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Quantitation of film coating on Zantac® 75 mg tablets and Epivir HBV® 100 mg tablets by ICP-AES

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Abstract

Purpose: To present a selective analytical Inductively Coupled Plasma-Atomic Emission Spectroscopy (ICP-AES) method developed and validated for the quantitation of tablet film coatings containing titanium. *Methods:* Tablet samples were decomposed by either digestion or dry ashing. The amount of film tablet coating was calculated based on titanium content of the sample. *Results:* The reported ICP-AES method was accurate, precise, sensitive and linear for determination of titanium concentrations from 2.9 to 8.6 ppm. *Conclusion:* This method provides an accurate determination of the amount of coating on a tablet and has general applicability for a variety of coating formulations containing different elements.

Keywords: Inductively coupled plasma; Tablet coating analysis; Quantitation of film coating; Titanium analysis; Atomic emission spectroscopy

1. Introduction

Tablets may be coated for aesthetic reasons as well as to provide taste masking or to control drug release. Manufacturers often desire to optimize the coating process, but in doing so, require an accurate measure of tablet coating. At present, analytical methods available to quantitate the amount of coating per tablet are either non-specific or imprecise [1–4]. Typically, rather than employing cumbersome, tablet specific analytical methods, manufacturers rely on methods based on percentage weight gain of an entire batch after coating [1]. This gives only an estimate of the coating level per tablet. Inaccuracies in this method are due to variability in tablet cores, attrition during coating and potential loss of moisture during the coating process.

An Inductively Coupled Plasma-Atomic Emission Spectroscopy (ICP-AES) method was developed which gives accurate, precise measurement of coating levels for individual tablets or for an entire

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batch. The method is reported herein. A related technique was reported previously for quantitation of ink on tablets [5].

The method for quantitation of coating is based on ICP-AES measurement of the amount of metal in the pigment of the film coating. The technique is selective for multiple elements and is quantitative to parts-per-billion (ppb) sensitivity [6–8]. These attributes suggest application to a wide variety of coating types. Typically, in the Pharmaceutical Industry, coatings contain titanium dioxide and iron oxides. The examples presented in this paper are titanium based.

In order to demonstrate the applicability of the method, we chose to examine two different tablets with different coatings: Zantac® 75 mg tablets and Epivir HBV® 100 mg tablets. Opadry® Pink coating is used for Zantac® tablets, and Opadry® \tf="DM8"\char178}}-
*Butterscotchcoatingisusedfor Epi*virHBV{^{\t-vir HBV® tablets. Both Opadry® coatings are formulated with iron oxide (Synthetic red iron oxide) and titanium. The other components are: Hydroxypropyl Methylcellulose, Triacetin, Polyethylene glycol and Polysorbate. The titanium dioxide is commonly used to opacify the film coat. Titanium is measured by this technique since its concentration in the Opadry® mixture is known. The measurement of titanium on the tablets is, therefore, directly correlated to the amount of Opadry® coating on the tablet and this can be measured easily and accurately using ICP-AES.

Two methods are presented for quantitation: one yields single tablet information and the other batch or composite data. As well, two methods for sample preparation are presented which allows possible application to a broad variety of tablet coatings.

2. Materials and methods

2.1. ICP-AES

The amount of titanium (emission wavelength of 334.94 nm), in the samples was determined using a Varian Liberty 100 ICP-AES (parameters listed in Table 1). The sample was introduced into the plasma as an aerosol generated by a nebulizer.

Table 1
Summary of Varian Liberty 100 ICP-AES program conditions

Condition	Value
Nebulizer pressure	150 kPa
Snout	OFF
Element	Titanium
Wavelength	334.941 nm
Line type	Analyte
View height	2 nm
Windows-search	0.080 nm
Windows-scan	0.120 nm
Integration	3.00 s
PMT	650 V
Power	1.00 kW
Plasma	15.0 ml/min
Aux	1.50 ml/min
Pump speed	25.0 rpm
BGC (background correction) mode	Dynamic
Units	ppm

2.2. Reagents

Concentrated sulfuric acid, nitric acid and ammonium sulfate were purchased from BDH (AnalaR grade). Titanium dioxide was purchased from BDH (purity was 98%). Titanium standard (1000 ppm) solution was purchased from SCP Science. Purified deionized lab water was used throughout the study.

2.3. Samples

Two different tablets were used: Zantac® 75 mg tablets and Epivir HBV® 100 mg tablets. Both tablets are coated with an Opadry® based film coating produced by Colorcon-Berwind [9,10]. The tablets were decomposed by digestion or dry ashing to dissolve the titanium dioxide for subsequent concentration of titanium [Ti] measurements by ICP-AES.

