A Case Study - 3D Powder Deposition onto Pharmaceutical Tablets

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Abstract
This paper presents the case study of a project conducted by Torrey Pines Research for Phoqus Pharmaceuticals wherein the requirement was to uniformly coat pharmaceutical tablets with various proprietary dry powders. This paper discusses the technical challenges, electrostatic constraints, solution options, and the resulting system solution.

Background and Problem Statement
Historically, pharmaceutical tablets have been coated in order to protect and seal the tablet, identify the drug, mask taste, and create a desirable appearance with brand identity. The traditional tablet coating process has been a batch process using a spray liquid mixing, tumbling, and drying process.

Problems with the current coating technology have included: (a) coating thickness variation, (b) damage to tablet features due to the aggressive tumbling process, (c) water and solvent based lacquer coating materials, potentially detrimental to certain drugs and environmentally unfriendly, and (d) a batch process resulting in an inability to tailor the coating to individual tablets and a large financial exposure if problems occur in the coating process (millions of tablets must be discarded).

Phoqus desired to be able to individually coat 3-D tablet surfaces with various dry powders using an in-line process. Their goals also included: (a) single system to coat many different tablet shapes and materials, with many different coating materials, (b) uniform and controlled coating thickness, (c) ability to utilize water soluble coating materials, (d) very low wastage, (e) speed consistent with manufacturing volumes (50K to 100K tablets per hour), and (e) an extendable process for coating with active drugs.

Phoqus contracted Torrey Pines Research (TPR), experts in using electrostatics to control the placement of dry powders as used in the electrophotographic and other electrostatic digital printing processes.

Technical Challenges
When TPR first considered the initial requirements as stated by Phoqus, the following three technical challenges were identified over those that were normally encountered in typical reprographic applications: 1) 3-D (three dimensional) surfaces - The vast majority of all reprographic applications involve writing images onto flat surfaces, such as paper. The pharmaceutical tablet application required a deposition system to be able to place uniformly thick layers of dry powder around all surfaces of a three dimensional tablet, 2) The use of many different powders and tablets - In a typical dry powder development system as used in an electrophotographic printer, the interaction between the dry powder and its development system, fusing system, and substrate are so complex that the dry powder and its development system and fusing system are designed and optimized as an integrated set (the notion of changing the dry powder material strikes fear and despair into the hearts of the system design team). In Phoqus' application, the requirement was to be able to change the dry powder material and/or the tablet material on a moment's notice, without there being significant system ramifications, and 3) Precision requirements - A typical electrophotographic printer, depending on the design and application requirements, deposits dry powder in the range from 0.5 to 1.0 mg/sq-cm, with a tolerance of approximately +/- 10%. Phoqus' requirement was to place the dry powder with a precision of +/- 2%.

Even faced with these unusual and challenging requirements, TPR believed that the electrostatic dry powder development technologies developed throughout the history of the electrophotographic printing industry, provided the basic platform from which improvements and clever extensions could evolve.

Solution Options and Methods
Material Resistivity
The first requirement in converging on a recommended dry powder deposition process was to determine the operating windows for the dry powder and the tablet from a material conductivity perspective. From the perspective of placing and moving electrical charges on and through a dielectric material, it was important to know whether the powder and tablet were insulative or conductive during the dwell time of the deposition process. In electrostatics, it is important to understand the concept of conductivity and resistivity within the time frame of the process. That is, a given material may be considered resistive in one process that occurs in a very short time, and that same material may be considered conductive in a process that occurs over a longer time frame. Thus, one must determine the time constant for the electrostatic charge transport phenomena in the process being studied. More on this later, but suffice it to say that for the time frames of the process envisioned for this tablet application, that a material may be considered conductive if its resistivity is less than 10^8 ohm-cm and is resistive if the resistivity is greater than 10^{11} ohm-cm. Unfortunately, as Mother Nature would have it, many materials are somewhere in between the above values, and will in fact change from being resistive to conductive depending on the moisture content of their environment. These materials would present the most difficulties, because once a process is designed to work with a set of materials with a given resistivity, the same process will not work if the

resistivity properties of the materials change from being considered resistive to conductive or vice versa.

