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Effect of Excipients on Salt Disproportionation during Dissolution: A Novel Application of In Situ Raman Imaging

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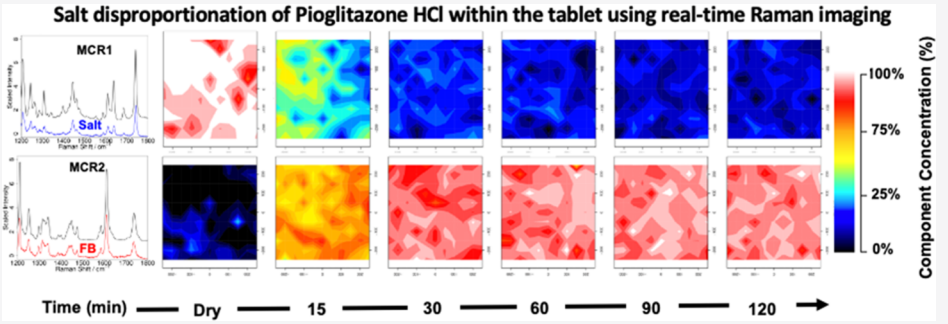

ABSTRACT: We have employed a bespoke setup combining confocal Raman microscopy and an ultraviolet−visible (UV−Vis) spectroscopy flow cell to investigate the effect of excipients on the disproportionation kinetics of Pioglitazone HCl (PioHCl) in tablets during dissolution. Three binary formulations of PioHCl, containing citric acid monohydrate (CA), lactose monohydrate (LM), or magnesium stearate (MgSt), respectively, were used as models to study the influence of excipients' physicochemical properties on the rate of salt disproportionation kinetics and dissolution performance in different aqueous pH environments. It was found that formulation excipients can induce or prevent salt disproportionation by modulating the microenvironmental pH regardless of the pH of the dissolution media. Incorporating CA in PioHCl tablets preserves the salt form and enhances the dissolution performance of the salt in the acidic medium (pH = 1.2). In contrast, LM and MgSt had a detrimental effect on in vitro drug performance by inducing salt disproportionation in the tablet during dissolution in the same acidic medium. Dissolution in the neutral medium (pH = 6.8) showed rapid formation of the free base upon contact with the dissolution medium. The Raman maps of the cross-sectioned tablets revealed the formation of a shell consisting of the free base around the edge of the tablet. This shell decreased the rate of penetration of the dissolution medium into the tablet, which had significant implications on the release of the API into the surrounding solution, as shown by the UV−vis absorption spectroscopy drug release data. Our findings highlight the utility of the Raman/UV−vis flow cell analytical platform as an advanced analytical technique to investigate the effect of excipients and dissolution media on salt disproportionation in real time. This methodology will be used to enhance our understanding of salt stability studies that may pave the way for more stable multicomponent formulations.

KEYWORDS: *disproportionation, dissolution, excipients, microenvionmental pH, Raman, real time*

1. INTRODUCTION

An estimated 50−70% of all developed small molecule drugs are administered as salts.[1,2] However, the success of using these ionized species in tablets significantly depends on their stability both before and during drug release,[3,4] as there is a tendency for the salt to convert back to its free (unionized) form under certain conditions via a reaction known as salt disproportionation.[4,5] Salt disproportionation is an acid−base reaction involving a proton exchange in the presence of water.[6−8] The conversion of the salt to the free form is undesirable since it may have detrimental effects on solid-state properties and pharmaceutical product performance, such as reduced dissolution rate and bioavailability.[4,7,9−14]

Salt disproportionation is influenced by a number of factors such as the physicochemical properties of the drug and environmental conditions during storage and dissolution.[10,14−16] Examples of drug physicochemical properties that mediate salt disproportionation include pH_{max}, the pH of maximum solubility, and the solubility difference between the

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salt form and the free form. pH_{max} is a critical concept in the chemistry of salts, which can be calculated from the following equation:

$$pH_{max} = pK_a + \log \frac{[B]_s}{\sqrt{K_{sp}}}$$

where pK_a is the negative log of the acid dissociation constant, $[B]_s$ is the solubility of the free base, K_{sp} represents the solubility product of the salt form, and $\sqrt{K_{sp}}$ is, therefore, the salt solubility.

The microenvironmental pH is another important factor that can influence salt disproportionation in both the solid state and solution phase. It refers to the hydrogen ion activity (i.e., pH) in the microscopic layer of water around the solid surface.[10,11,17] In the case of solid-dosage forms, the microenvironmental pH may be significantly impacted by the excipients possessing acidic or basic functionalities that are in intimate contact with the salt drug in multicomponent formulations. As a result, the salt propensity to disproportionate can be anticipated based on an assessment of the microenvironmental pH and knowledge of the salt pH_{max}.

For a salt of a weak base (Figure 1), when the microenvironmental pH is lower than the salt pH_{max}, the equilibrium is

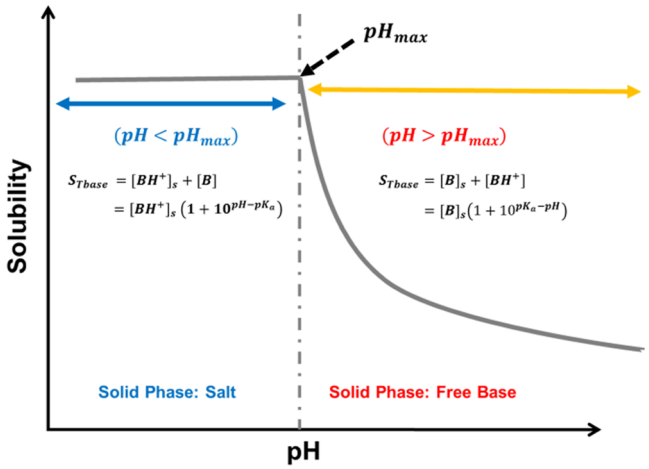

Figure 1. Schematic representation of the pH-solubility profile of a weak base drug presenting the pH_{max} point and indicating that the solubility may be expressed by two independent regions.[16]

between the solid salt, and the ionized form in solution and therefore salt disproportionation cannot occur. In contrast, disproportionation can potentially occur when the microenvironmental pH is higher than the pH_{max} of salt. In this case, excipients that can elevate the microenvironmental pH values above the drug salt pH_{max} can promote disproportionation.

The ability of some acidic or basic excipients to change the microenvironmental pH that influenced salt disproportionation in solid-dosage forms has been previously documented.[5,6,8,10,11,13,17−19] However, only a couple of examples of salt disproportionation during dissolution have been reported in the literature.[20,21]

Ewing et al.[20] investigated the salt disproportionation of formulated tablets, containing a sodium salt of a drug, during dissolution in different aqueous pH environments. Dissolution in acidic media led to rapid disproportionation upon contact with the medium, forming the free acid.[20] In the second study, binary mixture tablets of a new drug candidate HCl salt and Avicel (50:50% w/w %) were prepared to investigate the dissolution performance of the tablet in 0.1 M HCl and water.[21] The results revealed that HCl salt underwent conversion to free base when water was used as the dissolution medium. The data confirmed that the disproportionation mechanism follows solution-mediated phase transformation (SMPT), where the HCl salt initially dissolved before starting to precipitate as a free base.[21]

Both studies investigated the effect of aqueous media with different pH on drug salt disproportionation without exploring the role of the other formulation components (i.e., excipients) in inducing or preventing salt disproportionation during dissolution. Consequently, there is a gap in the current knowledge of how the physicochemical properties of excipients influence the salt disproportionation in tablets during dissolution. Therefore, the main aim of the present work is to understand the effect of excipients on salt conversion kinetics in the tablet matrix (solid state) during dissolution, i.e., to investigate competing kinetics of disproportionation (determined by microenvironmental pH) against dissolution and precipitation. This was attempted using Raman spectroscopic mapping in conjunction with a custom-designed flow cell dissolution system as the main analytical technique. The novelty of this system for investigating the salt disproportionation during dissolution derived from collecting Raman spectra in situ during the course of the dissolution experiment. Raman spectra were analyzed using alternate least-square multivariate curve resolution (ALS-MCR) mathematical approach, which originates from the use of concentrated maps of the tablet to explicitly track the changes as a function of time and space. In-line ultraviolet−visible (UV−vis) absorption spectroscopy was used in parallel with Raman spectroscopy as a complementary analytical technique that allows monitoring the changes in drug release from the tablet to be directly related to physicochemical changes that occur to the drug salt in the tablet matrix. This combination provides a holistic view of the effect of salt disproportionation on tablet performance.

