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Quantitative Determination of the Extent of Neutralization of Carboxylic Acid Functionality in Carbopol® 974P NF by Diffuse Reflectance Fourier Transform Infrared Spectrometry Using Kubelka-Munk Function

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Purpose. The purpose of this study was to develop an analytical method for the quantitative determination of the extent of neutralization of the carboxylic acid function in Carbopol® 974P NF using Diffuse Reflectance Fourier Transform Infrared Spectroscopy (DRIFT) with Kubelka-Munk function analysis.

Methods. Carbopol® 974P NF is a high molecular weight, chemically crosslinked polymer of acrylic acid, that has the C=O stretching band of the unionized carboxylic acid function at 1695 cm^{-1}. The quantitative determination of the extent of neutralization of the carboxylic acid function in Carbopol® 974P NF is based upon the asymmetrical C=O stretching of the carboxylate anion at 1570 cm^{-1} measured by DRIFT spectroscopy.

Results. To overcome spectral differences arising from sample preparation (powders, granules and tablets) and in an effort to increase the precision of the analytical method, the following approaches were used: (1) an internal standard, (2) first derivative of the spectrum to eliminate the effect of baseline drift and (3) the ratio of the first derivative of the C=O stretch of the carboxylate anion peak (1570 cm^{-1}) in the neutralized Carbopol® 974P NF to that of the peak of the internal standard (866 cm^{-1}). The above data treatment techniques proved to be superior to the usual methods of peak height or peak area. The calibration curve of the ratio of the first derivative (1570 cm^{-1}/866 cm^{-1}) was a linear function of the mass of sodium carboxylate over the range from 0.0% to 100.0% neutralization of the carboxylic acid function in Carbopol® 974P NF (Fig. 1a). No particle size or sample preparation effects were noted within the experimental error.

Conclusions. DRIFT spectroscopy using the Kubelka-Munk function is a powerful tool for the routine determination of the extent of neutralization of the carboxylic acid function in Carbopol® 974P NF in complex pharmaceutical formulations.

KEY WORDS: quantitative analysis; FTIR (DRIFT); Kubelka-Munk; neutralization; Carbopol® 974P NF.

INTRODUCTION

Historically, IR spectroscopy has been used solely as a qualitative technique, because of the sensitivity of IR absorption to geometry and instrument optics. For quantitative analysis, the same sample geometry and optics must be used for all samples. This is impossible to achieve across different laboratories using conventional IR spectroscopy. Recently, however, due to advancement in the application of optical theory, quantitative analysis can now be performed.

The well-known Beer-Lambert's law applies only to transmission measurements in lower concentrations (1–3). The absorbance A, and the concentration of the sample for transmission spectroscopy is as follows: $A = \varepsilon Ic$, where ε is specific absorptivity, I is thickness, and c is concentration. However, a linear relationship has also been reported for IR spectrum intensities, as a function of concentration, for Attenuated Total Reflection (ATR), Reflection-Absorption Spectroscopy (RAS), Diffuse Reflectance Spectroscopy (DRIFT), Emission, and Photoacoustic Spectroscopy (PAS).

Numerous diffuse reflectance theories have been proposed (4–10). The continuum theories are more general. They do not depend on a detailed knowledge of the medium since the scattering and absorbing processes are described by two phenomenological constants. The continuum theory views the sample powders as a homogeneous material. The scattering property and reflectivity are those of the powder as a whole. The diffuse reflectance is usually expressed in terms of the K-M function: $F(R_\infty) = K/S = (1 - R_\infty)^2/(2R_\infty)$, where S and K are constants that are related to the scattering and absorption properties, respectively, and R_∞ is considered to be the reflectivity of the infinitely thick sample. The reflectivity of the sample does not change as the infrared radiation cannot penetrate the sampling thickness any farther. The Kubelka-Munk equation is based upon the assumption of isotropic scatter, and has been used routinely for mid-IR spectroscopy (11–13). The Kubelka-Munk function is regarded as a limiting law (14) for essentially the same reason as the Beer-Lambert law. High energy throughout FT-IR has contributed to the successful application of this theory to quantitative analysis.