Given the above constraints, TPR defined the following matrix as the available "playing field" for the materials:

Operating Regions for Tablet and Powder Resistivity

	Insulative Tablet	Conductive Tablet
Insulative Powder	Acceptable	Acceptable
Conductive Powder	Acceptable	Unacceptable

As can be seen in the above table, TPR was able to envision an electrostatic dry powder deposition process that could be made to work in three of the four possible combinations of tablet and powder resistivities. The only combination that would not work was where the tablet and the powder were conductive. This makes sense because if both materials were conductive, then neither could support an electrostatic charge once in contact with the other and thus no electrostatic coupling force between the powder and the tablet could be established and maintained. As previously mentioned, a difficult problem with real world materials was that they tended to be in the critical zone of resistivity, that between 10^8 and 10^{11} ohm-cm. In that region, changes in the environment could transition a material from one region to the other, and thus result in a process that was unstable.

In working together with the chemists and material technologists at TPR and Phoqus, it was learned that tablets could be created that were in the conductive region more stably than if they were in the insulative region, and likewise, powders could be created that were always insulative. Thus, the operating region was established to be that in the upper right of the above table - conductive tablets and insulating powders. Typical tablet materials were Dibasic Calcium Phosphate and the powder materials were proprietary water-soluble formulations.

Deposition System Hardware

The next task facing TPR technologists was to architect a electrostatic deposition system that could reliably and controllably deposit powder under the above material constraints at the desired process speed. Since the driving science involved electrostatics, we had to be able to electrostatically charge the dry powder and move the charged powder in the presence of an electric field to the conductive tablet. There are two primary powder based processes used in the reprographics industry for creating images. These are known as single-component and dual-component development systems and are described below:

Single Component Development (SCD)

A typical SCD system is illustrated in Figure 1. The SCD system utilizes one critical consumable material, namely the powder to be deposited by the system. The purpose of the hardware in the SCD system is to triboelectrically charge the powder against the hardware components in the system: (a) developer roller, (b) supply roller and (c) trim bar, and then transport the charged material into the development zone wherein it is transferred to the substrate of choice using electrostatic forces.

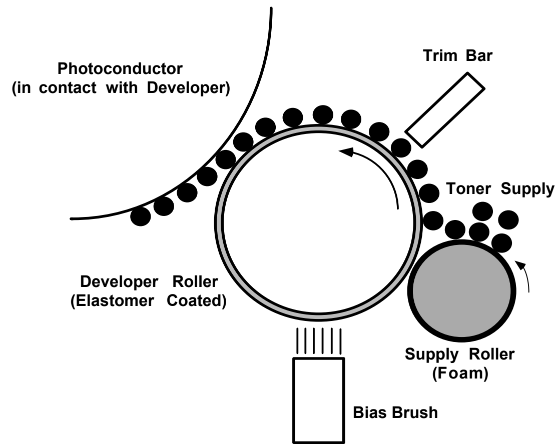

Figure 1

The primary advantages of SCD include: (a) no secondary consumable materials that might contaminate the tablet, (b) no powder concentration control system, (c) proven system in numerous EP products, and (d) relatively simple and inexpensive hardware.

The primary disadvantages of SCD include, (a) Speed - It was believed that the maximum process speed for which a single SCD system could support the deposition requirement was approximately 5 cm/sec. Thus, to achieve the desired throughput, multiple development systems would be required, (b) Less material flexibility - The SCD system is designed to generate charged dry powder due to triboelectric charge exchange between the dry powder and the hardware components in the SCD system as mentioned above. Thus, if new dry powder material is desired, a redesign of the surface properties of the fixed hardware components of the SCD system is required.

Dual Component Development (DCD)

DCD is one of the oldest of the reprographic development systems. It contains two critical consumable materials: (1) the powder material to be deposited, and (2) a coated metallic and magnetically active powder in the mix with the desired powder to be deposited on the tablet. As these two powders are mechanically combined, they electrostatically charge oppositely against each other. The relative proportion of these powders to each other must be carefully controlled in order to produce repeatable results.

As illustrated in Figure 2, the developer roll consists of a metal shell around a magnetic core. Various configurations of this roll have been commercialized. In the Phoqus application the magnetic core rotates and the outer shell was stationary. The lower part of the roll is immersed in the dual component powder mix.

