Short communication

Non-destructive determination of the coating film thickness by X-ray powder diffractometry and correlation with the dissolution behavior of film-coated tablets

Hiroyuki Yamada [a,b], Katsuhide Terada [c], Raj Suryanarayanan [a,*]

[a] *Department of Pharmaceutics, University of Minnesota, 308 Harvard Street SE, Minneapolis, MN 55455, USA*
[b] *Analytical Chemistry Research Department, Mitsubishi Tanabe Pharma Corporation, 3-16-89, Kashima, Yodogawa-ku, Osaka 532-8505, Japan*
[c] *Department of Pharmaceutics, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274-8510, Japan*

ARTICLE INFO

ABSTRACT

The goal of this project was to determine the effect of the thickness of the coating film on the dissolution behavior of tablets. Commercially available film-coated tablets containing aspirin, acetaminophen and caffeine, were used as the model system. First, a non-destructive X-ray microdiffractometric technique was developed to quantify the thickness of the film-coating in intact tablets. The same tablets were then subjected to dissolution tests. There was an inverse correlation between the cumulative amount of drug in solution at 5 min and the thickness of the coating film. As the coating thickness increased, the initiation of tablet dissolution was delayed, resulting in a decrease in the cumulative amount of drug in solution. Finally, the technique was applied to formulations marketed by different companies. The X-ray microdiffractometric technique has the potential to predict the dissolution behavior of tablets.

© 2009 Elsevier B.V. All rights reserved.

1. Introduction

X-ray diffractometry (XRD) is recognized as a powerful tool for the physical characterization of pharmaceutical solids [1]. XRD has been extensively used for phase identification, and more importantly, phase quantification in intact tablets [2–4]. Microdiffractometers, with two-dimensional area detectors, are commercially available wherein the X-ray beam is focused in a small sample area and the two-dimensional detector allows quick data acquisition [5,6]. Intact film-coated tablets, in a variety of shapes and sizes, have been analyzed, directly and non-destructively, using a microdiffractometer [7,8].

An appreciable fraction of marketed tablets is film-coated. The advantages of film-coating are well documented in the literature [9]. However, there are numerous processing and materials science issues with regard to film-coating. The reproducibility of the film-coating process is obviously of great concern. It is evident that the inter- and intra-batch variability in film thickness is well controlled [10]. Since the film-coating is usually conducted using an aqueous medium, there is a potential for interaction of the formulation components with water. This can be potentially serious if the API is in the amorphous state and crystallizes, either partially or completely,

when it comes in contact with water. This issue has received inadequate attention in the literature [11]. Finally the effect of coating thickness on the dissolution behavior of tablets is also of great interest [12,13]. This issue can be particularly important when rapid dissolution of the API is desired, for example in the treatment of pain.

The *in vitro* dissolution behavior of tablets is a very important quality control test, and can provide valuable information not only about batch (both within and between batches) consistency but also the biological availability [14,15]. The thickness of the coating film can be one of the determinants of the dissolution behavior of tablets. In order to determine the effect of the coating film thickness on the dissolution behavior, the same tablets should be subjected to both these measurements. Since the pharmacopeial dissolution tests are destructive, it is necessary to determine the film thickness by a non-destructive method and then subject the tablets to dissolution studies.

Conventionally microscopic methods have been used to measure the thickness of film-coated tablets [16]. While these approaches provide an accurate measure of film thickness, the techniques tend to be destructive. On the other hand, a number of spectroscopic approaches have been developed to characterize film-coating [17,18]. While these techniques are non-destructive, the techniques are of limited utility in determining the film thickness in the final product [19]. NIR has been used to quantify the coating material in tablets [20,21]. Recently, terahertz pulsed

---

spectroscopy, has enabled the characterization of formulation components as well as the coating film of tablets [22,23].

The specific object in this paper was to investigate the effect of the coating film thickness on the dissolution behavior of tablets. In order to accomplish this objective, a non-destructive X-ray microdiffractometric technique was first developed to quantify the thickness of the film-coating in tablets. The dissolution profiles were then experimentally obtained. This approach has the potential to predict the tablet dissolution behavior, based on the thickness of the coating film.

2. Materials and methods

2.1. Materials

Commercially available formulations containing aspirin, acetaminophen and caffeine as the active ingredients were used as the model system. Products marketed by three companies were purchased from a local pharmacy. From now on, these are referred to as I, II and III. All of them were film-coated capsule-shaped tablets. The label claim in each tablet was 250 mg acetaminophen, 250 mg aspirin and 65 mg caffeine. All the tablets contained hydroxypropyl methylcellulose and TiO_2, excipients typically used in film-coating.