Applications of diffuse reflectance measurements by infrared Fourier transform spectrometry for the determination of small amounts of organic compounds, including fractions from liquid chromatography, have already been reported (6,15). Using the exact value for the absolute reflectance of KBr powder yields excellent linear correlations between the Kubelka-Munk function and the sample concentration, even at low concentration (13). Application of DRIFT for quantitative determination requires caution, because the DRIFT signals can be strongly influenced by the size and shape of the sample particle and by the particle size of the diluent (7).

Near-IR spectroscopy has been used in the analysis of blends, granules, encapsulation matrices, and milled tablets. An early paper using near-IR spectroscopy in the analysis of pharmaceutical mixed powders was published in 1981 by Becconsall *et al.* (16). The authors cautioned that spectral interferences from other components in the sample matrix could complicate attempts at quantitation. Ciurczak and Torlini (17) published a paper on the analysis of solid and liquid dosage forms by near-IR. It was often observed that samples prepared in the laboratory were spectrally different from production samples due to differences in preparation methods, different processing parameters and the batch size. These authors concluded that quantitation using near-IR often led to unsatisfactory results.

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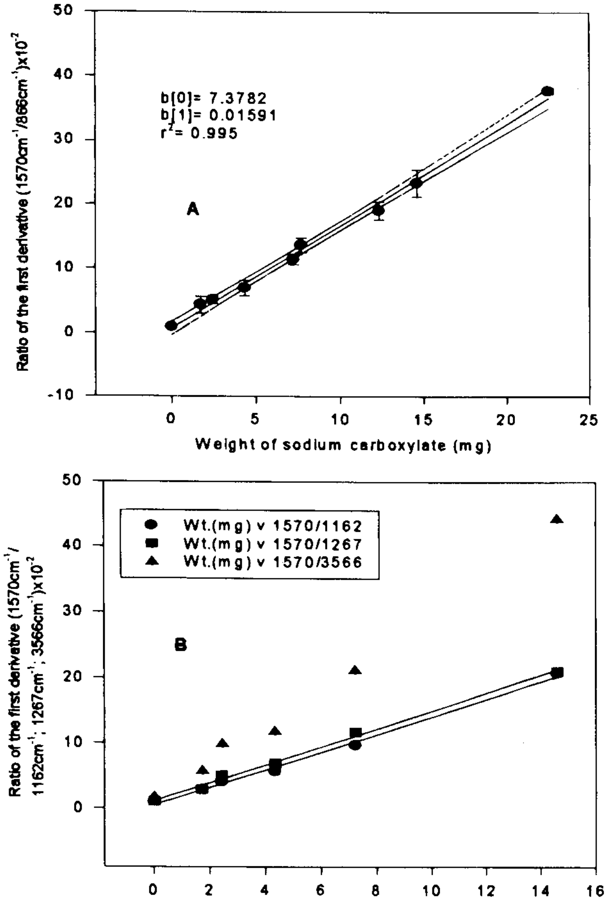

Fig. 1. (A) Calibration plot for ratio of the first derivative (1570 cm^{-1}/866 cm^{-1}) vs. weight of sodium carboxylate. (B) Plots for ratio of the first derivative (1570 cm^{-1} /either one of 1162 cm^{-1}; 1267 cm^{-1}; 3566 cm^{-1}) vs. weight of sodium carboxylate.

Diffuse reflectance Fourier transform infrared spectroscopy (DRIFT) using the Kubelka-Munk function has now been applied to the quantitative determination of the extent neutralization of the carboxylic acid function in Carbopol® 974P NF (poly acrylic acid) for wet granulation tablet formulations. The development of this quantitative method is described in this paper. The method has been validated. Finally, the method was used to determine the effects of the processing parameters on the extent of neutralization of the carboxylic acid function in Carbopol® 974P NF during process development.

