# 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 Hale[1]**

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***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 process 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:

$$y(m) = \int_0^m p(\mu) \times x(m - \mu)d\mu \qquad (1)$$

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

[1] Abbott Laboratories, D-49D, 1401 Sheridan Rd, North Chicago, Illinois 60064-4000.
[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:

$$Y(j\omega) = P(j\omega)X(j\omega) \quad \text{or} \quad P(j\omega) = \frac{Y(j\omega)}{X(j\omega)} \tag{2}$$

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

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

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

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

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

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

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:

$$\hat{P}(j\omega) = \frac{Y(j\omega) + Q(j\omega)}{X(j\omega)} = P(j\omega) + \frac{Q(j\omega)}{X(j\omega)} \tag{4}$$

in which $Q(j\omega)$ is the Fourier transform of the unknown noise function and $\hat{P}(j\omega)$ is the transformed transfer that includes the noise (note: $P(j\omega)$ 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 conductive 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:

$$\hat{P}(i/Nh) = \frac{Y(i/Nh)X^*(i/Nh)}{X(i/Nh)X^*(i/Nh) + \gamma C(i/Nh)C^*(i/Nh)};$$
$$i = 0, 1, \ldots N - 1 \tag{5}$$

in which: $N$ is the total number of points; $X(i/Nh)$ is the discrete Fourier transform (DFT) of the samples of $x(m) = x(kh)$ 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 $y(m) = y(kh)$. $\gamma C(i/Nh)C^*(i/Nh)$ 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:

$$DFT[x(kh)] = X(i/Nh) = \sum_{k=0}^{N-1} x(kh)\exp\left(-2\pi j\frac{ik}{N}\right);$$
$$i = 0, 1, \ldots, N - 1 \tag{6}$$

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):

$$IDFT[\hat{P}(i/Nh)] = \hat{p}(kh) = \frac{1}{N}\sum_{i=0}^{N-1} \hat{P}(i/Nh)\exp\left(2\pi j\frac{ik}{N}\right);$$
$$k = 0, 1, \ldots, N - 1 \tag{7}$$

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 Raghavarao (8):

$$P(|\bar{x} - \mu| \leq d) \geq 1 - \alpha \tag{8}$$

$$P\left(\left|\frac{\hat{\sigma}^2 - \sigma^2}{\sigma^2}\right| \leq r\right) \geq 1 - \alpha \tag{9}$$

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, $\hat{\sigma}$ 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 Raghavarao (8):

$$n = \frac{2z_{\alpha/2}^2}{r^2} + 2 \tag{10}$$

where $z_{\alpha/2}$ 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% ($z_{\alpha/2} = 1.96$), 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 tablets with a target weight of 1.134 grams were coated for this study. In order to evaluate the utility of the deconvolution method 400 tablets were sequentially numbered with a permanent marker and then weighed. The numbered tablets were then mixed with an appropriate number of unmarked tablets prior to coating.

Two separate coating experiments were performed in a 60.96 cm (24 inch) tablet coater (CompuLab; Thomas Engineering, Hoffman Estates, IL.). These experiments differed only in the amount of coating that was applied to the tablets. An aqueous coating solution, that consisted of 5% (W/W) solids, was applied at a rate of 85 grams/min using two spray guns with an atomizing air pressure of $2.38 \times 10^5$ Pa (20 psig). The exhaust temperature was controlled at 45°C and the processing air flow rate was kept at 14.16 $m^3$/min (500 cfm). The pan rotational speed was maintained at 8 RPM with a pan load of 8 kg. All numbered tablets were recovered and weighed individually after coating. The weight gain of each tablet was obtained by subtracting the uncoated tablet weight from the corresponding coated tablet weight. The coating weight distribution obtained from these measurements and from the deconvolution method were then compared. The data obtained during the two experimental runs are summarized in Table I.

