On-line Process Control and Process Analytical Technology: Integration of Chemical Engineering Practice into Semiconductor and Pharmaceutical Industries

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Abstract:

FDA's PAT Initiative provides an unprecedented opportunity for chemical engineers to play significant roles in the pharmaceutical industry. On-line process control, as an enabling process understanding tool and advanced quality control strategy, has been widely adopted in other industrial sectors. In the present manuscript, the authors will provide their perspectives on the need of chemical engineering principles in pharmaceutical development for a thorough process understanding. From the on-line process control perspective, we will discuss the following topics: (1) how can chemical engineering help meet the challenges from the semiconductor and pharmaceutical industries? (2) how can the chemical engineering practice be integrated into the semiconductor and pharmaceutical industries to achieve process understanding and the desired state of quality-by-design?

A real-world case study from the semiconductor industry will be presented to demonstrate how a classic chemical engineering concept, mixing homogeneity, can be implemented by inducing forced flow to ensure an excellent Copper Electrochemical Plating Process (Cu ECP, a key process in Cu technology) performance.

The concept of Dr.Taguchi's robust engineering design will be briefly discussed with a case study of brake system design. This case study will illustrate how the quality-by-design can be achieved through appropriate experimental design.

The third aspect of this manuscript deals with the comparison between a modern chemical plant and a pharmaceutical plant. From the engineering and quality perspectives, the disadvantages of the current pharmaceutical manufacturing mode, the advantages and challenges of Process Analytical Technology (PAT), and the roles of chemical engineering in facilitating and implementing PAT will be discussed. The case study of freeze-dried sodium ethacrynate will be presented to demonstrate the vital importance of controlling the processing factors to achieve the desired product stability.

On-line process control and PAT can help the pharmaceutical industry to realize the maximum benefits of the advancements in modern instrumentation, analytical technologies, and robust engineering design, and to achieve process understanding and the desired state of quality-by-design. On-line process control and PAT can maximize the output-to-input ratio at a reasonable cost. Chemical engineers can play a vital role in facilitation and implementation of PAT system in the pharmaceutical industry.

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1. Introduction

With the advancement of science and technology, process automation and computerized process control has gained broad applications in many industrial sectors, especially in the mass production environments such as those of petrochemical refining, metallurgical processing, precision instrument processing, optical fiber processing, and semiconductor manufacturing, etc. Significant benefits are: (1) tightened process control that leads to better product quality with reduced defective products; (2) automatic process control that enhances process understanding for the highly technical multivariate process; (3) high throughput for each individual process step as well as the entire manufacturing line. Consequently, the benign interaction between process technology and process product quality has not only greatly promoted the well-being of individual industry sectors, but also helped process industries to keep their competitive edge.

For on-line process control, in addition to the necessary peripheral support, a control system usually consists of two components: a control loop or algorithm and a process sensor that serves as the interface between the process space and control system. While the process industry has been the leader for developing advanced control strategies, in recent years much attention has been directed to the development of on-line sensors and probes [1-4], which enables the on-line process control. As one of the major tools in the FDA Process Analytical Technology (PAT) [5] domain, process control will be one of the key aspects which can help to design and ensure pharmaceutical manufacturing quality. In the following sections, we will discuss the similarities and differences among different industry sectors such as chemical, integrated circuit, and pharmaceutical industries, from a process analytical perspective. Some case studies will be presented to demonstrate how chemical engineering practice can be integrated into semiconductor and pharmaceutical industries, through on-line process control and the process analytical technology approach.

2. Comparison of process perspective between chemical plant and integrated circuit

Modern chemical plants involve high temperatures, high pressures, and catalysts. The process flow could be very complicated, and hence require the process control. Multiple control points are often necessary such as, temperature, pressure, flow rate monitoring and regulating at different locations within the manufacturing line. Depending on the degree of complexity of the device fabricated, the semiconductor industry normally uses many (up to hundreds) unit processes, including hot processing and ion implantation, pattern transfer, thin films, and process integration to finish the device fabrication [6]. A typical semiconductor manufacture mode for a CMOS fabrication is shown in Figure 2.1.
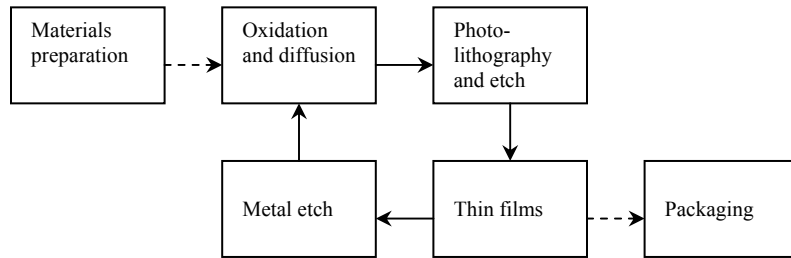
Figure 2.1 A typical semiconductor manufacture mode

In this typical semiconductor manufacture mode, the four major unit processes connected by solid arrows outline the major components of a typical fabrication line. Tremendous research, development, design and testing work was done on each process step and its integration prior to starting a manufacturing process line. This work enables fundamental process understanding and process control implementation. For this mode, the following QC and process control strategies have been utilized to reduce defects and improve yield:

- Strict QC system including SPC is exercised in each process step and between process steps;
- Monitor lots are placed at-line periodically;
- On-line process control is an essential and integral part of every process technology. The relationship between individual process and process equipment/tool starts at the R&D stage.

Although there is huge difference between a typical chemical plant and an integrated circuit (IC) in terms of size, it is interesting to compare them [7] from the process perspective, as listed in table **2.1**.

