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Tablet splitting: Product quality assessment of metoprolol succinate extended release tablets☆

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ABSTRACT

Metoprolol succinate extended release tablets comprise a multiple unit system containing metoprolol succinate in a multitude of controlled release pellets. Each pellet acts as a separate drug delivery unit and is designed to deliver metoprolol continuously over the dosage interval. Despite the flexibility that controlled release pellets may offer, segregation is one of the challenges that commonly occur during tableting for such drug delivery system. Since all commercial metoprolol succinate extended release tablets are scored, they are deemed suitable for splitting. The present study was aimed at utilizing an innovative technology to determine the dose uniformity for split tablets. Four marketed drug products consisting of innovator and generics were evaluated for effect of splitting on weight, assay and content uniformity. Novel analytical tool such as near infrared (NIR) chemical imaging was used to visualize the distribution of metoprolol succinate and functional excipients on the surfaces of the marketed tablets. The non-homogeneous distribution of directly compressed metoprolol succinate beads on the surface of the tablets as well as the split intersection explained the large variation in the split tablets' weight and content uniformity results. The obtained results indicated the usefulness of NIR chemical imaging to determine the need for content uniformity studies for certain split tablets.

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1. Introduction

The rapid and non-destructive nature of NIR spectroscopy analysis has gained its widespread use and recognition in the pharmaceutical industries. NIR spectroscopy applications in the pharmaceutical area range from raw material testing including active pharmaceutical ingredient (API) synthesis and purification through process monitoring to final finished product analysis (MacDonald and Prebble, 1993; Candolfi et al., 1999; Dou et al., 2007; Li et al., 2007; Luypaert et al., 2007; Moes et al., 2008). One of the steps needed to demonstrate enhanced understanding in the manufacturing process is to use tools that can provide greater understanding and insight into critical aspects of formulation and process variables that are essential for product performance.

Near infrared chemical imaging (NIR-CI) is one such analytical tool that delivers novel opportunities to explore and manage knowledge base manufacturing.

The direct analysis of tablet surface by using hyperspectral imaging techniques, which provide a NIR spectrum in each pixel of the image, generates a considerable amount of information nondestructively from the product. Focusing the interest in pharmaceutical research, several chemometric algorithms are demonstrating their usefulness in extracting the relevant information (i.e. quantitative determination of the component in one sample) in tablets with only one sample and without damaging it. With the recent advances in computer technology, NIR chemical imaging is nearly as fast as traditional NIR, taking only a few minutes to scan and analyze a sample. Applications have been reported in the pharmaceutical, industrial, as well as food and agricultural societies (Dubois et al., 2005; Nicolaï et al., 2006). Several reviews covered the general aspects of NIR and NIR chemical imaging including its application in pharmaceutical process monitoring as well as calibration and model development (Reich, 2005; Roggo et al., 2007; Gendrin et al., 2008; Ravn et al., 2008). In contrast to the traditional NIR spectrophotometer, the mapping capability of an NIR imager allows the visualization of distribution of interested components, API or an excipient, and determination of the presence of impurities (Cruz et al., 2009; Amigo and Ravn, 2009). One potential application of this technology is to assess the suitability of tablet splitting by monitoring the surface distribution and spatial uniformity of the active ingredient(s). While tablet splitting may

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not be appropriate in some cases, it remains a common practice that has been adapted by pharmacists worldwide to adjust the dose to be administered. According to a survey conducted in Germany, about one fourth of all tablets are split before ingestion including tablets that are unscored and tablets that are not allowed to split according to the package leaflet (Quinzler et al., 2006). Concerns are raised regarding the safety and potential loss of efficacy. However, any clinical relevance of tablets after splitting remains unknown in most cases.

