Tablet Dissolution Affected by a Moisture Mediated Solid-State Interaction Between Drug and Disintegrant

Brian R. Rohrs,[1,2] Thomas J. Thamann,[1] Ping Gao,[1] Dennis J. Stelzer,[1] Micheal S. Bergren,[1] and Robert. S. Chao[1]

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Purpose. To investigate the cause for decrease in delavirdine mesylate 200 mg tablet dissolution upon exposure to high humidity.

Methods. Dissolution testing was performed using the USP 2 (paddle) apparatus. Water in tablets was measured by Karl Fischer titration. ^{13}C CP/MAS NMR was used to identify and quantify delavirdine form changes in tablets. FT-IR spectroscopy was used to monitor delavirdine form change in tablets and component mixes, and to investigate a solid state reaction with the disintegrant.

Results. Dissolution extent of delavirdine mesylate 200 mg tablets was substantially decreased after exposure to high humidity. This effect is related to the amount of water present in the tablet matrix. ^{13}C CP/MAS NMR detected about 30% conversion from the mesylate salt of delavirdine to its free base form in the tablet matrix. FT-IR spectroscopy demonstrated that a solid state reaction occurs between the freed methanesulfonic acid and the carboxyl sites on the croscarmellose sodium disintegrant.

Conclusions. Water is thought to act as both a reaction medium and a plasticizer for croscarmellose sodium, facilitating protonation of the carboxyl sites on the disintegrant. This reaction has the potential to occur for any acid salt of a free base. The limiting solubility of delavirdine free base formed in the tablets accounts for much of the decrease in the extent of dissolution. A change in inter-particle bonding can explain the reduction in tablet deaggregation during dissolution.

KEY WORDS: dissolution; tablet stability; solid state reaction; croscarmellose sodium; disintegrant; infrared spectroscopy; CP/MAS NMR.

INTRODUCTION

Dissolution is a fundamental performance measure for solid oral dosage forms, and as such, is typically monitored in stability studies during drug development. There are many proposed factors affecting dissolution stability, (1,2) but the mechanisms for changes in dissolution performance are difficult to prove because of the complex nature of the physical processes involved. An exception to this is cross-linking of gelatin capsules, which has been demonstrated to lower dissolution of encapsulated material. (3) In addition, crystal form changes of the drug has been shown to both decrease (4) and increase (5) dissolution depending on the relative solubilities of the converted forms. Moisture has been implicated in many dissolution stability problems, (4–8) and often in the course of product development, formulations are exposed to high humidity conditions to characterize the effect of moisture on dissolution performance. These experiments allow one to choose an appropriate packaging system with the degree of protection needed to maintain adequate stability for the shelf life of the product.

Delavirdine mesylate is a non-nucleoside reverse transcriptase inhibitor developed for the treatment of Acquired Immune Deficiency Syndrome. Its molecular structure is shown in Fig. 1, and in its solid state, fourteen polymorphic and solvate forms have been characterized. (9) The registered form of delavirdine mesylate is Form XI, and it is formulated as direct compression tablets. Early in development, experiments showed that exposure to high humidity has a deleterious effect on tablet dissolution, and a packaging system with desiccant was chosen to protect product from moisture. This paper describes our investigations into the mechanism for change in dissolution behavior of stressed 200 mg delavirdine mesylate tablets.

MATERIALS AND METHODS

Delavirdine

The mesylate (methanesulfonate) salt Form XI bulk drug was obtained from a standard production lot. Delavirdine mesylate hydrate forms VI and XIV and the delavirdine anhydrous free base form were isolated in the Pharmaceutical Development research laboratories.

Delavirdine mesylate tablets consist of a direct compression formulation with a tablet strength of 200 mg on a salt basis. In addition to other excipients, tablets contain the super-disintegrant croscarmellose sodium. Placebo powder mix was prepared from proprietary excipient components to validate analytical methods for lack of interferences.

Croscarmellose

Croscarmellose sodium was obtained from FMC under the trade name Ac-Di-Sol. Acidified croscarmellose was prepared by suspending a quantity of the polymer in water with stirring, then adding concentrated hydrochloric acid while monitoring pH. At pH 2.0, the polymer suspension was allowed to stir for 30 minutes, then solids were collected using vacuum filtration.

