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Investigation of excipient and processing on solid phase transformation and dissolution of ciprofloxacin

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Abstract

Ciprofloxacin, a very slightly soluble antibiotics, is known to exist as both anhydrous and hydrous forms. This study was carried out to investigate the solid phase transformation of ciprofloxacin during conventional formulation processing that impacts the performance of solid dosage forms. In addition, alternative processing and formulation options were also evaluated to circumvent phase transformation. Anhydrate and hydrate of ciprofloxacin were characterized using differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), powder X-ray diffraction (PXRD) and powder dissolution. As expected, the anhydrate exhibited significantly higher dissolution rate than the hydrate. However, it rapidly converted to the hydrate upon exposure to aqueous medium. Interestingly, premixing the anhydrate with HPMC in the presence of water or ethanol was found to inhibit the processing-induced phase transition. Further studies demonstrated that wet granulation could be an option for preparing tablets with high loading of ciprofloxacin anhydrate through proper selection of excipients and control of processing conditions. Dissolution study of ciprofloxacin in HPMC based extended release matrix tablets indicated different dissolution rates between tablets containing the anhydrate and hydrate, suggesting transformation to the hydrate was significantly inhibited by HPMC in the gel layer of the hydrated tablets.

Keywords: Ciprofloxacin; Anhydrous; Hydrate; Phase transformation; Dissolution; Extended-release tablets

1. Introduction

Ciprofloxacin is a widely prescribed broad-spectrum oral fluoroquinolones available in more than 100 countries and has been approved for the treatment of 14 types of infections, especially urinary tract infections (UTIs), such as acute uncomplicated cystitis and chronic bacterial prostatitis (CIPRO, 2005a,b). Ciprofloxacin (Fig. 1) is a zwitterionic molecule with p*I* of 7.42 and apparent pK_a's of 6.09 and 8.74, respectively (Ross and Riley, 1990, 1992). Solubility of ciprofloxacin is pH-dependent, ranging from 6.19 mg/mL at pH 5 to 0.15 mg/mL at pH 7 at 37 °C. Recent studies based on cellular or in situ models have shown involvement of intestinal transporters including efflux proteins in the oral absorption of ciprofloxacin (Rodriguez-Ibanez et al., 2003; Volpe, 2004). This along with apparent lack of linear dose proportionality of AUC in human (CIPRO, 2005a) makes it challenging to classify ciprofloxacin according to biopharmaceutics classification system (BCS) guidance (Guidance for Industry, 2000). Nevertheless, the reported 70–85% absolute oral bioavailability suggests favorable intestinal absorption of ciprofloxacin (CIPRO, 2005a; Volpe, 2004). Therefore, oral absorption of ciprofloxacin is likely influenced by dissolution rate due to its required high dose (250–1000 mg) and low solubility at intestinal pH.

Different solid forms are known to influence the physicochemical and mechanical properties of solids including solubility and dissolution (Grant, 1999). The solid-state properties of the active ingredient must be understood in order to ensure consistent product performance (Zhang et al., 2004; Debnath and Suryanarayanan, 2004). When a predefined solid phase of a drug substance in a solid formulation is subjected to a variety of processing conditions during dosage form manufacturing, many phase transitions may take place including inter-conversion among polymorphs, solvates/hydrates, and the amorphous phases. If uncontrolled, these changes may negatively impact product quality and performance, such as stability,

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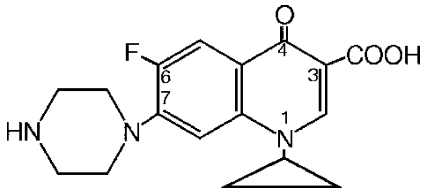

Fig. 1. Chemical structure of ciprofloxacin (MW: 331.4 g/mol).

dissolution or bioavailability (Zhang et al., 2004). A review of commercial products of ciprofloxacin shows that various solid forms are used. The hydrochloride salt is used in immediate release solid dosage forms while free base is used in suspension product (CIPRO, 2005a). Recently, a new extended-release tablet of ciprofloxacin containing a mixture of free base and hydrochloride salt was introduced into the market (CIPRO, 2005a).

