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The Use of Surface Analysis Techniques to Determine the Route of Manufacture of Tablet Dosage Forms

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ABSTRACT Analytical methods for determining the manufacturing process of tablet dosage forms have not been previously reported. The use of surface analysis techniques in particular X-ray Photoelectron Spectroscopy and Time of Flight Secondary Ionization Mass Spectrometry will be described and a model proposed which allows the prediction of the route of manufacture in calcium phosphate and cellulosic-based tablet formulations. Results of the application of this model to evaluate prototype tablet formulations prepared by wet granulation or direct compression will be reported. Strengths and limitations of the model will be discussed.

KEYWORDS Wet granulation, Direct compression, Lubricant, Excipient, Fracture, Surface analysis, XPS

INTRODUCTION

Tablets are the most popular medicinal dosage form accounting for over 70% of all ethical pharmaceutical preparations produced (Aulton, 1988). Increasingly, counterfeit products are appearing on the market. In the United States, the Food and Drug Administration are urging pharmaceutical companies to seek high technology solutions to overcome this problem (Klug, 2004). According to the World Health Organization, approximately 10% of all medicines sold worldwide are counterfeit with up to 25% of medicines consumed in Third World countries being counterfeit or substandard. Annual earnings from the sale of these products are estimated to be over $32 billion globally (World Health Organization, 2003). These counterfeit products may represent a safety, efficacy, or quality threat to patients. In many instances, the counterfeit product involves substitution of the active ingredient. This can be readily established using sophisticated analytical methodologies, e.g., LC-MS-MS. Another important element to consider is the manufacturing process of the product. The manufacturing route may also affect the rate and extent to which a drug is absorbed into the body.

Tablets contain both drug substance (sometimes referred to as active pharmaceutical ingredient or API) and excipients. Excipients can be sub-divided into various functional classifications, depending on the role that they are

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intended to play in the resultant formulation, e.g., fillers, disintegrants, binders, lubricants, glidants, etc.

There are two main manufacturing processes utilized in the production of tablet dosage forms. Tablets may be manufactured by incorporating a granulation step into the process or alternatively the formulation may be directly compressed. Granulation is a process of size enlargement of particles within a formulation. It facilitates an improvement in the flow properties of a formulation making it workable during the compression stage of manufacture. The process can be divided into two main sub-types:

- Wet granulation employs a fluid to facilitate granule formation.
- Dry granulation is a mechanical process where particle agglomeration is achieved by application of pressure.

Of the granulation processes described above, wet granulation is the most widely utilized (Ausberger & Vuppala, 1999). In this process, excipients are mixed with the granulation liquid and the agitation causes the liquid layers on the particles to coalesce forming loose agglomerates (Barlow, 1968). Partial dissolution of excipients in the formulation can lead to the formation of crystalline bridges between the particles when the resultant wet mass is dried. Further enhancement of bridge formation can be achieved by employing a binding agent dissolved in the granulating fluid (Rumpf, 1962).

Direct compression is a process where there is no requirement to use any particle agglomeration techniques. The excipients and API used in direct compression processes already possess the requisite flow and compression properties for the manufacture of a tablet dosage form.

The choice of whether a granulation or direct compression process is used during the manufacture is dependent on many factors some of which are shown in Table 1 (Record, 1980).

In trying to establish whether a tablet has been manufactured by the registered process, a technique capable of assisting in the identification of the manufacturing route would be valuable. This paper illustrates how prototype tablet formulations prepared by wet granulation and direct compression have been used to develop methods which are capable of distinguishing the granulation route that was utilized in the tablet manufacturing process.

MATERIALS AND METHODS

Materials

The materials used in this study are presented in Table 2 below. The list provides information on material grade and supplier.

Experimental

Samples of tablets were prepared using either a wet granulation (WG) or direct compression (DC) process. The formulations were identical and are presented in Table 3 below. Tablets were compressed on a Manesty tablet press, using 8 mm biconvex tablet tooling, to a target weight of 350 mg and hardness of 8–10 kP.