Stability Conditions

Tablets in open containers were exposed to 40°C/75%RH and 30°C/60%RH. Tablets were also placed in double polybags with desiccant between bag layers and exposed to the same conditions. This was done to determine whether the desiccant packaging system would adequately protect tablets between the times of manufacturing and packaging. At selected time points, tablets were removed from the stability ovens and sealed in glass vials with Teflon-lined caps. This closure system nominally prevents water loss from tablets prior to assay.

Dissolution

Tablet dissolution was performed using the USP Apparatus 2 (paddle) operated at 50 rpm. The dissolution medium was 900 ml of pH 6, 0.05 M phosphate buffer with 0.6% sodium dodecylsulfate surfactant added. Samples were pulled manually,

[1] Pharmaceutical Development, Pharmacia & Upjohn, Kalamazoo, Michigan 49001.

[2] To whom correspondence should be addressed. (e-mail: brian.r.rohrs@am.pnu.com)

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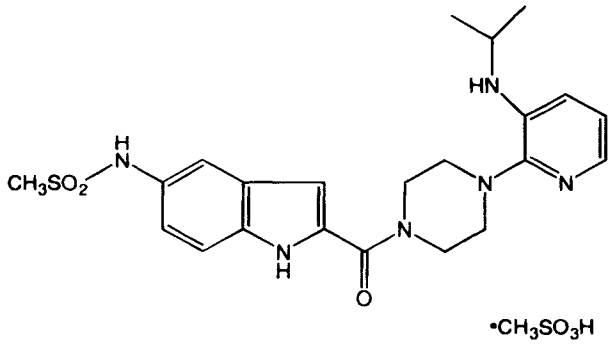

Fig. 1. Molecular structure of delavirdine mesylate.

filtered, then analyzed against prepared standards using an HPLC endpoint assay. Reported values are the mean and standard deviations of six tablets for initial and three tablets for subsequent time points.

Water

The amount of water in the tablets was measured by the volumetric Karl Fischer method using a commercially prepared single solution Karl Fischer Reagent (Fisher Scientific SK3). Samples were dissolved in heated 1:1 methanol/formamide solvent and the titration vessel was wrapped with heating tape to maintain it at 45°C. Tablets were crushed using a mortar and pestle, and a portion was rapidly weighed and introduced into the titration chamber. Water values (in percent by weight) are reported as the mean of three trials.

NMR

A Bruker MSL-200 NMR spectrometer with an Oxford wide-bore (89 mm) magnet was used. The static field of the superconducting magnet was 4.7T, and the spectrometer was operated at 50.3 MHz for ^{13}C and 200.055 MHz for ^{1}H. A doubly tuned, single-coil CP/MAS double gas bearing type probe (Bruker) was employed. The magic angle was adjusted using a KBr sample, which afforded a spinning angle of 54.7° ± 0.3°. (10) Hartmann-Hahn matching was optimized using admantane and kept for subsequent experiments on delavirdine. ^{1}H decoupling was applied with an on-resonance ^{1}H RF field of 72 kHz. Tablets for the NMR studies were crushed in a mortar and pestle and packed into ZrO_2 rotors. The samples were usually spun at a spinning speed of 4.5 kHz ± 2Hz. A H flipback pulse sequence was employed and the repetition time between successive sampling pulses was 5 sec. The acquisition parameters were: spectral width, 20 kHz; contact time, 0.75–3 ms; and 3.5 μs 90° ^{1}H pulse. Each spectrum was obtained with 2K data points, zero filling to 8K with 10 Hz line broadening prior to Fourier transformation. ^{13}C chemical shifts were calibrated indirectly to the higher field admantane peak (29.5 ppm relative to tetramethylsilane).

Infrared Spectroscopy

Samples were prepared as KBr pellets for infrared analysis. Data were collected from 4000 to 400 cm^{-1} at 4 cm^{-1} resolution on a Nicolet 760 spectrometer equipped with a TGS detector. Sensitivity, expressed as instrument gain, was 1. Data were processed as a Fourier transform utilizing a Happ-Genzel apodization function and plotted as absorbance vs. frequency. Spectra shown are the sum of 128 individual scans.

RESULTS

Dissolution and Water Content

Tablet dissolution results are shown in Fig. 2. Within one week, tablets exposed to 40°C/75%RH showed a greater than 20% decrease in the extent of dissolution at 60 minutes. For tablets exposed to 30°C/60%RH, the mean dissolution value did not drop below 70% until week four. Since dissolution samples are quantified by an HPLC separation method, one potential reason for the apparent dissolution change is chemical degradation of the parent. This explanation was immediately ruled out, however, since no degradation products appeared in the chromatographic tracings.