In spite of a long history of commercialization of this compound, literature search indicated that solid phases of ciprofloxacin have not been thoroughly investigated. The commonly known crystal forms of ciprofloxacin free base are anhydrous and hydrate. Little was reported about the thermodynamic relationship between different forms, possible solid phase change during processing and their potential impact on dosage form behaviors. Therefore, it is important to understand whether and how processing conditions might have resulted in solid phase changes and possible implications to dosage form performance. This study was carried out to (1) characterize certain basic solid state properties of anhydrate and hydrate of ciprofloxacin and conditions of their inter-conversion and (2) study effects of processing and excipients on phase transitions and potential impact on dissolution of dosage form.

2. Materials and methods

2.1. Materials

Anhydrous ciprofloxacin was supplied by Zhejiang Jingxin Pharmaceutical Co. Ltd., PR China (Lot# 041206) and was sieved through a 80 mesh screen (180 μm) before use. Hydroxy propyl methyl cellulose (HPMC), Methocel K100-LV was purchased from Colorcon (Lot# OJ01012N21). All solvents were analytical grade and obtained from commercial sources.

2.2. Characterization of anhydrate and hydrate of ciprofloxacin

2.2.1. Preparation of hydrate

Hydrate of ciprofloxacin was obtained using two different methods: (1) 200 mg of anhydrous drug was suspended in 100 mL water, heated to 100 °C for 10 min and then filtered. The precipitate was collected from the filtrate upon cooling and drying at room temperature. (2) Approximately 2 g of anhydrate was mixed with 2 mL of water using mortar and pestle for ∼3 min at room temperature. The solids were dried at 40 or 60 °C for 2 h.

2.2.2. Differential scanning calorimetry

Approximately 2 mg of sample was sealed in an aluminum pan with an empty encapsulated pan as a reference. The sample was scanned at a heating rate of 10 °C/min from 30–350 °C (Perkin-Elmer Model 1-DSC). The cell was purged with helium throughout the run.

2.2.3. Thermal gravimetric analysis

Approximately 5 mg of sample was heated in an open aluminum pan from room temperature to ∼250 °C (Perkin-Elmer Model Pyris 1) TGA at 20 °C/min under nitrogen purge.

2.2.4. X-ray powder diffraction

Approximately 200 mg of sample was exposed to Cu Kα radiation (45 kV × 40 mA) in a wide-angle powder X-ray diffractometer (ARL Inc., Switzerland, Model X'TRA). The instrument was operated in the step-scan mode, in increments of 0.05° 2θ over 5 to 40° 2θ, and the counts were accumulated for 1 s at each step. The data collection and analyses were performed with commercially available software (Origin, version 5.0).

2.2.5. Powder dissolution

Powder dissolution profiles of both anhydrate and hydrate of ciprofloxacin were obtained in a six-station USP II dissolution apparatus (Tianjin University Electronics Co., Model ZRS-8G) using 300 mg of sample (passed through 80 mesh) at 50 rpm, in 900 mL of distilled water (25 ± 0.5 °C). Samples were withdrawn at specific intervals and filtered through a 0.22 μm filter. The drug concentration was assayed by UV spectrophotometry at 278 nm (Shimadzu Model UV2450) after proper dilution. The experiment was run in six replicates.

2.3. Investigation of phase transformation and influence of excipients and processing

To evaluate the conversion between hydrate and anhydrous phases in the presence of water, anhydrous ciprofloxacin was wetted with water and triturated in a mortar using a pestle. The wet mass was then dried in an oven at 40 °C for 2 h before analysis by PXRD. In a separate experiment, ciprofloxacin hydrate was kept in an oven at 60 °C for 12 h before analysis by PXRD.