Sample Preparation

Differences in the elemental characteristics of the fresh fracture surfaces of tablets manufactured by WG and DC processes were investigated using surface anal-

TABLE 1 **Factors Determining Tablet Manufacturing Route**

Granulation	Direct compression
Improves flow properties (densifies materials)	Simple process
Uniform mixes reduces segregation	Reduced costs
Improve compression characteristics of the drug substance	Less degradation issues for materials sensitive to heat and water
Allows control of rate of drug release	Less complex formulation
Reduces dust improves safety	Only applicable to low drug loadings (~25% max)
Better homogeneity for low conc drugs	
Main method for high dose drugs	
Increases particle strength	
Improves handling characteristics	

TABLE 2 **Tableting Material Information**

Component	Supplier
Paracetamol	GlaxoSmithKline
Microcrystalline cellulose (Avicel PH101/102)	FMC International
Lactose (FastFlo)	Univar
Dibasic Calcium Phosphate	JRS Pharma
Polyvinyl Pyrrolidone (Kollidon 30)	BASF
Sodium Starch Glycollate (Explotab)	Roquette
Magnesium Stearate	Maprac

TABLE 3 **Model Tablet Formulations**

Component	Level
Paracetamol	6%
Diluent*	87%
Polyvinyl pyrrolidone	4%
Sodium Starch Glycollate	2%
Magnesium Stearate	1%

*The diluent consisted of one of the following: microcrystalline cellulose, lactose, microcrystalline cellulose/lactose (50/50), or calcium phosphate.

ysis techniques. The tablets were impact fractured by placing a clean scalpel blade on the outer surface of the tablet and lightly tapping the blade to induce a breakage and expose the fracture interface. It is this fracture interface that is of interest. The tablets were fractured down the middle (i.e., top to bottom) through the center of the tablets. Repeat fracturing and analysis reveals that variability of fracture was not an issue as the results were extremely repeatable within a batch of tablets.

X-ray Photoelectron Spectroscopy (XPS) (Ratner & Castner, 1997) analyses of fractured tablets were performed using a Surface Science Instruments (SSI) M-Probe spectrometer operating at a base pressure of 3×10^{-9} Torr. The samples were irradiated with monochromatic Al Kα x-rays (1486.6 eV) using an elliptical x-ray spot size of 1000 μm × 400 μm and 180 W power. Survey spectra were recorded with a pass energy of 150 eV from which the surface chemical compositions were determined. In addition, high resolution carbon (1s) and oxygen (1s) spectra were recorded for tablets comprising a cellulosic-based excipient formulation with a pass energy of 25 eV from which the carbon and oxygen chemical states were determined. All binding energy values were calculated relative to the carbon 1s photoelectron at a binding energy (BE) of 285.0 eV. Charge compensation for these electrically insulating materials was achieved using a beam of *ca*. 4–9 eV electrons at a flood current of *ca*. 0.1 mA, with an electrically grounded 90% transmission nickel mesh screen positioned *ca*. 1 mm above the sample surfaces. The standard take-off angle used for analysis was 35°, producing a maximum analysis depth in the range of 3–5 nm. All quantification is measured in At% (atomic percent), which is defined as the number of atoms of an element per unit volume divided by the number of atoms per unit volume of the substance containing the element.

For each tablet analyzed, a five point line scan was acquired across the fracture surface to determine variations in surface compositions, if any, and to improve significance in the calculated composition ratios used to differentiate between WG and DC manufactured tablets.

Time-of-Flight Secondary Ion Mass Spectrometry (ToFSIMS)

ToFSIMS spectra (Vickerman & Swift, 1997) were acquired under static conditions using a PHI 7000 instrument operating at a base pressure of less than 4.0×10^{-8} Torr. The instrument was equipped with a reflectron analyzer, a Cs^+ ion source (8 keV; pulse length 1.25 ns), and a pulsed electron flood source (50–70 eV) for charge compensation. Both positive and negative secondary ion mass spectra were acquired from areas measuring 250 μm × 250 μm over the mass range 0–1000.

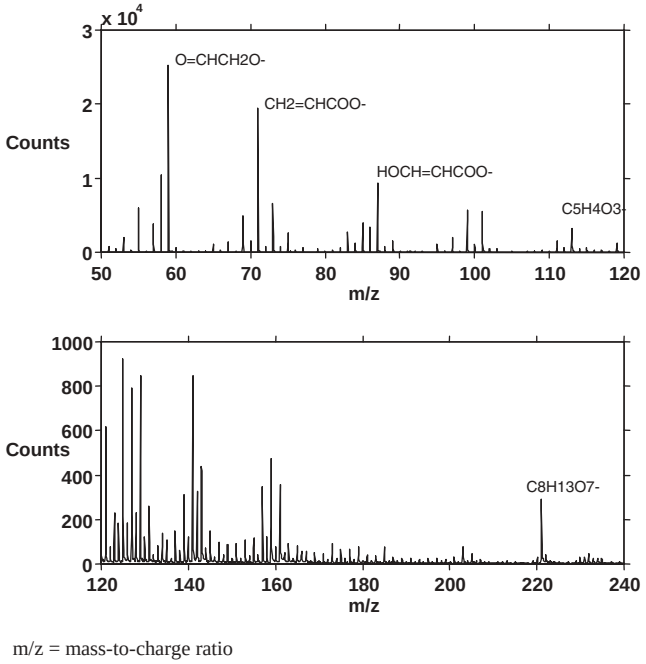
RESULTS AND DISCUSSION

Magnesium stearate is widely used as a lubricant in the production of tablets (Ertel & Carstensen, 1988), and was selected as the lubricant of choice for this investigation.

