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Multivariate wavelet texture analysis for pharmaceutical solid product characterization

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ABSTRACT

The application of multivariate wavelet texture analysis (MWTA) is presented and discussed as it is applied to three different types of pharmaceutical materials: (a) tablet cores, (b) wet granules and (c) controlled release tablets. The application of MWTA is initially proposed as a quantitative replacement to the human visual judgment of the textural appearance of the different materials. In all cases, the metrics obtained with MWTA agree with visual assessment on the progression of textural features such as erosion and surface roughness. This work further demonstrates that MWTA also represents a useful tool to increase the understanding of the manufacturing process, as it provides diagnostics to relate process parameters with textural features of the material that are difficult or costly to measure otherwise (such as granule size for wet material or surface appearance for a controlled release product). MWTA is also presented as a potential tool for real-time release for those cases where the textural features can be proven to provide accurate enough predictions of the final product performance; as shown here with the obtained prediction of dissolution from the controlled release tablet using the texture of the product as an input.

1. Introduction

The pharmaceutical industry is undergoing a dramatic shift in the approach towards the design of pharmaceutical products and operation of its manufacturing processes. These changes are a response to the guidance documents released by the Food and Drug Administration (2000, 2006a) encouraging the design and validation of pharmaceutical processes not only at one fixed set of processing conditions, but in a range of processing conditions referred to as the *design space*. Pharmaceutical companies are to provide evidence that the chosen design space will result in acceptable product for the patient, keeping safety and efficacy as the foremost priority. This concept is referred to as *Quality by Design* (*QbD*). A proposed design space is to be supported by the scientific understanding of the driving forces acting upon the complex network of interactions between materials, process and product. This scientific framework is to rely more on quantitative metrics of products and processes rather than qualitative metrics that are easily biased by human perception.

This need for quantitative metrics is clearly reflected in the massive amount of research in the area of process analytical chemistry (Workman et al., 2009) and is certainly an area of prolific growth in pharmaceutical research. Particularly in the use of spectroscopic instruments to analyze processes and to characterize drug product via chemical images (Gendrin et al., 2008). Although these tools are an important resource when it comes to characterizing and analyzing the chemical characteristics of a product, they can be limited when it comes to quantifying characteristics that are currently assessed by human perception, such as the visual appearance of a material or a product.

This work presents the use of multivariate wavelet texture analysis (MWTA) to quantitatively characterize the visual textural appearance of intermediate and final pharmaceutical products. The technique relies on simple digital grayscale images analyzed via wavelet analysis and multivariate latent variable methods. The metrics obtained with this technique can also be related to upstream conditions of the process and materials, or to downstream performance of the product. In this research, the MWTA approach is illustrated with three case studies: (a) the analysis of tablet erosion during film coating, (b) the characterization of wet granulated material and the prediction of its compaction behavior and (c) the characterization of a controlled release tablet and the prediction of its dissolution performance. The tablet erosion example is presented first since it is the simplest application of MWTA. The following examples are increasing the complexity of the analysis performed and include more than one model in their assessment.

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2. Multivariate wavelet texture analysis

The visual appearance of a given material can be decomposed by its color features and its textural features (Fig. 1). Color characteristics are widely studied with methods that range from the traditional ones as the CIE L^*a^*b method (CIE Colorimetry Committee, 1974) which requires the use of colorimeter; to new trends such as the use of Multivariate Image Analysis (MIA) that relies on simple color digital images and powerful mathematical methods to extract the color features of interest from the image (Yu et al., 2003; Yu and MacGregor, 2003, 2004). Color analysis methods are however limited when it comes to the characterization of the textural features of a surface.

The need for a quantitative characterization of surface texture was addressed by Bharati et al. (2004) with a technique that combined wavelet analysis and multivariate latent variable methods; specifically Principal Component Analysis (PCA) and Projection to Latent Structures (PLS). Their technique was referred to as multivariate wavelet texture analysis (MWTA) and was first applied as a monitoring tool for the mineral processing sector (Liu et al., 2004). This approach has been contrasted against other more traditional methods of texture analysis and proven to be superior in its ability to filter out light intensity variations and smudges in the images (Bharati et al., 2004).

Other reported applications of MWTA for monitoring includes that of polymer films (Gosselin et al., 2009) and paper formation (Reis and Bauer, 2009); fault detection for the semi-conductor industry (Facco et al., 2009); and monitoring of powder mixtures (Gosselin et al., 2008). Beyond the initial application of MWTA for monitoring a process; MWTA has also been applied as a classification tool for a mining process (Tessier et al., 2007) where the textural and color characteristics of the ore were used to determine the mineral composition of rocks. Other applications of MWTA for classification include medical imaging (Kucheryavski, 2007), ceramics, and foods (Prats-Montalban and Ferrer, 2007). Finally, the predictive power of MWTA was illustrated in the forensic field, where textural characteristics of bone remains were used to estimate the age of the victim (Kucheryavski et al., 2009).

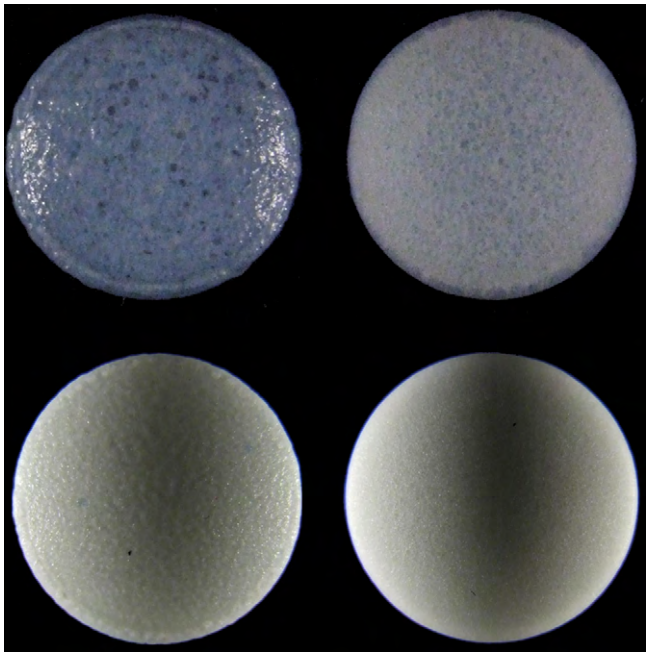

Fig. 1. Color differences (top tablets) and texture (bottom tablets) as different visual characteristics of a material.