As the core rotates, the magnetic field penetrating the shell causes some of the powder mix to be picked up and transported around the shell. Changing magnetic fields that cause the powder to alternately rotate also mechanically agitate the powder mix. This mechanical action has the effect of loosening the imaging powder from the surface of the magnetic powder.

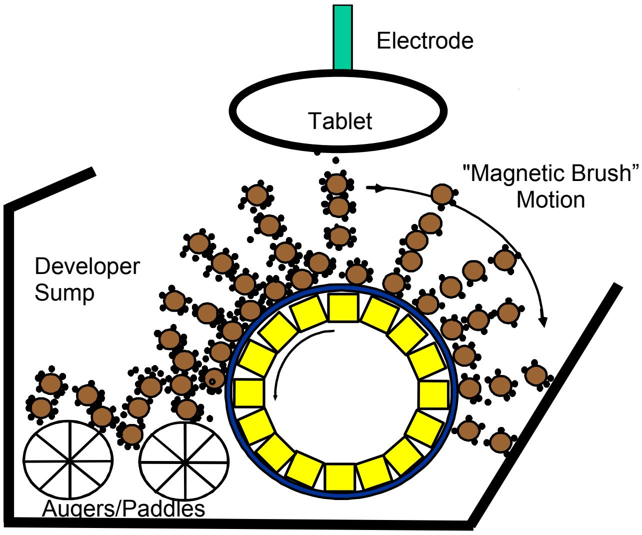

Figure 2

As the transported powder mix approaches the tablet, it begins to react to the electric field between the shell and the tablet. The electric field is set to be stronger than any remaining electrostatic forces holding the imaging powder onto the surface of the magnetic powder. This results in some of the imaging powder being attracted to the surface of the tablet where it is electrostatically held. The tablet is held at a fixed space above the roll and does not contact the powder mix on the surface of the roll.

The amount of powder coating on the tablet is controlled by the size the of the electric field between the tablet and the shell, the relative speed of the tablet and the shell, the duration of the applied field, and the electrostatic charge on the imaging powder. Imperfect, incomplete or non-uniform coating results if these parameters are not appropriately controlled.

The primary advantages of DCD include: (a) Established technology - One of the oldest (~50 years) and well understood development systems used in EP, (b) Speed - Has demonstrated ability to image at high process speeds, as high as 500 cm/sec, (c) Material flexibility - The dual component nature of the materials in the system, being the dry powder plus the metallic powder (called carrier), allows changing of powder materials to be accommodated by changing the material and surface properties of the carrier along with the ability to change certain process set points, without having to make hardware modifications to the development system.

The primary disadvantages of DCD include: (a) System complexity – DCD requires: (i) monitoring and control of the mass concentration of dry powder to carrier material, (ii) a metered toner addition system responding to a control system, and (iii) appropriate toner and carrier mixing hardware, (b) Carrier material–The material must be approved by the FDA since it comes in contact with the working powder and in some instances, could transfer directly onto the table.

Hardware Choice

After numerous periods of testing of both SCD and DCD systems, together with investigations into the potential material compatibility issues of a carrier material with DCD systems, eventually DCD was chosen as the working hardware for all ongoing system implementations. The magnetic roll coating hardware used for ongoing development work and pilot production activities is based on a commercial developer system used in the Heidelberg (now Kodak) 9110 high-speed printer and is illustrated in Figure 3.

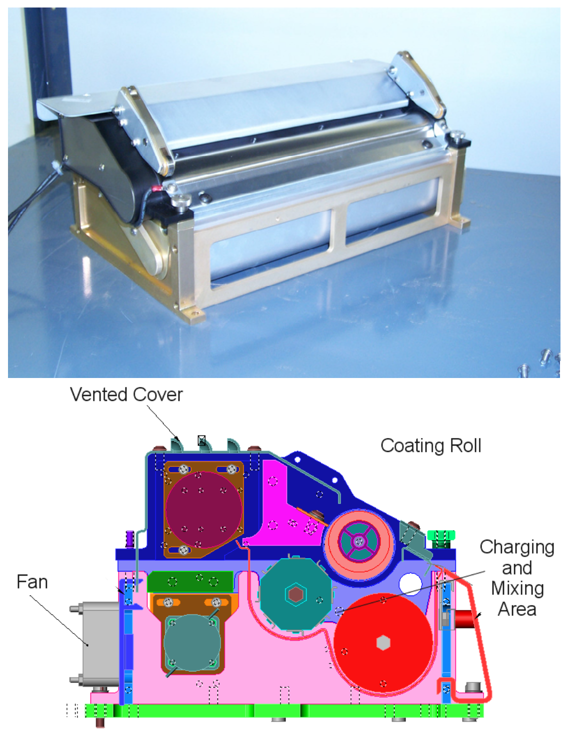

Figure 3

Materials

Coating Powder (Toner)