Pioglitazone HCl (PioHCl, Figure 2) was selected as a model drug salt system due to its reported low pH_{max} and the tendency

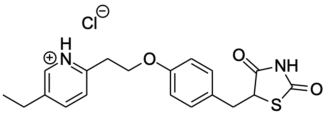

Figure 2. Two-dimensional (2D)-Chemdraw structure of Pioglitazone HCl.

to undergo disproportionation.[6,7,14,15] Binary mixtures of PioHCl with the respective excipients—lactose monohydrate (LM) (filler), magnesium stearate (MgSt) (lubricant), or citric acid monohydrate (pH modifier)—were compressed into tablets (Table 1). Drug salt only and binary mixture tablets were investigated at two different dissolution media: pH 1.2 and pH 6.8 to mimic the stomach and duodenum conditions, respectively.

2. MATERIALS AND METHODS

2.1. Materials. Pioglitazone HCl (Salt ≥98.5%) was obtained from Kemprotect Limited (U.K). Pioglitazone-free base (98%) was purchased from Sigma-Aldrich (U.K.). Both

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Mol. Pharmaceutics XXXX, XXX, XXX−XXX

Table 1. Pioglitazone HCl Formulations Compositions, Excipients Role, and the Mixture Weight Ratio of Each Formulation

formulation	excipient name	excipient role	measured pH[a]	Pio HCl: excipient weight ratio (w/w %)
F_α	citric acid monohydrate	acidic buffering agent	1.6	70:30
F_β	lactose monohydrate	binder-filler	6.3	20:80
F_γ	magnesium stearate	lubricant	8.5	90:10

[a]The pH values of concentrated slurries (10% w/v) of the excipient were measured in water.

Pioglitazone forms were used as received, without any further purification. Citric acid monohydrate (≥99%), magnesium stearate (Technical grade), and lactose monohydrate (Pharma grade) were purchased from Sigma-Aldrich (U.K.). All excipients were used as received, without any further purification. Raman spectroscopy confirmed the identity of the received chemicals. Fourier transform infrared (IR) spectroscopy (Agilent diamond attenuated total reflection (ATR)) was used to provide a complementary physical characterization data to confirm the chemical composition and the solid state of PioHCl and the free base. The IR spectra (Figure S1) of PioHCl and the free base demonstrate good agreement with the literature data.[15] Hydrochloric acid (12 M), sodium phosphate dibasic, and sodium phosphate monobasic were purchased from Sigma-Aldrich (U.K.) to prepare the dissolution media.

2.2. Formulation and Tablet Preparation. All excipients were ground and screened through a 50 μm sieve before mixing with the active pharmaceutical ingredient (API). The grinding and sieving were performed to narrow the particle size distribution, minimize segregation, and enhance blend homogeneity.[22] A binary mixture of the drug salt with the respective excipients was prepared at different weight ratios (Table 1). The selection of the excipients was mainly driven by the excipients used in the branded-drug tablet formulation.[23] Citric acid monohydrate was used to investigate the role of pH modifiers to prevent salt disproportionation during dissolution. The excipients were mixed with Pioglitazone HCl according to the ratio used in the branded-drug product (Actos)[23] or according to the standard excipient ratio stated in the Handbook of Pharmaceutical Excipients.[24] Tablets contains only the drug (without any excipients) were also prepared, as a control in the dissolution experiments, to distinguish the conversion of the salt to the free base resulting from the pH of the dissolution medium from those due to the effect of the excipients in the formulation.

The formulations were thoroughly blended for 15 min using a Turbula T2F mixer. The blended powders were then gravimetrically dispensed (approximately 50 mg for Pioglitazone formulations) into a 20 mL glass vial. Afterward, the mixture was compressed into tablets, 5 mm in diameter, using a manual hydraulic press (Specac). A consistent compression force of ca. 20 kN was applied for all tablets for 15−20 s. All tablets were stored in a desiccator prior to the dissolution experiment for a maximum of 24 h.

The acidic dissolution medium (0.1 M HCl) was prepared by diluting 8.30 mL of 12 M HCl in 1 L of deionized water, whereas the neutral dissolution medium (0.1 M sodium phosphate medium solution) was prepared by mixing 245 mL of 0.2 M of sodium phosphate dibasic and 255 mL of 0.2 M sodium phosphate monobasic, then making up the volume to 1 L using deionized water. It is anticipated to observe a decrease in the dissolution rate of PioHCl in the acidic dissolution medium (0.1 M HCl) due to the common ion effect.[25]

2.3. Raman Ultraviolet−Visible Flow Cell System. Raman spectroscopy in combination with a three-dimensional (3D)-printed flow cell was used to investigate the salt conversion during the dissolution of compressed drug/excipient formulations. Raman spectra were acquired using a Horiba LabRAM HR confocal microscope/spectrometer from 100 to 4000 cm^{-1}. Sample excitation was performed using a near-IR laser (785 nm) of 25 mW power. Spectra were acquired using a

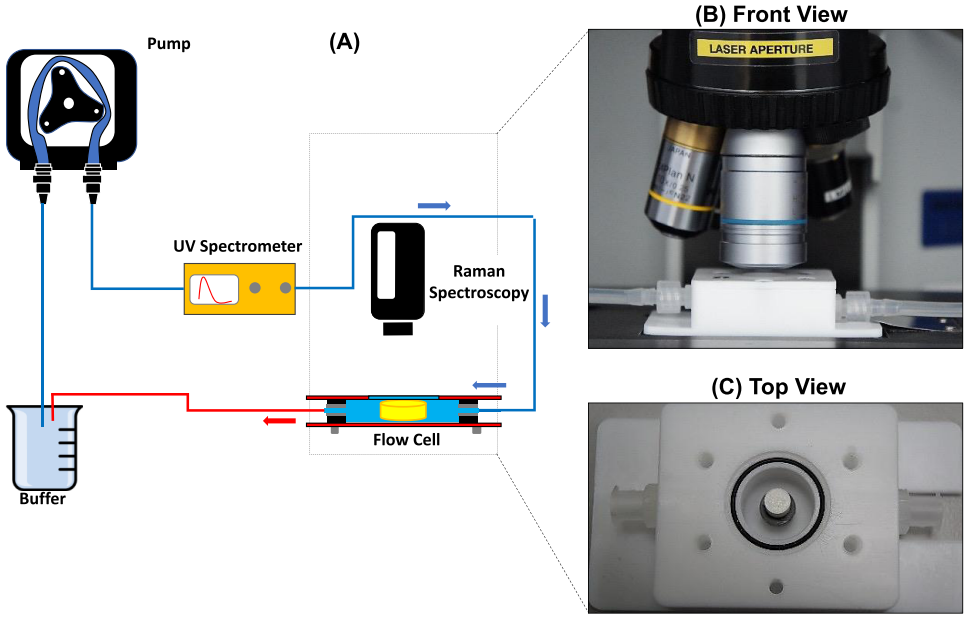

Figure 3. (A) Schematic diagram of the Raman ultraviolet−visible flow cell system. (B) Front view of the flow cell under the Raman spectroscopy objective. (C) Top view of the tablet placed inside the flow cell.