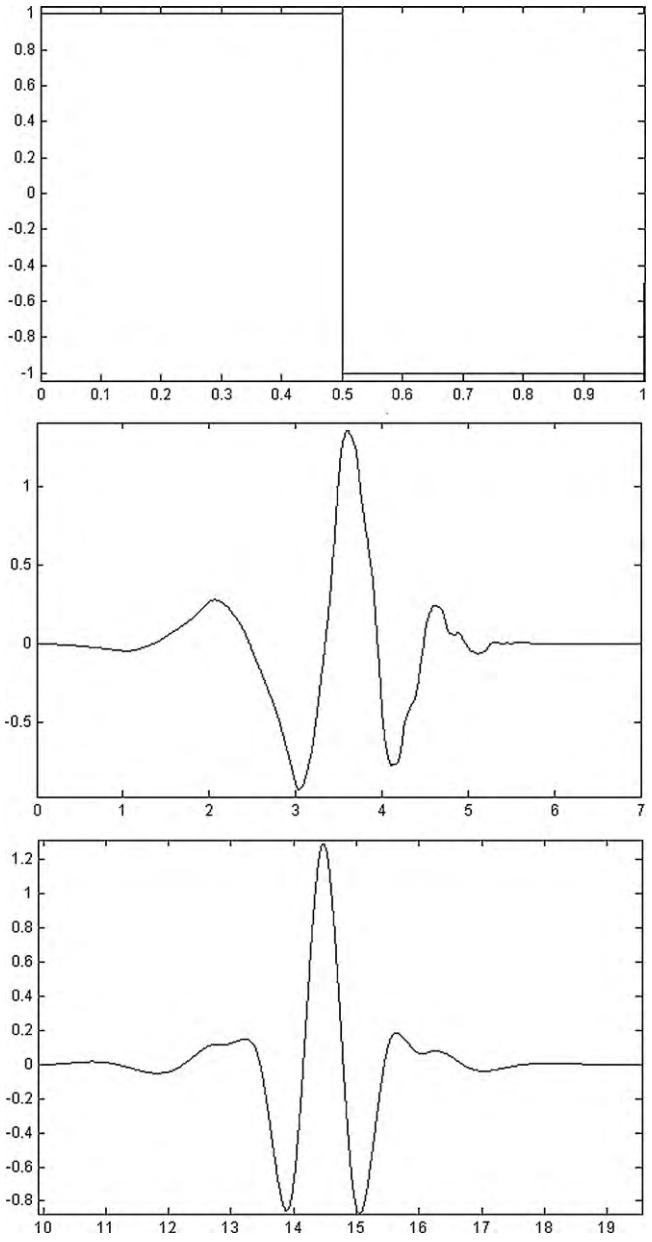

Fig. 2. Three different wavelet packet families, Haar (top), Daubechies (middle) and Coiflets (bottom).

MWTA is a two step process that involves a decomposition step and a feature analysis step. The decomposition step involves the use of wavelets to decouple the textural features of the image. In simple terms, wavelet analysis is similar to Fourier analysis where a signal is decomposed into multiple frequency-amplitude terms with two main differences (i) instead of using a sine function wavelet analysis uses a wavelet packet and (ii) most importantly, the basis function (the wavelet) is of finite duration, while the sine wave used in Fourier is not. These differences enable wavelet analysis to perform not only spectral, but also spatial decomposition of the signal. Fig. 2 illustrates three different types of wavelet packet families, the Haar (top), the Daubechies (middle) and the Coiflets (bottom). Wavelet analysis will decompose an image into an approximation image of the signal and d detail images of it. A property of this decomposition is that the addition of the details and the approximation is always equal to the original. The approximation can be said to be equivalent to the residuals since this is the portion of the image that is "leftover" after extracting the d details. The amount of white

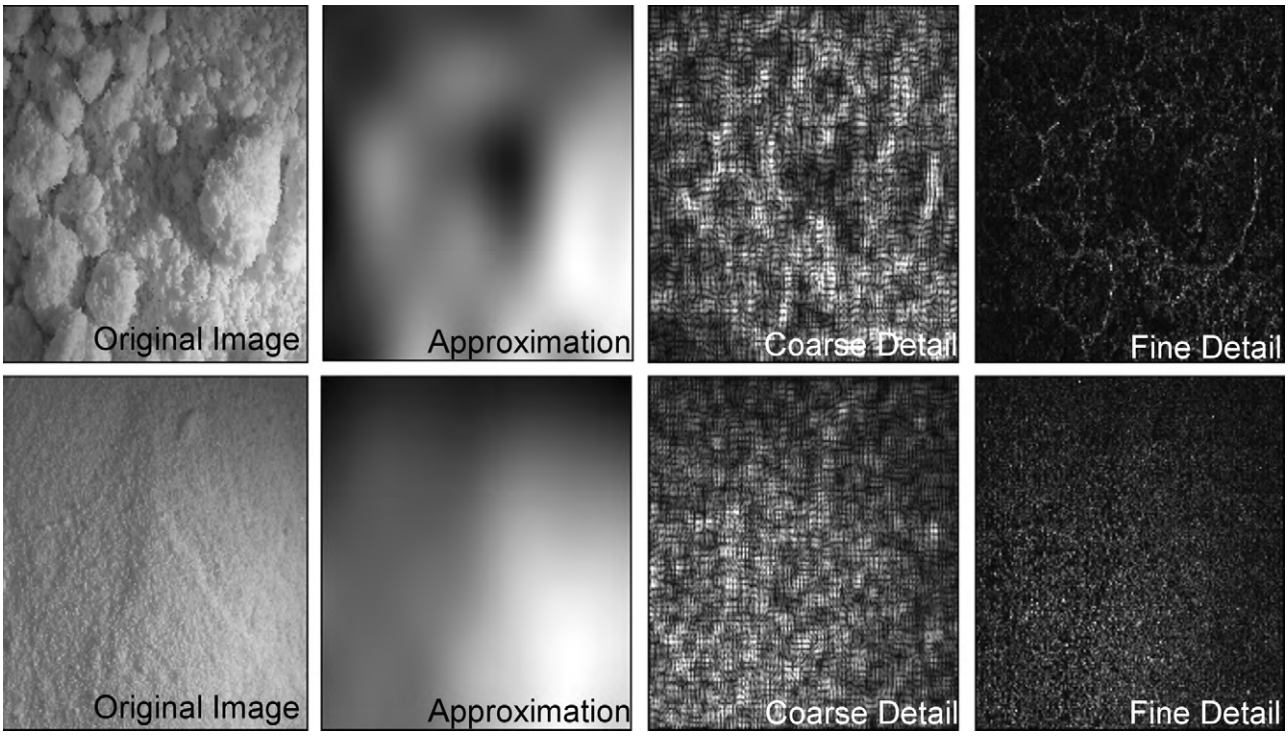

Fig. 3. Example of wavelet decomposition of two images: one with coarse features (top images) and one with fine features (bottom images).

in each of the detail images corresponds to the energy (analogous to the amplitude) that the original image has for that detail stage. Initial stages of detail decomposition will capture finer features of the signal (analogous to a higher frequency), and latter stages of detail will capture coarser features of the signal (analogous to lower frequency signal).