EXPERIMENTAL

Materials

Carbopol® 974P NF resin is a pharmaceutical grade of polymer. It is a synthetic, high molecular weight, chemically crosslinked polymer of acrylic acid (-$CH_2CHCOOH$-)$_n$ purchased from B. F. Goodrich (Cleveland, OH). Carbopol® 974P NF is slightly pre-neutralized (1–3%) by potassium salt. This pre-neutralization is done to precipitate polyacrylic acid in the polymerization solvent ethyl acetate. The maximum amount of the residual solvent content is 0.9% in the powder, which does not have an effect on the determination of extent of neutralization of carboxylic acid in Carbopol® 974P NF. The weight percentage of carboxylic acid was determined using titration by B. F. Goodrich. The equivalent weight of Carbopol® 974P NF can be calculated as follows:

$$\text{Equivalent weight of Carbopol® 974P NF} = (100/x)*45 \qquad (1)$$

x = weight percentage of carboxylic acid in Carbopol® 974P NF
45 = formula weight of carboxylic acid function (COOH)

Sodium phosphate dibasic anhydrous was obtained from Spectrum Chemical Mfg., Co. (Gardena, CA). Polyvinylpyrrolidone (PVP) K90 was purchased from ISP Technologies (Calvert City, KY). Lactose Spray-Dried was obtained from Foremost Farms (Baraboo, WI). Magnesium stearate was purchased from Mallinkrodt (St. Louis, MO). The model drug employed was simvastatin ($C_{25}H_{38}O_5$, m.w. 418.6), a water insoluble, nonionic compound.

Diffuse Reflectance Fourier Transform Infrared (DRIFT)

A Fourier transform infrared spectrophotometer (Digilab FTS-60) with a Triglycine Sulfate (TGS) detector and a diffuse reflectance attachment (Digilab DRIFT) was used. The spectrometer was scanned from 4000 to 500 cm^{-1} at 4 cm^{-1} resolution using a 1.12 kHz lower pass filter. One hundred and twenty-eight scans were monitored for each spectrum. The calibration voltage was adjusted between −6 and −7 volts.

The Kubelka-Munk (K-M) function was used to determine the percentage neutralization of the carboxylic acid function in Carbopol® 974P NF. The spectrophotometer was purged with nitrogen to reduce atmospheric water vapor. Single beam reflectance data were measured against high purity KBr and stored as the reference. The sample to KBr ratio was 1:9. IR quality KBr (Sigma) was used as the powder diluent. Each sample was measured four times. The "GRAMS" software from Digilab was used to analyze the spectrum. The Savitsky-Golay first derivative, 2nd degree polynomial with 10 convolution points from each peak, was used to re-analyze the DRIFT spectrum.

Sample Preparation

Samples for the Calibration Curve

Carbopol® EX-214 was received from B. F. Goodrich as the standard for determining the percentage neutralization of the carboxylic acid function in Carbopol® 974P NF. Carbopol® EX-214 is neutralized by sodium hydroxide by B. F. Goodrich. The standard sample used contained 7 wt % of non-neutralized carboxylic acid, which was determined by titration by B. F. Goodrich. The same absorption was observed on the DRIFT spectrum for both sodium carboxylate and potassium carboxylate forms of Carbopol® 974P NF. Consequently, no errors were introduced by using Carbopol® EX214 as an internal standard. Furthermore, the very low level of pre-neutralization (1–3%) Carbopol® 974P NF did not influence the determination of the extent of neutralization, as the calibration curve was based on the standard Carbopol® EX-214 with a known extent of neutralization.

A Carbopol® 974P NF blank sample was prepared to include all the components of the formulation except for Carbopol® 974P NF. Carbopol® EX-214 was weighed, spiked, and mixed with a weighed quantity of the Carbopol blank sample; then 50 mg of each spiked, standard sample was weighed, and mixed with 450 mg of KBr. This one-tenth weight percentage standard was used to establish the calibration curve. Figures 2a & 2b show true peak & first derivative for sodium/potassium carboxylate. Using the vertical distance between the peak and adjacent trough as a measure of first derivative reflectance, it was found that the intensity of the C=O stretching band of the carboxylate anion at 1570 cm^{-1} and the first derivative (1570 cm^{-1}) for the calibration samples increased as the percentage neutralization increased.

Four peaks (866 cm^{-1}; 1162 cm^{-1}; 1267 cm^{-1}; 3566 cm^{-1}) in the tablet formulation were examined as an internal standard peak. The calibration curves for the ratio of the first derivative of (1570 cm^{-1}/866 cm^{-1}) and (1570 cm^{-1}/either one of 1162 cm^{-1}; 1267 cm^{-1}; 3566 cm^{-1}) vs. weight of sodium carboxylate were all linear are shown in Figures 1a and 1b, respectively. The regression coefficients are 0.995, 0.995, 0.995, and 0.993 for 1570 cm^{-1}/866 cm^{-1}, 1570 cm^{-1}/1162 cm^{-1}, 570 cm^{-1}/1267 cm^{-1} and 1570 cm^{-1}/3566 cm^{-1}, respectively. In contrast, a highly variable calibration curve was observed when the peak height of sodium carboxylate vs. weight of sodium carboxylate was used.