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Mol. Pharmaceutics XXXX, XXX, XXX−XXX

50× objective and a 300 μm confocal hole. A 600 mm rotatable diffraction grating was used to scan a range of Raman shifts. Raman spectra were collected using a SYNAPSE CCD detector (1000 pixels). The flow cell was placed under the objective of the Raman microscope fixed to a motorized XYZ stage (Märzhäuser) for mapping. The spectra were collected as a function of time (15 min intervals) across a mapping area of 500 μm × 500 μm with 50 μm step along the x- and y-axes (121 spectra per map). The whole map required approximately 12 min as each spectrum was acquired for 2 s and repeated once to remove spectral artifacts, e.g., cosmic rays. The sample height was optimized between each map during the dissolution experiment.

Drug release data were collected using a combined miniature light source flow cell UV−vis spectrometer system (Ocean-Optics). A Z-shaped flow cell (FIAZ-SMA) with a 10 mm path length was simultaneously connected to a deuterium light source (DT-MINI-2) through optical fibers and a CCD spectrometer (USB2000). A peristaltic pump (IPS) pumped the room-temperature dissolution media through the UV−vis absorption spectroscopy flow cell and the Raman flow cell in a closed circle flow. Figure 3 illustrates the experimental setup of the system. The dissolution profile of Pioglitazone HCl formulations was acquired by measuring the absorbance at 270 nm every 10 s.

Each formulation was evaluated in acidic (pH = 1.2) and neutral (pH = 6.8) media for 2 h, which matches the mean residence time of tablets in the stomach and duodenum.[26] The total medium volume was 500 mL, and the flow rate was set at 10 mL/min.

2.4. Tablet Cross-Sectioning. The tablets that maintained their structural integrity after dissolution were cross-sectioned to perform further analysis. Raman mapping of the cross-sectioned tablet was performed to spatially identify the tablet's surface components and the inner core of the tablet after dissolution. Each tablet was placed perpendicular to the surface of the aluminum sample holder, embedded in an epoxy resin solution and allowed to dry at room temperature. A thin section of about 1.0 mm thickness was cut from the top of the sample with a razor. Then, each sample was placed in a die, which was subsequently leveled using a microtome (PowerTome XL CR-X Ultramicrotome) to permit smooth vertical cuts of the edge of the tablet to expose the interior using glass and diamond knives. The cross-sectioned tablets were stored in desiccators until the analysis was performed. The cross-sectioned tablets were placed under the objective of the Raman microscope fixed to a motorized XYZ stage (Märzhäuser) for mapping. The spectra were collected across a mapping area covering the whole tablet (around 3000 μm × 5000 μm) with a 100 μm step along the x and y-axes. The whole map required approximately 90−120 min as each spectrum was acquired for 2 s and repeated once to remove spectral artifacts.

2.5. Data Analysis. For Raman data analysis, spectra generated for each map were averaged to construct a single spectrum for each time point (15 min intervals). Averaging the as-produced spectra led to a spectrum with a good signal-to-noise ratio and facilitated the determination of any spectral changes occurring to the salt during the dissolution test. Also, false-color maps were mainly created using ALS-MCR. In ALS-MCR, a single data matrix, including all of the spectra collected and their concentration across the dissolution experiment at all time points, was produced to probe any salt conversion as a function of both x−y position and time. Numerical codes for statistical analyses were written in the "R" language (R software version 3.2.2), which is free, open-source software.[27] All numerical routines were adopted from previous studies.[27,28] Through this work, in MCR, the optimum number of components for each data set was determined based on a priori knowledge of the number of materials (i.e., API and excipients) in the formulation and using a trial-and-error approach to achieve meaningful data. In addition, constraints of non-negativity and unimodality were employed during MCR-ALS to help reduce the complexity of MCR. Colors from white/red to black/blue denoted the component concentrations from high to low. A continuum of white−red−orange−yellow−cyan−blue−black colors represents areas with a variable weighting of that phase. To simplify the data presentation and facilitate comparison between different systems, the total sum of the concentration of the MCR map for each component was calculated and plotted against each time point to generate kinetics plots for all of the tablet formulations investigated in this study. The total concentration was normalized for ease of comparison.

False-color maps of the cross-sectioned tablets were created using classical least squares (CLS) to produce an overlay chemical image, illustrating the distribution of each component across the map. Prior to the CLS chemical mapping, all spectra were baseline corrected and normalized to reduce the effect of variability in Raman spectra. In CLS analysis, the distribution of tablet components was identified using a computerized model function build in the LabSpec software (Horiba). The algorithm is based on modeling the spectra found in each pixel across the Raman map as the linear combination (the weighted average) of the pure component spectra (i.e., reference spectra). Throughout this work, in CLS, the blue color represented the salt component, the red color represented the free base component, and the yellow color represented the excipient (only in formulation tablets) component.

3. RESULTS AND DISCUSSION

3.1. Pioglitazone and Excipient Spectra. The Raman spectra of all tablet ingredients, including Pioglitazone (HCl salt and free base), citric acid, lactose monohydrate, and magnesium stearate (Figure 4), were analyzed separately. A clear spectral difference between the salt and free base of Pioglitazone was observed over the 1200−1800 cm^{-1} spectral region. Specifically, Pioglitazone HCl salt demonstrates two peaks located in the region 1600−1650 cm^{-1}, whereas the free base displays a unique single peak at 1610 cm^{-1}. This spectral difference can be

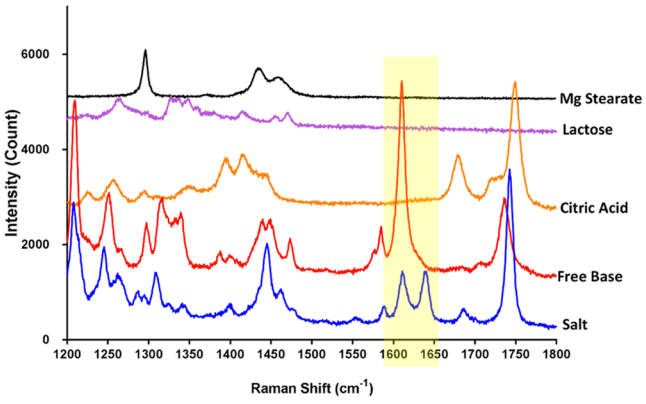

Figure 4. Raman spectra of Pioglitazone HCl salt, Pioglitazone-free base, and excipients used in formulations over the range 1200−1800 cm^{-1}.