Wavelet analysis is referred to as 2D wavelet analysis when it is applied to a matrix of numbers, such as the matrix extracted from a grayscale image, where each pixel is represented by a number between 0 and 255. In this 2D case the analysis can be performed in vertical, horizontal or diagonal direction across the matrix; this work utilizes decomposition in the three directions. These concepts are illustrated in Fig. 3, where the images of two different types of wet granules are shown along with their approximation and 2 stages of detail for a two-stage decomposition (the more stages implies the more detailed decomposition). Notice in the upper right most image of Fig. 3 (which shows the finest detail from the image of the coarse granule) how the fine particles adhered to the surface of the coarse lumps are identified, this feature is not apparent in the lower right most image (fine features of the fine granule) where the features of the powder are more homogeneous. This example also illustrates how the differences in illumination are kept in the approximations (left most images in the figure). To perform this decomposition, there are two parameters that have to be established: the number of details (d) and the wavelet family to use in the decomposition. The choice of the number of details will depend on the chosen wavelet family. The general guidance is to choose a wavelet family that will leave only illumination differences in the approximation (no textural characteristics), with the lowest number of details possible (lowest value of d). It is only until recently that a formal study was published providing some guidance and a systematic approach to the selection of wavelets to characterize surface characteristics (Kim et al., 2009).

After wavelet decomposition of one image; each of the grayscale images corresponding to the extracted details is read as a numerical matrix (since each pixel has a value between 0 and 255). Among multiple options to summarize the total energy in this image, for this work we chose the Frobenius norm due to its simplicity. The collection of the norms for all the details for one image is then collected into a feature vector called the *wavelet energy signature*. At this point, each of the images taken will be characterized by a feature vector of d elements, where d represents the number of details used to decompose the original images.

The resulting matrix from collecting the feature vectors for multiple images is then analyzed using a multivariate latent variable method (LVM) such as Principal Components Analysis (PCA) to study the unsupervised differences in the textural features of the images; or Projection to Latent Structures (PLS) to regress these textural image features to a response of interest. The use of LVM such as PCA and PLS is well established in the pharmaceutical sector, hence the details on these methods are not the scope of this work and can be found elsewhere in literature (Jackson, 1991; Burnham et al., 1999).

In the present work, MWTA is used as an unsupervised feature extraction tool in the assessment of tablet erosion, granule appearance and film-coat appearance; and as a soft-sensor when the features extracted with MWTA were used to predict the downstream manufacturability of the wet granulated material and the dissolution performance of a controlled release tablet. Although tablet surface and coating have been widely studied with other techniques such as confocal laser scanning microscopy (Ruotsalainen et al., 2003), terahertz spectroscopy (Zeitler et al., 2006, 2007; Ho et al., 2007), near infrared spectroscopy (Roggo et al., 2005), and Raman spectroscopy (Zhang et al., 2005; Sasic, 2007), the advantage of the method presented here is that it relies on simple grayscale images taken with a digital camera which are much less expensive and easier to operate than any of the aforementioned instruments.

3. Materials and process

The use of MWTA is illustrated with three separate case studies:

(a) Tablet erosion study

Table 1
Composition of the dry blend used in the wet granulation study.

Ingredient	% of total
Acetaminophen powder (MP Biomedicals)	23
Microcrystalline cellulose, Avicel PH-102 (FMC BioPolymer)	28
Lactose	44
FastFlo® 316, (Foremost Farms) – fine	
Lactose Direct Tableting, (Sheffield®) – coarse	
Polyvinylpyrrolidone, PVP K30 (BASF)	5
Total	100

Tablet cores were prepared using a placebo blend composed of 48.375% of microcrystalline cellulose (Avicel PH-102, FMC BioPolymer), 48.375% of Foremost® NF FastFlo® Lactose (Modified Spray Dried, Foremost Farms), 3% of Sodium Starch Glycolate (Roquette) and 0.25% Magnesium Stearate (vegetable derived). The blend was processed by dry granulation using a Gerteis Mini-Pactor® machine (Gerteis Maschinen + Processengineering AG) with a setting of 3 mm gap, 8 kN force, using knurled rolls and a 1 mm mesh screen. The granule was then compressed into a 400 mg SRC tablet using a Kilian T100 (IMA Kilian GMBH & Co.) press equipped with 9 stations operating at 55,000 tablets per hour with the necessary compression force for the resulting tablets to Exhibit 20 kP of hardness.

The tablets were then subject to tumbling at 20 rpm in a LDCS-5 (Vector Corporation) film coater (5 kg batch size) spraying 21.25 g of de-ionized water per minute using one Schlick ABC gun. A pattern air pressure of 4.9 psi was used as well as 40 ft^3/min of drying air at the necessary temperature to maintain the outlet air temperature at 45 °C. The thermodynamic conditions were calculated to match those when spraying a 15% solids solution of Opadry® II (Colorcon Inc.) aqueous coating. Tablets were sprayed for 53.4 min (theoretical time for the tablets to gather a 4 wt.% increase in coating if a 15% solids solution was used) and tumbled dried for 15 more minutes in the coater. Tablets were withdrawn from the coater to be analyzed by MWTA as follows: samples 1–8 were taken during spraying at approximately 6 min and 15 s apart, samples 9–21 were taken during the drying phase at 1 min interval. Each pulled sample consisted of 10–20 tablets; five randomly selected tablets per pull were imaged and further analyzed with MWTA.

(b) Characterization of wet granulated material

The eight different types of wet granules studied in this work were obtained with a full factorial experimental design carried out in a Collette Ultima PRO high shear wet granulator (Niro Pharma Systems). The three manipulated factors were (i) the particle size of a major component of the dry blend (see composition in Table 1), (ii) the impeller speed and (iii) the total amount of water added during the granulation process. The experimental design is shown in Table 2. The operation of the granulator was as follows: the dry blend was dry mixed for 1 min followed by the addition of water for a fixed period of 14 min and ending with a wet massing stage of 2 min. The impeller speed was only modified – according to the experimental design – during the water addition phase, otherwise it was kept at 450 rpm. For all runs, the chopper speed was kept at 2000 rpm.

Table 2
Experimental design used to produce the eight different wet granules used in this study.

Experiment	Impeller speed (rpm)	Water addition rate (ml/s)	Lactose (fine/coarse)
DOE1	200	0.4	Coarse
DOE2	600	0.4	Coarse
DOE3	200	0.54	Coarse
DOE4	600	0.54	Coarse
DOE5	200	0.4	Fine
DOE6	600	0.4	Fine
DOE7	200	0.54	Fine
DOE8	600	0.54	Fine

Table 3
Experimental design used to manufacture multiple controlled release tablets.