It was postulated that the distribution of the lubricant may be different in tablets produced via the two different processes. In WG, the lubricant is added to the granules prior to compression, and coats the surface of the granule (extra-granular). In contrast, the lubricant is more uniformly distributed within the direct compression formulation. The interaction of lubricant is dependent on both the excipient type and

the particle shape. As a result, formulations may possess either a continuous or discontinuous distribution of lubricant within the tablet matrix (Riepma et al., 1993). This distribution is exploited to determine differential parameters for WG and DC formulated tablets utilizing surface analytical techniques.

X-ray photoelectron spectroscopy (XPS) is the technique of choice since it is both surface sensitive and quantitative. Time-of-flight secondary ion mass spectrometry (ToFSIMS), in the first instance, has been used to identify the diluent (i.e., is the tablet a calcium phosphate or cellulosic-based formulation), the active and the lubricant for each tablet analyzed. From the ToFSIMS analysis, it is known which differentiation parameter (R_n) pathway to follow since the diluent is identified. Example ToFSIMS spectra illustrating the identification of the diluent and lubricant are shown in Fig. 1(a) – (c). In Fig. 1(a), the presence of a cellulosic-based diluent can be observed by the detection of the negative ions, m/z 71$^-$ (CH_2=CHCOO$^-$), m/z 87$^-$ (HOCH= CHCOO$^-$), m/z 113$^-$ ($C_3H_4O_3^-$), and m/z 221$^-$ ($C_8H_{12}O_7^-$). Figure 1(b) shows a calcium phosphate diluents where the important signals are observed at m/z 40$^+$ (Ca^+) and m/z 79$^-$ (PO_3^-). In Fig. 1(c), the lubricant can be identified as magnesium stearate via the detection of the negative ion at m/z 283$^-$ corresponding to the stearate anion,



m/z = mass-to-charge ratio

FIGURE 1(A) **ToFSIMS Spectra of Cellulose-based Diluent. m/z = mass-to-charge ratio.**