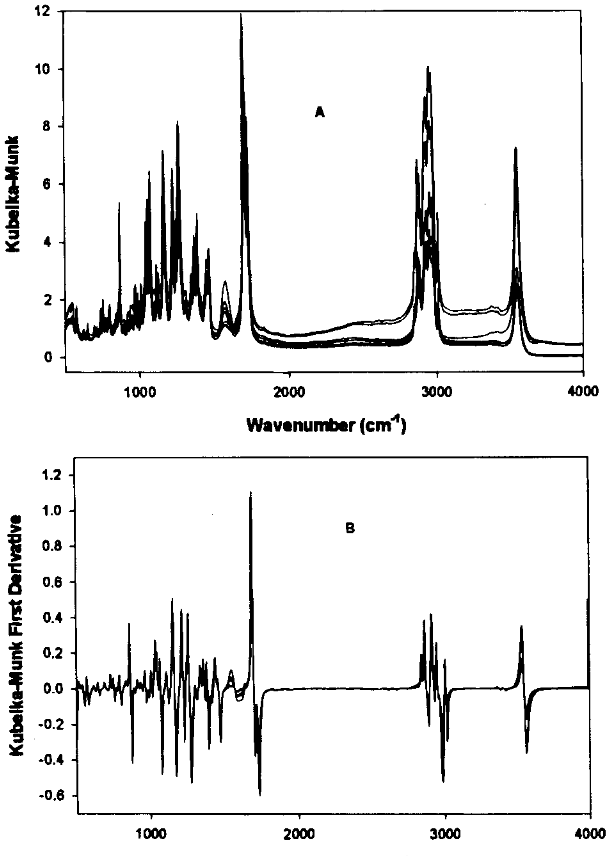

Fig. 2. (A) DRIFT spectra: peak of sodium carboxylate at 1570 cm^{-1} for the calibration samples are in the range of 0–100% neutralization of the carboxylic acid function. (B) DRIFT spectra: the first derivative of sodium carboxylate at 1570 cm^{-1} for the calibration samples in the range of 0–100% neutralization of the carboxylic acid function.

Samples for Drug Tablet

The tablet consisted of simvastatin, neutralizing agent, lactose, binder, magnesium stearate, and Carbopol® 974P NF. A mixed solvent of ethanol and water was used during the wet granulation process. The different extents of neutralization occurred as a result of using different processing conditions. Namely, different mixers' series, shear rates, spray rates, amount/ratio of granulating solvent and drying methods.

Samples for DRIFT FTIR

The granule or tablet samples were prepared by grinding in a mortar and pestle; then, 50 mg of each sample was weighed, and mixed with 450 mg of KBr.

Data Analysis

To determine the percentage neutralization of the carboxylic acid function, the calibration curve was established as the ratio of the first derivative (1570 cm^{-1}/866 cm^{-1}) vs. the weight of sodium carboxylate in Carbopol® 974P NF. The peak at 866 cm^{-1} identified as trisubstituted olefinic C-H wag from the drug was the most reproducible peak. The number of degrees of freedom used for calculation of percentage relative standard deviation (%RSD) was $f = n - 1$.

Method: Calculation of Sodium Carboxylate Content for EX-214

The definition and calculation of the weight percentage content of the carboxylic acid function and of sodium carboxylate in Carbopol® 974P NF or EX-214 are listed as follows:

$$c = (45/75) * (1 - x) * 100 \qquad (2)$$

c = weight percentage of the carboxylic acid function in the sample.
x = degree of the neutralization of the sample
75 = equivalent weight of Carbopol® 974P NF
45 = formula weight of the carboxylic acid function

$$a = (67/97) * x * 100 \qquad (3)$$

a = weight percent of sodium carboxylate in the sample
67 = formula weight of sodium carboxylate
97 = equivalent weight of fully neutralized Carbopol® 974P NF