Run ID	Gun to bed distance (in.)	Outlet temperature (°C)	Inlet temperature (°C)	Pattern air (SLPM)
DOE 1	7.5	35	52	50
DOE 2	7.5	35	52	30
DOE 3	7.5	25	38	50
DOE 4	7.5	25	39	30
DOE 5	4.5	35	52	50
DOE 6	4.5	35	52	30
DOE 7	4.5	25	38	50
DOE 8	4.5	25	39	30
Center point	6	30	46	40

The wet material was then imaged for MWTA analysis and then dried at the same conditions in a GPCG-1 fluid bed dryer (Glatt®) and milled in a Comil unit using a 1 mm screen. The final dry granule was analyzed in a compaction simulator (Huxley Bertram Engineering Ltd.) to determine the hardness-compression profile (hardness as a function of compression force) for each lot for tablets of 350 mg in total weight, using a 3/8 in. diameter standard round concave (SRC) tooling. Other tests conducted on the final dry granule were bulk and tapped density, particle size distribution using a laser diffraction instrument (Sympatec GmbH), and flow testing in a common a ring shear tester.

(c) Characterization and performance prediction for controlled release tablets

An experimental design was carried out in a HCT-60 (Vector Corporation) film coater to explore the impact of processing conditions on a controlled release tablet. The details on the formulation of the tablets are kept confidential for intellectual property reasons and are irrelevant for the scope of the work presented. The values and factors considered in the experimental design are listed in Table 3. Samples of produced tablets were imaged for MWTA while other samples were used to determine the dissolution performance by high pressure liquid chromatography (HPLC).

4. Methods

All images were taken using a Single-Lens Reflex (SLR) Fujifilm S91000 digital camera with 1/320 s of shutter speed with an aperture of F2.8 under low angle illumination using a Mini-Repro copy stand (Gruppo Manfrotto, Italy) with 4 fluorescent lights (14 W, 60 Hz, 200 mA). The images were taken at 9 megapixels of resolution in raw format, later converted to .tif format using the *Hyper-utility* software (version 3.1) provided by the camera's manufacturer. The distance of the objects to the lens, the use (or not) of a macro-focus and other optical decisions were made to enhance the textural features of interest for each application.

The wavelet analysis portion of the method was performed using functions from the *Wavelet Analysis Toolbox* in MATLAB® (version 2009b, The Mathworks™), LVM calculations were performed with in-house developed code.

To minimize the effects of amount and difference in the background, the images of individual tablets were cropped to an inner-rectangular section of the image where only the surface of the tablet would appear. This operation was automated with MATLAB®

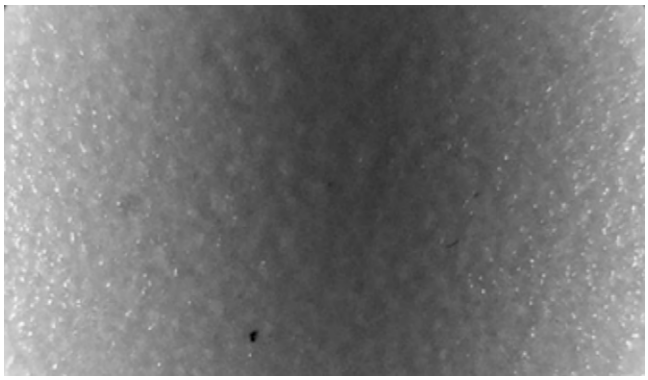

Fig. 4. Example of the cropped image of the surface of tablet.

and involved simple trigonometric calculations and an algorithm to detect the edge of the circular object in the frame. The edge of the tablets in the grayscale image was detected using the first derivative of the summation of the grayscale intensities by rows and columns, an example of the final image of a tablet surface is shown in Fig. 4. The images of the granules were already rectangular with no background in the frame and no cropping was required for these images. The resulting images were processed by MWTA and LVM according to the objectives of each study.

For the tablet erosion study, the images of the eroded tablet surfaces were decomposed using a Coiflets wavelet with 7 stages of detail. The set of 105 feature vectors (21 pull points and 5 images per pull point) was analyzed using PCA. The average score values (for the first principal component) of the 5 images taken per pull point made the erosion progression observable as verified by visual inspection.

In the characterization of wet granulated material case; there were multiple images taken of the wet material for each experimental point. The images were processed using a Coiflets wavelet and 8 stages of detail. PCA was applied to the matrix of average textural features per point in order to classify the images. Textural features were also analyzed against the parameters in the experimental design using a PLS model. Finally, the matrix of textural features was assessed as a potential predictor of the density, particle size, flow of the final dry granule, and the hardness compression of the final tablets. This analysis used a PLS model with 3 latent variables since the experimental design has 3 factors.

For the characterization and performance prediction of the controlled release tablets, the obtained images were decomposed using a Coiflets wavelet and 6 stages of detail. The obtained feature vectors were analyzed using PCA, where one principal component was sufficient to rank order the tablets according to their appearance, as verified by visual inspection. Two PLS models were also fitted: in the first one the textural features of the tablets were a response and the process parameters a regressor, this model was done to determine which factors in the process had an impact on the textural characteristics of the tablet (this is useful information for process development). In the second PLS model the textural features were the regressor and the dissolution measured at 9 h the response. This last model served to demonstrate the potential use of MWTA as a predictor of dissolution performance for a controlled release tablet.

The choices made about the type of wavelet to use and the number of decomposition stages were based on visual inspection of the wavelet features, the signal to be processed (a transversal cut of the surface to be analyzed) and the approximation image (the residual), recent studies propose a more systematic approach (Kim et al., 2009).

For this work it was considered that an approximation image was appropriate when it only exhibited illumination gradients and textural characteristics that were irrelevant for each case study.

During the evaluation of the multiple choices of a wavelet it was observed that the final results did not change dramatically when an alternative wavelet of similar features is chosen (e.g. a Daubechies versus a Coiflet wavelet, see Fig. 2). Nevertheless it is recommended to make a choice of a wavelet that will somehow resemble the transversal features of the texture to be analyzed. A completely off-choice of a wavelet will result in textural features to be left in the approximation (e.g. using the Haar wavelet – Fig. 2 – with sharp 90° features which are not typical of the transversal cut of the tablet surface). The comparison of the results obtained for different choices of wavelet packets is not the focus of this paper, a thorough study of wavelet packets can be found in the work by Kim et al. (2009).

5. Results

5.1. Case study 1: Tablet erosion

After wavelet decomposition, the wavelet textural features are fitted to a PCA model which captures 90.36% of the total variance with one principal component. Fig. 5 illustrates the values of the scores averaged per pull (left plot) and as a box plot on the right to illustrate the variability in the sample (composed of five tablets). As it can be seen in the average plot the textural features of the tablets continue to change up to pull point number 9 or 10 which is the point where the water spray was turned off. Images of selected