## RESULTS AND DISCUSSION

The normalized weight distributions of uncoated tablets were obtained by grouping the 400 numbered tablets into 25 equally spaced weight intervals between the minimum and maximum weights. The number of tablets in each weight interval was divided by the total number of tablets (400 in this case) to get the fraction of tablets in each weight interval. This fraction was then divided by the weight interval in order to obtain a normalized distribution. The integral of a normalized distribution function from its minimum weight to maximum weight is unity. Similarly, a normalized distribution for the coated tablets was also obtained.

Figure 1 shows the normalized weight distributions for coating experiments 1 and 2. The circles and triangles represent the uncoated tablets and coated tablets for experiment 1, respectively, while the partial filled squares and solid squares represent the uncoated tablets and coated tablets for experiment 2, respectively. The $x$ coordinate of each symbol in these figures corresponds to the middle point of its weight interval. The curves are Gaussian distributions for experiment 1, which were calculated from the means and standard deviations of the appropriate samples that are summarized in Table I. It is observed from the data in these figures that the weight distributions of both the uncoated and coated tablets are close but not precisely to Gaussian. The data are also somewhat noisy. This is due to the limited number of tablets that were measured as part of these experiments. Smoother weight distributions will be obtained as the sample size increases. However, for the purpose of this analysis, it is not practical or necessary to increase the sample size since most of this noise can be filtered out using the deconvolution technique.

As previously described, individual tablets were numbered sequentially and weighed before and after coating. The actual coating weight on each tablet is equal to its weight gain. Those measured coating weight distributions were normalized in the same manner as the weight distributions of the coated and uncoated tablets. These distributions were also calculated by deconvoluting the measured weight distributions of the uncoated and coated tablets.

Figures 2 and 3 compare the measured tablet weight gains (symbols) to the weight gains calculated using the deconvolution method (dotted curve) without removing the noise (i.e. the smoothing factor $\gamma = 0$), for coating experiments 1 and 2, respectively. It can be seen that the calculated coating weight distributions contain a lot of noise (as manifested by the numerous small peaks of the dotted curve in the figures). Therefore, deconvolution in the absence of smoothing (i.e. $\gamma = 0$) does not provide an accurate estimate of the coating weight distribution. This is a consequence of the noise in the measured uncoated and coated tablet weight distributions (refer to Figure 1). The noise in the measured uncoated and coated tablet weight distributions can be removed during the deconvolution operation in order to obtain a more favorable comparison between the calculated and measured coating weight distributions.

Figures 2 and 3 also compare the measured and calculated coating weight distributions (solid curve) after removing the noise from the experimental data, for coating experiments 1 and 2, respectively. The calculated distributions were obtained by filtering out the noise in the uncoated and coated tablet weight distributions with a smoothing factor of $\gamma = 500$. It is observed from these two figures that the agreement between the measured and calculated coating weight distributions is fairly good.

The calculated coating weight distributions (the solid curves in Figure 2 and Figure 3), were convoluted with the measured weight distributions of uncoated tablets (the open circles in Figure 1 and partially filled squares in Figure 2) for the coating experiments 1 and 2, respectively, in order to assess the accuracy of the method. The mathematical operation is defined by eq. (1), i.e. the measured distribution of coated tablets, $y(m)$, was calculated from the deconvoluted coating

**Table I.** Statistical Summary Data of Tablet Coating Experiments

| Item | Experiment 1 | | | Experiment 2 | | |
|---|---|---|---|---|---|---|
| | Uncoated | Coated | Coating | Uncoated | Coated | Coating |
| Sample Size | | 400 | | | 400 | |
| Minimum Weight (g) | 1.1188 | 1.1296 | 0.0005 | 1.1177 | 1.1287 | 0.0045 |
| Maximum Weight (g) | 1.1518 | 1.1645 | 0.0344 | 1.1483 | 1.1616 | 0.0190 |
| Average Weight (g) | 1.1336 | 1.1472 | 0.0136 | 1.1342 | 1.1456 | 0.0114 |
| Standard Deviation (g) | 0.00515 | 0.00538 | 0.00371 | 0.00530 | 0.00533 | 0.00145 |
| RSD (%) | 0.454 | 0.469 | 27.28 | 0.395 | 0.465 | 12.72 |