Since the quoted weight % of unionized carboxylic acid was 7% (B. F. Goodrich Certificate of Analysis for Batch # Y02350) lot of EX214, from equation (2), the degree of neutralization (x) for this specific lot can be calculated:

$$x = 0.883$$

Weight % of sodium carboxylate for lot of

$$\text{EX-214} = (67 / 97 * x) * 100 = 61.0\% \qquad (4)$$

67 = formula weight of sodium carboxylate
97 = equivalent weight of fully neutralized Carbopol® 974P NF
x = degree of neutralization

Therefore, the weight of sodium carboxylate was calculated for the calibration curve as follows:

$$\text{weight of sodium carboxylate} = \text{weight of EX-214 sample} * 0.610 \qquad (5)$$

Method: Calculation for the Percentage Neutralization of the Carboxylic Acid Function in Carbopol® 974P NF for Wet Granulation Processing

The weight content of sodium carboxylate for each tablet granulation can be obtained from the calibration curve of the ratio of the first derivative (1570 cm^{-1}/866 cm^{-1}) vs. weight of sodium carboxylate. The actual weight of sodium carboxylate (mg) in the tablet formulations includes any initial neutralization of the carboxylic acid function in Carbopol® 974P NF itself prior to wet granulation processing.

The percentage neutralization of the carboxylic acid function in Carbopol® 974P NF for the tablet formulations can be calculated as follows:

$$\%\ \text{neutralization} = (y/67) * (74.04/24) * 100 \qquad (6)$$

y = actual weight of sodium carboxylate for each formulation (mg)
67 = formula weight of sodium carboxylate
24 = amount of Carbopol® 974P NF in tablet formulation (mg)
74.04 = equivalent weight of Carbopol® 974P NF containing 60.78 Wt% of carboxylic acid

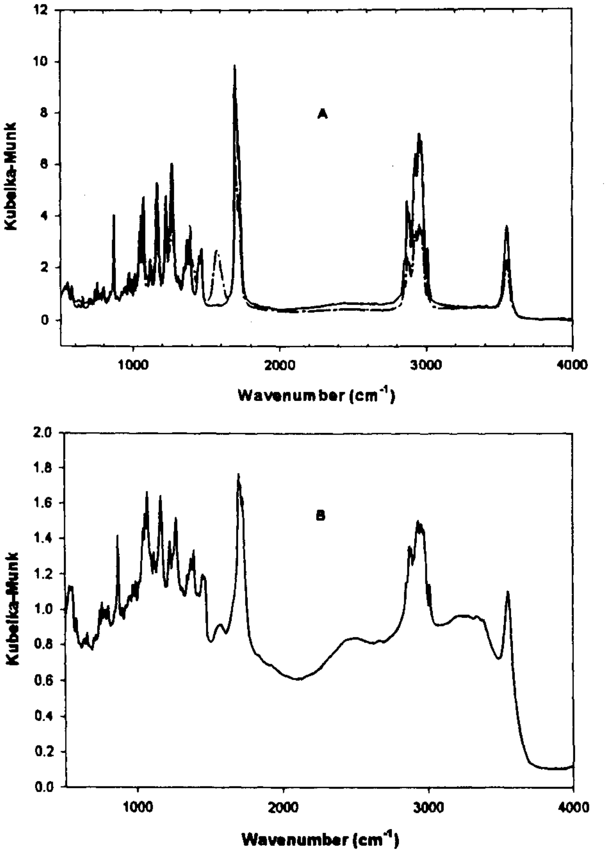

Fig. 3. (A) DRIFT spectra. A (solid line): Carbopol® 974P NF blank contains all components of the formulation except for Carbopol® 974P NF. B (dashed line): EX214 spiked into the Carbopol® 974P NF blank. (B) DRIFT spectrum for wet granulation tablet ground and mixed with KBr.

RESULTS AND DISCUSSION

Carbopol® 974P NF is a synthetic, high molecular weight, chemically crosslinked polymer of acrylic acid, that has a C=O stretching band of the carboxylic acid function at 1695 cm^{-1}. Carbopol® EX214 is a sodium hydroxide neutralized form of Carbopol® 974P NF that was supplied by B. F. Goodrich. Carbopol® EX214 has a strong asymmetrical C=O stretching band of the carboxylate anion at 1570 cm^{-1}.