Table **2.1** Comparison between chemical processing and integrated circuit

	Specific characteristics	Typical chemical plant	Typical integrated circuit
Similarities	Reaction rate (1st order)	10^6 l/moles/s	10^{10} l/moles/s
	Cost	$\$10^8 \sim 10^9$ /mi^2	$\$10^8 \sim 10^9$ /mi^2
Difference	Size	Macro-, meter	Sub-micro or nano-meter
	Raw material sources	many but depleting	electrical ground
	Number of species	10^2	2 (electron, hole)
	Transport via	pipe (10 inch. O.D.)	wire, metal interconnect (10^{-5} inch O.D.)
	Storage	tank (10^6 moles)	capacitor (10^{-10} moles)
	Pump	10 hp	10^{-9} hp (bipolar transistor)
	Flow rates	10^3 moles/s	10^{-11} moles/s
	Process control	gate valve on-off valve check valve	FET (field effect transistor) Transistor Diode
	Process mode	Continuous	Semi-continuous
	Number of reactions	many	Recombination/generation
	Diffusion coefficient	$10^{-2} \sim 10^{-5}$ cm^2/s	$10 \sim 10^3$ cm^2/s
	Unit operation	10^4 /mi^2	10^{16} /mi^2
Common ground	QC strategy	Statistical Process Control (SPC) and Engineering Process Control (EPC)	Statistical Process Control (SPC) and Engineering Process Control (EPC)

Table adopted from TABLE 1 in literature [7]. Courtesy of Professor Tim Anderson in University of Florida.

Even though a huge difference exists between these two areas, the process control strategy is the same, that is, reducing the process variability to achieve great product quality, through statistical process control (SPC) [8] and engineering process control (EPC) [9-10].

3. A case study from the semiconductor industry to illustrate how a semiconductor industry responds to the marketing pressure and technology driven force to innovate its manufacturing process continuously

As marked by the information explosion age, today's expectation by users and all of society towards the information processing speed has been increasingly higher than ever. The integrated circuit, is the core of the information-processing unit such as computer, has to meet this marketing challenge. On the other hand, the whole semiconductor industry has been striving to follow the famous Moore's Law, which in the original form states that the number of components (e.g., transistors) on a chip will be doubled every 18 months. In response to these challenges, the semiconductor industry needs to continuously develop its processing capability which can be used to fabricate integrated circuits with smaller dimension and faster responding speed. One of the critical unit processes is the metal interconnection, since the shorter the interconnection delays, the faster the IC responds.

The interconnect delays are imposed by the following equation:
$$t = RC \tag{3.1}$$
Where t stands for the interconnect time delay, R represents the metal line resistance, and C represents the capacitive coupling between metal lines. Figure 3.1 is the scheme of a resistor-capacitor (R-C) circuit, which can be used as the representative of a simplified IC.
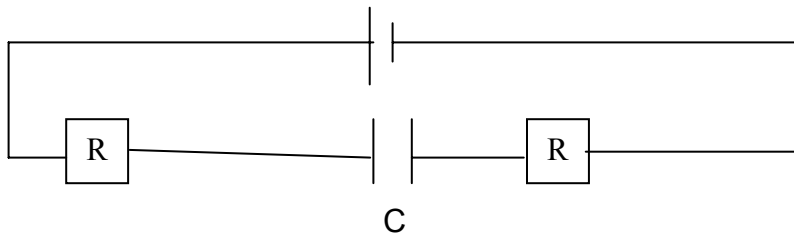

Figure 3.1 A resistor-capacitor (R-C) circuit

The interconnect time delay can be characterized by the R-C circuit time constant τ, as shown in Figure 3.1. The smaller the time constant τ, the shorter the charging process and the faster the circuit.
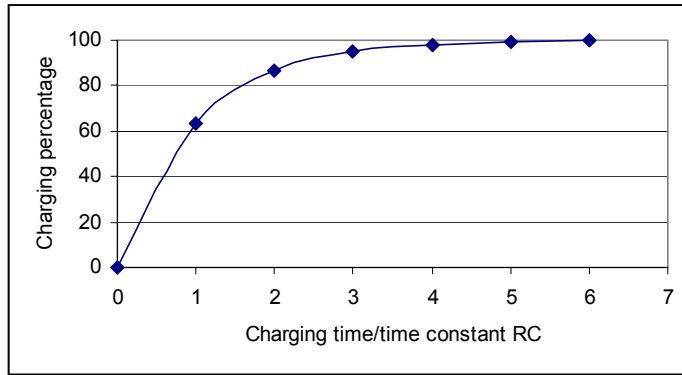
Figure 3.2 *R-C* circuit charging curve

One question will rise naturally: how to decrease the time constant? According to the definition, $\tau = RC$, several alternatives can be used to achieve this goal: (1) decrease the resistance R; (2) decrease the capacitance C; (3) decrease both R and C simultaneously.
R and C are related to the materials' properties by the following equations:

$$R = \frac{1}{\sigma} \cdot \frac{L}{A} \qquad (3.2)$$

$$C = \kappa \frac{\varepsilon_0}{d} \qquad (3.3)$$

Where σ is the electrical conductivity, L the length, a cross-section area, κ dielectric constant, ε_0 permittivity of the dielectrical material, d physical separation, R resistance, C capacitance, τ time constant.