In order to assess the effects of wet processing and excipients on phase transition of ciprofloxacin, fixed ratios of anhydrous ciprofloxacin to selected excipients (Table 1) were tested using

Table 1
Effect of excipient and processing on phase transition of anhydrous ciprofloxacin

Excipient	Anhydrous/ excipient	Solid phase in the granulation[a]	
		Method (1)	Method (2)
Lactose	1:1	Hydrate	Hydrate
MCC	1:1	Hydrate	Hydrate
Methocel K100-LV (HPMC)	1:1	Anhydrous	Anhydrous
Methocel K100-LV (HPMC)	5:3	Anhydrous	Anhydrous
PVP K30	1.9:0.1[b]	Hydrate	Hydrate

[a] Determined by PXRD.
[b] Granulated with 5% PVP solution.

Table 2
Composition of extended-release tablet of ciprofloxacin

Ingredient	A	B
Ciprofloxacin, anhydrous (%)	50	–
Ciprofloxacin, hydrate (%)	–	50
Methocel, K100-LV (%)	29	29
PVP K90 (%)	10	10
PVP K30 (%)	2.5	2.5
Avicel, PH 301 (%)	8.0	8.0
Magnesium stearate (%)	0.5	0.5
Tablet weight (mg)	1000	1000

two different methods described below. The batch size was 2 g for each experiment.

Method 1: The drug and excipient were mixed and granulated with water using a mortar and pestle. The wet mass was passed through a 20 mesh screen, dried in an oven at 40 °C for 2 h before analysis by PXRD.
Method 2: The drug and excipient were mixed and granulated with ethanol using a mortar and pestle. The wet mass was passed through a 20 mesh screen, dried at room temperature for 2 h before re-granulation with water following the same procedure as that described in Method 1.

2.4. Preparation of extended-release tablets

Tablets containing anhydrous ciprofloxacin were prepared according to Formulation A in Table 2. A weighed amount of 15 g of anhydrous ciprofloxacin and 8.7 g of Methocel K100LV were pre-blended in a plastic bag for ∼2 min. The powder blend was then dry mixed at low speed in a bench-top high shear mixer (Tianjing Dakang Electronics Co., Model SG–280) for 4 min followed by wet granulation via slow addition of about 6 mL of ethanol over 8 min at low speed. The granules were massed for 3 min at high speed upon addition of ethanol. The wet mass was screened through a 20 mesh screen, tray dried in an oven at 40 °C for 3 h. The dried granules were passed through an 80 mesh screen. 15.8 g of the dried granules obtained were weighed out and pre-blended with 2 g of PVP K90, and 1.6 g of microcrystalline cellulose in a plastic bag for ∼2 min followed by mixing in a bench-top high shear mixer at low speed for 4 min. Wet granulation was performed via slow addition of 10 mL of 5% aqueous solution of PVP K30 over 8 min at low speed. The granules were subsequently massed for 3 min at high speed upon addition of PVP solution and dried in an oven at 40 °C for ∼12 h.

Tablets containing ciprofloxacin hydrate were prepared according to Formulation B in Table 2. Ciprofloxacin hydrate, Methocel, PVP K90, and microcrystalline cellulose were pre-blended in a plastic bag for ∼2 min. Twenty grams of the powder blend was dry mixed at low speed in a bench-top high shear mixer for 4 min followed by wet granulation via slow addition of 10 mL of 5% solution of PVP K30 over 8 min at low speed. The granules were massed for 3 min at high speed upon addition of PVP solution. The wet granules were dried overnight in an oven at 40 °C for ∼12 h.

The above dried granulation was screened through a 20 mesh screen, blended with magnesium stearate for 2 min. Tablets of oval shape were prepared individually by weighing and compressing using a single punch tablet press (Tianqi Pharmaceutical Machinery Co. Ltd., Model THP-4). The tablet hardness was recorded using a hardness tester (Shanghai Huanghai Pharmaceuticals, Model 78X) and found to be similar between the two formulations (∼11 kg). The dimension of the tablet is 20 mm × 10 mm × 5 mm.

The solid phase of ciprofloxacin in both tablets was examined using X-ray powder diffraction following reducing the tablets into powders.