Figure 3a shows the DRIFT spectrum for the Carbopol® 974P NF blank and EX214 sample. Spectrum A of Figure 3a is that of the Carbopol® 974P NF blank consisting of all components of the tablet formulation except for Carbopol® 974P NF. Spectrum B of Figure 3a is that of Carbopol® EX214 spiked into the Carbopol® 974P NF blank, which has a stretching band C=O of the carboxylate anion at 1570 cm^{-1}.

In this study, the C=O band (1570 cm^{-1}) of the carboxylate anion is used to determine the extent of neutralization of carboxylic acid that occurred in Carbopol® 974P NF during the wet granulation process. The C=O band of the carboxylic acid at 1695 cm^{-1} cannot be used for the determination because some components of the tablet formulation have the same absorption band.

Figure 3b depicts the DRIFT spectrum of the ground tablet produced by wet granulation. The tablet was ground by mortar and pestle, then spiked into KBr for the measurement. This spectrum shows the upward drift of the baseline and the distortion of the spectrum for the tablet formulation (refer to Figure 3a for the blend sample of drug powder). This indicated that the process of wet granulation altered the reflectance of the sample, leading to the variable intensity of DRIFT signals between the granule and the standard powder blend spiked samples. Furthermore, a significantly larger variability (RSD up to 74%, n = 4) in the DRIFT signal was observed for the granule samples. Consequently, either using peak area or peak height would lead to a higher variation in the quantitative analysis. Therefore, application of DRIFT for quantitative determination requires caution because the sample treatment strongly influences the DRIFT signals (1).

To resolve the spectral differences between the dry powder calibration samples and the tablets, due to differences in preparation methods and or composition (e.g., different processing parameters such as volume and composition of the granulation solvent, spraying rate, batch size, milling conditions and tableting force), the first derivative of the DRIFT spectrum using the Kubelka-Munk function was used. Additionally, an internal standard peak was selected from both the powder blend calibration samples and the tablets for the quantitative analysis.

The peak of 866 cm^{-1} was selected as the internal standard because of greater reproducibility. The band of 866 cm^{-1} was primarily contributed by trisubstituted olefinic C-H wag from the drug, simvastatin. By using these techniques, the differences of particle size, physical properties and FT-IR instrumentation would not affect the quantitative results. A tablet was examined for the extent of neutralization of the carboxylic acid function in Carbopol® 974P NF using four different calibration curves (Figures 1a & 1b). The average extent of neutralization in the tablet was 20.0% (±3.6%) using all four calibration curves. This demonstrates that significant neutralization of the Carbopol® 974P NF has occurred during processing, since Carbopol® 974P NF is pre-neutralized to a level of only about 1–3%.

Method Validation

The DRIFT spectroscopy using the Kubelka-Munk function was validated in terms of linearity and range of the calibration curve, instrument precision, method precision, effect of sample preparation and reproducibility. The details are discussed as follows:

Linearity and Range

The calibration curve for the ratio of the first derivative (1570 cm^{-1}/866 cm^{-1}) vs. weight of sodium carboxylate was a linear relationship in the weight range of sodium carboxylate 0.00 mg–22.52 mg. This weight range covered from 0.0% to 100% neutralization of carboxylic acid in Carbopol® 974P NF for the sample tablets (Figure 1a). The linear regression correlation coefficient (r^2) was 0.995.

Instrument Precision

The RSD was 0.8% and 4.1% (n = 10) in the precision of the instrument for the standard, spiked sample (sodium carboxylate content: 7.68 mg) and sample tablet, respectively.

Method Precision

The RSD was 6.7% (N = 5) and 11.5% (N = 10) in the precision of the method for the standard spiked sample (sodium carboxylate content: 7.68 mg) and sample tablet, respectively. Each sample was measured four times (n = 4).

Effect of Particle Size Distribution

The effect of particle size distribution on the calculation of the percentage neutralization of the carboxylic acid function was determined by taking sieve fractions. Seven different particle size fractions were examined, including upper (>150 microns) and lower (<45 microns) sieve fractions, separately, to examine worse case scenarios (Table 1). The average percentage neutralization was 25.3% (RSD = 6.0%, N = 7; n = 4). However, within the experimental error, no particle size effects were noted (Table 1). These data indicated that there was no need for particle classification in order to achieve good measurement precision.