The purpose of this study was to evaluate the ability of NIR chemical imaging to generate chemical images that map the chemical composition of metoprolol succinate extended release (ER) commercial tablets from four different suppliers, to examine the distribution of API and excipients within a tablet, and to determine the need of content uniformity studies for tablets after splitting. Metoprolol succinate ER tablets of various strengths are scored in the middle and according to the label, can be divided; however, the whole and half tablet should be swallowed whole and not chewed or crushed. Metoprolol succinate ER tablets are formulated according to a multi-particulate novel drug delivery system principle where individual particles are film coated to control the drug release from the dosage form (see product package insert). For dosing convenience, these individually coated units are normally blended with other excipients and then compressed into tablets. Such a delivery system has the advantages of providing diverse drug release profiles and preventing dose dumping as commonly reported from a single film coated dosing unit. Metoprolol succinate ER tablets from four different suppliers were purchased from the pharmacy. NIR chemical imaging analysis in combination with traditional analytical testing was performed to compare the quality attributes of tablets before and after splitting. In addition, scanning electronic microscopy (SEM) pictures were taken on the beads after disintegration and beads after dissolution to examine the surface morphology and detect the presence of film rupture.

2. Materials and methods

2.1. Materials

Test samples of metoprolol succinate (25 mg) ER tablets obtained from four different suppliers were denoted as M1, M2, M3 and M4. All products had a minimum of 24-month shelf life at the time of purchase with the earliest expiration date 04/2010. Microcrystalline cellulose, methacrylic acid copolymer, nonperiel beads and ethylcellulose were purchased from Sigma (St. Louis, MO). Metoprolol succinate reference standard was purchased from United States Pharmacopeia (USP, Rockville, MD). HPLC grade acetonitrile, HPLC grade methanol, HPLC grade ethyl alcohol, USP grade monobasic sodium phosphate, HPCL grade monobasic potassium phosphate, ACS grade phosphate acid, ACS grade hydrochloric acid, and ACS grade sodium hydroxide were purchased from Fisher Scientific (Fair Lawn, NJ), Burdick & Jackson (Muskegon, MI), JT Baker (Phillipsburg, PA), and EMD (Gibbstown, NJ). All chemicals were used as received. HPLC ready 18 mΩ water was obtained from a Millie-Q Gradient A-10 water purification system (Millipore Corp., Bedford, MA). Nylon syringe filters were purchased from Sun SRI (Rockwood, TN).

2.2. Sample preparation and weight variation

Metoprolol succinate ER tablets from each supplier were split into two parts using a tablet-splitter (Apothecary Products, Inc., Burnsville, MN). Ten intact tablets and 20 split portions were individually weighed to determine the weight variation for each product.

2.3. Content uniformity and assay

Ten tablets were weighed individually and each was transferred to a 25-mL volumetric flask. To each flask, first add about 5 mL of water and sonicate for 15 min. And then add approximately 7.5 mL of ethyl alcohol and sonicate for another 30 min. Finally, add 0.1N hydrochloric acid to almost the volume and then sonicate for additional 30 min. At the end adjust the volume with 0.1N hydrochloric acid and then mix well before filtration the mixture through a 0.45-μm nylon membrane filter. 50 μL of filtrate is diluted to 1 mL with mobile phase before injection into the HPLC. The sample was determined by a validated HPLC method which is slightly modified from the USP monograph on Agilent 1090. The mobile phase was a mixture of pH 3.0 phosphate buffer and acetonitrile (3:1). A 150 × 4.6 mm ID column containing L7 packing (octylsilane chemically bonded to porous silica or ceramic microparticles, Luna C8 (2), 5 μm) was used. 10 μL samples were injected and eluted isocratically at a flow rate of 1.0 mL/min over 7 min and analyzed with UV detection at 223 nm. The retention time for metoprolol succinate is about 4 min. The amount of metoprolol succinate was calculated by comparing the peak area of the test solutions with those of the standard solutions of the USP metoprolol succinate reference standard where a calibration was established with appropriate concentrations.

The requirements for content uniformity are met if the acceptance value of the first 10 tablets is ≤15%. If the acceptance value is >15%, additional 20 tablets are weighed and the new acceptance value is calculated. The requirements are met if the final acceptance value of the total 30 tablets is ≤25% and no individual value was outside 75–125% of the labeled strength. The assay of the samples was determined by calculating the mean value of metoprolol succinate in the tablets analyzed for content uniformity testing.