Acetaminophen, aspirin and caffeine (anhydrous) powder samples were obtained from Sigma (St. Louis, MO, USA).

2.2. X-ray microdiffractometry

A microdiffractometric system with a two-dimensional area detector (D8 DISCOVER, Bruker AXS) was used, wherein X-rays (CuKα radiation; 45 kV × 40 mA) were collimated to a 0.8 mm i.d. spot size. The incident angle was 10° and detector position was fixed at 25°, which covered the angular range from 10 to 40°2θ. The data collection time was 180 s. The results were analyzed using commercially available software (JADE, Materials Data, Inc., Livermore, CA, USA).

2.3. Scanning electron microscopy

In order to determine the thickness of the coating film, the film-coated tablet was transversely sliced with a razor blade, mounted on the sample holder with double sided carbon tape, coated with platinum (50 Å) and observed under an electron microscope (Model: JSM-6500F, JEOL, Tokyo, Japan).

2.4. Dissolution profiles

The dissolution test was conducted using the USP Type II apparatus, where the paddles were rotated at 100 rpm, and 900 mL of deionized water, maintained at 37 °C, was used as the dissolution medium (NTR-6100A, Toyama Sangyo Co., Ltd., Osaka, Japan) [24]. The absorbance was measured at 295 nm, in 1 min intervals, using a UV-probe placed in the dissolution vessel (DM-3100, Otsuka Electronics, Osaka, Japan).

Since our objective was to monitor the effect of the coating thickness on the initial dissolution profiles, we did not monitor the concentrations of the individual APIs in the dissolution medium. Instead, the absorbance at 295 nm was used as a measure of the sum of the concentrations of the three APIs in solution. In order to validate this approach, aqueous solutions containing aspirin, acetaminophen and caffeine were prepared. The concentration ratio of aspirin to acetaminophen to caffeine was maintained at 50:50:13, the same as in the formulation. The absorbance at different concentrations (aspirin and acetaminophen ranging from 0 to 0.278 mg/mL and caffeine ranging from 0 to 0.072 mg/mL) was

measured and a plot of the absorbance versus concentration was linear. The absorbance of the solution containing 0.278 mg/mL of each aspirin and acetaminophen and 0.072 mg/mL caffeine was 1.81 ± 0.01 (mean ± SD; n = 6), and was close to the values of 1.89 ± 0.05 (n = 6), 1.88 ± 0.04 (n = 6) and 1.83 ± 0.02 (n = 6) for I, II and III, respectively, obtained after 60 min of dissolution. The results reflected the fact that the absorbance, irrespective of the commercial source, could be attributed predominantly, if not completely, to the APIs in the dosage form.

3. Results

3.1. Identification of API in film-coated tablets

X-ray powder diffractometry can be used to monitor the physical form of the active pharmaceutical ingredient in intact film-coated tablets [7,8]. Fig. 1(a) is a representative microdiffraction pattern of an intact tablet of I. In an effort to assign diffraction peaks to the different formulation components, the diffraction patterns of acetaminophen, aspirin and caffeine were also obtained [Fig. 1(b)–(d)]. Based on the positions of the characteristics peaks of the three active ingredients, the peaks observed in the XRD pattern of the intact tablet were assigned (Fig. 1(a)). The manufacturers had provided a list of excipients in the package. Two of the products had identical excipients. Most of the formulation components were completely or substantially amorphous. As a result, they will not exhibit sharp diffraction peaks. A few components are crystalline. However, none of them will exhibit a peak at 25.4°2θ except for TiO_2. This conclusion was based on evaluating the published XRD patterns of all the crystalline components in the Powder Diffraction Files of the International Centre for Diffraction Data (ICDD).

Therefore the intense peak at 25.4°2θ was attributable to the TiO_2 in the coating film. In the angular range where this peak was observed, there were no intense peaks attributable to the APIs or the crystalline excipients in the tablets [25–28]. Unfortunately, the diffraction peaks of caffeine overlapped with those of acetaminophen and aspirin. Moreover, the caffeine content in the formulation was low (65 mg per tablet; total tablet weight ~660 mg). Therefore the identification of caffeine was not possible.