The influence of temperature alone can be determined from the desiccated tablet results. Figure 2 shows that tablets stored in the double poly-bag/desiccant system had no change in dissolution out to four weeks at either the 30°C/60%RH or 40°C/75%RH accelerated stability conditions. We therefore concluded that exposure to moisture is the primary factor for disrupting tablet dissolution performance. Water content in the tablets was measured by Karl Fischer titration for all stability conditions and time points. The percent delavirdine dissolved at 60 minutes is plotted in Fig. 3 against weight percent water in the tablet. Between 4.4 and 4.6 weight percent water, dissolution extent drops from above 80% to less than 70% and continues to decrease as the amount of water in the tablet increases.

To further characterize the influence of moisture, tablet dissolution was studied at paddle speeds of 50, 75, and 100 rpm. Figure 4A contains the dissolution curves of the original tablets, and Fig. 4B shows dissolution results after 8 weeks of storage at 40°C/75%RH. For the initial tablets, paddle agitation speed significantly affects the dissolution curve shape, and the extent of dissolution is near 100%. The exposed tablets show two important changes. First, the maximum extent of dissolution is only about 70% of the 200 mg dose. Second, the dissolution

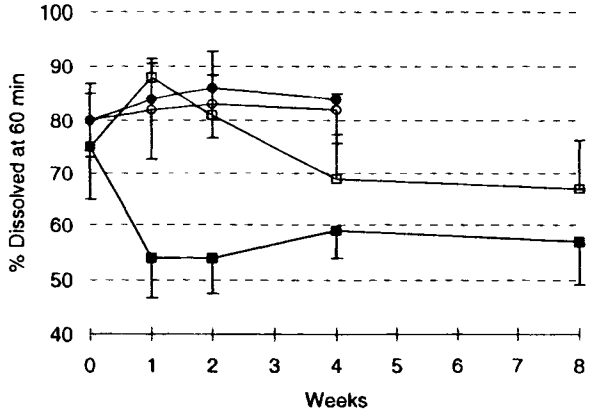

Fig. 2. Delavirdine mesylate 200 mg tablet dissolution stability. Plotted is percent dissolved at 60 minutes vs. time for tablets exposed in open containers at 30°C/60%RH (□) and 40°C/75%RH (■), and in poly-bags with dessicant at 30°C/60%RH (○) and 40°C/75%RH (●). Error bars represent one standard deviation.

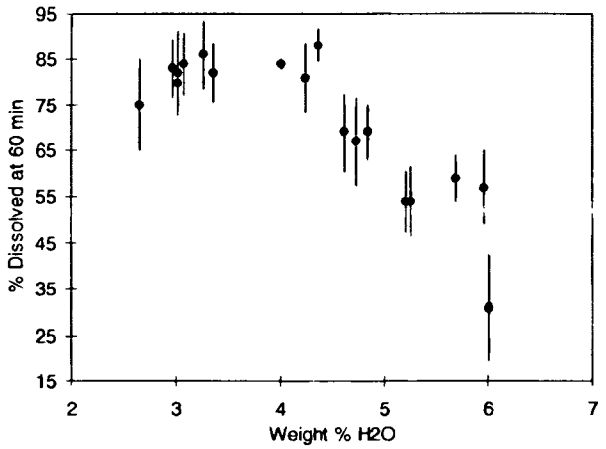

Fig. 3. Relationship between weight percent water in tablets on tablet dissolution. Error bars represent one standard deviation.

rate is not nearly as affected by paddle agitation rate. There appears to be an initial burst at higher rotation speeds which accounts for the positive displacement along the 'percent dissolved' axis, but the curve shapes are similar at all rotation speeds. Compared to the initial tablet dissolution in Figure 4A, the exposed tablets have a lower propensity for dispersion at high agitation rates.

SSNMR

Solid state NMR was used to characterize and quantify the forms of delavirdine in the tablet matrix. ^{13}C CP/MAS NMR techniques are sensitive to inter- and intra-molecular interactions and crystal packing in solids at a molecular level, and are therefore useful for distinguishing between closely related solid forms of the same molecular entity. Three crystalline forms (XI, VIII, and XII) of delavirdine mesylate have been recently characterized. (11) The distinct NMR features observed among these and other forms can be used for diagnostic purposes.