Table 1. Particle Size Effect on Percentage Neutralization of the Carboxylic Acid Function in Carbopol 974P® for Tablet Sample A

Sample #	>150 microns	75 microns	45 microns	<45 microns	% neutralization	%RSD[b]
A-1	100[a]	0	0	0	24.54	10.6
A-2	0	0	0	100	28.10	6.7
A-3	10	30	50	10	25.31	11.5
A-4	10	50	30	10	25.85	9.5
A-5	10	20	20	50	23.03	5.9
A-6	20	30	30	20	25.04	10.5
A-7	50	20	10	20	25.30	10.7
Average					25.31	
% RSD					6.0	

[a] Percentage by weight.

[b] Degree of freedom of the population was f = n − 1 for the calculation of RSD.

Reproducibility of the Calibration Curve

To examine the reproducibility of the calibration curve, the same standard, spiked samples were measured three times at three different intervals during two month, but the samples were only measured once. Then, the samples for the percentage neutralization of the five different particle size fractions were calculated based on these three calibration curves measured at three different periods. The average percentage neutralization was 24.4% (RSD = 12.0%, N = 5; n = 4) (Table 2). The RSD of 12% is considered to be the maximum level of variability, as the samples were made without measuring the calibration samples each time. Hence, for maximum precision, it is concluded that both the calibration samples and the granule samples are measured at the same time to further optimize the precision of the method.

Application for Determination of the Percentage Neutralization of the Carboxylic Acid Function in Carbopol® 974P NF for the Processed Samples

To demonstrate that the proposed method was capable of distinguishing the effect of each process parameter on the extent of neutralization of the carboxylic acid function in Carbopol® 974P NF, the following were evaluated: amount of granulation solvent (ethanol/water); solvent spraying rate/solvent pouring, high shear mixer/mortar & pestle and repeated batch manufacture. The higher water content of the granulation solvent was presumed to cause a higher extent of neutralization of carboxylic acid in Carbopol® 974P NF as more of the sodium phosphate could dissolve during granulation. The water content for each gram of granule was calculated as follows:

Water content (mL/g) = % volume of water content *
total solvent volume used (mL/g)

Table 2. Percentage Neutralization of the Carboxylic Acid Function in Carbopol® 974P NF for Sample Tablet Using Calibration Curve Measured at Three Different Time Periods in Two Months

	% Neutralization		
Sample #	Calibration I	Calibration II	Calibration III
A-1	25.31	21.01	26.59
A-2	25.85	21.46	27.16
A-3	25.04	20.78	26.31
A-4	25.30	21.00	26.58
Average	25.38	21.06	26.66
% RSD	1.3	1.4	1.3

Table 3. Process Effect on the Extent of Neutralization of the Carboxylic Acid Function in Carbopol® 974P NF

Formulation #	Granulating Solvent Ethanol: water= (v/v); (mL/g)	Solvent Spray/ Pouring	Water Content (mL/g)	% Neutralization
A	50:50 (0.20 mL/g)	Solvent Pouring	0.110	27.08
B	70:30 (0.29 mL/g)	Solvent Spraying	0.087	5.54
C	50:50 (0.25 mL/g)	Solvent Spraying	0.087	3.72
D	30:70 (0.20 mL/g)	Solvent Spraying	0.125	7.77
E	30:70 (0.20 mL/g)	Solvent Pouring	0.140	26.95
F	30:70 (0.20 mL/g)	Solvent Spraying	0.140	8.12
G	30:70 (0.20 mL/g)	Pestle & Mortar	0.140	60.97

Data are presented in Table 3 for the extent of neutralization of the carboxylic acid function in Carbopol® 974P NF for seven formulations that were manufactured with either a different composition/amount of granulation solvent or by a different process, in terms of higher shear mixer vs. pestle & mortar; solvent spraying vs. solvent pouring. The results show that (1) pouring of the granulating solvent using the same level of the water content could cause a significantly greater extent of neutralization (samples A & E) compared with spraying of the granulating solvent (Samples B, C, and F), and (2) Sample preparation using pestle & mortar showed a greater extent of neutralization (sample G) than granulation with either solvent spraying (sample F) or solvent pouring (sample E) in a high shear mixer. These differences can be explained in terms of overwetting, caused by pouring the granulation fluid onto a localized area of the powder bed, leading to a greater extent of dissolution of the soluble neutralizing agent in the formulation.