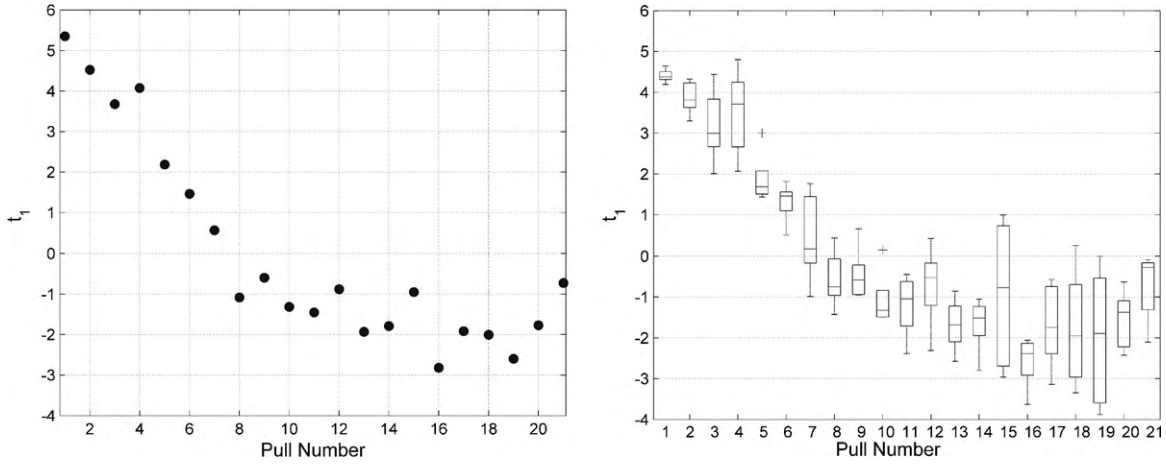

Fig. 5. Score values of the PCA model fitted on the textural characteristics of eroded tablets.

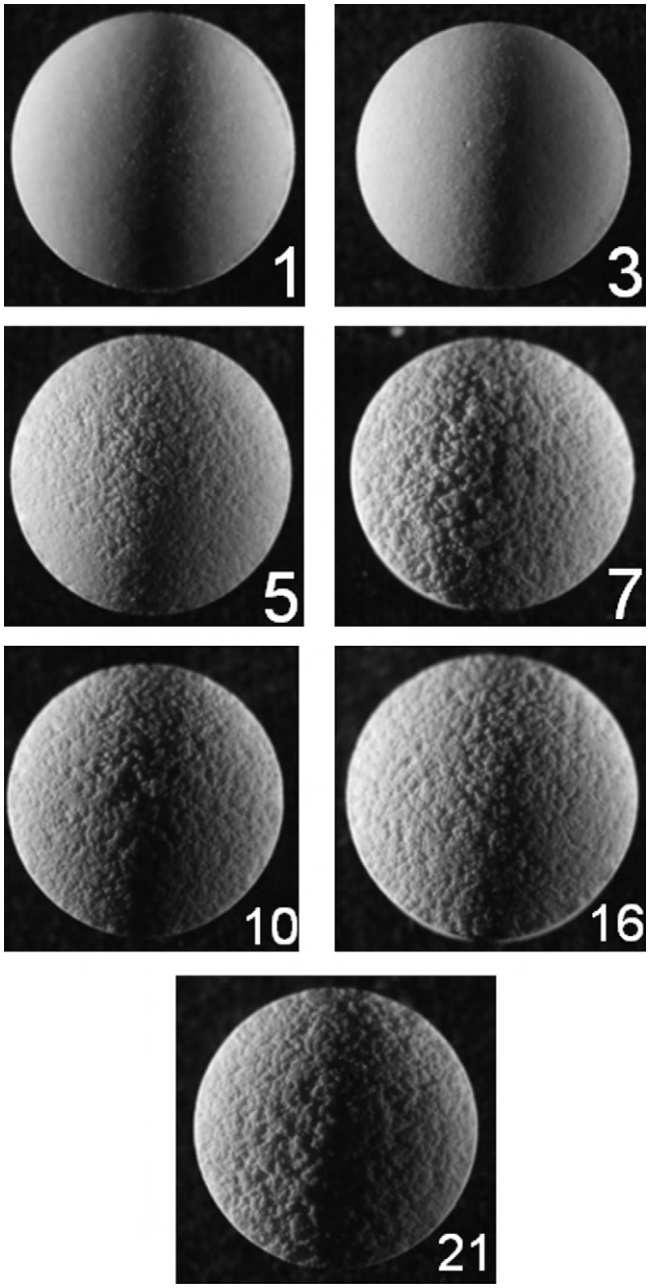

Fig. 6. Selected images for eroded tablets sampled from a film coater; numbers indicate the pull number.

tablets from pull point number 1, 3, 5, 7, 10, 16 and 21 are shown in Fig. 6. The changes in the values of the scores for this first principal component clearly correspond to increased erosion in the tablet surface.

5.2. Case study 2: Wet granules

Images of the eight different types of wet granulated materials obtained are shown in Fig. 7. The textural characteristics (average per point) of these granules were analyzed using a PCA model with 2 principal components (the third principal component was deemed insignificant since it introduces an eigenvalue of 0.76), the diagnostics for this model are shown in Table 4. Fig. 8 shows the values of the scores for the first and second principal component (t_1 and t_2) for all the wet granules; notice how the first component is capturing the major feature of the textural appearance: the size of the granules, with the wet material with large agglomerates on one extreme of the axis, and the material with finer granules on the other. In the same plot, notice that wet granules from experiment 5, 8 and 3 are relatively similar and hence fall close to each other in the score space (which can also be said for wet granules 1 and 2).

Table 4
Diagnostics from the PCA model fitted to the textural features of the wet granules.

PC#	Eigenvalue	R^2X (%)	R^2Xc (%)
1	6.05461	67.27345	67.27345
2	1.76634	19.62597	86.89942
3[a]	*0.76952*	*8.5502*	*95.44962*

[a] Insignificant component.

The textural characteristics were analyzed as a response using the experimental design parameters as a regressor for a two latent variable PLS model. This model explains close to 100% of the total variability in the water addition rate and type of lactose used (fine/coarse); but only 12.5% of the variability in impeller speed. This same model explains between 50% and 90% of the multiple textural characteristics (energy in details 1–9, D1–D9).

As discussed previously wavelet analysis decomposes an image into the energy of an approximation and details which represents the textural features of the image. The energy of the first stages of decomposition corresponds to finer feature of the images; energy of latter stages corresponds to coarser details of the image. Hence in these models the energy in the finer details is represented numerically in the variables D1–D4, variables D5 and D6 correspond to the medium size characteristics while the coarser characteristics are represented in the variables D7–D9.

With this in consideration, it can be seen that the loadings (Figs. 9 and 10) of the first latent variable (defined by the coefficients $\mathbf{w}_1^*$ and $\mathbf{q}_1$) reveal that the use of a coarser lactose and high impeller speeds are simultaneously correlated with an increase in the finer details of the images and a decrease in the coarser ones. The second latent variable defined by the coefficients $\mathbf{w}_2^*$ and $\mathbf{q}_2$) reveal that independently of the lactose and impeller speed used, higher rates of water addition are correlated with the appearance of coarser features in the image and the disappearance of the finer ones. These relationships can be explained from what is known about the fundamental mechanistic phenomena in the high shear wet granulation process, this discussion is provided in the following section.