In order for the electrostatic process to be completed and controlled in a similar way to that used in copiers and printers, the imaging powder (known as toner in the reprographic industry) must meet certain requirements. Simply put, the small powder particles must be moved around using only electrostatic forces. Particles will be most easily moved if they have relatively high electrostatic charge per unit mass. This property is known as the triboelectric charge to mass ratio, or more often, “tribo”.

One of the other critical requirements for the powder is that it should be easily fixed to the substrate (tablet) after imaging is complete. In most electrophotographic systems this fixing is accomplished by melting the powder. Since the bulk powder is usually contained in a large reservoir or bottle, it is also important that the powder not form aggregates or clumps in the reservoir.

This would inhibit its ability to flow from the reservoir into the imaging system.

Another important property of the toner powder is particle size. Ideally the powder must be made in a particle size range from about 5 µm to 15 µm. In the typical manufacturing process for toner, these sizes are routinely achieved using standard processing equipment.

Reprographic toner is generally made up of plastic resin, colorant, and additives. The additives are used to make changes in physical properties such as triboelectric charge characteristics, glass transition temperature, and flow.

The Phoqus application would result in a set of materials that must be approved for the pharmaceutical purpose by the FDA. Since the powder to be ultimately deposited was to be provided by the customer, Phoqus, those powders were already chosen to be FDA approved, however their characteristics as an imaging powder had to be modified by TPR chemists within the constraints of materials available with FDA approvals.

Carrier

The second powder in the system serves two functions. It is used to electrostatically charge the imaging powder and to transport the imaging powder to the coating area. This means that the two most important properties of the carrier are its magnetic properties and its electrostatic properties.

There are two broad types of magnetic carriers, those that are magnetically permeable but not permanently magnetized, and those that are permanently magnetized. The Heidelberg/Kodak developer system uses the latter type. Strontium Ferrite, approximately 50 microns in size with various coatings of acrylic and silicone was utilized.

In order to use the powder (toner) and carrier in a magnetic brush development system, the two powders must be blended in such a way that the electrostatic properties are optimized. Adjustment of the ratio of the materials, known as the toner concentration or TC may then be made and the experiment repeated until the desired charge per unit mass (Q/M or tribo) is achieved.

Tablet Holding Hardware

The task of designing the tablet holding hardware included: (a) securely holding the tablet in place, (b) making electrical contact with the tablet, and (c) not requiring cleaning due to contamination with imaging powder.

The tablet must be held in such a way that an electric field can be set up between the tablet surface to be coated and the coating system. The holding system must be electrically isolated from the tablet; otherwise the holder will also become coated with powder.

Figure 4 shows a cross section view of the tablet holding system. A vacuum is applied up the center tube and this holds the tablet in place throughout the process steps. The material in immediate contact with the tablet is a soft conductive elastomer so that the electric field can be applied by contact while insuring good conformability to the tablet surface. The outer shield is isolated from the tablet contact as shown. A voltage opposite in polarity to that on the tablet is applied to the outer shield. This system design relies heavily on technology and configurations developed for the reprographics industry, specifically for laser printers and copiers.