The identification of the existing drug form(s) in the tablet matrix involved verifying that no major interferences occur from the tablet excipients, and comparing the delavirdine spectral features with the previously characterized polymorphic, hydrate, and free base forms. Figure 5a shows the ^{13}C CP/MAS NMR spectrum of the 200 mg delavirdine mesylate tablets at the initial time point. The two sharp resonances between 20 and 25 ppm are characteristic of Form XI delavirdine mesylate. Figure 5b shows the tablet spectrum after 4 weeks exposure to 40°C/75%RH. Comparing Fig. 5b to Fig. 5a, some noticeable changes are observed. Two new resonances at 22 and 150 ppm appear in Fig. 5b. There are also noticeable intensity variations in the region of 120–150 ppm. A difference spectrum was obtained by subtracting Fig. 5a from Fig. 5b with a proper adjustment to ensure a complete cancellation of the resonances of form XI. (11) The difference spectrum is shown in Fig. 5c accompanied by the ^{13}C CP/MAS NMR spectrum of delavirdine free base shown in Fig. 5d. Although in the 60–110 ppm region of Fig. 5c, resonances of microcrystalline cellulose were not perfectly cancelled, the chemical shifts of the delavirdine resonances and their intensity pattern are essentially identical to those of the free base form, permitting an unambiguous identification of delavirdine free base in the stressed tablet.

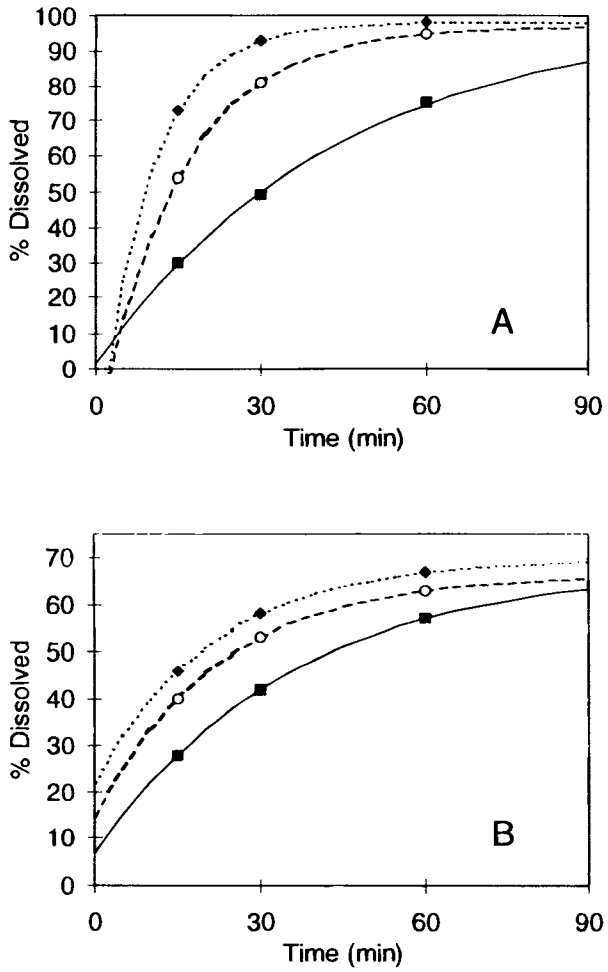

Fig. 4. Dissolution profiles of delavirdine 200 mg tablets (A) before and (B) after 8 weeks exposure to 40°C/75%RH, at paddle rotation speeds of 50 (■), 75 (○), and 100 (▲) rpm.

To quantify free base formation, the intensities of five diagnostic resonances of form XI and the free base were utilized. It was assumed that each tablet initially contained 200 mg of form XI and that the two component drug substances summed to 100%. The relative intensities were corrected by utilizing the relaxation constants of each form (11), then the average of the five resonances for each substance was determined. In Fig. 6, free base concentration is plotted against duration of storage at 40°C/75%RH in Fig. 6. Initially, the free base concentration increased monotonically, but reached a plateau of about 28% of the drug load beyond 4 weeks. An additional small increase in free base concentration of about 5% was observed when the exposure time was extended to 12 weeks.