2.4. Dissolution

Dissolution testing was performed on a calibrated USP II apparatus (Van Kel VK7000, Cary, NC) with paddles at 50 rpm. 500 mL dissolution medium was used and the temperature was set at 37 °C. Dissolution was conducted in phosphate buffer, pH 6.8 for both the whole and split tablets. An autosampler (Varian VK8000) was attached to the dissolution apparatus to withdraw 1.0 mL of sample into HPLC vials at preset sampling time points (1 h, 2 h, 4 h, 8 h, 12 h, 16 h, 20 h, and 24 h). The samples were injected to the HPLC using the same method as described in Section 2.3. without dilution. The amount of metoprolol succinate released was determined by comparing the peak area of the test solutions with those of the standard solutions of the USP metoprolol succinate reference standard where a calibration was established with appropriate concentrations.

2.5. SEM

Surface morphology and shape of beads were investigated by SEM (JSM-6390 LV, JEOL, Tokyo, Japan) measurements at the working distance of 15 mm and an accelerated voltage of 20 KV. Beads from Products M1 to M3 were separated from the rest excipients by sieving through a proper sized screen after disintegration or 24-h dissolution. All beads were golden coated with sputter coater (Desk V, Denton Vacuum, NJ, USA) before SEM observation under high vacuum and high voltage10 mV to achieve film thickness of 30 nm.

2.6. Chemical imaging analysis

In this work, a qualitative method to chemically map different commercial metoprolol succinate tablets is proposed by

using Sapphire® chemical imaging system (Malvern, Westborough, MA) with SapphireGo® data acquisition system (version 1.4). The system consists of a liquid crystal tunable filter (LCTF) coupled with a NIR sensitive focal plane array (FPA) detector. The diffuse reflectance image of the sample is passed through the LCTF. The tunable filter element rapidly selects wavelengths over a spectral range of 1200–2450 nm. A series of images are then captured by the indium–gallium–arsenide near-infrared FPA detector with a total acquisition time of ~2 min per sample. Each pixel in the detector array corresponds to ~1600 μm^2 (40 × 40 μm) area of the tablet surface and the resulting data set contains 125 wavelength increment scans per spectrum. The data sets are generally referred to as image cubes or hyperspectral image cubes. As the spectral responses obtained from a NIR chemical imaging measurement contain information from both the sample and the instrument, it is necessary to correct for the instrument response by using a background reference. The raw data from the data acquisition is thus relative NIR diffuse reflectance data ($R = R_{sample}/R_{background}$) organized in a 3D structure (hyperspectral data cube). The high-reflectance standard Spectralon™ (Labsphere, Inc., North Sutton, New Hampshire) was used as background reference in this study.

To get representative information about each product, the tablets' concave surfaces were smoothed by using a filer to obtain flat surfaces exposing underneath components. The tablet surface was filed to almost half of the tablet thickness to expose the bulk of the tablet and remove any surface effect due to the dust and the lubricant. The filed material was removed by applying a jet of air to minimize the contamination of the tablet surface with the removed powder. The smoothed and split tablets from each supplier were scanned eight times and averaged on the imager. Pure compound reference samples of the drug and the excipients spectra were used to create a spectral library against which each tablets' spectra were analyzed. For this purpose, approximately 250 mg of each raw material was compressed into 10 mm diameter tablets on a hydraulic tablet press (Carver Inc.) using 10 kN pressure for 10 s. Prior to data analysis, all raw reflectance data (R) were transformed into absorbance (A) by the relation $A = -\log_{10}(1/R)$. The raw NIR diffuse reflectance spectra obtained from a NIR chemical imaging measurement contain both chemical and non-chemical information about the solid sample (Borer et al., 1998). The source of the non-chemical information may be from the sample (e.g. uneven sample surface or differences in sample density) and/or the instrumentation (e.g. changes in lamp intensity or detector response). The effects are typically observed as spectral baseline offsets or a sloping baseline. As it is the chemical information that is of interest, the non-chemical biases are sought and removed by different preprocessing techniques. These preprocessing techniques are routinely used in conventional NIR spectroscopy and their effects on hyperspectral NIR images have also been investigated (Burger and Geladi, 2007). The most common preprocessing approaches used in NIR chemical imaging experiments on pharmaceutical solid dosage forms are first and second Savitzky–Golay derivative transformation (Savitzky and Golay, 1964), standard normal variate (SNV) (Barnes et al., 1989), multiplicative scatter correction (MSC) (Geladi et al., 1985) or a combination hereof. The best performance in visualizing the obtained data was found with third order polynomial Savitsky–Golay derivative with a filter width of 11 data points. The hyperspectral NIR image data were then translated into concentrations to produce the NIR chemical images by partial least squares regression (PLS-2) analysis. In order to spatially visualize either the smoothed or split tablets for each product, a library was built from the pure component spectra representing metoprolol succinate, methacrylic acid copolymer, microcrystalline cellulose, nonpareil beads and ethylcellulose as classes I, II, III, IV, and V, respectively.