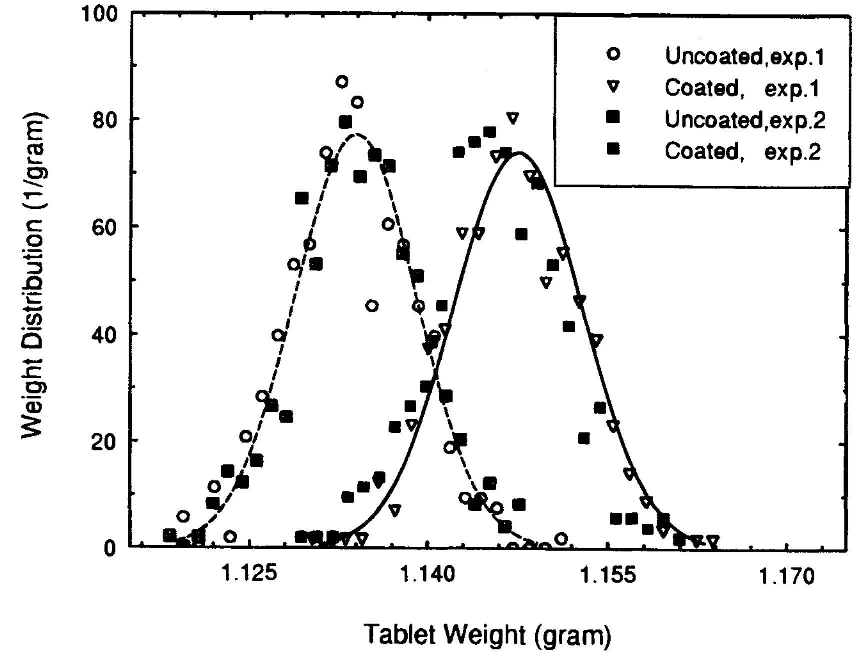


**Fig. 1.** Weight distributions of uncoated and coated tablets for coating experiment 1 and 2.

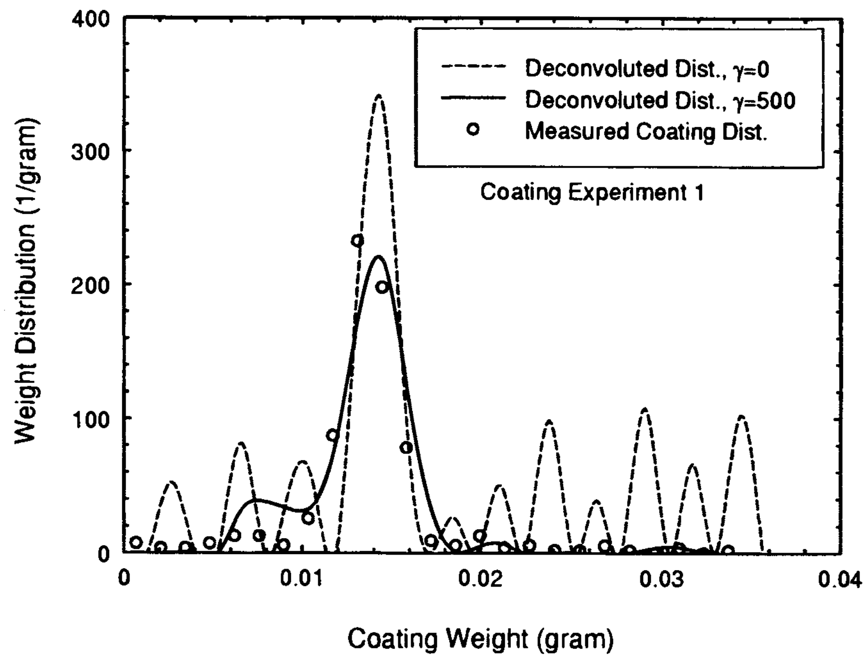


**Fig. 2.** Comparison of measured and calculated (deconvoluted with and without removing noise) coating weight distributions for coating experiment 1.

distribution and the measured weight distribution of uncoated tablets. These results for the coating experiments 1 and 2 are plotted as dotted and solid curves in Figure 4, respectively. The symbols in these figures represent the measured weight distribution of coated tablets for the coating experiments. The good agreement between the measured and convoluted weight distributions of coated tablets provides assurance that the deconvolution method with filtration of noise can be used to approximate the coating weight distribution from separate random measurements of uncoated and coated tablet weights.