3.2. Estimation of the thickness of the coating film by XRD

In order to investigate the relationship between the coating film thickness and XRD peak intensity, the same tablet was subjected
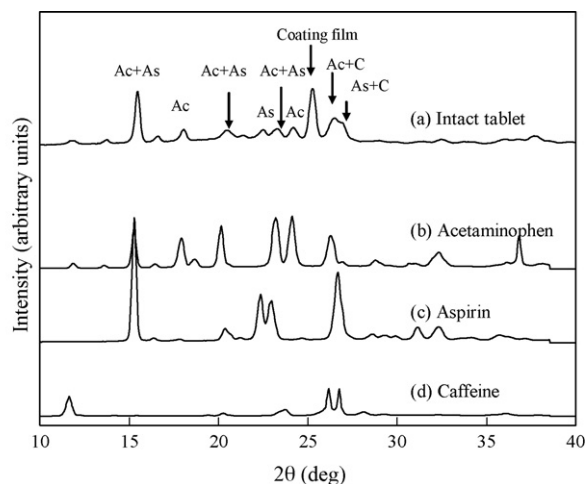

Fig. 1. Microdiffraction patterns of (a) intact tablets of I, (b) acetaminophen, (c) aspirin and (d) caffeine. Diffraction peak at 25.4° is from the coating film. Ac, As and C represent acetaminophen, aspirin and caffeine, respectively.
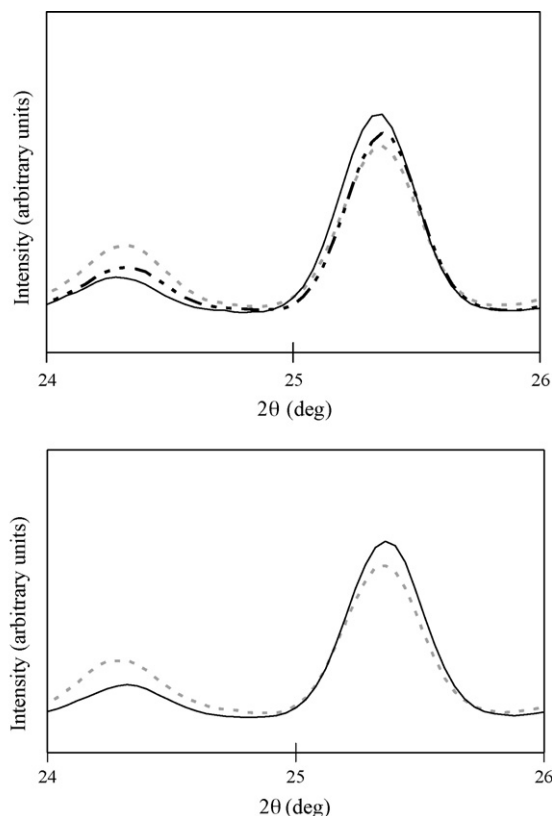
Fig. 2. Microdiffraction patterns of intact tablets of I. The diffraction peaks at 24.3° and 25.4° were from the core tablet (acetaminophen) and coating film, respectively. Five tablets were subjected to the microdiffraction. Each curve is the diffraction pattern of an individual tablet. In an effort to facilitate visualization, the XRD patterns have been divided into two clusters.

Fig. 3. A plot of the intensity of the 25.4°2θ peak of TiO$_2$ as a function of the thickness of the coating film. The coating film thickness was determined by SEM. In each tablet, the coating thickness, as well as the XRD intensity, was determined at 3 locations.

to XRD measurement followed by scanning electron microscopy (SEM). Five intact tablets of I were subjected to XRD. The intensity of the peak at 25.4°2θ due to diffraction by TiO$_2$, a component in the coating film, was monitored. The intensity of the peak at 24.3°2θ, due to diffraction by acetaminophen in the core tablet, was also monitored. As shown in Fig. 2, as the intensity of the TiO$_2$ peak increased, the acetaminophen peak intensity decreased. The attenuation of X-rays by the coating film is expected to increase as the coating film thickness increases, resulting in a decrease in the diffracted intensity of the crystalline components in the core tablet.