Currently, the majority of material for metal interconnection is aluminum whose electrical conductivity σ is 3.65 ohm^{-1}m^{-1} [11]. To reduce R, one can choose a more conductive material for metal interconnection. Copper is a good candidate for this since its electrical conductivity σ is 5.88 ohm^{-1}m^{-1}. To reduce C, we need to make use of materials with smaller k; this explains the motivation of developing low k materials. Regardless of the challenges that the industry has to face for Cu integrated with low k materials, and the Cu technology itself presents a great challenge to the thin films and Cu removal areas. Compared to the matured Al metal interconnection, Cu metal interconnection has to face the following challenges:

- Al sputtering is a dry process, but Cu electrochemical plating is a wet process. There are at least three challenges for the Cu process, such as electrochemical plating (ECP) chemistry development, electroplating bath quality control, and electroplating defect control.
- Al can be etched to create pattern, but Cu can not be etched away. Instead, Cu removal has to use chemical mechanical polishing (CMP) or other alternative [12].
- Cu wiring integration issues need to be resolved before the Cu process can be commercialized.

In order to realize the metal interconnection transition from Al to Cu, semiconductor industry-wide resources including R&D, fabrication line, and equipment vendors have been

teaming up to tackle Cu technology, low k materials, and Cu/low k integration vigorously. Significant progress has been made in the Dual Damascene Copper Process Technology including Cu electroplating, Cu removal, and Cu low k integration, etc. [13~15]

3.1 A case study of on-line process control in copper electrochemical plating area: Cu ECP chemical control

3.1.1 Brief review of Cu ECP chemistry development

Cu electroplating is an old technology that has been widely used in the plating and metal finishing industry. However, conventional Cu plating cannot be directly applied to the semiconductor industry for wafer plating, due to a variety of reasons. For example, (1) Si wafer is not conductive; (2) small features with high aspect ratio in the Si patterned wafers can not be filled seamlessly. This stimulated the development work on the Cu electroplating chemistry study. In addition to the inorganic components such as Cu^{+2}, Cl^{-1} and acid, more research has been focused on organic components. Two-components chemistry (accelerator and suppressor) and 3-components chemistry (accelerator, suppressor, and leveler) have been in the market place for a few years, although their chemical structures and properties still remains as trade secrets. Each individual component has its specific function to help the electrochemical plating process, as listed in Table **3.1**.

Table **3.1** Functions of individual component in the electrochemical plating of Cu

Individual component	Function in the electrochemical plating process	Two component chemistry	Three component chemistry
Cu^{2+}	Being reduced and deposited at the wafer surface	yes	yes
Cl^-	Help additive (organic component) function	yes	yes
Acid	Adjust pH and conductivity	Yes.	yes
Accelerator	Grain refiner; directly involved in deposition mechanism	Yes. Usually contains pendant surface atoms	Yes. Usually contains pendant surface atoms
Suppressor	Adsorb at the Cu surface and polarize the interface	Yes. Polyethers or polyoxyethers, high molecular weight	Yes. Polyethers or polyoxyethers, high molecular weight
Leveler	Adsorb at the Cu surface	no	Yes. Nitrogen-containing surfactants; protonated in acidic solutions

3.1.2 Cu ECP bath quality control

For the Cu ECP process, its plating chemistry plays a significant role as stated below:
- the degree of gap-filling is determined to a large extent by the action of organic additives;
- organic additives affect many deposition properties such as stress, crystallography, etc;
- the impurities introduced by organic additive breakdown may pose a problem;
- organic additives are consumed during plating.

Therefore, to ensure void-free gap fill and decrease the number of defects, it is necessary to monitor Cu ECP bath quality on-line. Furthermore, it is critical to replenish individual components and/or dump the bath solution as needed, in order to maintain the bath quality.
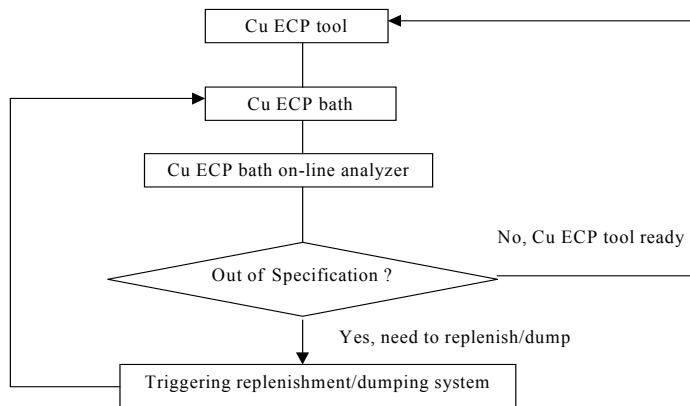
Figure 3.3 A typical Cu ECP on-line bath quality control algorithm

Figure 3.3 outlines a typical Cu ECP bath control algorithm. Some of the field data of accelerator concentration of Cu ECP bath are shown in Figure 3.4. Based on the on-line concentration chart and replenishment/dumping data, the consumption rates of the accelerator are shown in Figure 3.5.
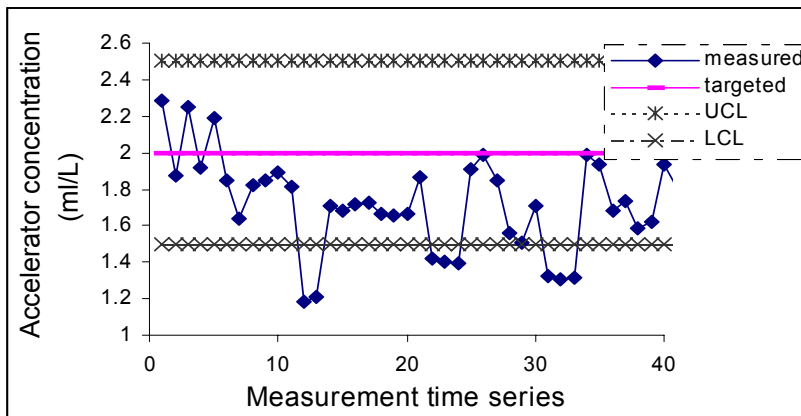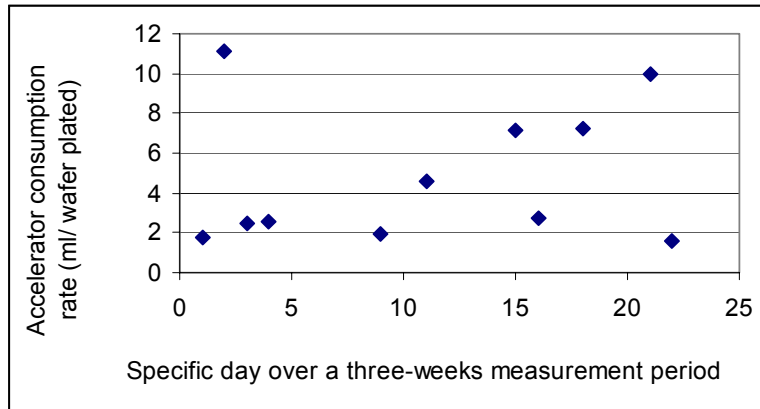