2.5. Tablet dissolution test

Dissolution profiles of the extended-release tablets were determined in a six-station USP II dissolution apparatus (Tianjin University Electronics Co., Model ZRS-8G) operating at 100 rpm. Nine hundred milliliters of 0.1N hydrochloric acid solution was used as dissolution medium (37 ± 0.5 °C) in order to maintain sink condition (Talwar et al., 2001). About 5 mL of samples were withdrawn at specific intervals and filtered through a 0.22 μm filter, and the drug concentration in the filtrate was properly diluted before analyzed by UV spectrophotometry at 278 nm (Shimadzu Model UV2450). At each data point, the lost 5 mL was replenished by 5 mL of fresh dissolution media maintained at the same temperature. Sufficient sensitivity and linearity of the UV method was obtained for the sample assay (linear range of 2–10 μg/ml, $R^2 = 0.9996$). Lack of interference from excipients was confirmed by UV scanning of tablet formulation devoid of the active. Six tablets were tested for each formulation.

3. Results and discussion

3.1. Characterization of solid phases

DCS and TGA: DSC scan of the anhydrous ciprofloxacin shows a single melting endotherm with an onset temperature of 270.8 °C. The DSC thermogram of the hydrate exhibited two endothermic transitions. The first broad peak with the onset temperature of 101.7 °C was attributed to the dehydration process. This was confirmed by corresponding weight loss at the same temperature range during TGA scans. The second endotherm at 269.9 °C was due to melting of the dehydrated phase.

The stoichiometry of the hydrate was determined by the percentage of weight loss at the desolvation temperature observed in TGA experiment. The results indicate a weight loss of 18.7% (w/w) taking place between approximately 100 and 120 °C. This weight corresponds to a loss of approximately 3.5 water molecules per molecule of ciprofloxacin.

The powder X-ray diffraction patterns of both hydrate and anhydrate are overlaid in Fig. 2. The PXRD patterns of the two substantially crystalline phases are distinctly different. The hydrate has characteristic peaks at 5–7° 2θ while the anhydrate has characteristic peaks at ∼14° 2θ. Therefore, the phase

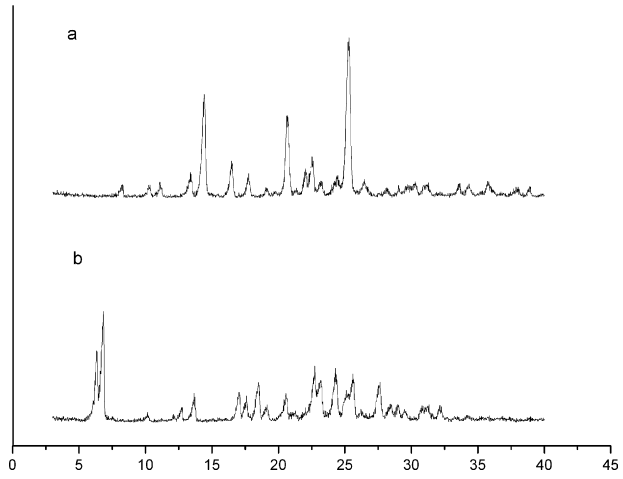

Fig. 2. Powder X-ray diffraction patterns of crystal forms of ciprofloxacin: (a) anhydrate; (b) hydrate.

transition between these two crystalline forms can be readily monitored by PXRD.

3.2. Powder dissolution

The powder dissolution profiles of the two crystal forms of ciprofloxacin indicate that the anhydrous form has a significantly higher dissolution rate than the hydrate, essentially reaching maximum concentration within 1 min (Fig. 3a). However, it was found that almost immediately after a peak concentration was reached, the percent dissolution started to decline, decreasing almost 50% at the end of the 60-min experiment (Fig. 3b). This observation can be attributed to the crystallization