3. Results and discussion

The weight variation of tablets before and after splitting is presented in Table 1. Similar to what has been previously reported (McDevitt et al., 1998; Rosenberg et al., 2002; Polli et al., 2003; Gupta et al., 2008; Ellison et al., 2008; Hill et al., 2009), the weight variation increased significantly after splitting compared to the intact tablets. The relative standard deviations (RSD) of the four products are 1.5, 1.7, 1.0, and 1.0 for the intact tablets compared to 4.2, 6.4, 7.4, and 5.8 after splitting, respectively. Despite the fact that all products are scored in the middle, the two halves are often uneven and fragmental along the cutting edge during splitting thus giving weight variation for the split tablets. One tested product is so small in size that it adds to the difficulty to split evenly.

Table 1
Weight variation of tablets before and after splitting (mg).

Tablet #	Product M1		Product M2		Product M3		Product M4	
	Tablet	Split	Tablet	Split	Tablet	Split	Tablet	Split
1	168.4	85.6	111.6	56.3	338.9	179.1	166.4	81.8
2	169.8	81	110.3	50.5	337.7	144.7	170.1	84.8
3	171.5	83.5	107.4	49.7	342.9	174.5	167.2	88.3
4	168.6	87.8	111.1	59.4	342.5	160.6	167.4	81.2
5	169.7	87.4	107.9	49.7	346.8	170.2	166.8	85.1
6	169.2	83.2	105.3	55.6	343.5	167.0	169.5	81.5
7	172.5	88.5	110.6	51.1	341.7	179.4	168.6	78.1
8	167.1	81.4	107.6	55.7	347.5	164.8	170.2	86.9
9	171.0	88.2	110.9	47.4	345.5	175.3	168.5	76.5
10	172.5	80.4	108.4	55.5	350.7	172.1	168.5	84.7
11	168.0	90.1	108.8	49.2	341.1	164.8	169.7	94.6
12	169.6	80.8	107.6	57.4	340.5	167.1	171.4	76.6
13	171.7	87.1	110.5	51.1	345.3	142.9	168.6	83.3
14	172.5	81.9	108.6	55.9	342.3	189.3	168.4	83.4
15	173.8	84.7	108.1	52.1	346.3	170.2	166.9	87.8
16	166.8	87.2	109.7	58.1	345.6	170.1	172.8	77.8
17	173.5	90.6	107.8	52.3	347.3	148.5	169.2	80
18	167.4	78.8	107.4	55	341	190.7	166.2	88.9
19	164.1	81.9	108.4	56.1	340.7	170.3	168.7	78.1
20	169.5	86.7	104.8	50.9	338	169.7	170.4	87.4
Average	169.9	84.8	108.6	53.5	343.3	168.6	168.8	83.3
Range	164.1–173.8	78.8–90.6	104.8–111.6	47.4–59.4	337.7–350.7	142.9–190.7	166.2–172.8	76.5–94.6
RSD (%)	1.5	4.2	1.7	6.4	1.0	7.4	1.0	5.8

Table 2
Content uniformity of tablets before and after splitting (%).