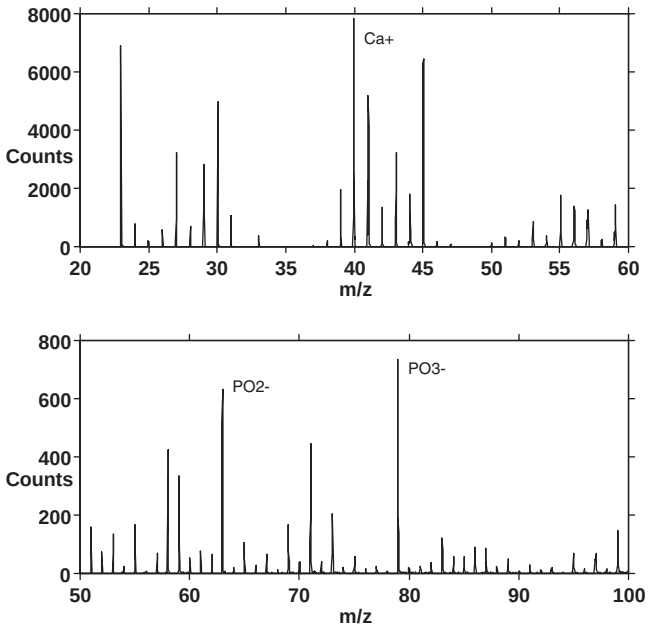


FIGURE 1(B) **ToFSIMS Spectra of Calcium Phosphate-based Diluent.**

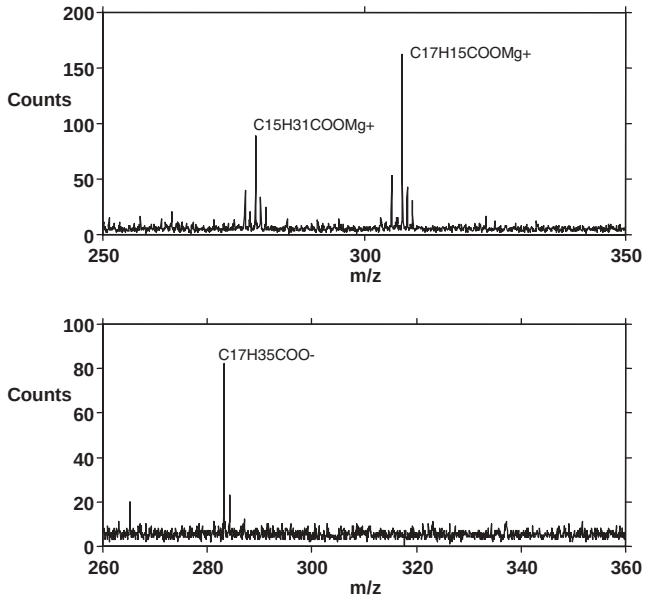


FIGURE 1(C) **ToFSIMS Spectra of Magnesium Stearate Lubricant.**

$C_{17}H_{35}COO^-$, and the Mg^+ ion in the positive ion spectrum. Hence, initial information concerning tablet formulation allows the differential parameter route to be chosen readily.

Calcium Phosphate Differentiation Parameter, R_{CP}

For tablets formulated with calcium phosphate as diluent, a clear quantitative difference has been identified between WG and DC formulations, an example of which is shown in Fig. 2 and Table 4. Higher levels (in atomic %) of calcium and phosphorus and concomitantly lower levels of carbon (associated with presence of magnesium stearate) are consistently observed at the fracture surface for DC formulations compared to WG formulations. This implies that the magnesium stearate distribution is different for these two processes, namely, at the fracture interface of a WG tablet the lubricant is more prevalent than at the fracture interface of a DC formulated tablet. Inclusion