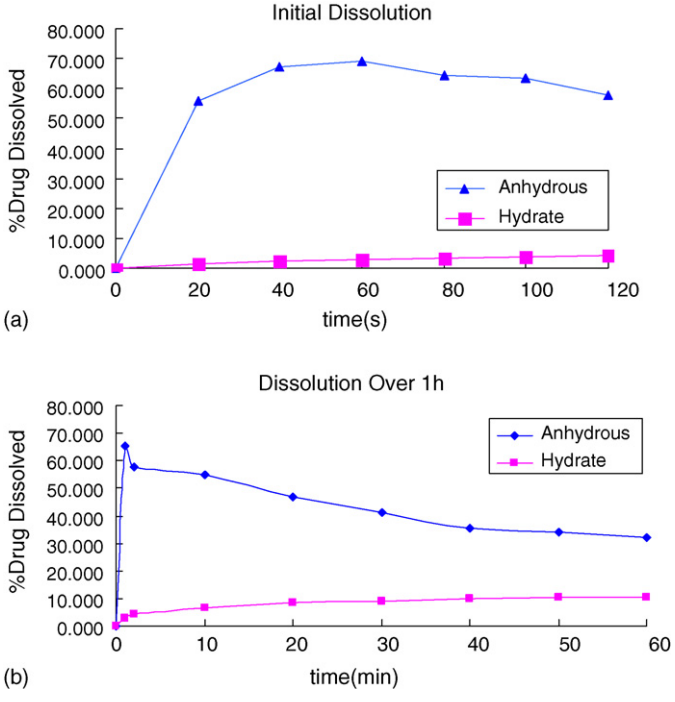

Fig. 3. Powder dissolution of anhydrous and hydrate ciprofloxacin: (a) profiles in the first 2 min; (b) profiles over 60 min.

of ciprofloxacin hydrate that has a significantly lower solubility. Thus, the anhydrate curve is expected to converge with the hydrate profile should the experiment be carried out over a longer duration. Interestingly, this solution-mediated phase transition was visually apparent during the dissolution test. Following addition of anhydrate powder to the dissolution vessel, the solid particles dissolved rapidly, resulting in a nearly clear solution that subsequently turned turbid within minutes. The results indicate that the transformation from anhydrous ciprofloxacin to the more stable hydrate is very rapid in aqueous medium. Thus, transition during aqueous processing is also possible. It should be noted that the observed difference in powder dissolution is attributed to the solubility difference between the two solid phases considering immediate and rapid decrease in concentration of the anhydrate upon reaching its peak value.

3.3. Effect of excipients and processing on phase transformation

In a preliminary study of conversion between hydrate and anhydrous phases monitored by PXRD, the anhydrous ciprofloxacin was found to convert to the hydrate form on exposure to water through triturating and subsequent drying at 40 or 60 °C for 2 h. The anhydrous form can be obtained from dehydration of the hydrate upon drying at 60 °C for 12 h. Since these conditions are within the range of parameters often used in the processing of various solid dosage forms, it is important to understand the impact of wet processing on the phase conversion and possible ways to prevent or control such changes irrespective of which solid form is used as the starting material.

Inhibitory effect of additives or excipients, such as polymers, on solid phase transition have been reported (Matsumoto and Zografi, 1999; Katzhendler et al., 1998). For example, polyvinylpyrrolidone (PVP) and HPMC have been reported to influence amorphous to crystalline or crystalline to crystalline transformations for different drugs. In a study of effects of excipients on hydrate formation in wet masses, the highly water absorbing silicified microcrystalline cellulose was found to inhibit the formation of theophylline monohydrate in wet masses at low moisture contents even following an overnight equilibration (Airaksinen et al., 2003). Therefore, phase transformation of ciprofloxacin was evaluated in the presence of excipients, including polymers commonly used in solid dosage forms.

The effect of excipients at different ratios on the anhydrate to hydrate transition was assessed under conditions that resemble the actual wet processing of solid dosage forms. The results summarized in Table 1 show that at a 1:1 ratio of drug to excipient, inhibition from anhydrate to hydrate was observed with HPMC (Fig. 4), but not with microcrystalline cellulose or crystalline lactose as monitored by PXRD. At a higher drug to HPMC ratio (5:3) that is similar to the ratio in a formulation, the inhibition of phase transition remains effective. Granulating anhydrate with aqueous PVP solution did not prevent hydrate from forming, a likely result of the very high drug to PVP ratio. Use of ratios similar to those of HPMC is impractical due to the gumming nature of wet drug–PVP mixture. According to the literature (Talwar

