing one raw material in each container, followed by the next material and so on. Likewise, the process of coating application can be sped up by arranging several test panels in a row in the spray booth, and then applying paint to the entire row of panels simultaneously.

Another consideration is to think through the quantities of materials that are produced. Especially in the early stages of coating development, small volumes of material are all that is needed to screen a variety of resins, catalysts, crosslinkers, additives, solvents, etc., in order to begin to select the key ingredients for the coating. For these early stages, 10–50 ml of formulation is probably sufficient in contrast to 100 mL–1 L batches that are typically used now. Conducting these experiments in small volumes means that more compositions can be prepared without needing larger amounts of raw materials or generating additional waste.

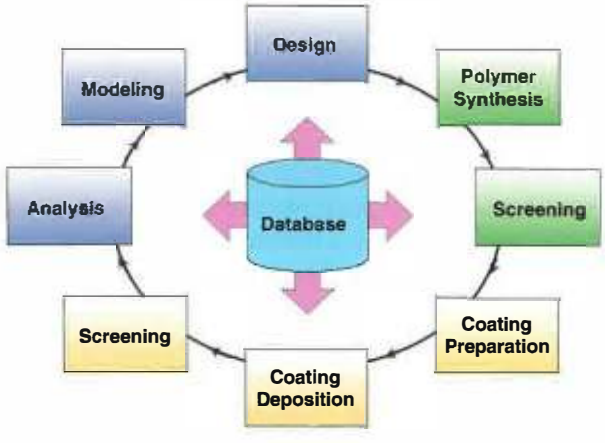
Capturing all of the compositional information and also the experimental results in a searchable database is another consideration at this stage as well. Just think where most organizations would be today if they had been gathering formulation and property information in a searchable database over the past 10 or 15 years. This is especially critical since the amount of data generated increases substantially as a result of the increasing number of experiments that are conducted as high throughput methods are implemented. Conventional database software or integrated laboratory information management systems can be used for building a database.

The next logical step is to think about adding some automation to the process. There are many liquid-dispensing robots on the market that are relatively economical to purchase. Implementing software to capture compositions and analysis results in electronic form is critical in being able to develop correlations between the compositions and results when a large number of compositions are prepared.

THE ULTIMATE GOAL: AUTOMATED WORKFLOWS

The ultimate goal is to accelerate the process of experimentation by at least an order of magnitude. Realizing this goal requires the automation of all of the operations performed in the development of coating formulations. While not completely realized as of now, a number of significant steps have been taken in instrumentation that automates many of the important stages and screening methods. A complete workflow is illustrated in *Figure* 2 and includes the steps of experiment design, polymer synthesis, polymer screening or characterization, coating preparation, coating deposi-

Figure 2—Complete coatings research and development workflow.



tion or sample preparation, coating property screening, and, finally, data analysis and modeling. In a fully integrated workflow, all of the compositional and analysis information is captured in a database for future analysis and use in constructing models.

This workflow is really not all that different from the workflow illustrated in *Figure* 1. The main difference is that each step of the workflow involves multiple samples instead of a single sample. Each major phase in the workflow may also consist of additional steps. In designing the methods used in each step of the workflow it is important that the throughput of each stage is closely matched. Otherwise, bottlenecks can be introduced that impede the overall throughput of the entire workflow.

Design

Successful high throughput experiments begin with a good design. A good design is even more important when conducting high throughput experiments since a bad design wastes a significant amount of resources. Both full factorial and fractional factorial design approaches can be taken when designing high throughput experiments and newer approaches specifically amenable to combinatorial experiments are also being developed.[5-8] When high throughput methods are used, large experimental designs can be run in a single experiment.

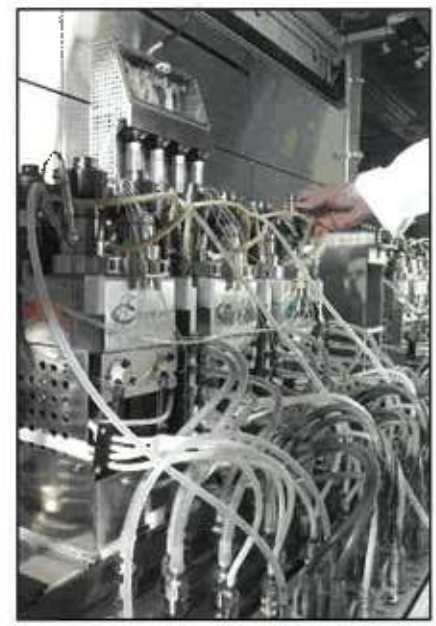
Polymer Synthesis

The polymer or resin system is a crucial part of any coating binder system. Initially, high throughput synthesis of polymers has employed chemical synthesizers or simple batch reactors.[9-18] Most monomers are low viscosity liquids and are readily dispensed using automated pipettes or syringes. Solid initiators or catalysts can be dissolved in solvent for dispensing into the individual reactors. These batch reactors usually employ vortex mixing or magnetic stirring; therefore, polymerizations have to be carried out under dilute solution conditions to ensure that the viscosity remains low enough for good mixing. A unique advantage of these automated synthesizers is that they can usually be set up with online GC or HPLC/GPC systems, which allows them to be used for kinetic analysis of polymerization reactions.[19-22] Emulsion polymerization can also be carried out in an automated synthesizer.[23] Only recently have reactor systems been introduced for polymerization reactions that employ mechanical stirring.[24] Chemspeed has introduced a sophisticated parallel polymerization reactor system with mechanical stirring, individual temperature control, and the capability to feed reagents to the reactor over time (*Figure* 3). Free radical, anionic, and ring opening polymerizations have been effectively carried out in the simple batch reactor systems; however, there have been no reports of the high throughput synthesis of alkyd or polyester resins yet. Particular challenges with these types of polymers include the high viscosity, the high polymerization temperature, and the need for removal of reaction byproducts.