Tablet #	Product M1		Product M2		Product M3		Product M4	
	Tablet	Split	Tablet	Split	Tablet	Split	Tablet	Split
1	106.9	93.1	88.9	119.1	108.9	107.9	97.5	103.1
2	98.2	117.1	102.4	105.6	105.2	96.0	100.7	99.6
3	108.8	108.6	109.1	87.5	99.4	116.7	110.6	121.2
4	105.8	114.2	104.4	148.2	111.6	106.2	98.6	90.7
5	105.7	115.5	106.4	103.8	101.2	98.4	103.0	111.6
6	105.5	118.8	103.0	133.4	103.4	89.4	103.6	108.3
7	108.1	117.2	104.0	122.9	96.0	113.5	97.5	111.5
8	102.9	82.6	95.9	97.6	104.1	105.2	97.4	95.0
9	107.9	105.9	105.6	109.3	103.5	101.8	100.1	113.9
10	93.2	105.4	98.5	109.1	105.0	111.2	105.8	117.7
Average	104.3	107.8	101.8	113.7	103.8	104.6	101.5	107.3
Range	93.2–108.8	82.6–118.8	88.9–109.1	87.5–148.2	96.0–111.6	89.4–116.7	97.4–110.6	90.7–121.2
RSD (%)	4.8	10.9	5.8	15.6	4.3	8.0	4.3	9.3
AV (%)	12.0	28.4	14.2	42.7	10.7	20.2	10.4	23.9

Similar to the weight variation, significant higher acceptance value (AV) was observed in the content uniformity of the split tablets (see Table 2). All four products passed the content uniformity L1 testing with AVs within 15% before splitting but all failed after splitting with AVs over 20%. Five out of ten halves were outside of 85–115% range for Products M1 and M2. One out of ten halves was outside of 85–115% range for Product M3 and two out of ten for M4. Part of the large variation can be explained by the increased weight variation after splitting. However, due to the large size difference between the drug loaded beads and the direct compressible excipients, segregation may happen during powder filling for multi-particulate beads compression. This may cause the beads to preferably reside on one side of the tablet than the other or at the bottom of the tablet than on the top (Wagner et al., 1999). These factors would result in uneven distribution of metoprolol succinate coated beads inside the tablet matrix and therefore add to the variation of content uniformity between the two halves after splitting.

The assay of the samples was determined by calculating the mean value of metoprolol succinate in the tablets analyzed for content uniformity testing. The assays of all products before and after splitting were within 85–115% of the labeled strength. Since the assay testing was performed right after tablet being split, degradation or loss of potency was not expected. The differences in the assay values are likely caused by weight difference among products. In general, the whole tablets showed assay values much closer to the target (100%) as compared to the split tablets.

The drug release profiles in 500 mL of phosphate buffer, pH 6.8 were illustrated in Fig. 1. All four products showed slightly different release characteristics. Products M1 and M4 showed linear release up to 16 h and then leveled off afterwards. Product M2 exhibited linear release during the 24-h period with approximately 85% release by the end of the testing. Product M3 showed biphasic release pattern with an initial burst release followed by sustained release over the course of 24 h. As a unique feature of multi-particulate drug delivery system, tablet splitting has little, if any, impact on the drug release property for all products as seen from Fig. 1 despite of the variations observed in weight and content uniformity.

The SEM images of the drug beads from Products M1, M2 and M3 after either disintegration or dissolution are presented in Fig. 2. After disintegration, the beads of M1 and M2 products appeared spherical in shape while the beads of M3 appeared oblong. The shape difference among the products indicated different preparation methods that might have been employed to obtain those beads. The compression of a modified release beads with a release controlling coating could have severe impact on the integrity of the coating layer and resulted in a dose dumping and altered release characteristics (Habib et al., 2002). SEM images for the beads from the