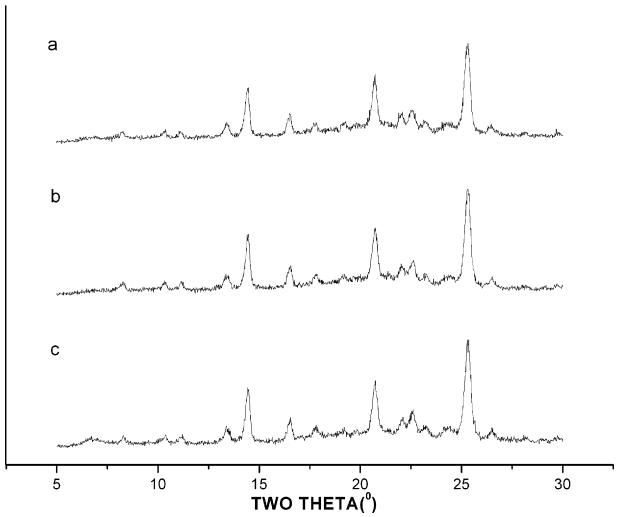

Fig. 4. Powder X-ray diffraction patterns of various mixtures of anhydrous ciprofloxacin and HPMC using different mixing methods following aqueous granulation and drying [(a) 1:1, Method 1; (b) 1:1, Method 2; (c) 5:3, Method 1].

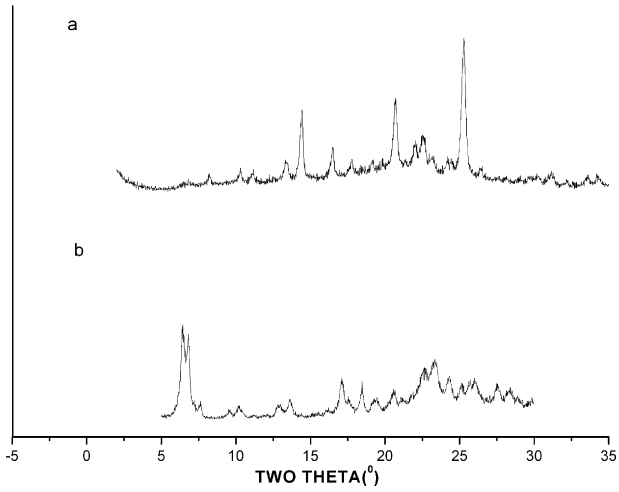

Fig. 5. Powder X-ray diffraction patterns of ground samples of Tablets A (a, anhydrate) and B (b, hydrate).

et al., 2001), dry granulation process, such as roller compaction, has been used in preparing solid dosage forms of ciprofloxacin. The dry process was presumably utilized to improve powder flow and compressibility due to the required high drug loading, as well as to avoid phase changes. This study indicates that use of a wet process may also be feasible for ciprofloxacin if proper excipients, processing steps and conditions are selected.

3.4. Effect of processing and solid phase on tablet dissolution

Product performance, such as dissolution, is known to be dependent on the solid state of the drug substance, formulation composition and the processing conditions (Zhang et al., 2004). In addition, phase transformations during processing as well as during dissolution can also influence the observed dissolution rates. In studying crystalline properties of an insoluble drug, carbamazepine, in a hydrophilic matrix system, Katzhendler et al. (1998) found that the rate controlling polymer, HPMC, inhibited the solid phase transformation to less soluble dihydrate from the anhydrous form in the hydrated gel layer during drug release. They postulated hydrogen bonding as the primary mechanism for the observation and concluded that these types of changes could have direct impact on the in vivo drug absorption as well as swelling and erosion characteristics of the delivery system.