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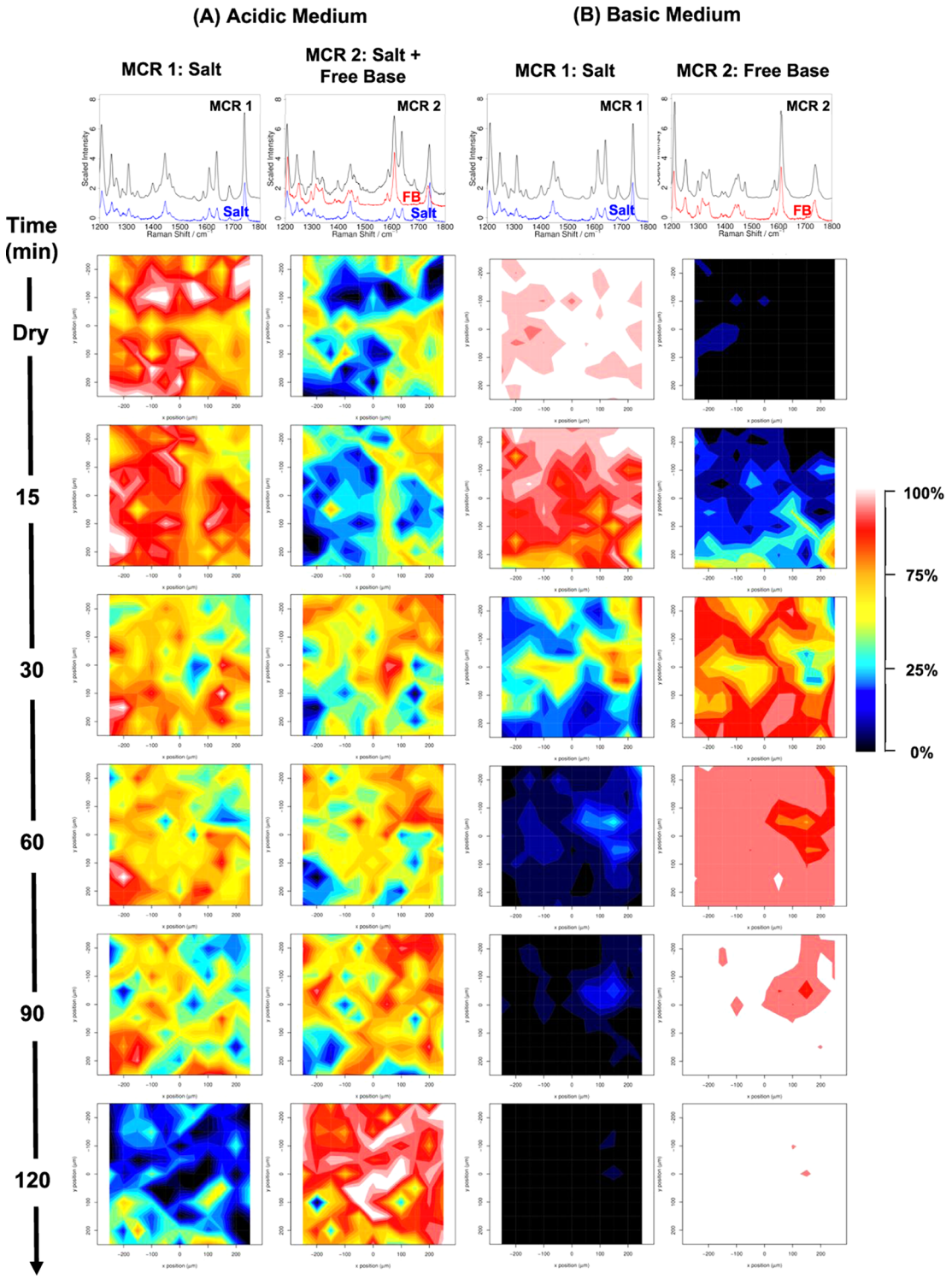

Figure 5. Raman maps of Pioglitazone HCl only tablet during dissolution in (A) acidic medium and (B) neutral medium as a function of time, generated by MCR analysis.

explained by the protonation of Pioglitazone that changes the vibrational modes of the pyridine ring and the carbonyl group.[29−31]

With respect to the excipient spectra, the excipients used in the formulations are largely Raman inactive in this specific region (1600−1650 cm^{-1}). Therefore, this spectral range will be used to differentiate between the salt and the free base peaks with minimum interference from the excipient spectra used in this study.

3.2. Dissolution Experiments. *3.2.1. Effect of the Dissolution Media.* Tablets containing only the drug salt (control tablets) were prepared to study the dissolution behavior of the salt in acidic and neutral environments. This type of experiment was employed to discriminate the role of excipients in inducing or preventing salt disproportionation

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Mol. Pharmaceutics XXXX, XXX, XXX−XXX

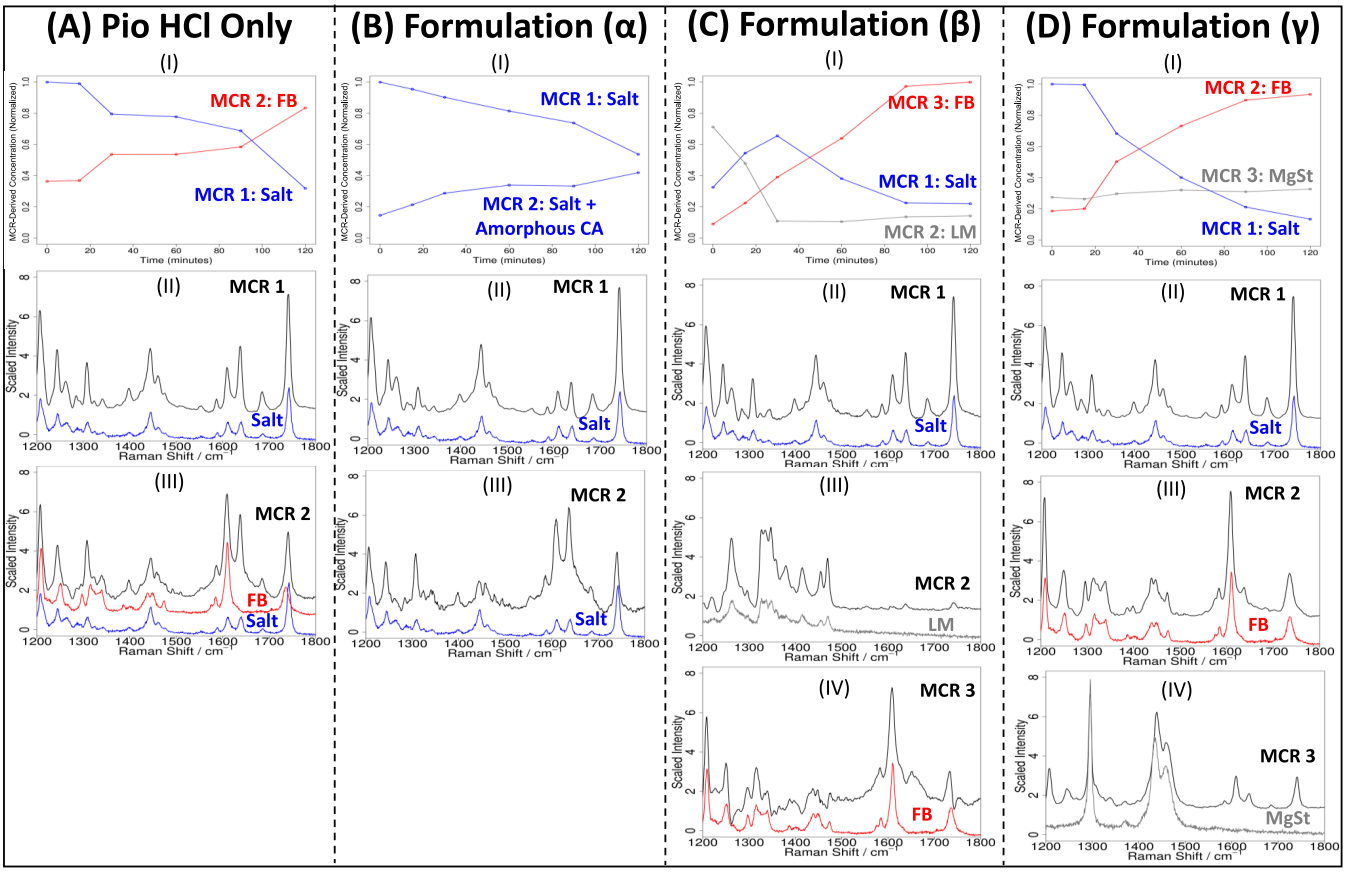

Figure 6. Salt disproportionation kinetic plots (I) and MCR components (II–IV) of (A) PioHCl only, (B) formulation (α), (C) formulation (β), and (D) formulation (γ) dissolution experiments in the acidic medium.

from the dissolution media effect. The pH_{max} of Pioglitazone HCl published by Nie et al. indicates a pH_{max} of 2.8.[15] Therefore, at pH values below 2.8, the salt is expected to be the most stable form, whereas the free base will be more stable above pH 2.8. The acidic environment may thus stabilize the salt, whereas the neutral medium may lead to the conversion of the salt into the free base. MCR analysis was employed to spatially and spectrally deconvolute any change in the salt state during dissolution in acidic and neutral pH (Figure 5). MCR data can be presented as loadings, which illustrate the spectrum of a specific component, and maps that provide the spatial distribution of the corresponding component.

