Determination of Tablet Coating Distribution by Deconvolution of Uncoated and Coated Tablet Weight Distributions

Ji Zhou,1,2 Todd Williams,1 Herman Swopes,1 and Thomas Hale1

Received September 21, 1995; accepted December 16, 1995

Purpose. The purpose of this research is to obtain the tablet coating distribution from weight distributions of uncoated and coated tablets. Methods. The method of deconvolution with digital smoothing was used to calculate the distribution of coating applied to a tablet population from separate random measurements of individual uncoated and coated tablets. Results. It was demonstrated that the calculated coating weight distribution agrees well with the measured distribution. The effect of the smoothing factor on the solution is illustrated. Conclusions. This method can be used during development to facilitate process scale-up/optimization. In routine production, the method can assess the reproducibility and consistency of a coating process.

KEY WORDS: coating distribution; deconvolution; noisy data.

INTRODUCTION

Coating is a unit operation that is commonly performed during the manufacture of pharmaceutical products. Tablet coatings are used to: 1) control the rate and site of in vivo drug release, 2) mask unpleasant tastes or odors, 3) enhance physical or chemical stability, 4) improve easy of swallowing and appearance, and 5) provide product identity. In the ideal coating process an identical amount and distribution of coating is consistently applied to each tablet. This helps to assure that all tablets within and between batches are of comparable quality. Coating uniformity is particularly important in controlled release applications where the thickness of the coat can affect safety and efficacy. In reality, the amount of coating that is applied to individual tablets during a typical coating procedure exhibits a normal distribution. In a well designed coating process the width of this distribution will be as narrow as possible. The objective of this work is to describe a method that can be used to quantify the uniformity of coating in a tablet population. This tool can facilitate the development and optimization of pharmaceutical coating processes.

Several methods are currently used to evaluate coating uniformity. These methods include qualitative as well as quantitative techniques. The human eye is very sensitive to the physical appearance of tablets but can only provide qualitative information. Analytical methods, on the other hand, are more objective and quantitative. For example, dissolution profiles of marker compounds in core tablets or coatings (1) have been used to quantify the quality of tablet coats. These procedures, however, are very time consuming and costly. Consequently, sample sizes are usually small, and as a result, may not be representative of the overall tablet population. The quantitative method of reflective color analysis has also been used by Porter and Saraceni (2) to determine inter tablet color uniformity. Unfortunately, this technique is tedious, time consuming and not applicable for colorless coatings. Thus, it is desirable to identify a quantitative method that can be used to rapidly and inexpensively evaluate the uniformity of coating that is applied during a coating process.

Quantifying the mass distribution of coating in a batch of coated tablets is complicated by the fact that uncoated tablets do not exhibit a uniform weight distribution. Recently, Fourman and co-workers (3) have estimated the coating weight distribution of a tablet population by recording the weight of 40 marked tablets before and after coating. Even with a very small sample size, this approach is clearly not convenient or practical especially during routine commercial production.

In this study, an alternative quantitative technique to evaluate inter tablet coating uniformity is proposed. The method of deconvolution of noisy data is used to determine the weight distribution of coating material from the weight distributions of separate random samples of uncoated and coated tablets. This technique overcomes many of the disadvantages associated with other approaches since it does not require knowledge of the weight gain of individual tablets.

METHODOLOGY

The weight (distribution) of coating that is applied during a coating process can be calculated from the weights of separate random samples of coated and uncoated tablets by using the technique of deconvolution. Simply stated, the output (response) of a linear system or process is related to an applied input (stimulus) by its transfer function. The transfer function is a property of the system. In a linear process, a change in the magnitude of the stimulus results in a proportional change in the response of the system. A pharmaceutical coating operation is a linear process since the coating material does not react chemically with other processes or formulation variables.

In a coating process the weight of a coated tablet (output) is equal to the weight of the uncoated tablet (input) plus the weight of the coating (system) that is applied to that tablet. This interpretation assumes that for a given process the weight distribution of coating that is applied remains constant from batch to batch but allows for inter-batch variations in the weight distribution of uncoated tablets. This can be expressed mathematically as:

\[ y(m) = \int_{0}^{m} p(\mu) \times x(m - \mu) \, d\mu \]  

(1)

in which: \( y(m) \) is the weight distribution of the coated tablets (output distribution), \( x(m) \) is the weight distribution of uncoated tablets (input distribution), \( p(m) \) is the transfer function (i.e. weight distribution of coating that is applied to the tablets), \( m \) is weight and \( \mu \) is a variable of integration. Equation (1) accounts for the fact that a distribution of coating, \( p(m) \), is applied to a distribution of uncoated tablets, \( x(m) \), to create a distribution of coated tablets, \( y(m) \). This equation can be used

---

2. To whom all correspondence should be addressed.
to directly calculate the distribution of coated tablets from the distribution of uncoated tablets and the known transfer function for the system. Alternatively, the transfer function, which is the object of this analysis, can be calculated from the known system input and output by using the method of deconvolution. Deconvolution is widely used to interpret pharmacokinetic data. The main difference between pharmacokinetic and coating applications is that the former pertains to time distributions whereas the latter involves weight distributions.