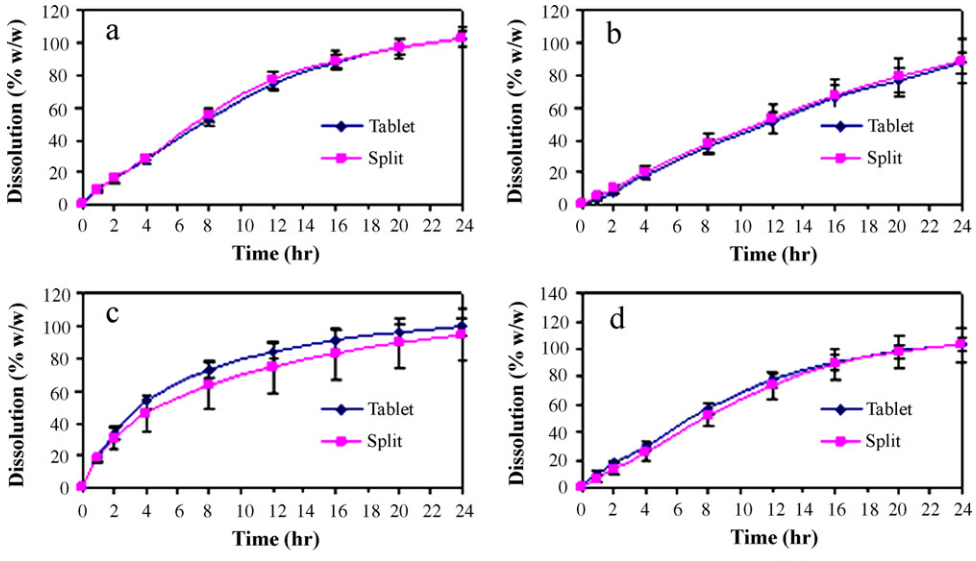

Fig. 1. Dissolution of (a) Product M1, (b) Product M2, (c) Product M3, and (d) Product M4 before (♦) and after splitting (■).