Finally, Fig. 11 is an illustration of the quality of the predictive model for the downstream manufacturability properties of the dry granule. This figure illustrates the percentage of the total variability (R^2) that the model captures for each metric by each of the three latent variables in the PLS model. The first four bars in Fig. 11 represent the R^2 for the as is, tapped, and bulk volumes as well as density. The next six bars represent the hardness obtained when the tablet was compressed as a function of force (hence the labels '5 kN', '10 kN', '15 kN', . . ., '30 kN'), the subsequent six bars correspond to particle size metrics and the last one to the flow function coefficient (or FFC). Notice in this plot that the hardness-compression behavior of the dry granule (represented by the bars labeled as '5 kN', '10 kN', '15 kN', . . ., '30 kN') is the best predicted property with an accuracy close to 80% (which is quite acceptable given the variability in the testing of the hardness of a tablet). These numbers are of course subject to using the same processing conditions in the drying and milling step. In a complete framework to study the behavior of the dry granule, the characterization of the wet granule (with MWTA) would be complemented with information on how the drying and milling step affect the properties of the dry granule as well. This work is not intended to provide such a framework but only to illustrate the potential use of the quantitative textural characteristics

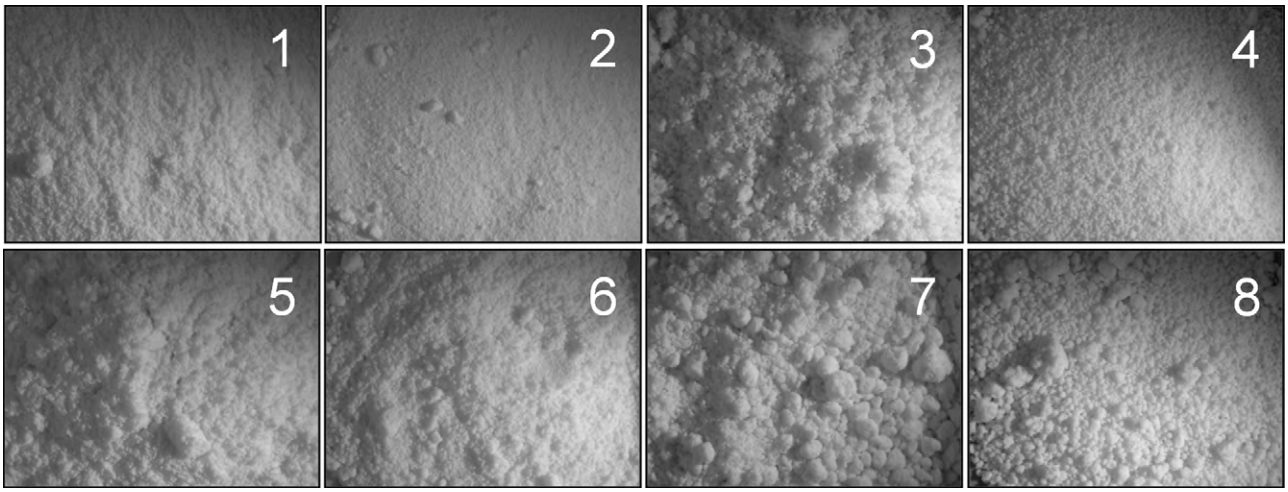

Fig. 7. Selected images of the eight different wet granules studied.

of the wet material as a predictor of the downstream performance of the material.

5.3. Case study 3: Controlled release tablets

The first result from this case is similar to the one from the tablet erosion case, with the difference that the textural differences for this material are in the polymeric coating material rather than the tablet core. Fig. 12 is a plot of the rank order scores values for the first principal component of a PCA model fitted onto the textural features of the tablets. Although the intermediate tablets are not shown, it is visually clear (and confirmed with the complete set) that the increase value of t_1 corresponds to a smoother surface of the tablets, this score value is a quantitative representation of the textural features of the tablets and could be used for numerical comparison with other samples (e.g. to compare if texture of the tablets obtained at full scale resemble the texture of the tablets obtained at small scale).

Fig. 13 is the result of an upstream analysis exercise to determine which process parameters in the film-coating step where affecting the *color* characteristics of the tablets – as extracted by Multivariate Image Analysis (MIA) using features extracted with the covariance method (Yu and MacGregor, 2003; García-Muñoz and Gierer, 2010) – and which parameters were affecting the *texture* characteristics of the tablets (as extracted with MWTA). The results from two PLS models (one for color and one for texture) are summarized in the Very Important for the Projection (VIP) plot. By analyzing this plot it was clear that the two most important parameters (for color and texture) were the total amount of solution sprayed, and the flow of pattern air in the guns, these plots however identified the ther-

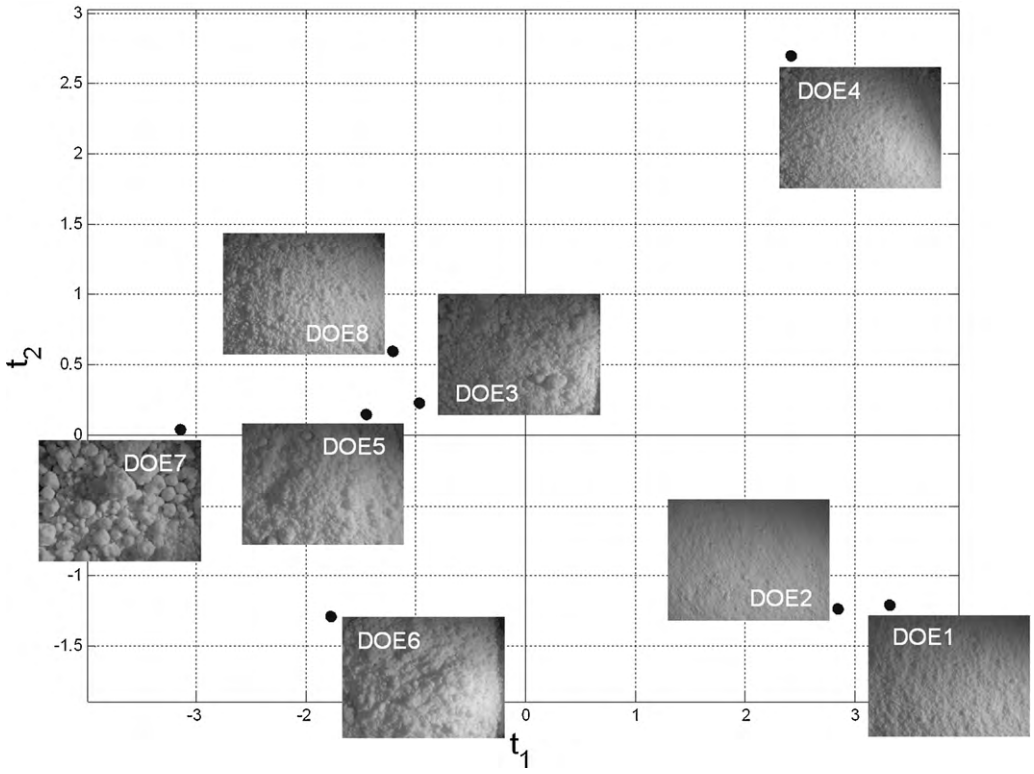

Fig. 8. Score mapping of the wet granules according to their textural features.