Starting with the acidic medium (pH = 1.2), two components were required to deconvolute the mapped data (Figure 5A). Comparison with the reference spectra indicates that the first component, MCR1, can be associated with the salt (two peaks with the range 1600–1650 cm^{-1}). The second component, MCR2, can be associated with mixtures of both the salt and free base. The analysis of the spectra shows an increase in the 1610 cm^{-1} intensity over the second peak. The increment in the 1610 cm^{-1} peak intensity could indicate the presence of a physical mixture of the Pioglitazone salt and free base, which has been reported previously.[15] The score plots show that the salt (MCR1) is distributed throughout the mapped compact surface before the dissolution experiment start. Corresponding MCR2 score plots indicated coexistence of salt and the free base material in the mapped area of the dry compact. This may be explained by the formation of the free base due to the presence of atmospheric humidity during the powder mixing and tablet compression. Alternatively, compression-induced local amorphization has been reported before to increase the rate of salt disproportionation reaction in some tablets compared to powder blend.[32]

During the dissolution of the tablet containing only the drug (control tablet), the amount of the salt-free base mixture (MCR2) increased at the expense of the pure salt (MCR1). This is probably due to the control tablet undergoing preferential dissolution of the salt component in the acidic medium, which explains the reduction in the pure salt component concentration (MCR1). In contrast, the free base formed during tablet manufacture, remained undissolved in the tablet matrix, resulting in the slight increase in the salt-free base mixture component concentration (MCR2). Alternatively, free base seed crystals (possibly formed during tablet compression) may potentially act as nucleation substrates. If present, these seeds may facilitate the nucleation and growth of the free base dissolved in the medium from the surface of the free base crystals located in the tablet matrix.[33]

The results from the dissolution experiments in the neutral medium (pH = 6.8) significantly differ from those recorded in the acidic medium (Figure 5B). Comparison of MCR loadings with reference spectra clearly shows that the data has been resolved into two components, which agree remarkably well with Pioglitazone HCl salt (MCR1) and Pioglitazone-free base (MCR2). These results confirmed that there was a rapid formation of the free base after the neutral medium contacted the tablet. A complete conversion of the salt to the free base occurred 60 min after the dissolution experiment started.

Salt disproportionation is likely linked with the rise of the medium pH above the pH_{max} of the salt, which facilitated the

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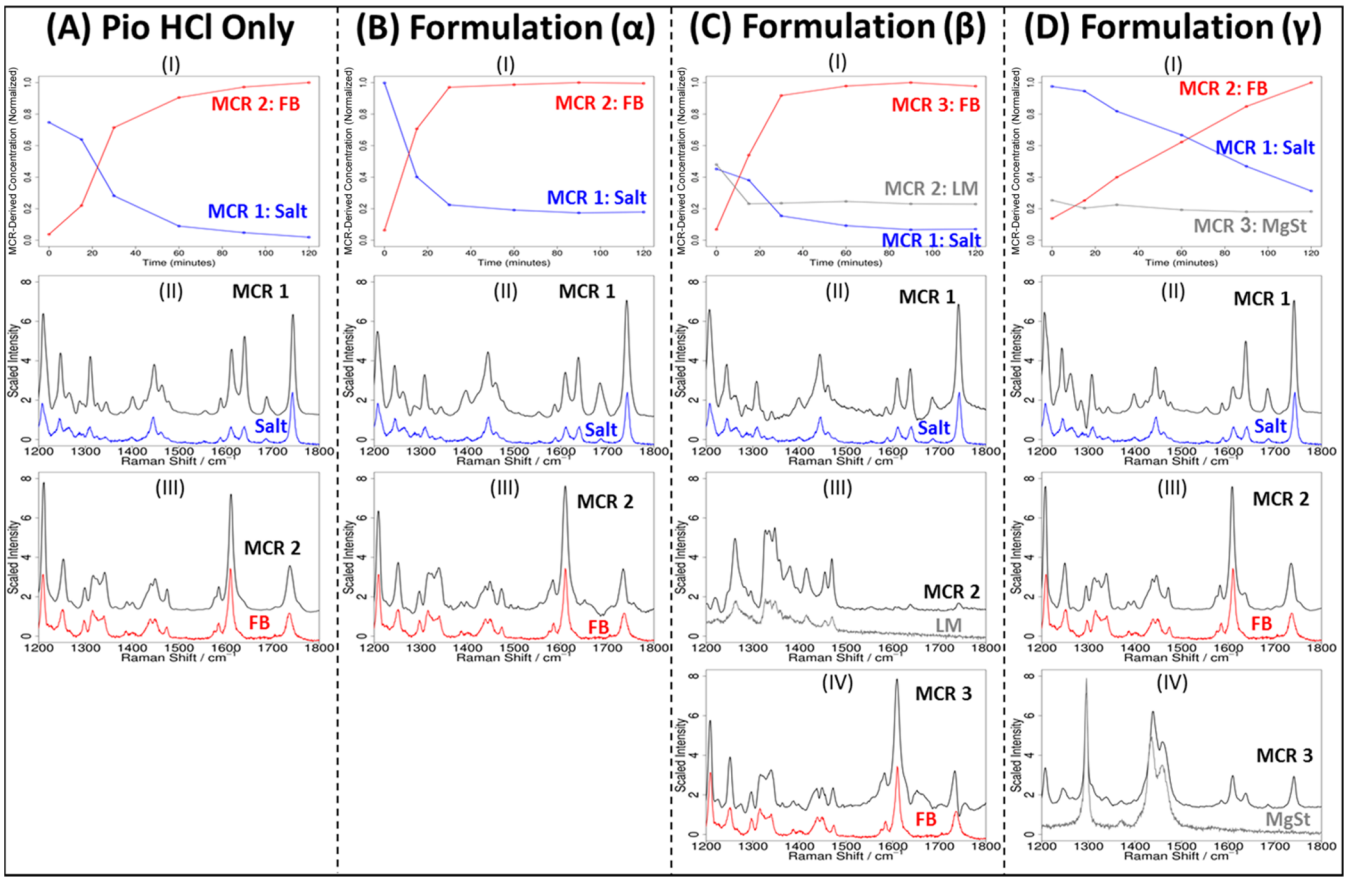

Figure 7. Salt disproportionation kinetic plots (I) and MCR components (II–IV) of (A) PioHCl only, (B) formulation (α), (C) formulation (β), and (D) formulation (γ) dissolution experiment in the neutral medium.

solution-mediated phase transformation (SMPT) of the salt. It is well known that SMPT consists of three phases; (i) initial dissolution of the metastable phase (i.e., salt) to reach supersaturation; (ii) nucleation of the stable phase (i.e., free base); and (iii) crystal growth.[34] Therefore, it is likely that the increase of the pH above the pH_{max} of the salt in the neutral medium led to an increase in the supersaturation of the unionized form (i.e., free base) in the solution. This high supersaturation led to the precipitation of the free base to reach equilibrium.[7,14,15,32,35] This precipitation of the free base on the surface of the tablets was observed in the Raman maps and was observed visually on the surface of the dissolution media container.