Application of the Fourier transform to equation (1) yields the following equation in the Fourier domain:

\[
Y(\omega) = P(\omega)X(\omega) \quad \text{or} \quad P(\omega) = \frac{Y(\omega)}{X(\omega)} \quad (2)
\]

in which \( j = \sqrt{-1}, \omega \) is frequency, \( Y(\omega), P(\omega) \) and \( X(\omega) \) are the Fourier transforms of \( y(m), p(m) \) and \( x(m) \), respectively. The Fourier transform of any function \( f(m) \) is defined as:

\[
F(\omega) = \int_{-\infty}^{+\infty} f(m) \exp(-2\pi j \omega m) dm
\]

whereas, the inverse Fourier transform of \( F(\omega) \) is defined as:

\[
F^{-1}[F(\omega)] = f(m) = \int_{-\infty}^{+\infty} F(\omega) \exp(2\pi j \omega m) d\omega
\]

The actual coating weight distribution, \( p(m) \), can be determined by taking the inverse Fourier transform of \( P(\omega) \) from Equation (2):

\[
p(m) = F^{-1}[P(\omega)] = \int_{-\infty}^{+\infty} P(\omega) \exp(2\pi j \omega m) d\omega \quad (3)
\]

In practice, experimental data usually contain random noise and measurement errors that can affect the accuracy of subsequent calculations. Mills and Duduković (4) have considered these errors by modifying Equation (1) to include an unknown noise function, \( q(m) \). The transformed form of this modified equation is:

\[
P(\omega) = \frac{Y(\omega) + Q(\omega)}{X(\omega)} = \frac{Y(\omega)}{X(\omega)} + \frac{Q(\omega)}{X(\omega)} \quad (4)
\]

in which \( Q(\omega) \) is the Fourier transform of the unknown noise function and \( P(\omega) \) is the transformed transfer that includes the noise (note: \( P(\omega) \) is the transformed transfer function in the absence of noise).

In most situations the transformed equation is solved numerically since analytical solutions are usually not available. In this work, Equation (4) was cast into a form that is more conducive to rapid solution via fast Fourier transform. This approach, which is described in the literature (4,5), utilizes inverse linear filtering techniques. In this method, the transformed transfer function, at a discrete sampling point; \( i \), is given by:

\[
\hat{P}(\omega) = \frac{Y(i/Nh)X^*(i/Nh)}{X(i/Nh)X^*(i/Nh) + \gamma C(i/Nh)C^*(i/Nh)}
\]

\[
i = 0, 1, \ldots, N - 1
\]

in which: \( N \) is the total number of points; \( X(i/Nh) \) is the discrete Fourier transform (DFT) of the samples of \( x(m) = x(\omega k) \) where \( h \) is the weight increment of the input distribution and \( k = 0, 1, 2, \ldots, N - 1 \). \( Y(i/Nh) \) is the analogous DFT of \( y(m) = y(\omega k) \). \( \gamma C(i/Nh)C^*(i/Nh) \) is the digital filter that removes noise from the measured experimental data. \( \gamma \) is a smoothing factor and * denotes the complex conjugate. Details of the inverse filtering method are described by Hunt (6). The magnitude of \( \gamma \) determines the amount of filtering that is applied in the algorithm. If \( \gamma \) is too large the solution will be over-smoothed whereas an overly noisy solution will result if \( \gamma \) is not large enough. In the limit of \( \gamma \rightarrow 0 \) Equation (5) reduces to a discretized form of Equation (2) which is the transformed solution in the absence of noise. The DFT of \( x(m) \) is defined by:

\[
\text{DFT}[x(kh)] = X(i/Nh)
\]

\[
\sum_{k=0}^{N-1} x(kh) \exp\left(-2\pi j \frac{ik}{N}\right)
\]

\[
i = 0, 1, \ldots, N - 1
\]

A similar equation can be obtained for \( Y(i/Nh) \).

Ultimately, the weight domain transfer function is obtained by taking the inverse discrete Fourier transform (IDFT) of the solution calculated from Equation (5):

\[
\text{IDFT}[\hat{P}(i/Nh)] = \hat{P}(\omega) = \frac{1}{N} \sum_{i=0}^{N-1} \hat{P}(i/Nh) \exp\left(2\pi j \frac{ik}{N}\right)
\]

\[
k = 0, 1, \ldots, N - 1
\]

DFT's and IDFT's can be calculated using standard computer software such as that available in the IMSL Mathematical library (7).

**EXPERIMENTS**

Meaningful distributions can only be obtained when sample sizes are properly selected. In the case of tablet coating a sample size should be chosen to satisfy the following two equations for estimation of sample mean \( \mu \) and standard deviation \( \sigma \) according to Desu and Raghavaro (8):

\[
P(\bar{x} - \mu \leq \alpha \leq \bar{x}) \geq 1 - \alpha \quad (8)
\]

\[
P\left(\frac{\bar{x} - \mu}{\sigma} \leq r\right) \geq 1 - \alpha \quad (9)
\]

where \( P \) is the probability function, \( \bar{x} \) is the best unbiased estimation of the true mean \( \mu \), \( d \) is the maximum absolute error of estimation in mean, \( 1 - \alpha \) is the desired probability level, \( \tilde{\sigma} \) is the best estimation of the standard deviation \( \sigma \) and \( r \) is the maximum relative error in standard deviation.

Estimation of the standard deviation \( \sigma \) generally requires larger sample size than estimation of mean \( \mu \). Mathematically, if equation (9) is satisfied, equation (8) is almost always true. An approximation to the sample size \( n \) satisfying equation (9) is given by Desu and Raghavaro (8):

\[
n = \frac{2\tilde{\sigma}^2}{\alpha^2} + 2 \quad (10)
\]

where \( \tilde{\sigma}/2 \) is the upper 100(\alpha/2) percentile point of the normal distribution. For example, in order to control the relative error \( r \) at 15% \( (r = 0.15) \) for sample deviation \( \sigma \) with a probability of at least 95% \( (\tilde{\sigma}/2 = 1.96) \), the sample size \( n \) should be larger than 344 according to equation (10).

In this study a sample size of 400 tablets was used to estimate the necessary weight distributions. Oval shaped core