Figure 3.4 Field data of Cu ECP bath

Figure 3.5 Consumption rate of ECP bath

Field data for Cu ECP bath (not shown here) tells us a few more facts: (1) the accelerator is not stable over time in the system; it will degrade in the Virgin Make-up Solution (VMS). There is idle consumption even when the Cu ECP tool is not operating. (2) Bath mixing homogeneity needed improvement since measurement results at different times followed by replenishment are different. While there is not much we can do for the accelerator stability due to the chemistry constraints, we can improve the bath mixing homogeneity through engineering approach. From the fluid mechanics perspective, we have two options: (1) form forced convection by using propelled mixer; (2) form forced flow for better mixing. The first option can be expensive given the Cu ECP bath being very corrosive and hence only stainless steel would be the choice of materials. The second option virtually does not cost anything since we only need to change the sampling point from the top of the bath container to the bottom of container. Figure 3.6 outlines such a strategy.
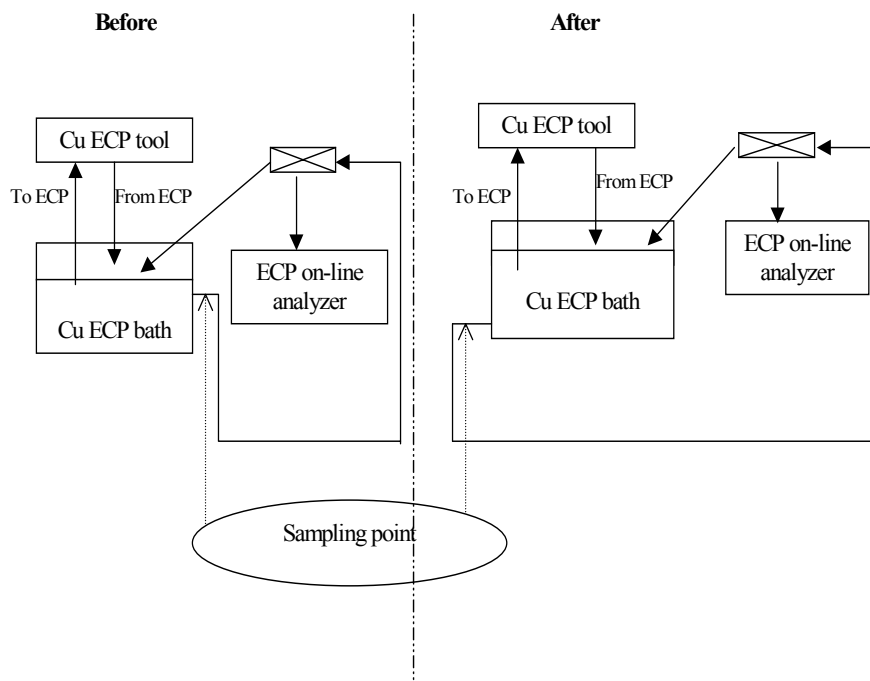
Figure 3.6 Engineering implementation for improving bath mixing homogeneity by changing the sampling point from the top of the bath container to the bottom of the bath container

The benefits from such an engineering implementation can be easily appreciated when we look at the accelerator consumption rate for a period of two weeks as shown in figure 3.7.
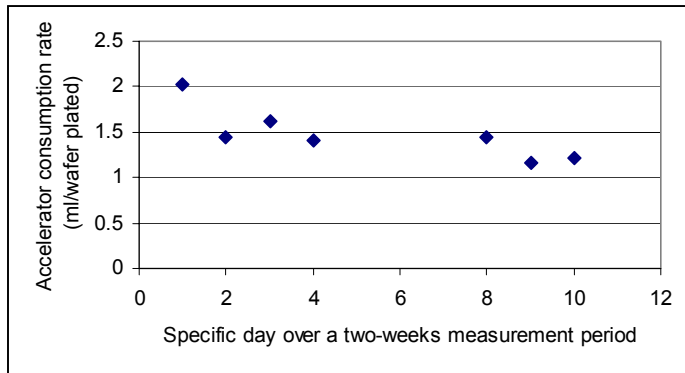

Figure 3.7 Accelerator consumption rate after improving bath mixing homogeneity

If we compare this figure to Figure 3.5, the following observations can be made:
(1) the accelerator consumption rate is dropped to around 1.5 ml/plated wafer;
(2) the accelerator consumption rate is reasonably stable.