2.4. Zantac® 75 mg tablets

2.4.1. Digestion

Zantac® 75 mg tablet samples were prepared by hot plate digestion. Ammonium sulfate (2 g) and concentrated sulfuric acid (5 ml) were added to each sample in a 100 ml tall form beaker. The samples were heated until copious fumes of sulfur trioxide appeared. Samples were then heated for an additional 20 min to ensure that all of the titanium dioxide was dissolved. Concentrated nitric acid (15 ml) was added and samples were refluxed to digest the organic material and dissolve any particulate matter that may plug the nebulizer during ICP-AES analysis. Solutions were refluxed until transparent and orange in color, allowed to cool, and diluted with purified water to a final volume of 200 ml.

2.4.1.1. Standard. A 200 ppm titanium standard solution was prepared by addition of the titanium standard solution (40 ml) into a Zantac® digestion blank solution (see below) and diluting to volume in a 200 ml volumetric flask. A 50 ppm standard was prepared by diluting the 200 ppm standard titanium solution with purified water.

2.4.1.2. Zantac® digestion blank. The blank solution consisted of ammonium sulfate (2 g), concentrated sulfuric acid (5 ml) and concentrated nitric acid (15 ml).

2.5. Epivir HBV® 100 mg tablets

2.5.1. Dry ashing

The Epivir HBV® 100 mg tablets could not be completely digested using the digestion sample preparation used for the Zantac® 75 mg tablets. Variations on the digestion technique were attempted without success. Dry ashing techniques were investigated for sample preparation of Epivir HBV® 100 mg tablets and optimal conditions were established.

The samples were prepared by dry ashing at 575 °C for 4 h prior to the dissolution of titanium dioxide, in concentrated sulfuric acid (5 ml) and ammonium sulfate salt (2 g), on a hot plate. Upon appearance of sulfur trioxide fumes, samples were heated until the complete disappearance of titanium dioxide. Tablets were heated for an additional 10 min. If charred particles were present, concentrated nitric acid was added dropwise until the solution was clear. Samples were cooled to room temperature, quantitatively transferred, and diluted to volume in a 200 ml volumetric flask with purified water.

2.5.1.1. Standard. A 5 ppm titanium standard solution was prepared by addition of the titanium standard (1.0 ml) into a Epivir HBV® dry ashing blank solution (see below) and diluting to volume in a 200 ml volumetric flask.

2.5.1.2. Epivir HBV® dry ashing blank. The blank solution was prepared by adding ammonium sulfate (2 g) and concentrated sulfuric acid (5 ml) to a beaker. The solution was heated on a hot plate for 4 h, an equivalent time period as for the samples. The blank solution was transferred and diluted with purified water to 200 ml in a volumetric flask.

3. Results and discussion

3.1. Zantac® 75 mg tablets

The ICP-AES method was assessed for reliability and accuracy by performing recovery, accuracy, precision, and linearity experiments. Furthermore, the titanium dioxide content of Opadry® Pink was analyzed and verified against the manufacturer's claim of 29.2% w/w (9). Known amounts of Opadry® Pink were weighed and analyzed for titanium dioxide content. The amount of titanium dioxide determined from two separate experiments, was 28.6% w/w. When compared to the theoretical value of 29.2% w/w, the recovery was calculated to be 98.0% (Table 2). The theoretical value for titanium dioxide content was therefore confirmed and used in subsequent calculations.

In a preliminary experiment to evaluate the applicability of the method, the amount of coating on tablets with four different theoretical amounts of coating (3.50, 4.05, 4.50 and 4.95% w/w) was

Table 2
Verification of Opadry® Pink (Zantac® tablets) titanium dioxide content vs. theoretical value (29.2% w/w)

TiO_2 (mg) detected	Opadry® (mg)	TiO_2 standard recovery factor (%)[a]	TiO_2 detected (%)	Detected vs. theoretical (%)
2.58	9.965	90.50	28.61	98.0
2.64	10.064	91.70	28.60	97.9
Mean			28.60	98.0

[a] Correction factor to compensate for matrix differences between standards and samples. Standards were prepared in water and not in blank samples for this experiment.

determined (theoretical percent coating was determined using the percent weight gain method after defined time periods of coating). Determinations were made on both single tablets and composite (10 tablets) samples. Although considerable tablet to tablet variation was found, the relationship between the theoretical and experimental determined amount of coating was linear, with correlation coefficients of 0.9983 and 0.9801 for the single tablet and composite sample, respectively. The single tablet determination method yielded the following regression equation:

$$y = 1.0056x - 0.6589, \quad r = 0.9983,$$

$$95\%\ \text{CI for slope} = (0.825–1.186),$$

$$95\%\ \text{CI for intercept} = (-1.432–0.114),$$

where y stands for the experimental % (w/w) coating, r stands for the correlation coefficient, 95% CI stands for the 95% confidence interval value for the slope and the intercept.