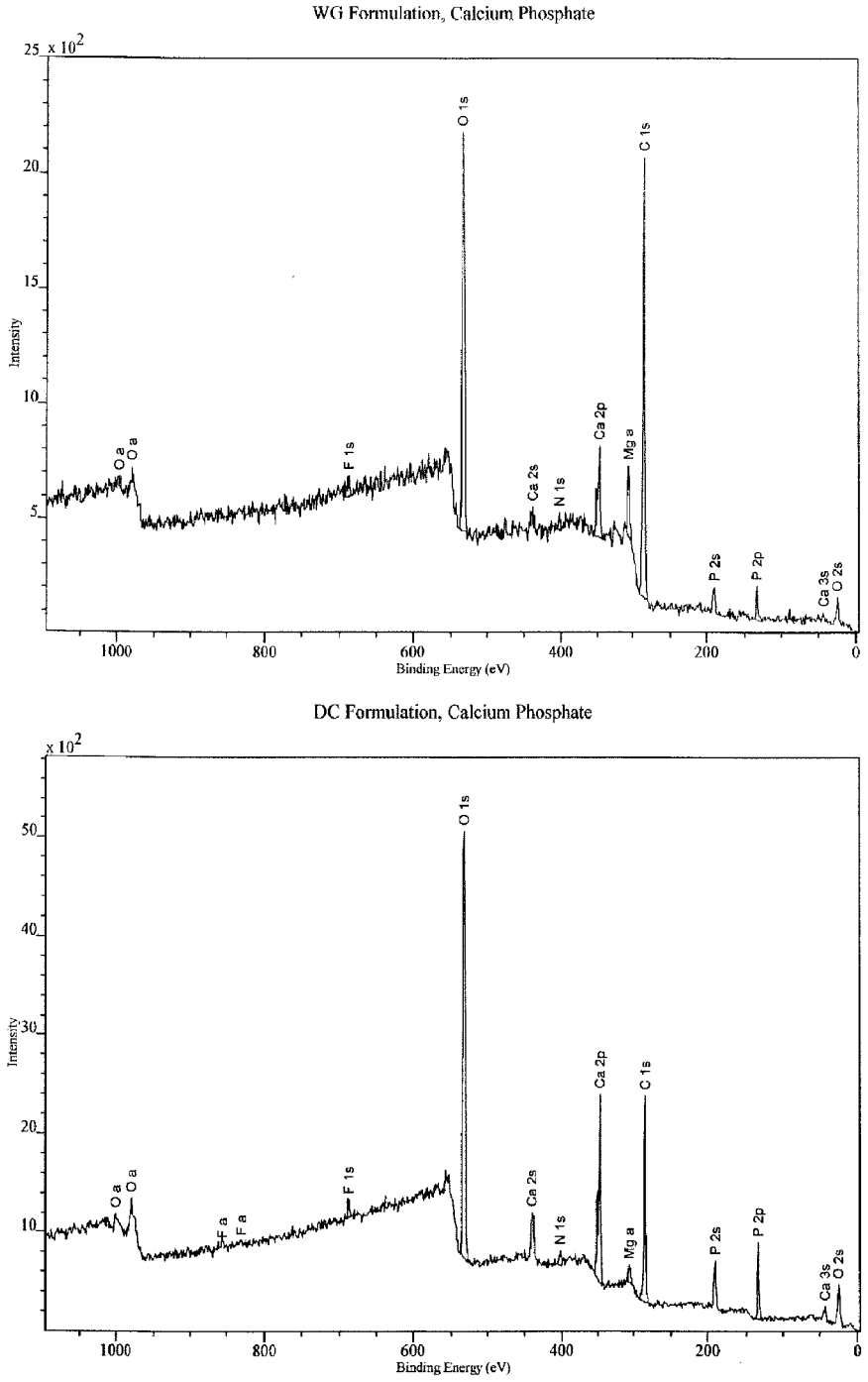


FIGURE 2 **XPS of DC vs. WG Tablets for Calcium Phosphate Formulations.**

TABLE 4 Calcium Phosphate Fracture Interface Compositions in At%

	DC	WG
Carbon	38.3	62.8
σ	0.8	0.9
Oxygen	39.6	25.6
σ	0.7	0.7
Nitrogen	1.7	1.2
σ	0.4	0.5
Calcium	8.8	3.4
σ	0.3	0.4
Phosphorus	9.6	3.7
σ	0.4	0.4
Magnesium	0.9	2.2
σ	0.2	0.3

of data associated with both the diluent (i.e., calcium) and the lubricant (carbon and magnesium), it is possible to produce a parameter for differentiation between the two tabletting methods.

Hence, by combining ratios of calcium:magnesium and carbon:oxygen the parameter for differentiation between WG and DC calcium phosphate formulations, R_{CP} can be defined as:

$$R_{CP}: (\text{At\% O})/ (\text{At\% C}) \times (\text{At\% Ca})/ (\text{At\% Mg}) \quad (1)$$

Repeated testing on series of calcium phosphate produced tablets from both WG and DC formulations indicated a clear barrier for differentiation between the two types of formulation; i.e., the parameter R_{CP} was always below 7 for WG and above 7 for DC formulated tablets, hence, the equation

$$\text{Where } R_{CP} = \text{WG} < 7 < \text{DC} \quad (2)$$

Cellulose Differentiation Parameter, R_C

The cellulose-based diluents comprise the same major elements as the lubricant, namely carbon and oxygen. As such, simple wide scan data, as acquired for calcium phosphate-based tablets, are not sufficiently different to determine a parameter for differentiation between WG and DC formulations. However, by acquiring narrower scan high resolution spectra for carbon (C 1s) and oxygen (1s), it is clear that there are significant and reliable differences in the relative chemical states of these elements for DC and WG formulations at the fracture surface. An example of the C 1s data is shown in Fig. 3 and Table 5.

Theoretically, the C 1s peak of a pure cellulose material comprises only two chemical states (Beamson & Briggs, 1992), C–O–C (at a binding energy of ca. 286.5 eV) and O–C–O (at a binding energy of ca. 288.0 eV) in an approximate ratio of 4:1, respectively. The C 1s peak of a pure magnesium stearate material should show two chemical states, C–C, C–H (at a binding energy of *ca.* 285.0 eV) and O–C=O (at a binding energy of *ca.* 289.0 eV) in an approximate ratio of 16:1, respectively. Relating this theoretical information back to the model, a ratio incorporating the C–C, C–H, and O–C–O carbon chemical states above will provide a parameter that is dependent on the coverage of the hydrophilic cellulosic excipient by the lubricant. In the presence of an active component comprising a nitrogen heteroatom, this ratio is compromised due to the overlap of the C–O–C component of the cellulose with the C–N component of the active which both appear at a binding energy of *ca.* 286.5 eV. The contribution of the C–N component is negated by multiplication of the carbon state ratio with the ratio of C–O–C/N–C=O components in the O (1s) peak. Through the analysis of multiple samples of WG and DC formulations containing cellulosic excipients, the parameter, R_C, for differentiating between WG and DC cellulosic formulations has been defined as:

$$\frac{\text{Carbon (O-C-O)At\%} \times \text{Oxygen (C-O-C, C-OH)At\%}}{\text{Carbon (C-C, C-H)At\%} \times \text{Oxygen (O=C-N)At\%}}$$

Where $R_C > 1.5$ = DC or $R_C < 1.5$ = WG.

Both the R_{CP} and R_C differentiation parameters have been rigorously tested using a series of formulations and have been shown to be reliable in predicting the method of manufacture for calcium phosphate-based and simple cellulosic-based formulations, respectively. Data are presented in Fig. 4 and 5 below.