Voids

Voids-free

0.14um Trench 1000A PVD Cu Seed Layer
Bad bath control

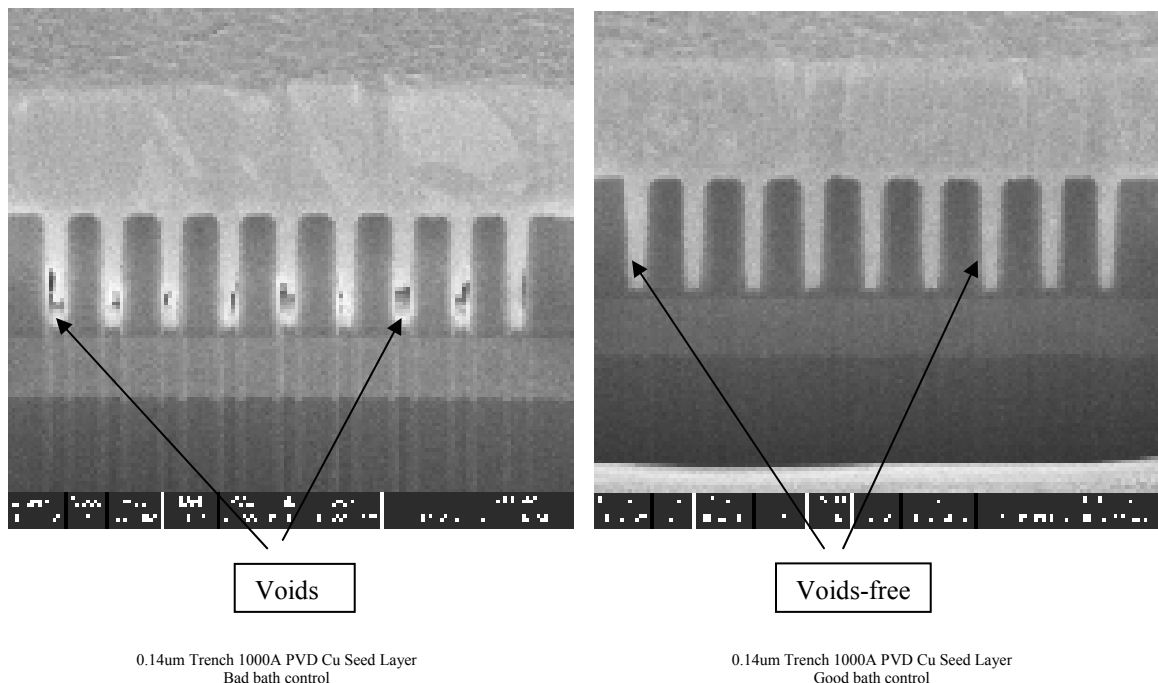0.14um Trench 1000A PVD Cu Seed Layer
Good bath control

Figure 3.8 Focused Ion Beam (FIB) images to compare the gap-filling capability of bad and good ECP bath control

Another comparison can be made in terms of gap-filling performance. Figure 3.8 shows two Focused Ion Beam (FIB) pictures of two plated wafers with 0.14 µm trenches (aspect ratio of

5.4). One was plated with bad bath control condition; the other was plated with good bath control condition. While voids are easily found at the bottom of trenches for bad bath control, essentially voids-free gap-filling was achieved by good bath control. This is an example demonstrating that good on-line process control ensures good Cu ECP performance.

4. Quality-by-design: an example in the automobile industry

The Taguchi Methods for Robust Engineering[TM] was created after World War II, when Dr. Genichi Taguchi was leading a group to develop a new phone system with better connection performance for Japan. Over the past 40 years, this methodology has been applied to different industry sectors such as automobile, chemical, semiconductor, aerospace, etc., with excellent results. The idea is based on identifying the "ideal function(s)" for a specific technology or product/process design, and relies on selectively choosing the best nominal values for design parameters that optimize performance reliability (even in the presence of factors causing variability) at the lowest cost. One example of applying the Taguchi method to achieve quality-by-design is the design of brake pad material [16]. Figure 4.1 illustrates the concept of signal-to-noise in the brake system design.

$$S/N = \frac{\text{Energy Transformed to Perform the Intended Function (Work Done by Signal)}}{\text{Energy Transformed to Other Than the Intended Function (WOrk Done by Noises)}}$$
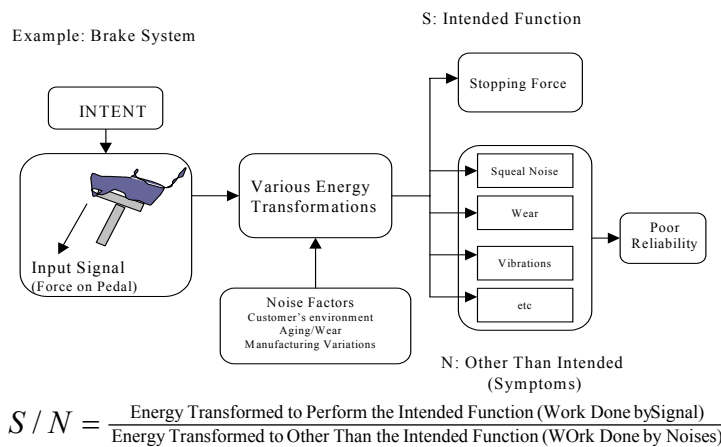
Figure 4.1. Concept of Signal-to-Noise Ratio (adopted from literature [16])