The composite sample determination yielded the following regression equation:

$$y = 0.8883x - 0.1078, \quad r = 0.9801,$$

$$95\%\ \text{CI for slope} = (0.340–1.436),$$

$$95\%\ \text{CI for intercept} = (-2.455–2.240),$$

where y stands for the experimental % (w/w) coating, r stands for the correlation coefficient, 95% CI stands for the 95% confidence interval value for the slope and the intercept.

To test the accuracy of the method, tablet cores were spiked with known amounts of titanium dioxide and analyzed. Duplicate samples representing 50, 75, 100, 125 and 150% of titanium dioxide present in 4.95% w/w tablet coating were prepared and analyzed. The percent recovery ranged from 95.6 to 100.3% with an overall mean recovery of 97.9% for 10 samples (Table 3).

To test the precision of the method, 10 samples were prepared by spiking the homogeneous mixture of 10 Zantac® 75 mg tablet cores with 4.95% w/w titanium dioxide. Ten separate aliquots of approximately 150 mg of mixture (representing one tablet weight) were weighed and prepared for analysis. Precision was evaluated in two separate tests.

First, system precision was verified by analyzing one sample 10 times with the same standard. A relative standard deviation (RSD), value below 2.0% demonstrated the system precision. The RSD value of 1.46% calculated from the mean of 10 analyzes demonstrated acceptable system precision (Table 4).

Secondly, method precision was verified by duplicate analysis of the 10 individual samples. The RSD of the relative response per unit weight of sample was calculated. An RSD value below 2.0% demonstrated repeatability. The RSD value of 1.4% calculated from the mean of 10 samples indicated the method used to prepare the samples for ICP-AES analysis was repeatable (Table 5).

To determine the linear range of titanium quantitation by ICP-AES, Zantac® digestion blank solutions were spiked with varying amounts of titanium standard. A concentration range of 50–150% of the theoretical concentration estimated at 4.95% w/w (100%) was used. Quantitation was linear from 2.90 to 8.60 ppm, and the resulting regression equation was:

$$y = 62,843x - 25.8, \quad r = 0.9997,$$

where y stands for the intensity and r stands for

Table 3
Accuracy results for Opadry® Pink (Zantac® tablets) samples prepared by digestion

% of Nominal concentration	Actual TiO_2 (mg)	Detected TiO_2 (mg)	Recovery (%)	Mean recovery (%)
50	1.095	1.042	97.1	98.7
	0.983	0.966	100.3	
75	1.441	1.408	99.7	100.0
	1.433	1.409	100.3	
100	1.962	1.893	96.5	96.5
	1.699	1.608	96.6	
125	2.337	2.189	95.6	96.4
	2.456	2.341	97.2	
150	2.833	2.707	97.5	97.7
	2.909	2.790	97.9	
			Overall mean	97.9

Table 4
System precision using one sample of Opadry® Pink (Zantac® tablets)

Sample	Concentration (%w/w)
1	4.99
2	4.77
3	4.78
4	4.79
5	4.80
6	4.85
7	4.83
8	4.90
9	4.76
10	4.85
Average	4.83
SD	0.07
RSD (%)	1.46

the correlation coefficient. The limit of detection (LOD) was found to be estimated at 0.025 ppm based on a 3:1 signal to noise ratio. The limit of quantitation (LOQ) was estimated to be 0.25 ppm titanium from the LOD ($10 \times$ LOD) and five replicate determinations at this concentration yielded a RSD value of 0.13% (results not shown).

3.2. Epivir HBV® 100 mg tablets

To demonstrate confidence in the dry ashing sample preparation, validation was performed to assess accuracy and precision of the method. Linearity, LOD and LOQ were not repeated since modifications of sample preparation do not affect these parameters. Furthermore, the titanium dioxide content of Opadry® Butterscotch was determined and verified against the theoretical value of 16.31% w/w (10).

To verify accuracy, duplicate samples of Epivir HBV® 100 mg tablet cores were spiked with known amounts of titanium dioxide and analyzed. Amounts representing 50, 75, 100, 125, and 150% of titanium dioxide present in 2.5% w/w tablet coating were established. The recovery ranged from 100.6 to 103.9% with an overall mean recovery of 102.4% for the 10 samples (Table 6).