After the XRD measurement, the coating film thickness in each tablet determined by SEM. In each tablet, the thickness of the coating film was measured at 3 different locations. The RSD in 5 tablets ($n = 3$ for each tablet) ranged between 3.4 and 5.8% indicating that the film-coating was uniform. The non-destructive nature of XRD permitted us to use the same tablets for both XRD and SEM. The intensity of the TiO$_2$ peak, determined by XRD was plotted as a function of the film thickness, determined by SEM (Fig. 3). The diffraction intensities correlated with the coating film thickness ($r = 0.989$). With an increase in the thickness of the coating film, there was a proportional increase in the diffracted intensity. It is therefore possible to determine the thickness of the coating film, non-destructively, by XRD.

3.3. Effect of the coating film thickness on the dissolution profile

The coating film must dissolve or rupture in order for the core tablet to come in contact with the dissolution medium. The thickness of the coating film can therefore be a key determinant of the
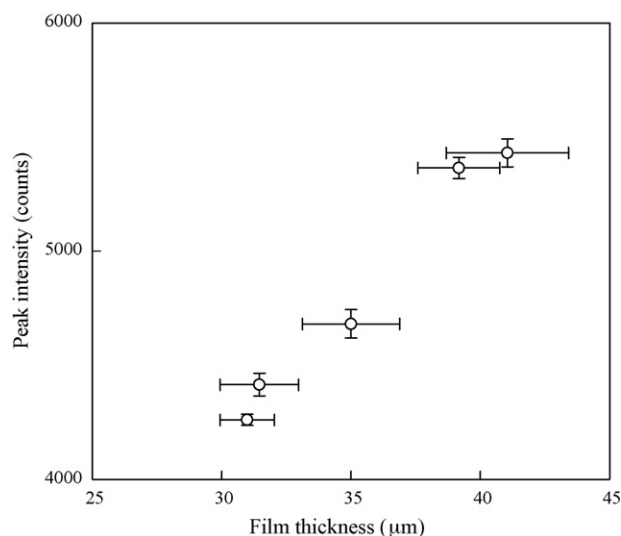
dissolution profile, particularly at the early stage of dissolution. The effect of the coating film thickness on the dissolution profile was next investigated.

After the non-destructive determination of the film thickness by XRD, the same tablets were next subjected to dissolution studies. In all the tablets, based on the absorbance measurement, the dissolution was complete in ~20 min (data not shown). However, as is evident from Fig. 4(a), there were pronounced tablet-to-tablet differences in the initial dissolution profile. Since the slope values appear to be substantially similar [Fig. 4(b)], the differences are likely attributable to the thickness of the coating film. With an increase in coating thickness, the lag time for dissolution is expected to increase. However, once the dissolution of the core tablet is initiated, the dissolution rates appear to be substantially similar.

Since our interest was the performance of the formulation soon after it was placed in contact with the dissolution medium, the cumulative amount in solution at 5 min was used as a measure of the initial dissolution behavior. In Fig. 5, the percent dissolved in 5 min was plotted as a function of the intensity of the TiO$_2$ peak. The increase in the thickness of the coating film, reflected in the increased intensity of the TiO$_2$ peak, caused a marked decrease in the initial dissolution rate.

As mentioned earlier, our goal was to determine the influence of coating film thickness on the dissolution behavior of tablets. However, the dissolution test, as well as the technique used to measure the coating film thickness (such as SEM), is destructive. It is therefore impossible to perform both these tests on the same tablets. By developing a non-destructive XRD method for determining the film thickness, we are able to establish the influence of the coating film thickness on the initial tablet dissolution behavior.