Obviously the higher the S/N ratio, the better is the quality. Improving the signal-to-noise ratio is an important objective for the pad design. Parameter design, as it specifies the proper nominal values of the design parameter settings (levels), will make the design robust against noise. Control factors were used to optimize the product/process for robustness against noise factors. Figure 4.2 shows an example of how to use the parameter design to obtain a robust pad design.
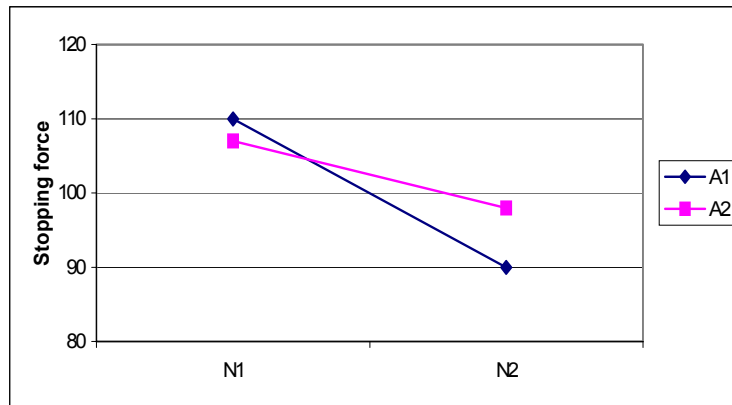
Figure 4.2 Interaction between control and noise (adopted from literature [16])

Here response variable is the stopping force generated by a brake. Control factor A is the amount of additive in brake pad (A1=5%, A2=8%). Noise factor N is the customer's usage condition (N1=new pad and dry condition, N2=worn pad and wet condition). From figure 4.2, for new pad and dry condition, the two designs (A1 and A2) will generate approximately the same stopping force, although A1 design is a little bit better. However, for worn pad and wet condition, A2 design will generate a bigger stopping force (~98) than A1 design (~90). Therefore, A2 design is more robust than A1.

5. Comparison between a modern chemical plant and a pharmaceutical manufacturing plant: process perspective

There are many fundamental aspects of similarity between the chemical industry and pharmaceutical industry. As examples, unit operations such as fluidized bed drying and crystallization are widely used in both chemical and pharmaceutical industries. While many unit operations in the chemical industry are accompanied by chemical reactions such as gas absorption with chemical reaction in an agitated tank [17], (e.g. reaction absorption of SO_2 gas in purification section of the ammonia synthesis production line), understanding these processes is more challenging. On-line process control helps gain process understanding and improve reactor design and unit operation equipment design. On the other hand, the nature of unit operations in the pharmaceutical industry is more physical than chemical, as outlined in Table **5.1**; therefore, the process steps are relatively simple compared to their counterparts in modern chemical and semiconductor manufacturing lines. However, the slurry phase in the pharmaceutical system makes it hard to implement on-line process control due to several reasons. Usually solid or slurry phase is not easily conveyed as liquid is, also the deposition of the materials on the probe/sensor would bias the measurements, and hence present a challenge to PAT in the pharmaceutical industry.

Table **5.1** Comparison between a modern chemical plant and a pharmaceutical manufacturing plant

	Specific characteristics	Modern chemical plant	Typical pharmaceutical plant
Similarities	Mass transfer	Dry, mix, crystallization	Dry, blend, crystallization
	Heat transfer	Dry (spray dry and rotating dry)	Dry (fluid bed drier or oven drier)
	Momentum transfer	Fluid flow	Slurry flow
	Reaction	Synthesis and conversion (high T, P)	Synthesis
Differences	Species handled	Most gas/liquid, less solid	Most solid/liquid, less gas
	Operation mode	Continuous	Batch
	Process state	Steady state	Semi- or unsteady state
	Process volume	Large	Small in many cases
	Equipment	Process-specific	Multiple-use
	Process control	Computerized	Lab-intensive
	Regulatory agency	EPA	FDA
Common ground	Start-up and maintains	Unsteady state	Unsteady state

6. Typical pharmaceutical process mode by direct compression and its inherent disadvantages

Taking a coated tablet as an example, a typical pharmaceutical process mode may be shown in Figure 6.1.
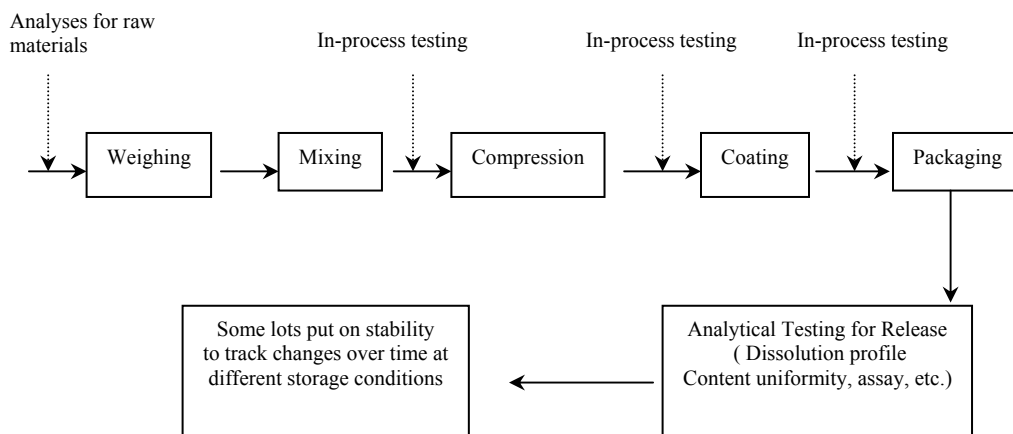
In-process testing now: sample and complete analytical testing,
-if all specifications are met, go to the next process step
-if all specifications are not met, reject or rework the batch

Figure 6.1 Typical pharmaceutical process mode

There are some inherent disadvantages for the current pharmaceutical process mode, such as:
(1) It requires extensive off-line lab testing, hence it is lab intensive and less efficient. This is essentially test-into-quality, not quality by design (built-in). Often unnecessary rejections lead to waste since no assignable cause can be made.
(2) It is batch operation mode, not continuous mode, therefore produces low efficiency.
(3) Additional time is required in the total manufacturing process to complete testing.