A logical flow diagram presents the decisions made during the differentiation process, see Fig. 6. The flow diagram enables the reader to follow the process when carrying out the prediction experiments for a tablet of unknown formulation. Initially, the tablet is fractured as per the method described in the method section. At this point, the fracture mechanics can be investigated using microscopy but do not yield a reliable method

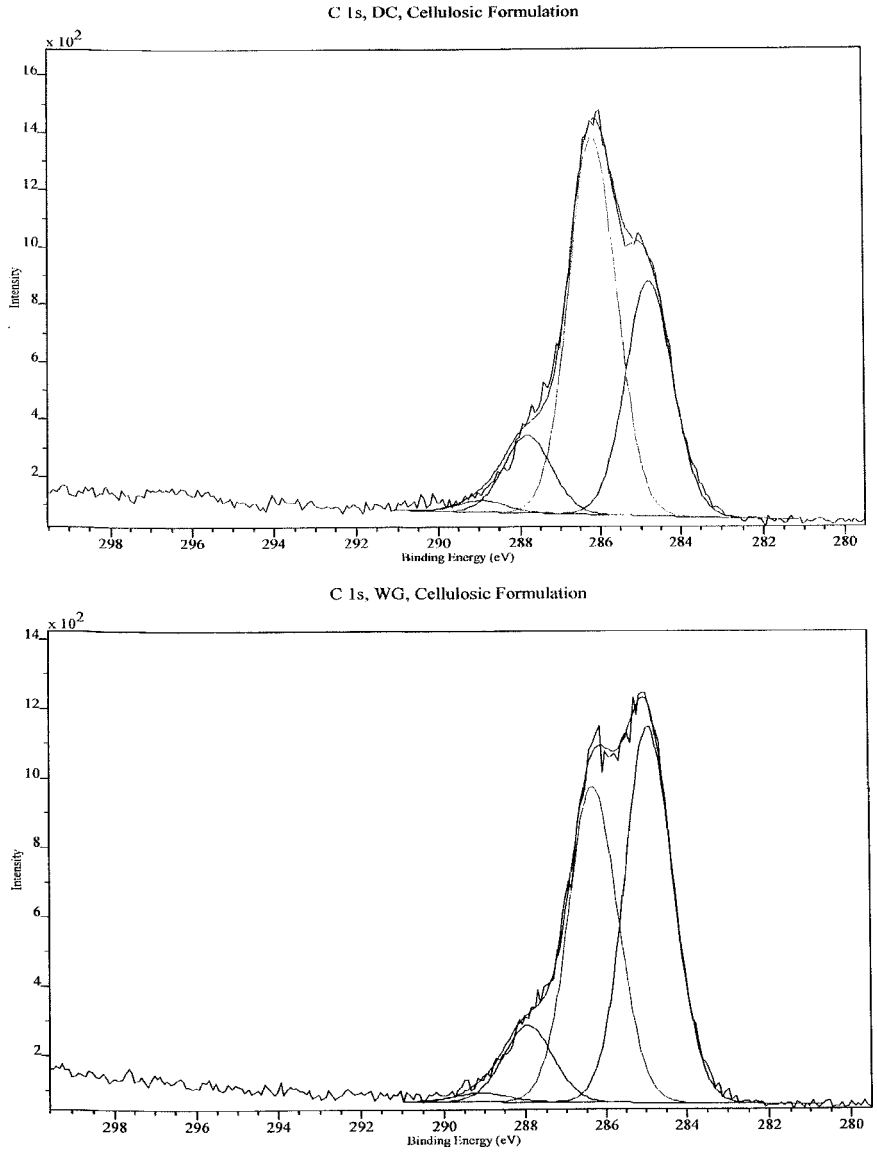


FIGURE 3 **C 1s Data of DC vs. WG Tablets for Cellulosic Formulations.**

TABLE 5 **Cellulosic Fracture Interface Carbon Compositions in At%**

Carbon state	DC	WG
C–C	21.5	33.4
C–O–C	34.6	28.0
O–C–O, C=O	7.1	6.8
O–C=O	1.1	0.8

for differentiation. The first point of analysis is to determine the diluent used, and for this, ToFSIMS analysis is used. Once the diluent is known, there are two possible routes: R_{CP} for calcium phosphate diluents or R_C for cellulosic diluents. For R_{CP}, XPS wide scans are acquired from five areas per fracture surface followed by the R_{CP} calculation described above. If calcium phosphate is not the diluent then the R_C route is followed. Again five areas per fracture surface are analyzed, but for R_C, both wide and narrow scans are acquired. After the acquisition, the data is manipulated using calculations, as described above, to produce the differential parameter for cellulosic-based diluents.

The model was further challenged with a series of 16 tablet formulations manufactured by WG or DC processes, selected at random, containing a wider range of excipients, and drug loadings. In this case, the prediction of granulation route success rate was 75%. The model failed to predict correctly where the tablets contained greater than 55% drug loading as at this level the properties of the API predominate.