Infrared Spectroscopy

Solid-state NMR provides a good tool for quantifying the delavirdine mesylate salt to free base conversion process, but it is a relatively labor intensive method for qualitative screening purposes. An alternative characterization method is infrared spectroscopy. Like SSNMR, IR spectroscopy is sensitive to crystalline form changes. Since it is inherently based on molecular vibrations, IR also has the advantage of being sensitive to functional group changes in low or non-crystalline materials.

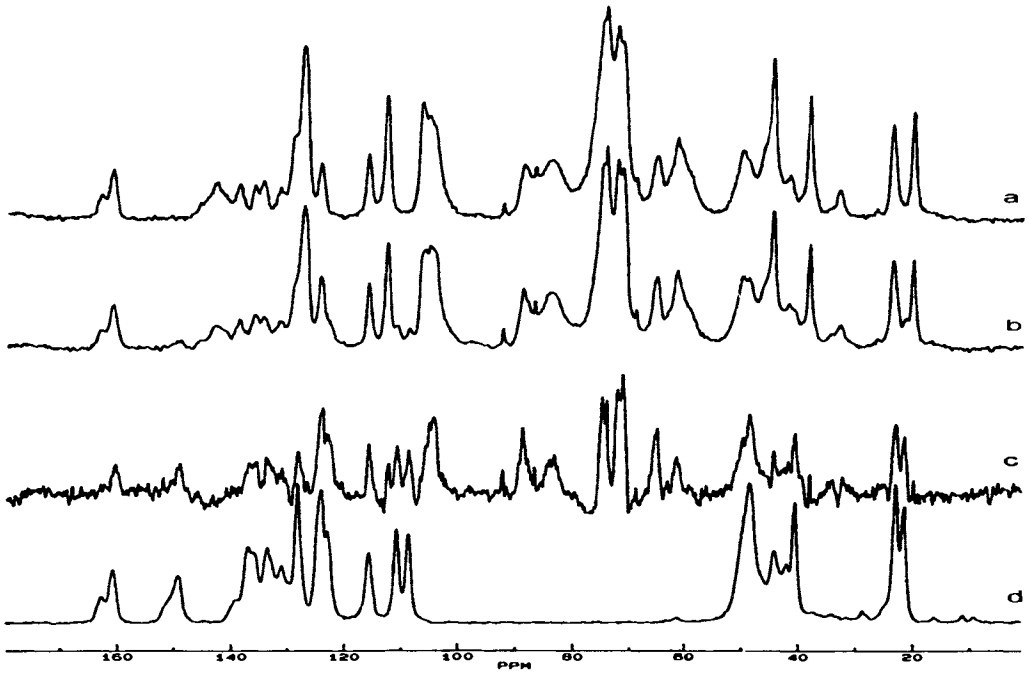

Fig. 5. ^{13}C CP/MAS NMR spectra of (a) tablet at initial time point, (b) tablet after four weeks at 40°C/75%RH, (c) spectral difference between stressed and initial tablet, and (d) delavirdine anhydrous free base.

Figure 7 demonstrates that IR is sensitive to the delavirdine mesylate salt (top spectrum) to free base (bottom spectrum) conversion in the region from 1540–1640 cm^{-1}. A shift occurs in the carbonyl stretching frequency from 1613 cm^{-1} for the salt to 1597 cm^{-1} for the free base. The frequencies associated with the pyridinium ring deformations also change. The 1577 cm^{-1} peak in the free base spectrum is especially distinctive.

To determine which excipients participate in the salt to free base conversion, tablet mixes were prepared successively leaving out one component. This resulted in six different mixes of drug minus one excipient, which were then compressed into pellets. The 'N-1' study design allows one to determine not only if a single excipient is responsible for the conversion as in binary mixtures, but also if certain combinations of components

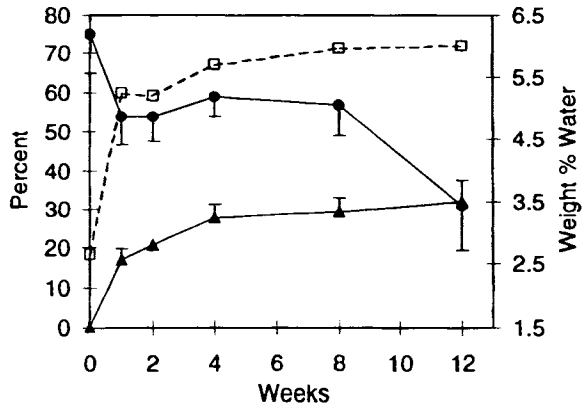

Fig. 6. Relationship over time between percent dissolved at 60 minutes (●), percent free base formation (▲), and weight percent water (□, right axis) in delavirdine mesylate 200 mg tablets exposed to 40°C/75%RH. Error bars represent one standard deviation.