3.2.2. Effect of Excipients. It has been reported that excipients possessing acidic/basic functionalities can modulate the microenvironmental pH within adsorbed moisture located at surfaces of the salt.[4−7,11−15,18,32,35] The change in the microenvironmental pH may induce or prevent salt disproportionation depending on the pH_{max} of the drug salt. In this investigation, we focused on three excipients: citric acid monohydrate (pH modifier), lactose monohydrate (filler), and magnesium stearate (lubricant). Citric acid (CA) is a widely used pH modifier in pharmaceutical formulations, primarily to adjust the microenvironmental pH of tablet matrices.[24] pH modifiers, such as citric acid, have been used previously as an effective tool to modulate the microenvironmental pH to enhance stability[18,36−38] and minimize salt disproportionation during manufacturing and dissolution.[39−42] Lactose monohydrate (LM) and magnesium stearate (MgSt) are widely used functional excipients in solid-dosage forms.[24] It is well-documented that magnesium stearate induces and accelerates disproportionation reactions when blended with weak base salts due to its alkaline nature.[6,10,15,43]

Therefore in this study, Pioglitazone HCl was formulated with citric acid to prevent disproportionation during dissolution. Lactose monohydrate and magnesium stearate were selected based on the FDA-approved Pioglitazone HCl tablet formulation (Actos), which contains both excipients as filler and lubricant, respectively.[23] Different binary formulations were tested in acidic and neutral media, and kinetics plots were generated from MCR maps and presented in Figures 6 and 7, respectively. MCR maps of different formulations in acidic and neutral media can be seen in the Supporting data (Figures S2–S7).

In the acidic medium, the MCR analysis for tablet formulation (α) required two MCR components to deconvolute the mapped data (Figure 6B). Increasing the number of components to three or more generated noise components or components with no significant variation from the first two. The first MCR component unambiguously correlates with the pure salt reference spectra (two peaks between 1600 and 1650 cm^{-1}), as shown in Figure 6B.II. The second component showed two peaks in the region 1600–1650 cm^{-1}, which were also correlated with the salt spectra. However, a broad peak at 1600 cm^{1} was also seen in the second component that is not entirely comparable to the salt or the free base reference spectra (Figure 6B.III). It is likely that the broad feature observed in the second MCR component (Raman shift 1550–1700 cm^{-1}) and which

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Mol. Pharmaceutics XXXX, XXX, XXX−XXX

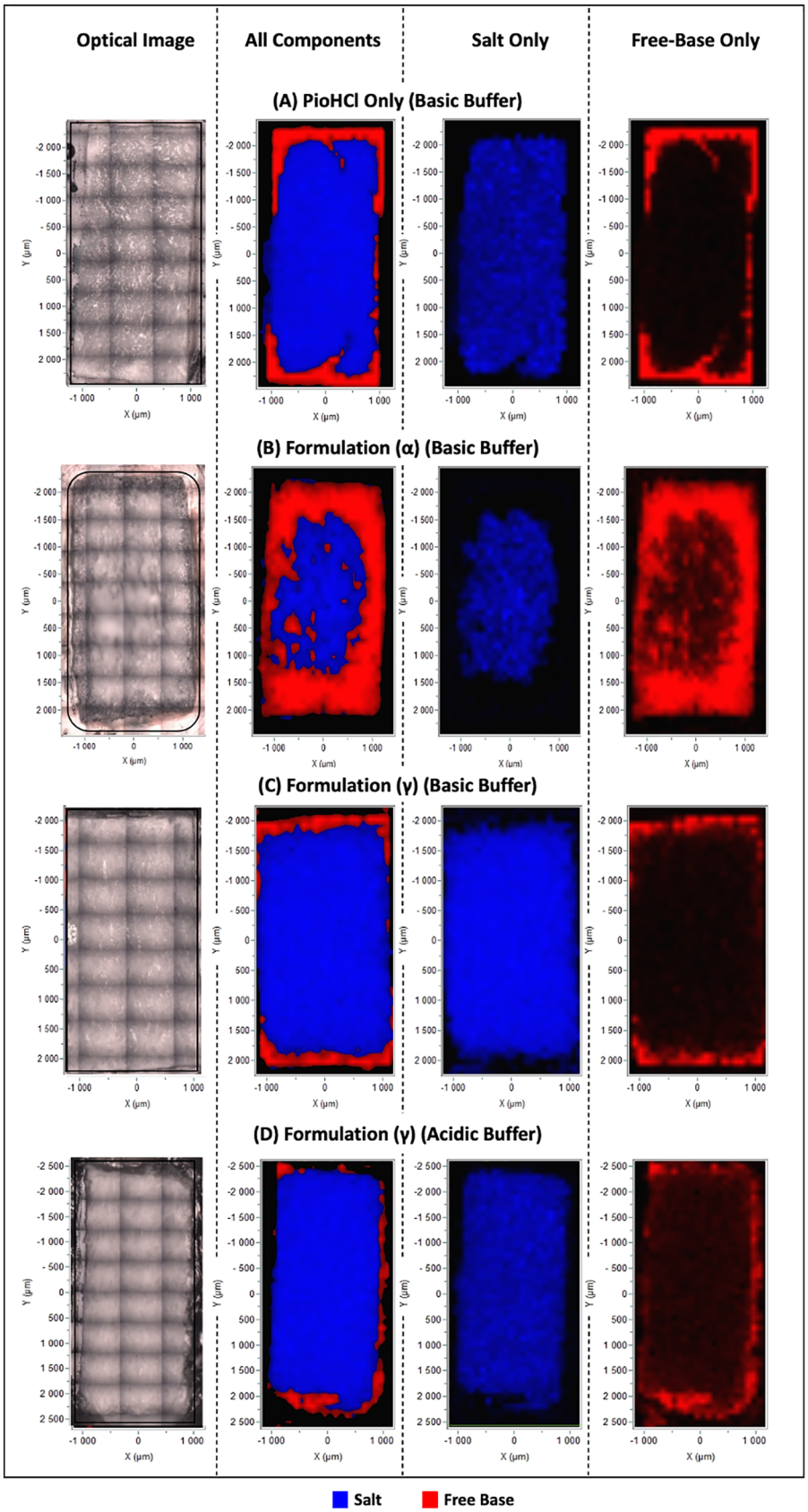

Figure 8. CLS maps of the cross-sectioned tablets for (A) PioHCl only (basic medium), (B) formulation (α) (basic medium), (C) formulation (γ) (basic medium), and (C) formulation (γ) (acidic medium). Blue and red color represent the salt and free base component, respectively.

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Mol. Pharmaceutics XXXX, XXX, XXX−XXX

can also be seen in the single point Raman spectrum (Figure S8) is due to a very high local concentration of citric acid in solution. For comparison, the reported Raman spectrum of aqueous citric acid found in ref 44 contains a similar broad feature in this spectral region. There was no spectroscopic evidence of conversion from the salt to the free base during this experiment in any of the measured data. Incorporation of citric acid in the Pioglitazone HCl tablet formulation prevented the formation of the free base during tablet preparation by lowering the microenvironmental pH surrounding the salt and minimizing free base formation. A similar effect using a pH modifier has been reported previously.[39]

The MCR analysis of formulation (β) and formulation (γ) tablets generated three distinctive components related to the salt, the free base, and the excipient spectra (Figure 6C,D). In formulation (β), MCR1, MCR2, and MCR 3 can be attributed to the salt, lactose monohydrate, and the free base, respectively. Figure 6C.I shows that after 30 min, the amount of lactose monohydrate (MCR2) had reduced significantly, which could be related to the high solubility of lactose monohydrate in the acidic medium. Inversely, salt component (MCR1) showed a clear increase after 30 min, which could be explained by the exposure of new surfaces containing the salt after the rapid dissolution of lactose monohydrate.