3.4. Comparison of the products marketed by different companies

Tablets obtained from three different companies were subjected to detailed characterization. Fig. 6 contains the XRD patterns of tablets from the different sources. The XRD patterns of tablets I and II were substantially similar. In the case of tablet III, while the peak positions substantially matched with that of tablets I and II, the intensities were different (Fig. 6). In III, the intensity of the peak at 25.4°2θ, due to the TiO$_2$ in the coating film, was much lower than that in I and II. Therefore, the film-coating thickness in III should be
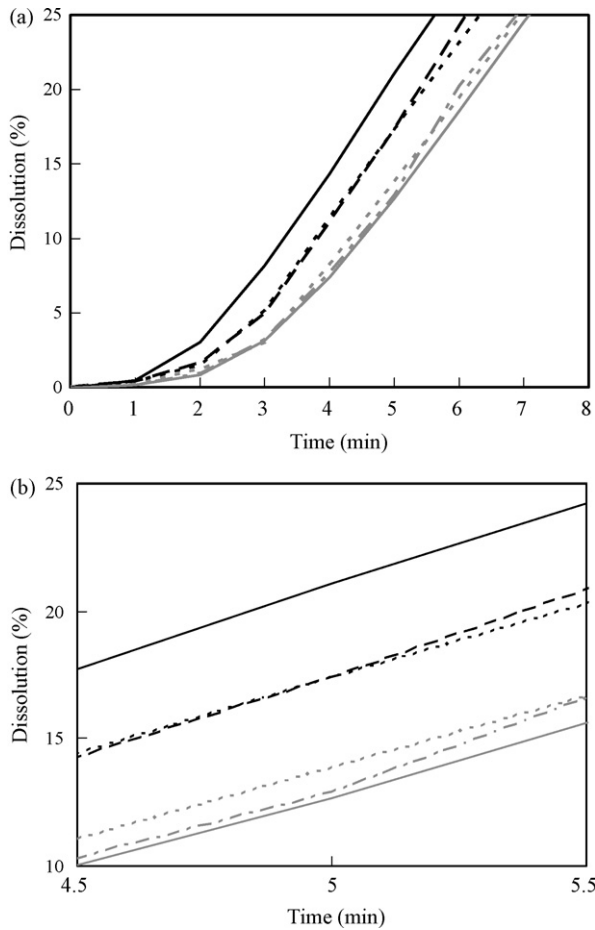
Fig. 4. (a) Dissolution profiles of tablets of I. Six tablets were used for the measurement. The dissolution rates were monitored every 1 min using an *in situ* UV-probe. (b) The dissolution profiles between 4.5 and 5.5 min are shown in expanded axes.
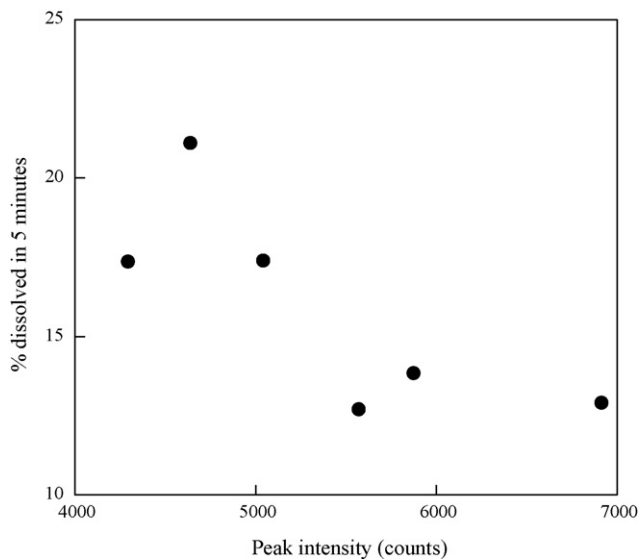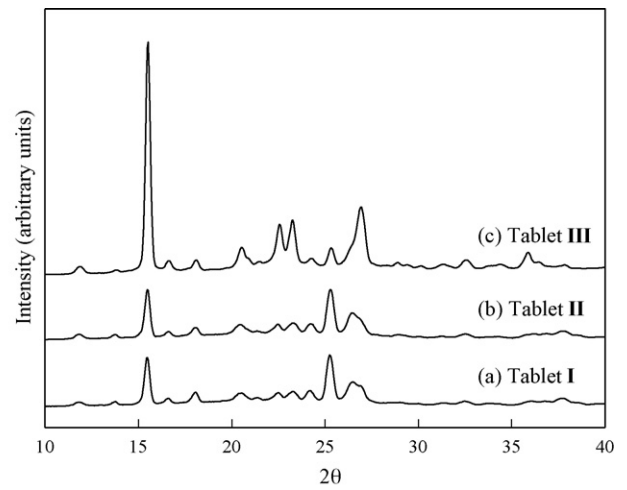

Fig. 6. Microdiffraction patterns of intact film-coated tablets: (a) tablets I, (b) tablets II, and (c) tablets III. Diffraction peak at 25.4° is from the coating film.

less than that in I and II. As a consequence, the peaks attributed to the core tablet components were more intense in III. The integrated intensity of the $25.4°2\theta$ peak of TiO_2 can be used as an approximate measure of the thickness of the film-coating. The TiO_2 peak intensity in tablets of III (1936 ± 577 counts; $n = 10$) was about one-third of I (5505 ± 787 counts), and II (5363 ± 603 counts).