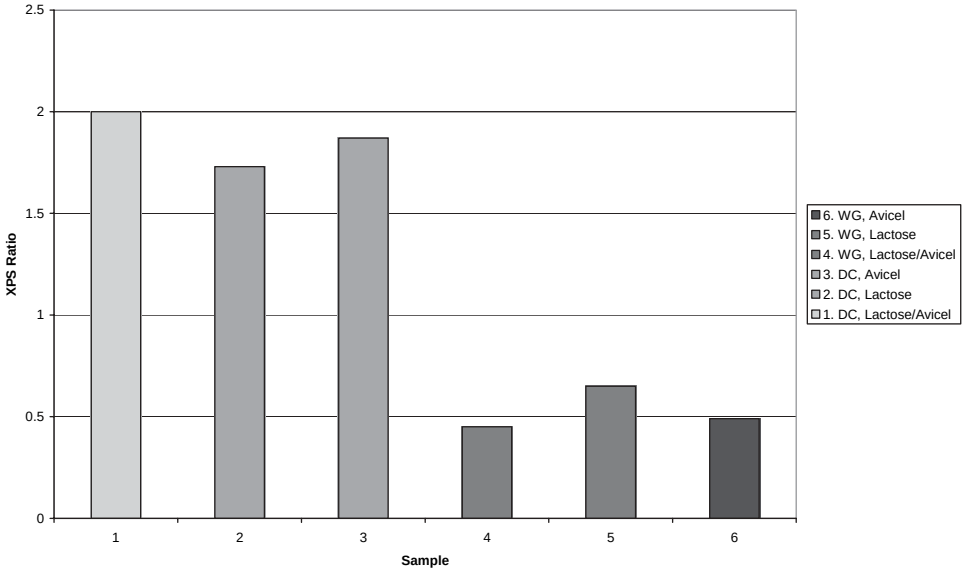


FIGURE 4 **Microcrystalline Cellulose (Avicel) and Lactose Tablets—Prediction of Route of Manufacture.**