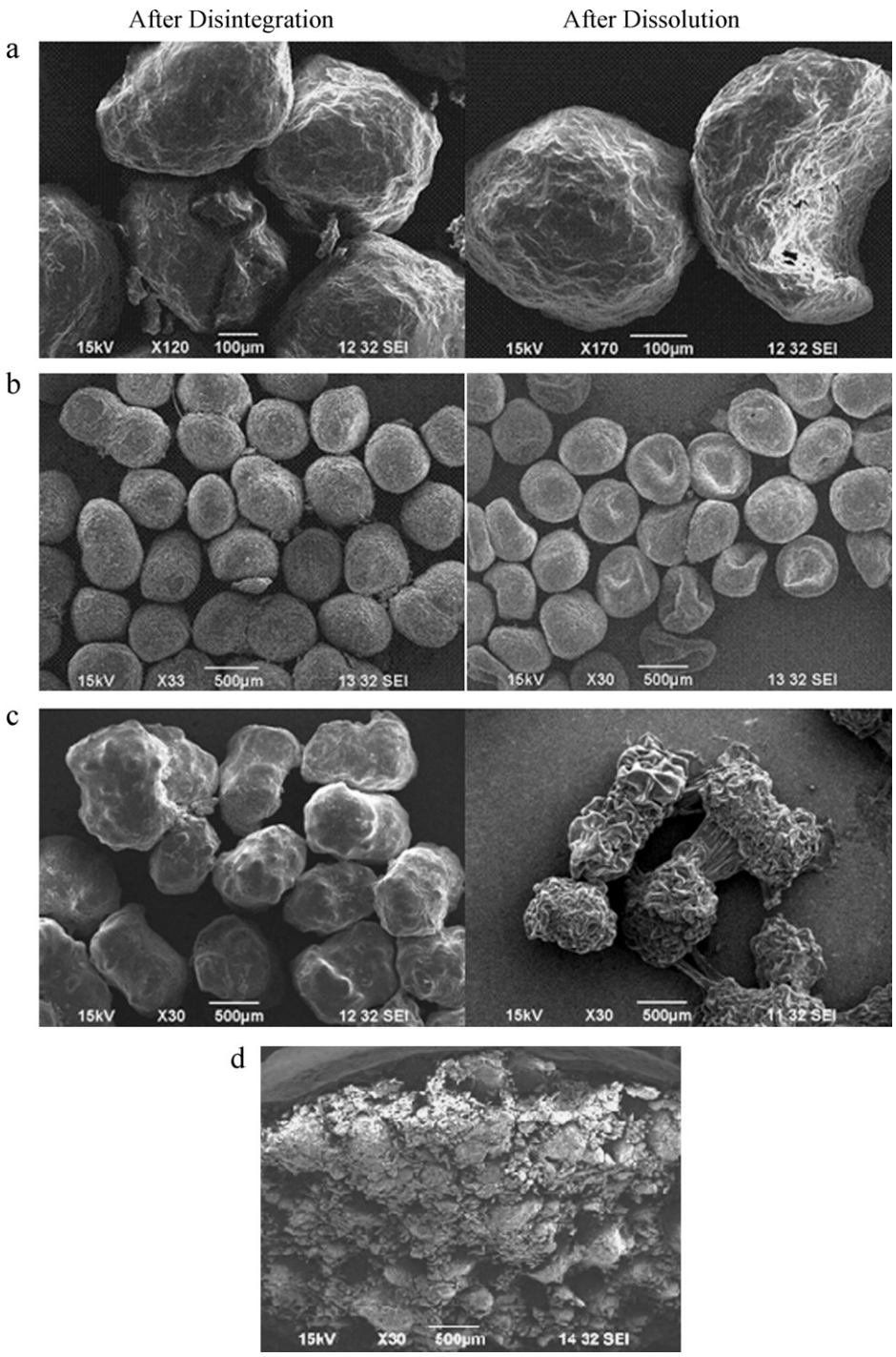

Fig. 2. SEM images of the isolated beads from (a) Product M1, (b) Product M2, and (c) Product M3 after disintegration and after dissolution, respectively, as well as (d) the fracture of split tablets of Product M2.

three products after disintegration showed no apparent film rupture indicating the effectiveness of the cushioning agents employed for tableting of these products. On the other hand, some surface defects were observed in M1 and M2 beads after dissolution. Most of the beads shrank after dissolution due to negative pressure produced inside the beads as drug and/or any soluble excipients released through the polymeric sheath around the beads. Fitting the dissolution data to different release kinetics, zero, first and diffusion models, showed highest correlation coefficients for the diffusion mediated release mechanism for the four products (data not shown). The M3 beads shrank so much that it was not possible to detect any surface property. This observation along with the kinetics data could insight that the mechanism involved for drug release might be diffusion controlled.

Examining the fracture of the split tablets by SEM showed that a nonfunctional coating of the tablets was applied (Fig. 2d). Because of the low depth penetration power of NIR beam as well as the presence of the cushioning matrix and non functional coating, filing the concave tablet surface was done to expose the inner components for the NIR beam. Fig. 3 shows the chemical images with respect to factor index of metoprolol succinate, methacrylic acid copolymer, microcrystalline cellulose, nonpareil beads or ethylcellulose