The thicknesses of the film-coating were also determined by SEM. In case of II, the coating thickness ($37.1 \pm 3.8 \mu m$; $n = 5$) was approximately the same as in I ($35.5 \pm 4.5 \mu m$). The coating thickness in III ($13.0 \pm 5.7 \mu m$) was about one-third of I and II. Thus, the XRD and SEM results were in good agreement.

When the XRD peak intensity ($25.4°2\theta$ peak of TiO_2 in the coating film) was plotted as a function of the film thickness (determined by SEM), an approximately linear relationship was observed ($r = 0.995$, Fig. 7). Since the peak intensity was proportional to the coating film thickness in tablets obtained from 3 different commercial sources, the TiO_2 concentration in the film-coating is expected to be approximately the same in all the tablets.

Finally, the dissolution rate (measured as percent dissolved in 5 min) was plotted as a function of the XRD ($25.4°2\theta$ peak of TiO_2
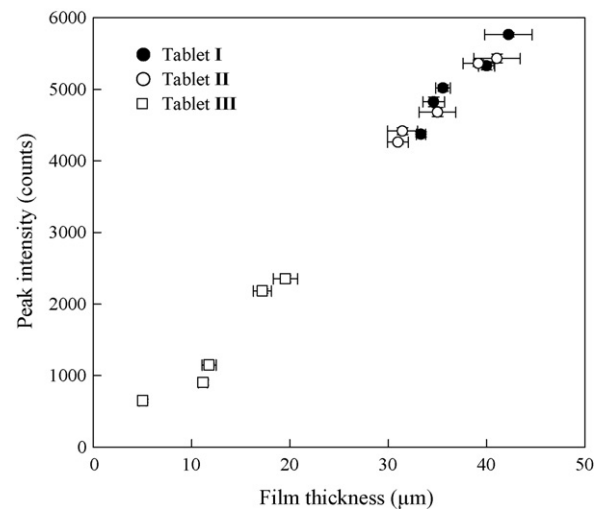

Fig. 5. Correlation between XRD intensity of the coating film and the % dissolved in 5 min. XRD intensity was determined from the peak area of the coating film. Dissolution profiles of the tablets were shown in Fig. 4.

Fig. 7. A plot of the intensity of the $25.4°2\theta$ peak of TiO_2 as a function of the thickness of the coating film. The coating film thickness was determined by SEM. In each tablet, the coating thickness, as well as the XRD intensity, was determined at 3 locations: (●) tablets I, (○) tablets II, and (□) tablets III.
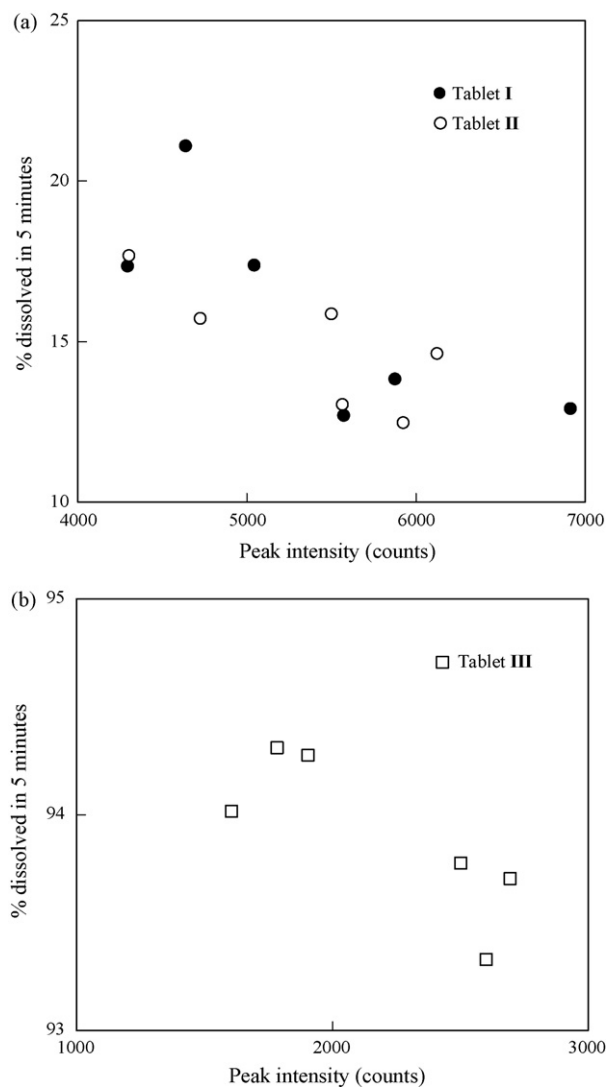
Fig. 8. Correlation between XRD peak intensity of the coating film and the % dissolved in 5 min. XRD peak intensity was determined from the peak area of the coating film: (a) tablets I and II and (b) tablets III.