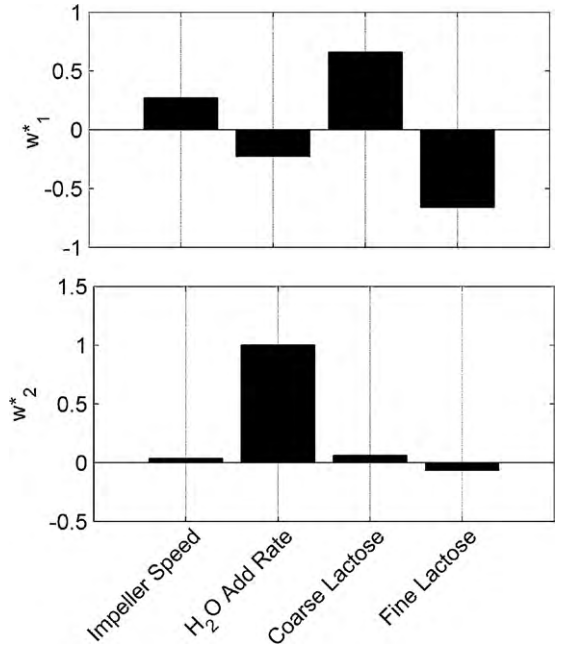

Fig. 9. Loadings for the regressor of the PLS model fitted between wet granulation process parameters and the textural features of the wet material.

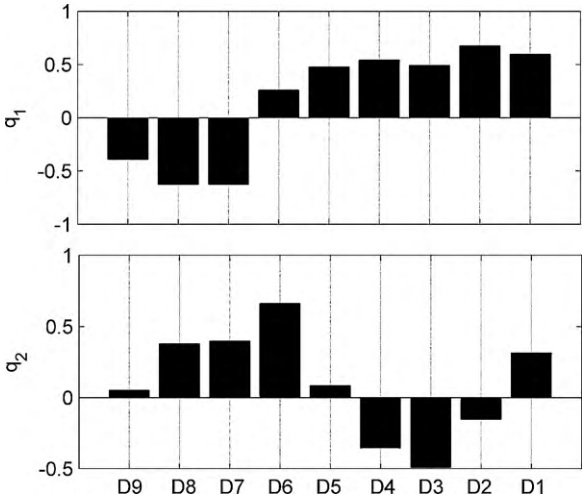

Fig. 10. Loadings for the responses of the PLS model fitted between wet granulation process parameters and the textural features of the wet material.

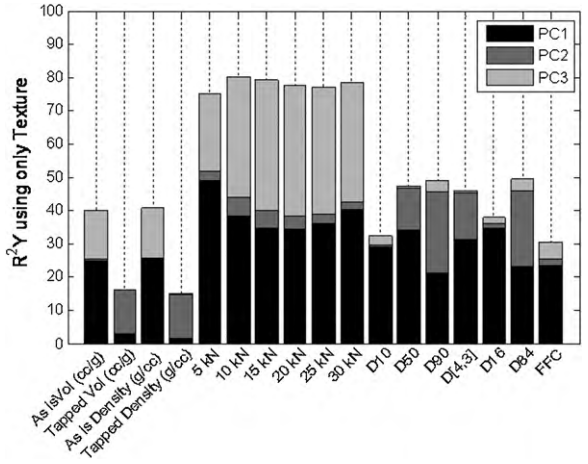

Fig. 11. Percentage of total variance captured by a PLS model fitted between the wet material textural features and the multiple indices characterizing the dry granule.

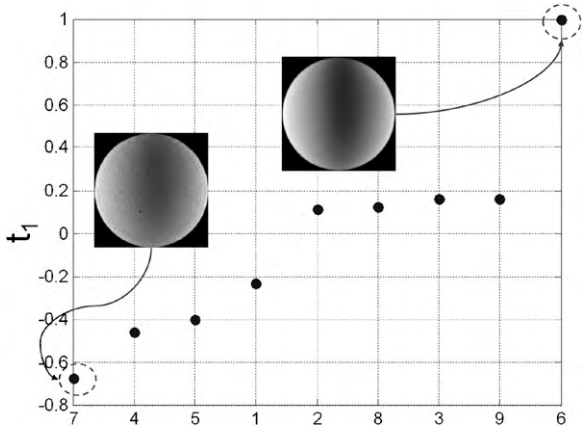

Fig. 12. Rank ordered score values for the textural appearance of a controlled release tablet.

mal conditions of the coater as the third most important factor for color, while the gun to bed distance was identified as the third most important factor for texture.

Finally, the textural characteristics of the tablets were assessed as a potential predictor of the dissolution performance, which is of upmost importance since these are controlled release dosage forms. Fig. 14 shows the predicted values for the dissolution of the tablets as well as the 95% confidence intervals, calculated with the same approach as in (Nomikos and MacGregor, 1995). The implications of such predictive potential are discussed below.

6. Discussion

The results obtained for the tablet erosion study indicate that the erosion of the tablets progresses steadily when the tablets are tumbled and subject to the aqueous spray, and that this erosion is less dramatic when the spray is off and the tablets are dry tumbled. This is inferred by the fact that the average score values become stable (no change in the average textural features of the tablet images) roughly after sample number 9 or 10 (Fig. 5) and knowing that the spray was stopped at the time sample number 8 was taken. The box plot of this same diagnostic indicates that the variability in textural features increases, but not necessarily the baseline. This is, after the spray is stopped some tablets will become more eroded while the erosion for other tablets will stop to progress.

For the three presented studies, it was observed that the score values (Figs. 5, 8 and 12) of a PCA model fitted on the wavelet textural features provide a quantitative framework to characterize materials and are in agreement with visual inspection thus providing a non-biased tool to replace human visual appreciation. This quantitative framework is particularly useful for materials that are hard to characterize otherwise (like wet granules), or where containment restrictions prevent direct contact with the product. Furthermore the characterization and classification of materials with MWTA is shown to be related to downstream manufacturability and product performance (as illustrated in Figs. 11 and 14). These results justify the use of an MWTA based characterization method to be used as part of a *Quality by Design* (Food and Drug Administration, 2006b) exercise or a continuous quality assurance strategy.

Aside from the statistical verification of the predictive potential in the textural features of a material it is also shown that these textural features can be used to advance the process understanding of the system where the materials were produced.