Five formulations were manufactured using different amounts/compositions of granulating solvent (Table 4). These five formulations had the same granule composition and were manufactured under the same processing conditions in terms of high shear mixer, mixing time periods, spraying rate of granulation solvent and drying time periods. The results for the extent of neutralization are listed in Table 4. The data demonstrate that the higher the water content of the granulating solvent used during wet granulation, the higher the extent of neutralization. Sample A using a granulating solvent: ethanol:water = 30:70 (v/v), 0.29 mL/g, had the highest water content (0.203 mL/g) for each gram of granule which led to the greatest extent of neutralization (15.1%, RSD = 4.9%; N = 3). Under the same processing conditions, the extent of neutralization of the carboxylic acid function in Carbopol® 974P NF increased linearly as the water content of the granulating solvent increased (Fig. 4). These results can again be explained in terms of increased water content leading to increased solubility of the neutralizing agent in the formulation.

Table 4. Percentage Neutralization vs. Water Content (mL/g) of Granulating Solvent

Batch #	Granulating Solvent Ethanol:water (v/v)	Granulating Solvent (mL/g)	Water Content (mL/g)	% Neutralization	% RSD
A	30:70	0.29	0.203	15.07	4.9
B	30:70	0.20	0.140	8.12	12.4
C	50:50	0.25	0.125	7.77	14.7
D	70:30	0.20	0.060	3.72	7.0
E	70:30	0.29	0.087	3.01	19.3

The results demonstrate that the DRIFT methodology using the Kubelka-Munk function is capable of determining the extent of neutralization of the carboxylic acid function in Carbopol® 974P NF from different processing conditions; namely, amount of granulation solvent, mixer, mixing time and method of addition of the granulation solvent.

CONCLUSIONS

When the following analytical techniques are utilized in conjuction with DRIFT spectroscopy using the Kubelka-Munk function, they produce superior results for the quantitative determination of the extent of neutralization of the carboxylic acid in Carbopol® 974P in powder systems. These techniques are: (1) the first derivative of the DRIFT spectrum, (2) selection of the internal standard peak (866 cm^{-1}) and (3) the ratio of the first derivative of the sodium carboxylate anion (1570 cm^{-1}) over that of the internal standards peak (866 cm^{-1}) to construct the calibration curve and for sample measurement.

This methodology was developed and validated in terms of (1) precision of instrument (RSD = 0.8%–4.1%) (2) precision of the method (RSD = 6.7%–11.5%) (3) linearity (r^2 = 0.995) (4) percentage neutralization range 0.0%–100%, and (5) absence of particle size effects within the experimental error (RSD = 10%). Sample preparation and measurement were straightforward, with no requirements to select a specific particle size distribution or different instrument settings to have good

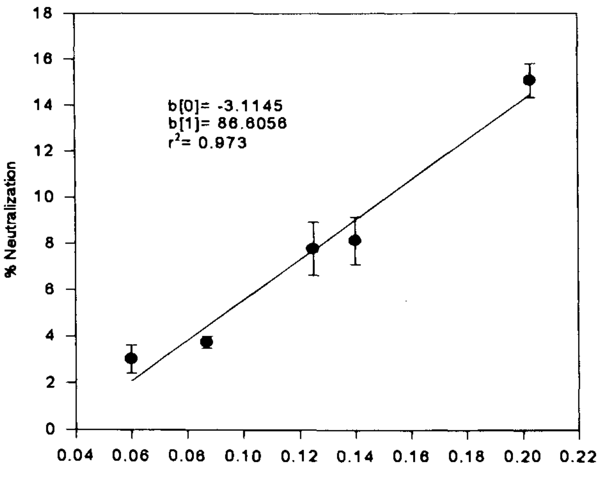

Fig. 4. Percentage neutralization of carboxylic acid in Carbopol® 974P NF during wet granulation vs. water content of granulation solvent used.

measurement precision. The technique is convenient, simple, robust and reliable for the quantitative analysis of the tablet and granule samples.

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