in the coating film) peak intensity (Fig. 8). As the TiO_2 peak intensity increased, there was a pronounced decrease in the dissolution rate. Although the trends observed in I, II and III were qualitatively similar, III (panel b in Fig. 8) dissolved much faster than I and II (panel a in Fig. 8). The film-coating in III disintegrated much faster (<1 min) than in tablets I and II (~20 min). In addition to the effect of the thickness of the coating film, there might be formulation effects—the disintegrant in III might be more effective than in I and II.

Characterization of the tablets marketed by different companies (tablets I, II and III) by XRD, SEM and dissolution testing indicated that I and II were substantially "similar". On the other hand, the coating thickness in III was much less than in I and II, leading to rapid disintegration followed by dissolution. Microdiffractometry can readily identify the differences between these products and the technique is non-destructive.

4. Discussion

In film-coated tablets, the thickness of the coating film is expected to influence the dissolution behavior of tablets. However, in order to determine this effect, the film thickness and the dissolution testing should be conducted in the same tablets. The non-destructive microdiffractometric method enabled us to determine the film thickness in intact film-coated tablets. This was followed by dissolution testing (destructive analysis) of the same tablets.

Using this approach, we were able to explain the subtle differences in the dissolution behavior of film-coated tablets obtained from different commercial sources. While the non-destructive measurement of the film thickness is an important component of the paper, our broader goal is to relate the tablet properties (film thickness in this case) to the observed tablet dissolution behavior. While spectroscopic techniques can be used to determine film thickness, we believe that this is the first report directly *relating* film thickness to dissolution behavior.

In addition to the non-destructive determination of the coating film thickness, XRD will also provide information about the physical form of the crystalline ingredients (aspirin, acetaminophen and caffeine in this case) in the dosage form. Thus if there are any processing or storage induced phase transformations, they could be identified and possibly quantified. In this system, since none of the crystalline ingredients exhibited processing-induced phase transformation, we did not utilize all the unique features of the technique. We had earlier demonstrated the feasibility of quantifying the different physical forms of the API, in intact film-coated tablets, by XRD [8].

5. Conclusion

A non-destructive X-ray microdiffractometric technique was developed to quantify the thickness of the film-coating in intact tablets. The same tablets were then subjected to dissolution tests. The effect of the thickness of the coating film on the tablet dissolution behavior was established. The X-ray microdiffractometric technique has the potential to predict the dissolution behavior of tablets.

Acknowledgments

References

[1] R. Suryanarayanan, X-ray powder diffractometry, in: H.G. Brittain (Ed.), Physical Characterization of Pharmaceutical Solids, Marcel Dekker, New York, 1995, pp. 187–221.
[2] W. Cao, S. Bates, G.E. Peck, P.L.D. Wildfong, Z. Qiu, K.R. Morris, Quantitative determination of polymorphic composition in intact compacts by parallel-beam X-ray powder diffractometry, J. Pharm. Biomed. Anal. 30 (2002) 1111–1119.
[3] S. Yamamura, Y. Momose, Quantitative analysis of crystalline pharmaceuticals in powders and tablets by a pattern-fitting procedure using X-ray powder diffraction data, Int. J. Pharm. 212 (2001) 203–212.
[4] R. Suryanarayanan, C.S. Herman, Quantitative analysis of the active tablet ingredient by powder X-ray diffractometry, Pharm. Res. 8 (1991) 393–399.
[5] B.B. He, Introduction to two-dimensional X-ray diffraction, Powder Diffr. 18 (2003) 71–85.
[6] B.B. He, Microdiffraction using two-dimensional detectors, Powder Diffr. 19 (2004) 110–118.
[7] H. Yamada, R. Suryanarayanan, Calculation of the penetration depth of X-rays in intact pharmaceutical film-coated tablets by microdiffractometry, Pharm. Res. 23 (2006) 2149–2157.
[8] H. Yamada, R. Suryanarayanan, X-ray powder diffractometry of intact film coated tablets—an approach to monitor the physical form of the active pharmaceutical ingredient during processing and storage, J. Pharm. Sci. 96 (2007) 2029–2036.
[9] M.K. Kottke, E.M. Rudnic, Tablet dosage forms, in: G.S. Banker, C.T. Rhodes (Eds.), Modern Pharmaceutics, 4th edition, Marcel Dekker, Yew York, 2002, pp. 287–334.
[10] M. Ruotsalainen, J. Heinämäki, J. Rantanen, J. Yliruusi, Development of an automation system for a tablet coater, AAPS Pharm. Sci. Tech. 3 (2002), Article 14.