Proceeding with the analysis, the salt (MCR1) concentration decreased while the concentration of the free base (MCR 3) increased until it reaches a maximum concentration at 90 min. Similar results were found in formulation (γ), where the concentration of the free base (MCR2) was increased after 30 min (Figure 6D.I). In contrast to the lactose in formulation (β), the concentration of magnesium stearate did not change during the dissolution of the formulation (γ) tablet due to the limited solubility in aqueous media.

In comparison to the drug-only tablet (Figure 6A), formulations (β) and (γ) showed a significant difference in the kinetics of salt disproportionation. A complete salt conversion to the free base, within the limit of the system detection, was recorded in both formulations (β) and (γ) during dissolution in the acidic medium. It is possible that both excipients elevated the microenvironmental pH significantly, which impacted the salt stability in the tablet. It is interesting to note that the free base formation appears to have been initiated in the area surrounding the region of high magnesium stearate concentration (Figure S4 from t = 30 min onwards). This confirms the deleterious effect of basic excipients, such as magnesium stearate, in inducing salt disproportionation in weak base salt formulations.[6,15] Although lactose monohydrate is considered a neutral excipient, the measured pH of lactose monohydrate (pH = 6.3) is above the pH_{max} of PioHCl (2.8), which may enhance the rate of disproportionation. In addition, lactose monohydrate has been reported before to interact with moisture-sensitive APIs (similar to PioHCl) and affected the stability of the drug.[45,46]

Weak base salts have a high tendency to revert to the free base in basic pH conditions, found in the duodenum and small intestine. Therefore, it was expected that PioHCl would undergo salt disproportionation at neutral pH. However, acidic pH modifiers, like citric acid, can be employed to modulate the microenvironmental pH below the pH_{max} of salt regardless of the bulk dissolution medium pH, and thus reduce the salt disproportionation tendency.[47,48] Figure 7B.I shows the salt disproportionation kinetics of formulation (α) in the neutral medium. MCR data analysis shows that the data have been resolved into two components, which agree remarkably well with Pioglitazone HCl salt (MCR1) and Pioglitazone-free base (MCR2) in Figure 7B.II and B.III, respectively. The data shows a rapid conversion from the salt to the free base in less than 30 min.

The salt conversion in the formulation (α) was faster than that in drug-only tablet during dissolution in neutral media (Figure 7A). It is likely that the highly water soluble citric acid leached from the tablet matrix, possibly leaving pores upon contact with the neutral medium. These pores may have increased the ingress of the neutral medium inside the tablet and exposed more surfaces of the salt drug to the medium, resulting in rapid and significant conversion to the free base, an effect that has been previously reported.[48−50] Similarly, formulation (β) showed a rapid conversion of the salt drug to the free base in less than 30 min (Figure 7C.I). The high solubility of the lactose monohydrate is thought to have facilitated the ingress of the neutral dissolution medium into the tablet matrix and enhanced the salt disproportionation rate.

Formulation (γ) (Figure 7D.I) demonstrated significantly slower kinetics for the salt to free base conversion when dissolved in the neutral medium than obtained using the other formulations (drug-only (Figure 7A.I), formulation (α) (Figure 7B.I), and formulation (β) (Figure 7C.I)). A possible explanation for these different disproportionation kinetics is the hydrophobic nature of the magnesium stearate and the limited salt solubility in the neutral medium. It is postulated that the hydrophobic surface coverage of the salt by the MgSt led to a decrease in the water ingress inside the tablet and a reduction in the salt dissolution rate. Consequently, the reduction in the dissolution rate might increase the time required to reach the supersaturation concentration to start precipitating the free base.

3.2.3. Postdissolution Analysis. At the end of the dissolution experiment, most of the tablets exposed to the acidic medium disintegrated completely, and it was not possible to recover any residue of the tablets. However, the formulation (γ) tablet stayed intact after the dissolution in the acidic medium and was recovered from the flow cell. Similarly, tablets dissolved in the neutral medium were recovered except for the formulation (β) tablet, which disintegrated completely due to the dissolution of lactose monohydrate that accounts for ∼70% of the tablet mass. Tablets successfully recovered from the flow cell were cross-sectioned using an ultramicrotome to expose the interior of the tablets. Raman spectroscopic mapping was then performed to analyze the exterior and the core composition of the cross-sectioned tablet.

Raman maps generated by CLS are presented in Figure 8. It is apparent from the maps that salt disproportionation of the Pioglitazone HCl salt to the free base occurs on the outside of the tablet (top and bottom surface and edges), with the interior consisting of the unchanged salt form. Under neutral conditions, Pioglitazone salt disproportionation resulted in the formation of the free base of the drug that initially manifested itself as an impermeable layer around the outside of the tablet, thus inhibiting the ingress of the dissolution medium. High-solubility excipients such as citric acid can enhance the penetration of the neutral medium (pH = 6.8) into the tablet matrix, which led to an increase in the thickness of the free base shell in formulation (α) tablet in comparison to the drug-only tablet, as shown in Figure 8B.

The presence of magnesium stearate in formulation (γ) led to the formation of the insoluble free base shell in acidic and neutral media (Figure 8C,D, respectively). These findings illustrate the

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Mol. Pharmaceutics XXXX, XXX, XXX−XXX