In order to evaluate whether the above findings can be applied to the processing of tablet formulation and confirm the influence of solid phase on tablet dissolution, extended release tablets with 50% drug loading were prepared using wet granulation process. Tablets A and B used anhydrous and hydrate ciprofloxacin as the starting material, respectively, and met the same physical specifications, such as dimension and hardness. PXRD analysis of ground tablets confirmed that solid phase in both tablets remained essentially unchanged after undergoing wet granulation, drying and compression processes (Fig. 5). This is consistent with the previous results where both forms did not undergo phase change upon milling for 30 min with a mortal and pestle. This study demonstrated that tablets containing more soluble anhydrous ciprofloxacin could be obtained using wet granulation process via choosing a polymer that was shown to inhibit hydrate formation. The tablets containing hydrate could be prepared by controlling drying condition, such as temperature and drying time. It should be pointed out that although a two-step granulation process (Method 2) was used to prepare anhydrate granulation of Tablet A to ensure minimum probability of phase conversion during processing, simpler alternatives are likely to work as well on the basis of the above findings. For example, anhydrate tablets may also be prepared using a single step wet granulation of anhydrate and HPMC with either water or ethanol followed by drying, sizing, blending with other excipients and compression.

To indirectly confirm the control of solid phase in the tablet dosage form and demonstrate inhibition of in situ phase transition by HPMC during dissolution, in vitro dissolution test was carried out to compare Tablets A and B. Fig. 6 shows anhydrate tablets exhibited a higher dissolution rate than hydrate tablets.

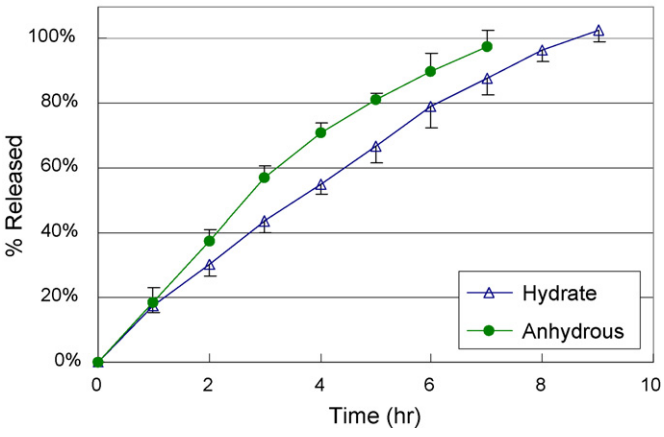

Fig. 6. In vitro dissolution of extended release tablet containing anhydrous and hydrate ciprofloxacin (mean ± S.D., $n = 6$; USP II, 100 rpm, 0.1N HCl, 37 °C).

The drug release profiles can be approximated by zero-order kinetics, suggesting a primarily erosion controlled release mechanism. This observation is consistent with the release behavior of a hydrophilic matrix system containing a compound of low solubility and low viscosity grade of rate-controlling polymer (Liu et al., 2006). Curve fitting of the data up to approximately 90% of total release yielded the dissolution rates of 0.143% h^{-1} ($R^2 = 0.975$) and 0.118% h^{-1} ($R^2 = 0.998$) with intercepts of 0.09 and 0.07 for Tablets A and B, respectively. The higher dissolution rate observed with anhydrate tablets is primarily because of the higher solubility. Similar rates observed in the first hour may be attributed to the rapid phase transition of the surface anhydrous drug that is not protected by HPMC. The apparent lack of significant in situ phase transformation from anhydrate to hydrate during tablet dissolution is most likely due to the presence of high concentration of HPMC in the hydrated gel layer of the tablets. If there were no such an inhibitory effect in the gel layer, the anhydrate would have rapidly converted to hydrate and the dissolution rates would have been the same. It should be pointed out that a more soluble solid form, such as anhydrate, is sometimes desired to ensure rapid dissolution of the solid drug particles following their release from an ER delivery system for an insoluble drug. This study shows that solid phase transition needs to be understood and controlled should one intend to use anhydrate for such purpose.

4. Summary

Investigation of anhydrate and hydrate of ciprofloxacin showed that anhydrate exhibited significantly higher dissolution rate. Upon exposure to aqueous medium, the anhydrous form rapidly converts to the hydrate. However, premixing of anhydrate with HPMC in the presence of water or ethanol was found to inhibit the processing-induced phase transition. Further studies demonstrated that wet granulation could be an option for preparing tablets with high loading of ciprofloxacin anhydrate through proper selection of excipients and control of processing conditions. Dissolution study of ciprofloxacin in extended release hydrophilic matrix tablets suggested that transformation to the hydrate was inhibited by HPMC in the hydrated gel layer of the tablets.

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