High Throughput Polymer Characterization

Following synthesis, the polymers need to be characterized. In many cases for modest workflows (~20–50 samples per experiment) commercially available analytical test systems with autosamplers can be used. These would include commercially available HPLC, GC-MS, GPC, and DSC systems. For rapid molecular weight determination using GPC, rapid GPC systems are available from Symyx and Polymer Laboratories. A rapid GPC measurement can take as little as 10 minutes per sample in contrast to 30–45 minutes per sample for conventional systems. Matrix assisted laser desorption-ionization time of flight mass spectroscopy (MALDI-TOF) is a rapid method for measuring polymer molecular weight and it has been applied to the analysis of polymer libraries.[25-27] For compositional analysis, a high throughput FTIR system is available from Bruker[28] and Pike offers several high throughput accessories for a variety of FTIR spectrometers.[29]

Figure 3—Chemspeed Autoplant A-100 Reactor system for parallel polymer synthesis.



Coating Formulation

Coating formulation involves the dispensing of resins, crosslinkers, solvents, pigments, and various additives, followed by mixing of these to form a liquid coating formulation. A number of automated liquid handling robotic dispensing systems are commercially available and many of these have been employed for dispensing of coating materials. A particular challenge is that many of the materials used are relatively high in viscosity where dispense accuracy using volumetric pipettes can be less than optimum. Mixing of high and low viscosity materials can

Figure 4—Symyx Coatings Formulation System with automated viscometer.

also be a challenge. Magnetic mixing is the simplest to implement. An alternative is to employ mechanical mixing. The Symyx Coatings Formulation system is a typical approach (*Figure* 4). It incorporates an automated liquid dispensing system, magnetic stirring, and also includes a viscometer for measuring the viscosity of coating formulations.[2] This system has recently been used to automatically determine the pot life of two-component coating formulations.[30]

Several systems have been developed for the automated dispensing of free-flowing powders such as pigments. Dispensing of powders is usually less accurate than dispensing liquids and a common practice is to determine the actual dispensed weight and then adjust the remainder of the formulation in proportion to maintain the proper ratios.

Coating Application

After mixing of the coating ingredients the coating must be deposited and cured to form a solid film that can be screened for key properties. Symyx and BASF have developed automated drawdown methods for the application of coating films to a variety of substrates.[2,6] GE developed a silicone template and a unique heated centrifuge to prepare arrays of coating samples.[31] Inkjet printing of polymer solutions can also be applied to the deposition of liquid coatings.[32-35] Another approach is to deposit coating formulations into the bottom of standard microtiter plates. Often the method and format of application is determined by the screening test to be employed.

Coating Property Screening

Following application, the coatings must be screened for key properties. Often one or two properties may be identified as primary screens and tests developed to screen for these key properties. A number of methods for measuring physical and mechanical properties of coating films have been developed and described in the literature. In some cases, depending on the format of the sample array, conventional instruments for measuring gloss and color can be used. These instruments are also available with computer interfaces so that the data can be collected in a database. Specialized systems have been developed to characterize coating surface energy,[2,36,37] coating hardness using nanoindentation methods,[38] abrasion resistance of coatings,[39] coating adhesion,[40] scrub resistance of latex paints,[41] and vapor barrier properties.[42] A parallel dynamic mechanical thermal analysis (DMTA) system has been developed to measure the viscoelastic properties of polymers.[43] The parallel DMTA system analyzes 96 samples in one experiment and can be used to determine glass transition temperature, bulk modulus, and crosslink density of thermoset materials. A recent book describes a number of additional characterization and screening methods used for polymer film characterization.[3]

Data Analysis

Gathering all compositional and analysis data for each experiment carried out is required in order to maximize the usefulness of the methodology. A number of approaches have been described and several commercial software packages are available that assist in data collection and analysis.[4,44,45] Data can be analyzed using statistical software programs, such as *DesignExpert*, *JMP*, or *Minitab*. Multivariate data can be visualized and analyzed using *Spotfire*. Data from well-designed experiments can be used to develop models of the effect of key independent variables on the properties of the resulting materials.[46] These models have predictive potential: compositions that have not been prepared yet can be identified that have an optimum combination of properties.

FUTURE CHALLENGES

While a lot of progress has been made in the development of automated high throughput systems for coating development in the past five years, there are a number of significant challenges for the future. A particular challenge is accurate and automated dispensing and mixing of high viscosity "liquids" that do not form free-flowing powders. Another challenge is dispersion of pigments on a small scale. In addition, a workflow has not yet been reported for the development of powder coatings. Additional tools for automated characterization of key properties are also needed. Small-scale simulation of coating application equipment has not yet been addressed. However, now that the revolution

has been started, it is expected that new tools and methods will continue to be developed.

CONCLUSIONS AND OUTLOOK

High throughput methodology is a radical change in how experiments are carried out and can revolutionize how laboratories operate in the future. As these methods become more widespread, organizations that do not adopt high throughput methods will be at a significant disadvantage. Simple steps can be taken to begin moving toward high throughput methods now. A number of automated methods have been described in the literature and many additional methods for sample preparation, characterization, and screening continue to be developed. In the future it is expected that these methods and systems will be as commonplace and indispensable to the process of coatings and material development as the personal computer is today.

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