(4) Off-line test data may not reflect the real situation due to:
- o Surrogated sample size from the population is not the best way to predict the overall behavior in the process. It may just capture a portion of what has been happening in the process due to lack of representativeness of the sampling.
- o Some changes (such as moisture content, particle segregation, etc) may take place after sampling, during transferring and storage of the samples.

7. FDA's Process Analytical technology (PAT) Initiative

7.1 An example showing process factors affecting pharmaceutical product quality and formulations

A freeze-drying process is often used to prepare stable parenteral formulations of drugs that are unstable in aqueous solution. The physical form, chemical stability and dissolution characteristics of these products can be influenced by process conditions [18]. For example, sodium ethacrynate could be freeze-dried to form a chemically stable crystalline form or a less stable amorphous form, as illustrated in Figure 7.1 and Figure 7.2 (adopted from Fig. 2 and Fig. 3 in literature [18]).
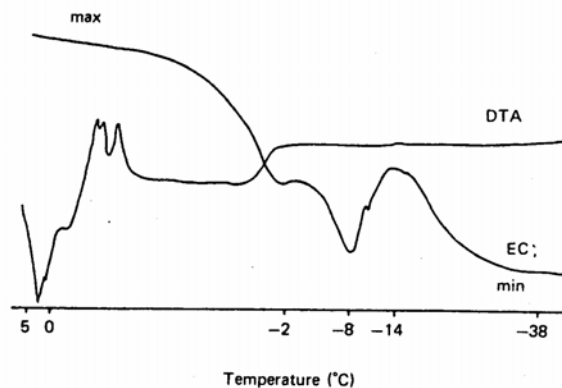

Figure 7.1 DTA and EC profiles of 4% w/w aqueous solution of sodium ethacrynate cooled to – 140 ^{0}C (20 ^{0}C/min) and warmed at 1.5 ^{0}C/min (adopted from Fig. 2 in literature [18])

In Figure 7.1, the EC (electrical conductivity) profile shows a surge peaking around -14 ^{0}C which demonstrates that more crystalline form is being formed. Meanwhile, a transition occurring between –40 ^{0}C and –14 ^{0}C indicated by a shallow DTA endotherm was observed, which characterizes the transformation from amorphous form to crystalline form in that temperature range.
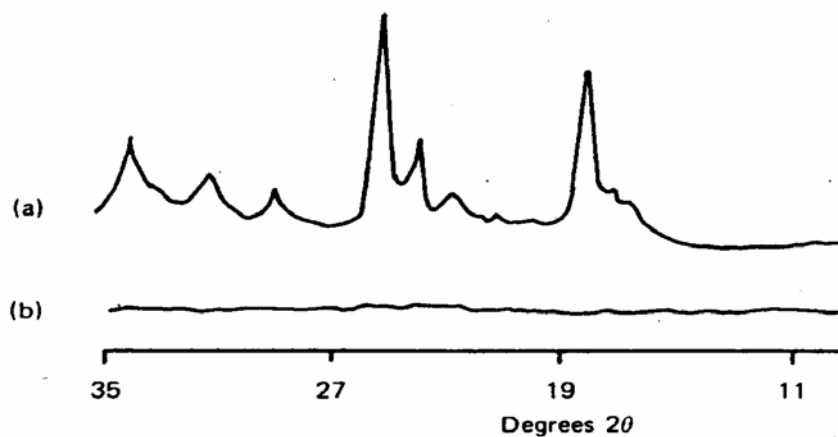
Figure 7.2 X-ray powder diffraction patterns of (a) slow cooled and (fast) freeze-dried sodium ethacrynate (adopted from Fig. 3 in literature [18])

In Figure 7.2, at freeze-dried condition (fast drying), sodium ethacrynate is essentially an amorphous form since its X-ray power diffraction patterns show nothing but an almost flat line. Because the cooling speed is so fast there is not enough time for the phase transformation (in this case crystallization) to take place. Whereas at slow cooled condition, multiple characteristic peaks show up in the X-ray powder diffraction patterns, which clearly indicate that some crystalline forms have been formed during the cooling processes.

While this case study only serves as an example to illustrate the importance and necessities of controlling process factors precisely in the production of freeze-dried pharmaceutical products, it also highlights some of the benefits that PAT can bring into the pharmaceutical industry, which are discussed below.

7.2 PAT in the pharmaceutical industry

"FDA considers the PAT to be a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality. It is important to note that the term *analytical* in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner. The goal of PAT is to understand and control the manufacturing process, which is consistent with our current drug quality system: quality cannot be tested into products; it should be built-in or should be by design." [5]

Process analytical technology (PAT) has enormous advantages for the pharmaceutical industry. From the process perspective, the benefits of PAT include:
- understanding the process. On-line or real time process control leads to a better understanding of the process and better assured product quality by reducing variability in the process;
- quality is built-in. Quality control starts at the R&D and design stage, and penetrates through the entire life cycle of the product. In this sense, it is an integrated quality control concept;

- it can reduce reject/rework and lead to a more efficient process.

While implementing PAT in the pharmaceutical industry can help shift the quality paradigm from testing-into-quality to quality-by-design, many challenges are required to be addresses:

(1) Industrial challenges

For legacy products, the industry has been making them that met cGMP requirements. While trying to bring PAT into these products, a lot of issues may arise. In fact, the manufacturing of some of these products is more arts than science and engineering. For those products, implementation of PAT may need to redesign the process.