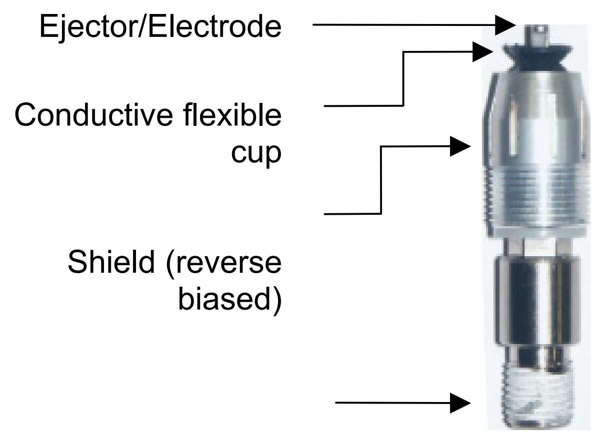

Figure 4

Process Integration

The initial experimental work was aimed at understanding the coating process using commercially available toners. TPR blended these toners with available carriers to determine the combinations that could provide good charge characteristics. The aim was to produce a combination of materials, known as developer, with an approximate ratio of 1 part toner to 9 parts carrier by weight. That yields a toner concentration or TC of 10%. Ideally this combination will have a charge per unit mass, or tribo, in the range of 15 to 35 micro coulombs per gram.

After a satisfactory developer blend was created it was loaded into the magnetic brush developer and run to assess its suitability as a developer. Some material blends created a dust cloud when run in the developer, indicating that the charge relationship between the powders was insufficient for maintaining adequate performance. This may have been due to its mechanical characteristics or some other quality.

After the system was well understood with commercially available toners, real Phoqus powders were introduced and system optimization began.

Three Dimensional Coating

In typical reprographic applications, the electrical field between the developer roller and the substrate is uniform due to the flat nature of most substrates. Since the electric field is a function of voltage and the distance between the roller and the substrate, the electric field in this tablet application was NOT uniform.

Therefore, a novel approach was developed to utilize the “theory of field collapse”. That is, the tablet speed through the development zone was set such that there was enough time for the powder to be developed to the tablet at each location around its surface to satisfy the electrical field, or in other words, to neutralize the field and develop the powder until the effective field was zero. In so doing, a uniform coating thickness was achieved during the process as demonstrated in Figure 5.

Figure 5

Figure 6

Summary

Using enhancements and extensions of electrostatic dry-powder deposition technologies, novel combinations of hardware, materials, and process set points were successfully established to enable the three dimensional coating of pharmaceutical powders on tablets to a uniform thickness. The combination of conductive tablets, insulating powders, dual component magnetic brush development, and a novel electric field collapse process, achieved the desired results. See Figure 6 for fully coated examples.

This work established that: (a) electrostatics can be adapted for specialized needs in powder coating, including variable distance & shape, production process speeds, and thickness uniformity, (b) the printer/copier industry provides a mature technology base, and (c) these technologies eliminate the use of solvents and provide new capabilities in pharmaceutical tablet manufacture and potentially many other applications.

Author Biographies

J. Randolph Sanders is currently President of Torrey Pines Research (TPR) and has been with TPR since shortly after its inception in 1986. He has 30-years experience in the design and development of digital printing products ranging from high-speed & high-performance to low-speed & low-cost monochrome and color systems. Mr. Sanders' responsibilities have included technical program management and strategic product planning for individual products and complete product lines. Mr. Sanders' areas of expertise include mechanical and electromechanical design, subsystem integration, paper handling, dry powder and liquid toner development, fusing, and high-resolution color systems Mr. Sanders, a frequent lecturer at industry conferences and technical seminars, earned his BS & MS in Mechanical Engineering, from the University of Florida.

Peter J. Mason is currently Senior Vice President and General Manager of Torrey Pines Research. He has more than 30-years experience in the development of printers and copiers including more than 20 years at Xerox Corporation. He is an early developer of laser printing and holds several of the basic patents in the field He also worked for several years in the famed Xerox "Skunk Works." Mr. Mason's technical expertise includes technology evaluation and selection, product architecture, program management, and monochromatic and color electrophotographic process physics with an emphasis on development and fusing. Mr. Mason maintains a close awareness of new products and technologies and their potential applications.

Marshall Whiteman, PhD, is a registered pharmacist and chartered chemical engineer. His current role is VP, Technical Development at Phoqus Pharmaceuticals Limited, where he is responsible for all aspects of technology and product development for the exploitation of Phoqus' novel electrostatic deposition and drug delivery systems. Dr. Whiteman gained both his B.Pharm. and his Ph.D. (in Powder Technology) from the School of Pharmacy, University of London. Since then, he has spent the last 18 years working in Pharmaceutical Research and Development with American Home Products, SK&F/SmithKline Beecham, Colorcon and, most recently, Phoqus.