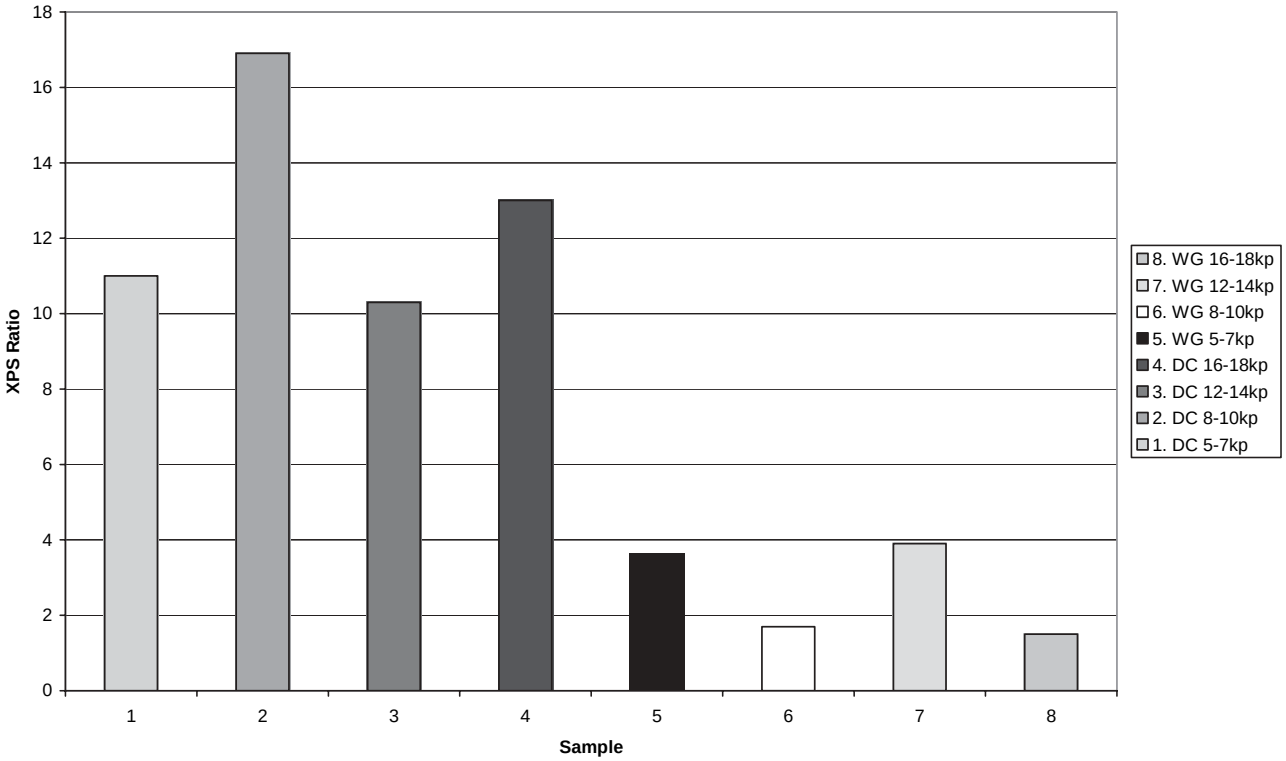


FIGURE 5 **Dibasic Ca Phosphate Tablets—Prediction of Route of Manufacture.**

CONCLUSIONS

A technique has been developed which enables the differentiation of tablets manufactured by wet granulation or direct compression processes. The model described exploits the use of XPS as a technique for quantifying common elements present at a fresh fracture surface of a tablet, in particular the distribution of the lubricant, magnesium stearate. Although the model was developed with tablet formulations containing dibasic calcium phosphate, microcrystalline cellulose, and lactose diluents, it was also largely

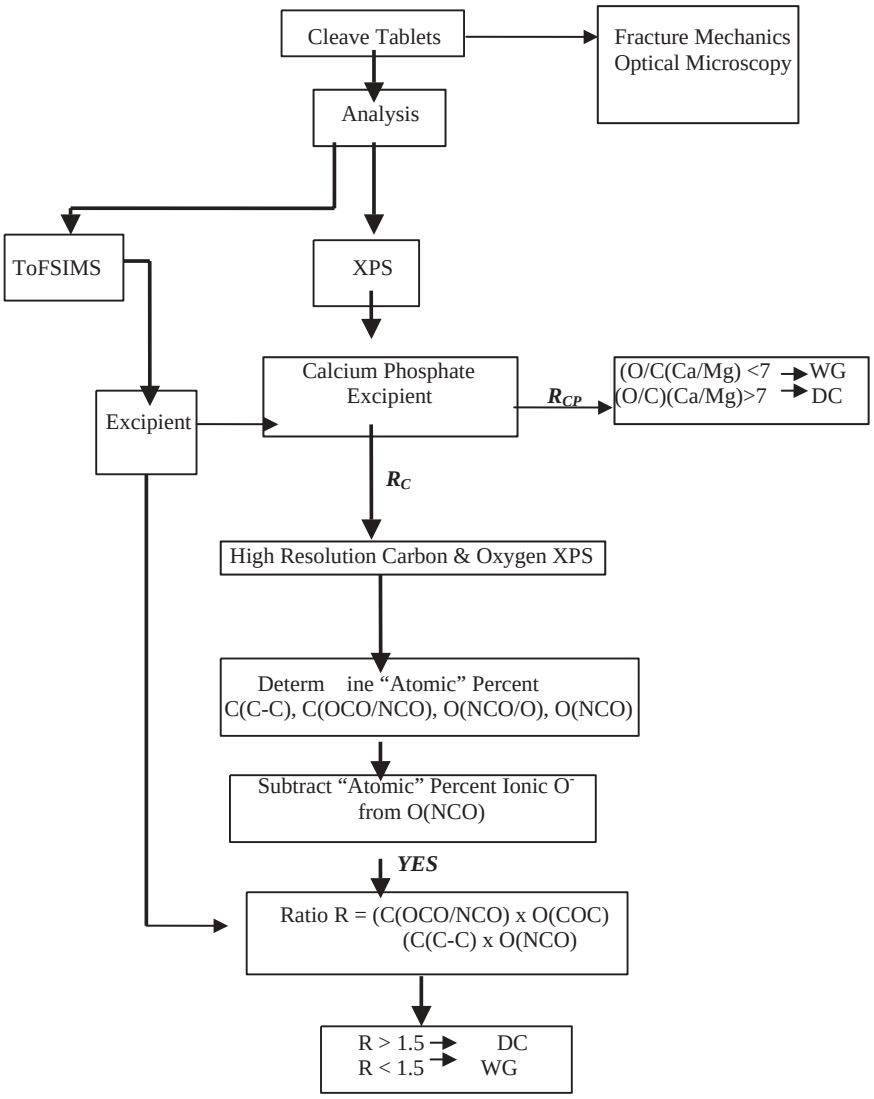


FIGURE 6 **WG vs. DC Decision Tree.**

successful in predicting the manufacturing processes for an uncontrolled group of tablet formulations. In principle, the success rate of the model could be increased with further refinement.

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