Generally speaking, the magnitude of $\gamma$ will have a profound effect on the shape of the calculated distribution. As $\gamma$ decreases, the main peak in the calculated distribution becomes larger and the noise level (as magnitude of oscillations) in the solution increases. This effect is illustrated in Figure 5, which shows the measured coating weight distribution for coating experiment 1, plotted simultaneously with calculated solutions that are deconvoluted with $\gamma = 100$ and $\gamma = 500$. In practice when using the deconvolution method to calculate the weight distribution of coating from the weight distributions of uncoated

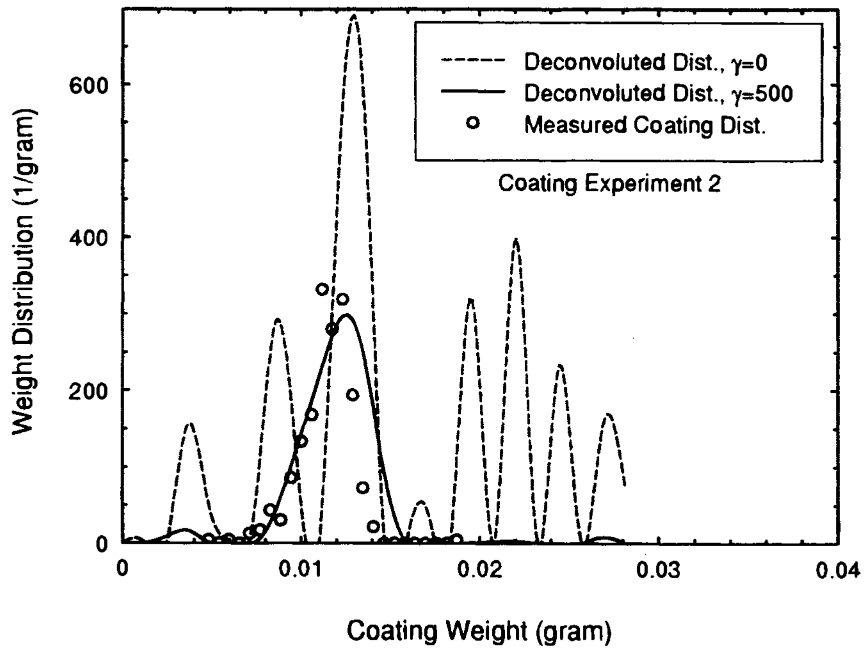


**Fig. 3.** Comparison of measured and calculated (deconvoluted with and without removing noise) coating weight distributions for coating experiment 2.