To test the repeatability of the method, 10 samples were prepared from a homogeneous mixture of 10 Epivir HBV® tablets cores, which were spiked with 2.5% w/w of Opadry® Butterscotch powder. Samples were mixed until homogeneous. Approximately, 225 mg of the mixture (representing one tablet weight) was weighed and prepared for analysis. The RSD value of 2.0% was calculated from the mean ($n = 10$) of the relative response per unit weight of sample indicating that the method used to prepare the samples is repeatable (Table 7).

To verify the titanium dioxide content of Opadry® Butterscotch (16.31% w/w), 10 samples of known amounts of Opadry® Butterscotch were analyzed. The Opadry® Butterscotch samples were prepared according to the sample preparation procedure with the exception of the heating step in the muffle furnace. The mean percent

Table 5
Method precision using Opadry® Pink (Zantac® tablet) samples and multiple standard solutions

Sample	Sample weight	Detector response	Relative sample response (response/mg)
1	1.911	342 200	179 069
1	1.911	350 600	183 464
2	1.992	352 700	177 058
2	1.992	357 600	179 518
3	1.944	352 700	181 430
3	1.944	356 600	183 436
4	1.898	348 300	183 509
4	1.898	343 400	180 927
5	1.924	350 300	182 069
5	1.924	356 800	185 447
6	1.812	336 400	185 651
6	1.812	334 300	184 492
7	1.862	345 400	185 499
7	1.862	349 100	187 487
8	1.926	349 200	181 308
8	1.926	352 700	183 126
9	1.821	341 800	187 699
9	1.821	346 100	190 060
10	1.839	341 800	185 862
10	1.839	338 400	184 013
Average			185 520
SD			2498
RSD (%)			1.4

titanium dioxide found experimentally in Opadry® Butterscotch was $16.12 \pm 0.26\%$. The experimental value found for titanium dioxide is in agreement with the theoretical value of 16.31% w/w (mean recovery = 98.8%) (Table 8).

4. Conclusion

A quantitative method for the determination of the amount of film coat present on a tablet is an essential tool for optimization of tablet coating.

Table 6
Accuracy results for Opadry® Butterscotch (Epivir HBV® tablets) samples prepared by dry ashing

% of Nominal concentration	Actual TiO_2 (mg)	Detected TiO_2 (mg)	Recovery (%)	Mean recovery (%)
50	0.589	0.607	103.0	102.5
	0.480	0.490	102.0	
75	0.680	0.684	100.6	101.6
	0.679	0.696	102.5	
100	0.956	0.991	103.7	102.8
	0.992	1.011	101.9	
125	1.179	1.223	103.8	102.4
	1.142	1.155	101.1	
150	1.391	1.446	103.9	102.6
	1.322	1.338	101.2	

Table 7
Method precision using Opadry® Butterscotch (Epivir HBV® 100 mg tablets) (dry ashing)

Sample	Sample weight (mg)	Detector response	Relative sample response (response/mg)
1	223.9	193 700	865.3
2	226.7	194 100	856.3
3	227.3	199 200	876.5
4	225.0	198 600	882.8
5	226.6	193 500	853.7
6	224.9	194 600	865.1
7	223.2	196 200	879.1
8	226.6	201 900	891.1
9	225.8	196 300	869.4
10	225.3	205 400	911.7
Mean			875.1
SD			17.4
RSD (%)			2.0

Table 8
Results of the verification of the amount of TiO_2 in Opadry® Butterscotch (Epivir HBV® tablets)

Sample	Opadry® (mg)	TiO_2 detected (%w/w)	Detected vs. theoretical (%)
1	2.736	15.84	97.1
2	4.707	16.22	99.4
3	5.631	15.73	96.4
4	6.934	15.85	97.2
5	8.402	15.97	97.9
6	2.726	16.37	100.4
7	4.563	16.41	100.6
8	5.631	16.15	99.0
9	7.115	16.19	99.3
10	8.056	16.47	101.0
Mean		16.12	98.8
SD		0.26	
RSD (%)		1.62	

The ICP-AES method presented herein, based on quantitation of titanium is a reliable and accurate method for determination of coating level. This method was shown to be precise, sensitive and linear in the titanium concentration range of 2.9–8.6 ppm. Two different sample preparations were developed using Zantac® 75 mg tablets and Epivir HBV® 100 mg tablets. Dry ashing prior to the dissolution of titanium in sulfuric acid was shown to be a more effective sample preparation technique for the Epivir HBV® 100 mg tablets in comparison to the sulfuric and nitric acid digestion method. This ICP-AES method has general applicability for a wide variety of coating formulations containing different elements and can provide coating information on a single tablet as well as on an entire batch.

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