In the case of the wet granulation example, the loadings from the PLS model (Figs. 9 and 10) indicate that the use of a coarser material with a slower rate of water addition and a faster agitation will lead

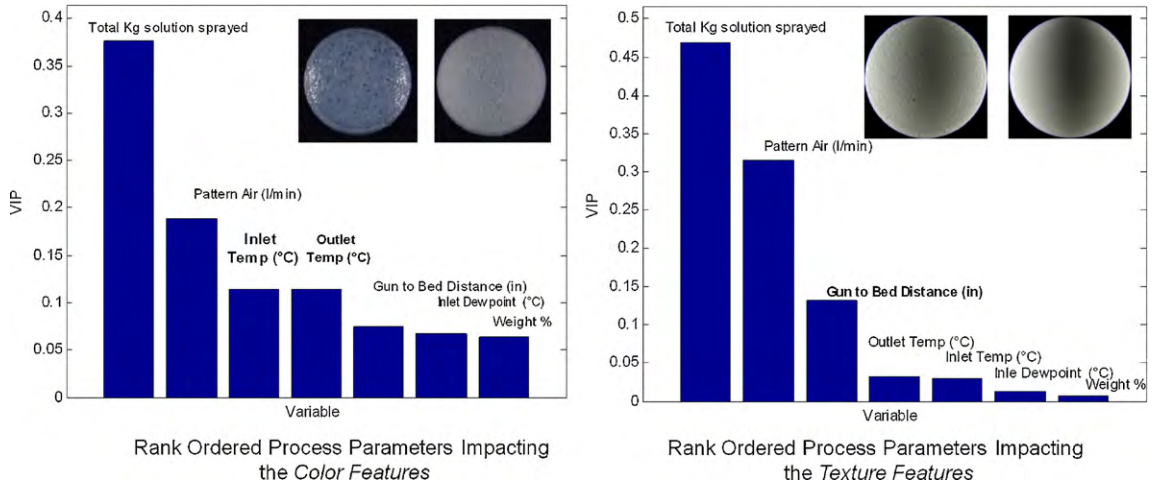

Fig. 13. Very Important for the Projection plots to determine film-coating parameters affecting color and textural features of a controlled release tablet.

to an increase of the finer (D6–D9) textural details (granule size) and decrease of coarser ones (D1–D3). This is in agreement with the mechanistic understanding of wet granulation since a larger particle size in the dry material will result in a smaller surface area that will not promote the nucleation and aggregation of granules as much as a finer material with a larger surface area for bonding. The slower addition of water at a higher agitation rate will result in a better distribution of water (smaller droplets) and yield a more homogeneous granule lacking of large agglomerates, this also justifies the loadings for the second latent variable that indicates a higher rate of addition will result in the increase of coarser (D2–D4) textural features (agglomerates) of the image and a decrease of the finer ones. Even though these results are in agreement with prior knowledge of high shear wet granulation, they may not be apply for other formulations where the differences in the texture of the granule are less apparent. The latter situation could be potentially solved by increasing the power of the optics used to acquire the images of the materials.

The results obtained in the analysis of the textural features for a controlled release tablet indicate that the overall visual appearance of the tablets is strongly dependant of the amount of solution sprayed (thicker layers will look different) and the pattern air (Fig. 13). The latter is agreeable since a change in pattern air will directly affect the droplet size distribution of the spray which will affect the total mass of polymer deposited by each drop and may affect the drying mechanism and phase separation of the water soluble and insoluble polymer mixture used to coat the tablets.

The importance of the inlet/outlet temperature and the gun to bed distance can be interpreted as the effect of the drying mechanism of the droplet onto the visual appearance of the tablets; the inlet and outlet temperatures will determine the thermodynamic conditions of the coater and the gun to bed distance will dictate the total time a droplet will be exposed to such conditions. Both mechanisms will affect the drying phenomena of the droplet on the surface of the tablet.

This model (which relates process parameters to visual appearance) could be potentially used in conjunction with the model that relates textural features to the dissolution of the tablet in order to determine the feasibility of having a set of process parameters for a tablet designed with certain desired esthetic appearance features while still reaching a target dissolution performance (i.e. using MWTA as a design tool rather that an analysis one). The successful use of MWTA for design purposes is documented for the polymer industry (Liu and MacGregor, 2005), these experiences could easily be translated to the pharmaceutical field.

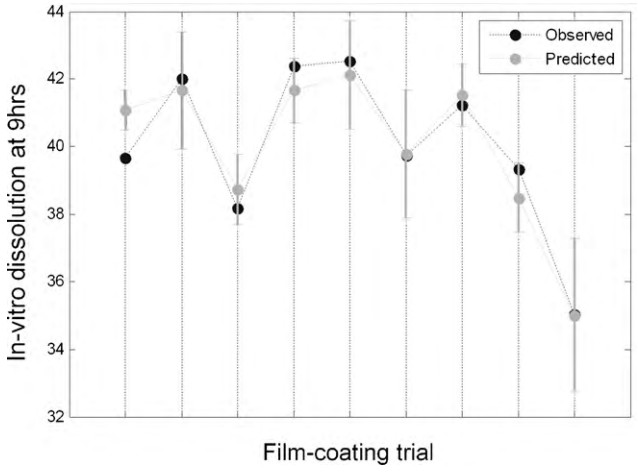

Fig. 14. Predicted and observed dissolution at 9 h, as predicted with PLS with the textural characteristics of a controlled release tablet as a regressor.

7. Conclusions

Multivariate wavelet texture analysis was applied to study three different types of pharmaceutical materials: tablet cores, wet granulated material and a controlled release tablet.

From the analysis of the progression of erosion in tablets, it was seen that the erosion only progresses while the tablets were sprayed and tumbled. This result casts doubt on the use of the traditional friability test as a way to diagnose potential problems in the film-coating step since this test is done on dry tablets.

The analysis of wet granulated material revealed relationships among textural features of the granule and the process conditions used that were in agreement with prior knowledge about the mechanics of high shear wet granulation. This study also showed the potential predictive power of MWTA with respect to downstream manufacturing indexes of the dry powder (such as flow and compression) such results indicate that the use of MWTA is a cost effective addition to the battery of tests done for wet granulated material.

Finally the results of the analysis of a controlled release tablet indicate that the textural features of the tablet surface could be used for process understanding and potentially to predict the in vitro

performance of the product. These results (especially considering the low cost and simplicity of performing MWTA) support the use of MWTA for real-time release of product or as a complementary tool in a continuous quality assurance strategy, given that enough GMP provisions are taken (as they are for the use of any spectroscopy based technique).

A *Quality by Design* framework must (by definition) include all the characteristics of the product and the process that will impact either safety or efficacy. This framework should be based on robust, reproducible metrics, able to be subjected to validation and audits. A method based solely on human perception cannot be an accepted metric in such a framework since it is inherently biased by the judging person and may require panels of judges with stringent guidelines to be understood and interpreted.

This work presents the use of multivariate wavelet texture analysis (MWTA) as a cost effective replacement to such a human judgment of visual appearance. MWTA has shown to provide quantitative metrics that are in agreement with the visual differences in the textural characteristics of multiple pharmaceutical materials and with the knowledge on the fundamental mechanics of the processes involved. Furthermore, the obtained metrics are shown to form a continuum where the gradual change of appearance can be measured and systematically verified, offering an attractive tool for product development and manufacture.

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