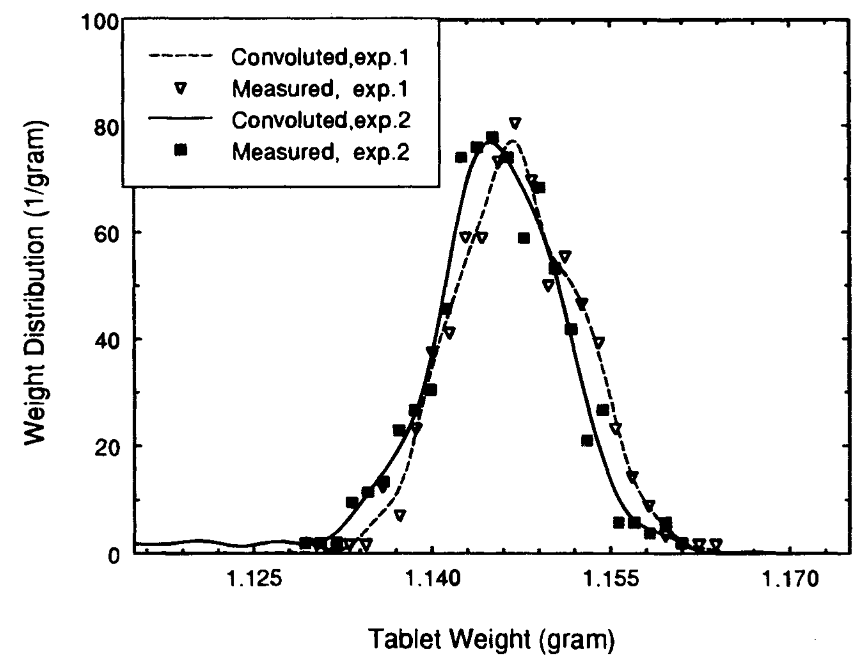


**Fig. 4.** Weight distributions of coated tablets determined from measurements, and from the convolution of coating and uncoated tablet weight distributions, experiments 1 and 2.

and coated tablets, one should start with smaller smoothing factors and increase its value gradually until the deconvolution curve is relatively smooth. Too large a smoothing factor could result in an over-smoothed solution. The accuracy of the result should be confirmed by comparing the coated tablet weight distribution, obtained from the convolution of the calculated coating weight distribution and the measured uncoated tablet weight distribution, to the measured coated tablet weight distribution.

## CONCLUSIONS

It has been demonstrated that the method of deconvolution with digital filtering can be used to accurately approximate the coating weight distribution from separate random measurements of coated and uncoated tablet weights. The advantage of this method is that it is not necessary to determine the weight gain of individual tablets. As a result, it provides a rapid, inexpensive and convenient method to determine the

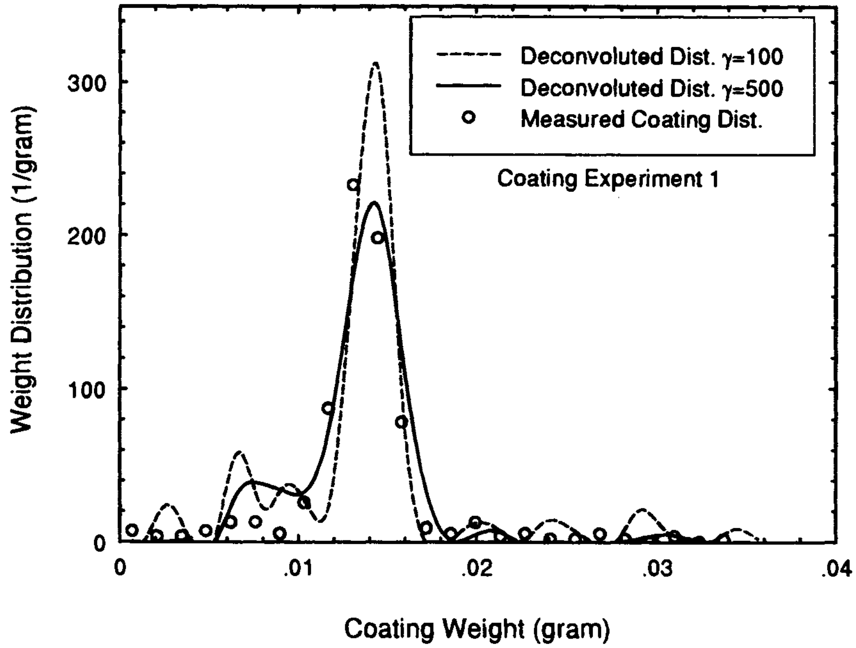


**Fig. 5.** Comparison of measured weight distribution of coating gain with the calculated weight distribution after removing noise ($\gamma = 100$ and $\gamma = 500$) for coating experiment 1.

distribution of coating that is applied during a tablet coating operation. This technique can be used during development to help facilitate process scale-up and optimization or during routine production to assess the reproducibility and consistency of a particular process.

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