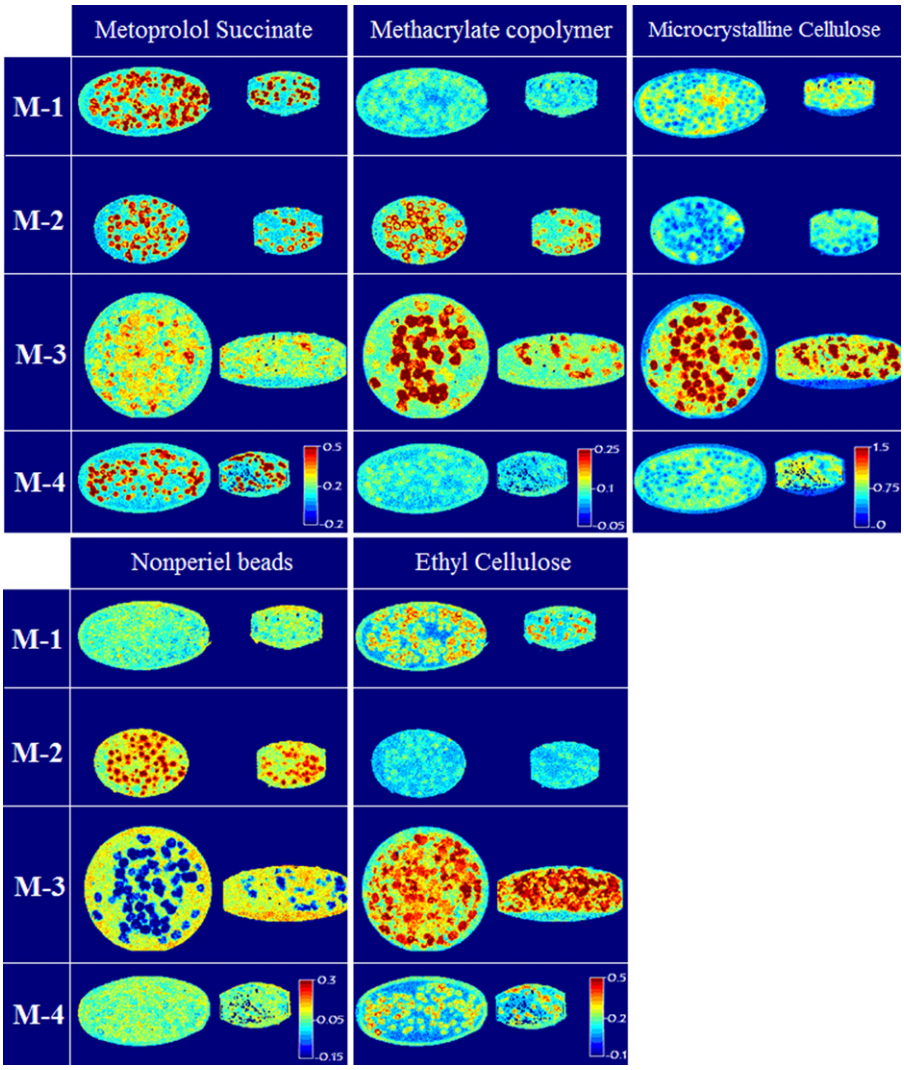

Fig. 3. Chemical images of smoothed and split tablets' compositions from each supplier generated from data processing using PLS-2. The chemical images show the distribution of the five components under investigation. High/low (red/blue) color intensities relates to high/low concentration of the component of interest. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

for tablets analyzed by PLS-2 method using its best performing preprocessing treatment. The images show the distribution of the five components at the surface of either the smoothed or split tablets. High/low (red/blue) color intensities relates to high/low concentration of the compound of interest. An observation at the composition of all tablets from all suppliers revealed that all the tablets designed as a multiple-unit formulation containing metoprolol succinate in the form of individual drug delivery units (pellets). Sandberg et al. (1990) described metoprolol extended release tablets as a matrix containing spherical cores of the drug that is coated with a polymeric membrane of mainly ethylcellulose which controls the drug release from the pellets. It was observed that all the formulations had metoprolol succinate coated pellets having a particle size of about 0.2–2 mm with larger pellets for M3 compared to the other marketed tablets. It was found that M3 pellets were manufactured using cores of microcrystalline cellulose while the other products were formulated using nonpareil beads upon which metoprolol succinate forms a compact layer on the core and this compact layer was further covered with a release controlling polymeric membrane. It was observed that M1 and M2 tablets' surfaces showed heterogeneity in the distribution of the drug as compared to other products. This finding could expalin the higher variation in the results of the content uniformity testing for both products. The obtained results might have implications on split tablets since splitting them into halves equally by weight might still contain unequal amounts of the drug in the split portions due to unequal distribution. Visual inspection of the chemical images of M3 pellets revealed that two types of pellets existed as follows: (a) immediate release pellets to provide the burst effect of the drug to attain the minimum effective concentration in the blood, and (b) extended release pellets to sustain the drug release for a period of 20 h. Irrespective of the other products, this finding might explain the results obtained from the release studies wherein biphasic release pattern existed, an initial burst release followed by sustained release. A careful evaluation at the composition of tablets from the package insert revealed that all the four products used either ethylcellulose, methacrylic acid copolymer or their combination to retard the drug release from the prepared pellets. Methacrylic acid copolymer and its combination with ethylcellulose were the release retarding agents for M2 and M3, respectively. On the other hand, ethylcellulose coats were used to extend the drug release from M1 and M4. Consequently, NIR chemical imaging allowed for obtaining qualitative information and mapping the surface distribution of the investigated excipients as well as the drug in each marketed formulation. Moreover, it allowed for explaining the quality attributes of the final products such as variations in content uniformity and drug

release patterns. The non-homogeneity of beads distribution indicates the usefulness of content uniformity studies for split tablets. Obviously the two cores would result in varying amounts of metoprolol as reflected in the content uniformity studies.

4. Conclusions

Effect of tablet splitting on metoprolol succinate content uniformity was evaluated by performing physical and chemical analysis such as weight, assay and content uniformity as well as NIR chemical imaging. Among the four marketed metoprolol succinate ER tablets, it was found that split tablets showed higher rate of failures as compared to whole tablets in terms of weight and content uniformity comparisons. NIR chemical imaging offered an estimation of the real distribution of metoprolol succinate and functional excipients in the marketed tablets, being very useful when the total homogeneous distribution in the tablet or in a splitting process is pursued.

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