(2) Engineering challenges

While implementing PAT, engineering issues can be great challenges to the pharmaceutical industry. If we take the manufacturing mode described in Figure 6.1 as an example, some possible challenges may include:
- How to put the variability of raw material and/or in-coming materials characteristics (chemical, physical, etc) into design consideration so that the product/process can accommodate the variability from the system level?
- How to deal with the blend uniformity issues? How does the type of blender impact the blending results? The blend uniformity issue may be associated with dead spots in the blender/mixer, sampling techniques, data quality, and possible segregation after blending. Process engineers will have to familiarize themselves with knowledge in equipment design and sampling theory, and be able to make good judgment about the data quality, and have awareness of engineering-related issues during material handling and transferring.
- How does the compression process impact the physical properties of the in-process materials and the final drug product attributes?
- How to convey solid? Settling of particles may block pipelines. Moisture may promote formation of cake, which may cover the view window of the equipment. If a probe is placed there for data acquisition, artifacts and bias will be a difficult issue. This issue may occur during blending and coating process.
- Does the packaging material interfere with the efficacy and strength of the final dosage form?
- How to handle the inherent variability of the dissolution test? Dissolution profile might be affected by a lot of chemical and physical properties of the drug products, such as formulation parameters, compression force, tablet hardness, coating materials and coating thickness, and microstructure of the drug matrix, etc. The variability of the dissolution process itself due to content inhomogeneity of substance and hydrodynamics in the dissolution vessel has been well appreciated in chemical industry, but not yet in the pharmaceutical industry.
- How to handle the materials characterization issues associated with the process such as content uniformity issue? How to use off-line laboratory data to generate model for on-line process control?
- How do process factors and storage conditions impact product stability and product shelf-life [18]?

- How to deal with process/equipment scale-up challenge so that laboratory and pilot plant results can be scaled up to manufacturing line [19]? R&D will face this challenge during the technology transfer. In chemical engineering practice, dimensionless group method [20] and scale-up rule study [21] have been proved to be an efficient way for engineering scale-up. In the drug regulatory area, scale-up and post-approval change (SUPAC) [22-23] has been setting up a good example for science-based decision making.
- How to use multivariate statistics [24] to establish the correlation among the formulation parameters, process conditions, and final dosage quality attributes? How to establish the causal link [25] between these parameters so effective control strategies can be developed?

In the semiconductor industry, one single device may involve hundreds of processing steps. To increase the process yield and device liability, the Motorola initiated the famous six-sigma concept which has been widely adopted in the semiconductor industry. If a process achieves six-sigma, there will be only about 2 parts per billion of defective products. As a contrast, the pharmaceutical industry has very few processing steps. Further, most of these steps are physical in nature even for the most complicated process lines. If the concept of quality by design and process control strategies that have been widely adopted in the semiconductor industry are implemented and executed in the pharmaceutical industry, the probability of product failure should be much smaller. However, today's reality for the pharmaceutical industry is pressing because of an increasing trend toward manufacturing-related problems. For example, the number of prescription drug recalls in the US market has been increasing from 176 in 1998 to 254 in 2003 [26]. As part of the FDA strategic plan "FDA Critical Path Initative", PAT provides an exciting opportunity for quality by design, process control, and quality improvement in the pharmaceutical industry.

7.3 The roles of chemical engineering in implementing and facilitating PAT

When the unit operation concept was first introduced by AIChE in 1922, it typically dealt with the simplest physical separation such as gravity sedimentation and evaporation. As promoted by large-scale industrial production, a lot more sophisticated unit operations such as reactive crystallization, reactive distillation, and vacuum-freeze drying [27], have been developed and commercialized. Many non-traditional chemical engineering courses such as biotechnology, materials characterization, microelectronic processing, computer languages, process control and information theory, have been introduced to the chemical engineering curriculum over the last decade. In this sense, chemical engineers are well equipped with modern chemical engineering knowledge and should have better-than-ever opportunities to meet challenges that emerge from process industries including the pharmaceutical manufacturing industry.

PAT represents one of such opportunities. The pharmaceutical industry provides an exciting platform for the chemical engineering professional to play a significant role during implementing and facilitating PAT. Some examples include,

- mechanistic understanding of the process and performing process modeling from a first principles approach;

- taking a lead role to integrate engineering considerations into the prototype design and test at the R&D stage of process and product development;
- taking a lead role in the product/process/equipment scale-up and technology transfer;
- contributing to the manufacturing process by leading PAT implementation;
- engaging process control to deal with pharmaceutical unit operations and resolve any engineering-related issues;
- taking the primary role in the process optimization.

In his famous speech titled as "How will chemical engineering influence pharmaceutical engineering practice" in 2000, late chemical engineering professor at the University of Florida and particle engineering pioneer in the world, Dr. Brian Scarlett, said that chemical engineers "control and design processes in order to make products," as well as "design and control products." Product design and process design are like the left and the right hand. He concluded that chemical engineers can help the pharmaceutical industry move forward from being an inventing and testing industry to a design industry.

8. Concluding remarks

The availability of on-line process control tools coupled with FDA PAT Initiative have provided wonderful opportunities to chemical engineering discipline and chemical engineers. PAT, as an emerging technology from the pharmaceutical industry, could serve as a spring board for integration of chemical engineering practice into the pharmaceutical industry. The principles of quality-by-design with on-line process control, a fundamental understanding of unit operations, principles of mass and energy transfer can maximize the output-to-input ratio of pharmaceutical products at a reasonable cost. Chemical engineers can play a vital role in introduction/implementation of PAT to the pharmaceutical community.

The views and opinions expressed in this paper are only of authors, and do not necessarily reflect the views or policies of the FDA.

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