[11] N. Pourkavoos, G.E. Peck, Evaluation of moisture sorption by tablet cores containing superdisintegrants during the aqueous film coating process, Pharm. Res. 10 (1993) 1212–1218.

[12] Zs. Muskó, K. Pintye-Hódi, P. Szabó-Révész, P. Kása Jr., I. Erős, D. Deák, Measurement of film thickness on the surface of coated pellets and its influence on drug dissolution rate, Pharmazie 55 (2000) 465–466.

[13] Zs. Muskó, K. Pintye-Hódi, R. Gáspár, J. Pintye, P. Szabó-Révész, I. Erős, G. Falkay, Study of in vitro and in vivo dissolution of theophylline from film-coated pellets, Eur. J. Pharm. Biopharm. 51 (2001) 143–146.

[14] G.S. Rekhi, S.S. Jambhekar, Bioavailability and in-vitro/in-vivo correlation for propranolol hydrochloride extended-release bead products prepared using aqueous polymeric dispersions, J. Pharm. Pharmacol. 48 (1996) 1276–1284.

[15] V. Pillay, R. Fassihi, Unconventional dissolution methodologies, J. Pharm. Sci. 88 (1999) 843–851.

[16] C.A. Nguyen, Y.N. Konan-Kouakou, E. Allémann, E. Doelker, D. Quintanar-Guerrero, H. Fessi, R. Gurny, Preparation of surfactant-free nanoparticles of methacrylic acid copolymers used for film coating, AAPS Pharm. Sci. Tech. 7 (2006), Article 63.

[17] J.D. Perez-Ramos, W.P. Findlay, G. Peck, K.R. Morris, Quantitative analysis of film coating in a pan coater based on in-line sensor measurements, AAPS Pharm. Sci. Tech. 6 (2005), Article 20.

[18] T. Sovány, K. Nikowitz, G. Regdon Jr., P. Kása Jr., K. Pintye-Hódi, Raman spectroscopic investigation of film thickness, Polym. Test. 28 (2009) 770–772.

[19] M. Andersson, B. Holmquist, J. Lindquist, O. Nilsson, K.G. Wahlund, Analysis of film coating thickness and surface area of pharmaceutical pellets using fluorescence microscopy and image analysis, J. Pharm. Biomed. Anal. 22 (2000) 325–339.

[20] B.R. Buchanan, M.A. Baxter, T.S. Chen, X.Z. Qin, P.A. Robinson, Use of near-infrared spectroscopy to evaluate an active in a film coated tablet, Pharm. Res. 13 (1996) 616–621.

[21] J.D. Kirsch, J.K. Drennen, Near-infrared spectroscopic monitoring of the film coating process, Pharm. Res. 13 (1996) 234–237.

[22] P.F. Taday, I.V. Bradley, D.D. Arnone, M. Pepper, Using terahertz pulse spectroscopy to study the crystalline structure of a drug: a case study of the polymorphs of ranitidine hydrochloride, J. Pharm. Sci. 92 (2003) 831–838.

[23] A.J. Fitzgerald, B.E. Cole, P.F. Taday, Nondestructive analysis of tablet coating thickness using terahertz pulsed imaging, J. Pharm. Sci. 94 (2005) 177–183.

[24] (USP 32/NF 27) The United States Pharmacopeia, United States Pharmacopeial Convention, The United States Pharmacopeia, Rockville, MD, 2009, pp. 1393–1394.

[25] Powder Diffraction File 21-1272, International Centre for Diffraction Data, Newtown Square, PA, 1997.

[26] Powder Diffraction File 00-054-2055, International Centre for Diffraction Data, Newtown Square, PA, 1997.

[27] Powder Diffraction File 00-012-0850, International Centre for Diffraction Data, Newtown Square, PA, 1997.

[28] Powder Diffraction File 00-051-1953, International Centre for Diffraction Data, Newtown Square, PA, 1997.