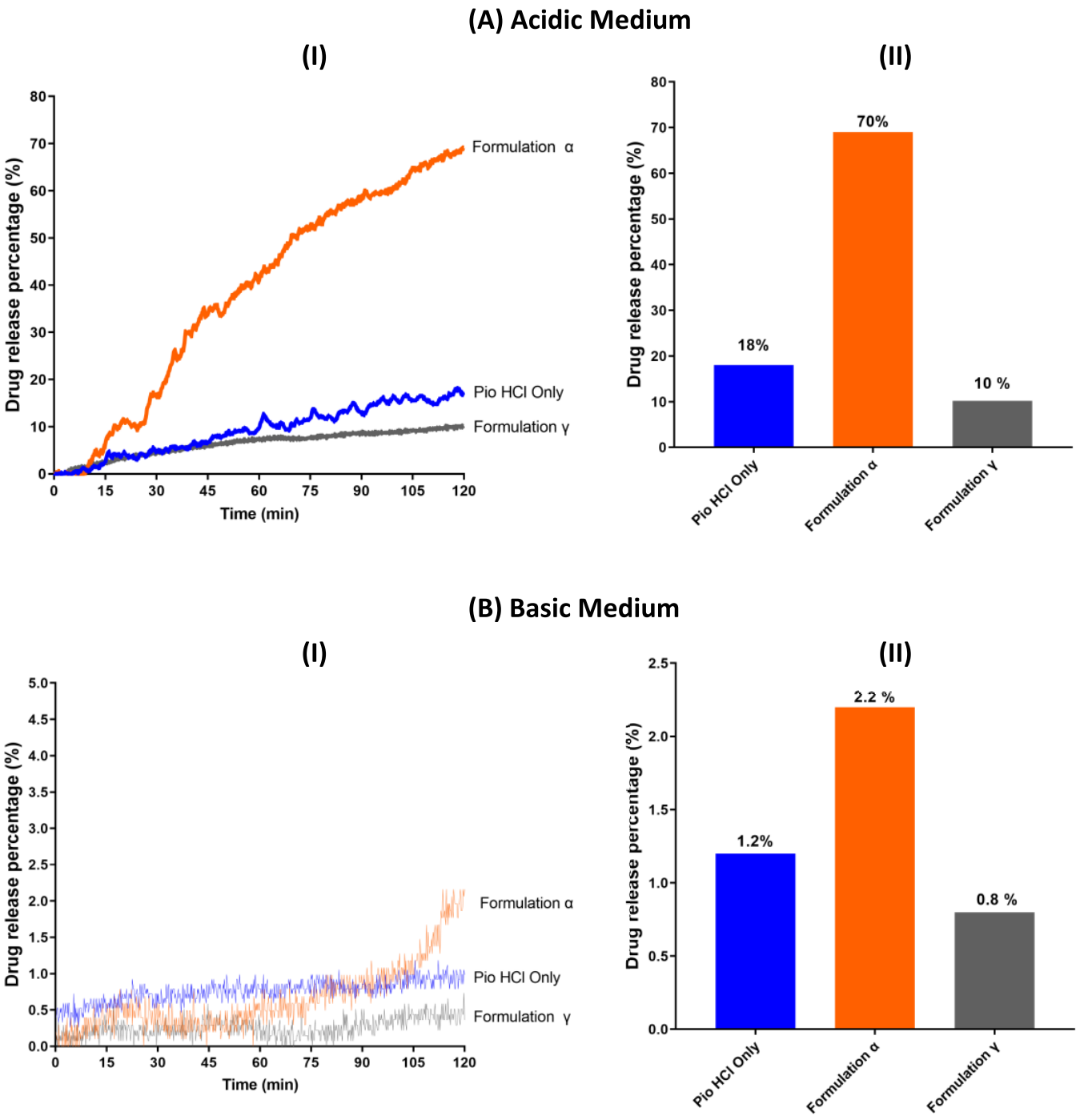

Figure 9. Dissolution experiment in (A) acidic and (B) neutral media. (I) Dissolution profiles obtained using UV−vis absorption spectroscopy detection that presents the percentage of Pioglitazone released from the tablet as a function of time for the pure drug and different formulations.

detrimental effect of magnesium stearate on the dissolution performance in both acidic and neutral media when formulated with the salt of the weakly basic drug. The free base shell may have a significant impact on the amount of the drug released into the surrounding medium, which was explored using the in-line UV−vis absorption spectroscopy.

3.2.4. Dissolution Profile: Ultraviolet−Visible Data. To provide additional analytical insight, the dissolution profiles of Pioglitazone HCl released from drug only, formulation (α), and formulation (γ) tablets were obtained in parallel with the flow cell experiment in acidic and neutral media. (Note: Formulation (β) UV−vis absorption spectroscopy data were excluded due to the overlapping absorbance spectra of lactose monohydrate and Pioglitazone[51]).

Figure 9 demonstrates the amount of Pioglitazone released from tablets (drug only, formulation (α), and formulation (γ)) in the acidic and neutral media, which was determined using the calibration plot (Figure S9). In the acidic medium (Figure 9A), tablets containing citric acid showed rapid drug release during the measurement period, releasing 70% of the drug in 120 min. In contrast, the dissolution rate of the tablets containing PioHCl only and magnesium stearate showed slower drug release than the tablet containing citric acid. Pioglitazone salt only tablet has a higher drug release compared to the magnesium stearate

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Mol. Pharmaceutics XXXX, XXX, XXX−XXX

(formulation (γ)) tablet, where 18 and 10% of Pioglitazone was dissolved after 120 min, respectively.

The UV−vis absorption spectroscopy dissolution profiles supported the Raman spectroscopic images recorded for the experiments and thus confirm the link between the salt disproportionation in the tablet and the percentage of the drug released from the tablet. For example, the Raman MCR analysis of formulation (α) tablet dissolution in acidic medium (Figure 6B) shows that there was no detectable formation of the free base in the mapped area across the experiment time. As a result, the inhibition of the salt disproportionation resulted in a significant release of Pioglitazone as shown in the UV−vis absorption spectroscopy dissolution profile for this formulation (Orange line within Figure 9A). The higher drug release observed in a formulation (α) could be attributed to the pore formation and, consequently, rapid hydration of the tablet matrix, thus enhancing the drug release.[52] In addition, citric acid could modulate the pH in the stagnant diffusion layer surrounding the API particle to enhance the dissolution of Pioglitazone, an effect that has been previously reported.[53] Raman MCR analysis of the drug-only tablet (Figure 6A) and formulation (γ) tablet (Figure 6D) showed salt conversion to the free base during dissolution, which contributed to the low drug release in the UV−vis absorption spectroscopy dissolution profile for drug-only tablet (Blue line) and formulation (γ) (Black line) presented in Figure 9A. Further, the common ion effect might contribute to the low drug release observed for both tablets.[25] These findings confirm the protective role of citric acid in preventing salt disproportionation by lowering the microenvironmental pH below the pH_{max} of the drug. In contrast, the deleterious effects of magnesium stearate in inducing salt disproportionation during dissolution are due to the elevation of microenvironmental pH above the pH_{max} of the drug.

The drug release in the neutral medium is presented in Figure 9B. All tablets showed an extremely low drug release (1.0−2.0%), which reflects the tablet's failure to dissolve in the neutral medium. The observed increase in drug release from formulation (α) after 105 min in the neutral medium could be attributed to the functional role of citric acid in lowering the pH of the diffusion layer around the API particles and forming pores in the tablet matrix, similar to that described for the acidic medium above. These results were in agreement with the Raman MCR kinetic plots (Figure 7) presented previously showing the rapid conversion of the salt to the free base after the neutral medium contacted the tablet surface.

4. CONCLUSIONS

The disproportionation of Pioglitazone HCl upon dissolution was tested as a function of both the pH of the dissolution media and the nature of the excipients. Raman spectroscopy was employed to detect chemical changes of the drug in the solid-dosage form during dissolution and these were correlated with changes in the concentration of drug in solution as measured by in-line UV−vis absorption spectroscopy. For Pioglitazone HCl tablets during dissolution in the acidic medium ($pH < pH_{max}$), the Raman imaging data revealed that salt conversion to the free base did not occur in formulations consisting of drug only, and drug plus citric acid. Moreover, introducing citric acid as a pH modifier (i.e., acidifiers) into the tablet formulation can minimize the disproportionation of Pioglitazone HCl in tablet manufacturing and storage. In contrast, tablets containing excipients, such as lactose monohydrate and magnesium stearate, underwent salt disproportionation to the free base during dissolution. Excipients, such as lactose monohydrate and magnesium stearate, have previously been reported to induce drug salt disproportionation in neutral and basic buffered environments.[6,10,15,43] However, the role of excipients in inducing salt disproportionation in solid-dosage forms during dissolution in acidic media has not previously been elucidated. Our results indicate the vital role of microenvironmental pH, the ability of excipients to influence it, and the effect on drug release from a solid-dosage form. At neutral pH, Pioglitazone HCl salt converted to the free base in all tablets as the pH of the dissolution medium was well above the pH_{max} of the drug. The Raman spectroscopic mapping of the cross-sectioned tablets reveals the formation of a shell of the free base around the edge of the tablet. This shell significantly reduced the rate of penetration of the dissolution medium into the tablet and the resulting structural change reduced the release of the API into the surrounding media as determined by the UV−vis absorption spectroscopy drug release data.

We have demonstrated the utilization of Raman spectroscopic imaging combined with a UV−vis absorption spectroscopy flow cell is a valuable tool for the investigation of problematic multicomponent pharmaceutical formulations, specifically where disproportionation kinetics depend on the pH microenvironment. This approach can enhance our understanding of the interplay between drug and excipient properties, and their influence on disproportionation kinetics, ultimately, helping to mitigate disproportionation of API salts in tablets and enabling pharmaceutical scientists to develop more reliable products with improved drug stability.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.molpharmaceut.1c00119.

Infrared (IR) spectra of the as-received Pioglitaozne salt and free base to confirm the chemical composition and the solid state of both materials; Raman MCR maps of all formulation tablets investigated during dissolution in acidic and basic media; a single-point Raman spectrum of formulation (α) tablet during dissolution in the acidic medium at $T = 120$ min showing the broad feature in the 1550−1700 cm^{-1} spectral region; and a UV−vis calibration curve showing the concentration of dissolved Pioglitazone vs. absorbance at 270 nm (PDF)

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Notes

The authors declare no competing financial interest.

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Mol. Pharmaceutics XXXX, XXX, XXX−XXX