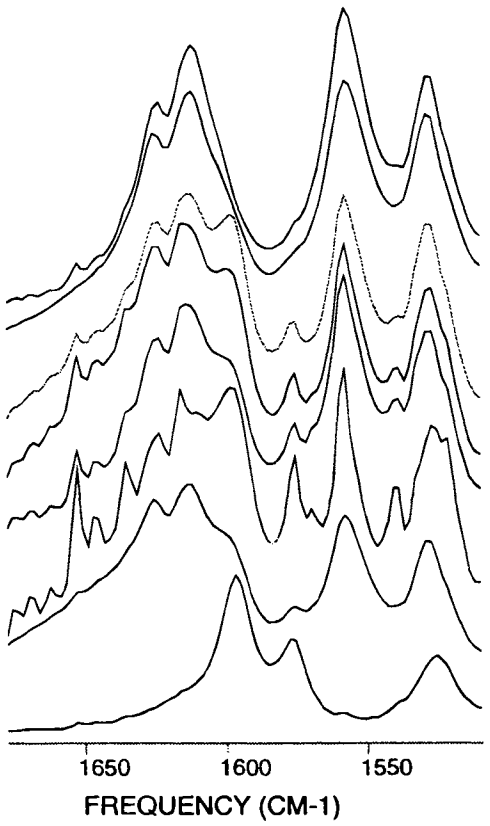

Fig. 7. Portion of the IR spectra of Form XI delavirdine mesylate (top), and delavirdine free base (bottom). Bracketed in order from top to bottom are spectra from pellets of tablet mix minus: croscarmellose sodium, SiO_2, HPMC, lactose, microcrystalline cellulose, and magnesium stearate, all exposed for one week to 40°C/75%RH.

have an effect. Figure 7 shows the IR spectra of the pellets after one week exposed to 40°C/75%RH. Spectra of delavirdine mesylate and the free base bracket the pellet spectra, and it is clearly evident from the absorption band at 1577 cm^{-1} that free base has formed in all mixes except the one missing croscarmellose sodium. The presence of croscarmellose sodium in the tablet matrix is therefore necessary for the delavirdine salt to free base conversion to occur.

Purely from a chemical balance perspective, as a molecule of the delavirdine mesylate salt is converted to the free base, an acidic proton is made available. The croscarmellose sodium disintegrant contains sodium carboxylate groups which could react with that proton to form carboxylic acid. This would result in a shift in the carbonyl stretching frequency. To characterize the extent of that frequency change, acidified croscarmellose sodium was prepared (see Materials section for details) and the IR spectrum collected. Figure 8A contains spectra of both the original and the acidified materials. The carbonyl stretching frequency shifts from 1629 to 1736 cm^{-1} as the carboxylate functional group is converted from the salt to the acid form. The top spectrum in Fig. 8A represents a mixture of the two forms whereas the second spectrum contains predominantly the sodium salt form. The protonated C = O stretching frequency is sufficiently removed from other tablet matrix IR peaks such that if acidification occurs in the tablet matrix, it may be evident in the IR spectrum. The signal, however, should be very weak because not only is there a relatively low level of croscarmellose in the formulation, but also the carbonyl absorption bands are very broad since croscarmellose is a non-crystalline polymer.

Figure 8A contains spectra from the initial tablet and a tablet after 2 weeks stored at 40°C/75%RH. The delavirdine free base peak at 1577 cm^{-1} is readily apparent in the stressed tablet spectrum as discussed above. In addition, a small deflection in the baseline can be observed between 1700 and 1780 cm^{-1}. This deflection is absent from the initial tablet spectrum and corresponds to the frequency range over which the acidified carboxylate absorbs. This can be seen more clearly in Fig. 8B. The stressed and initial tablet spectra are overlaid for comparison. Spectral subtraction of initial and stressed tracings results in a peak which corresponds to the carbonyl absorption band from the acidified croscarmellose, confirming the carboxylate to carboxylic acid conversion in the stressed tablet.

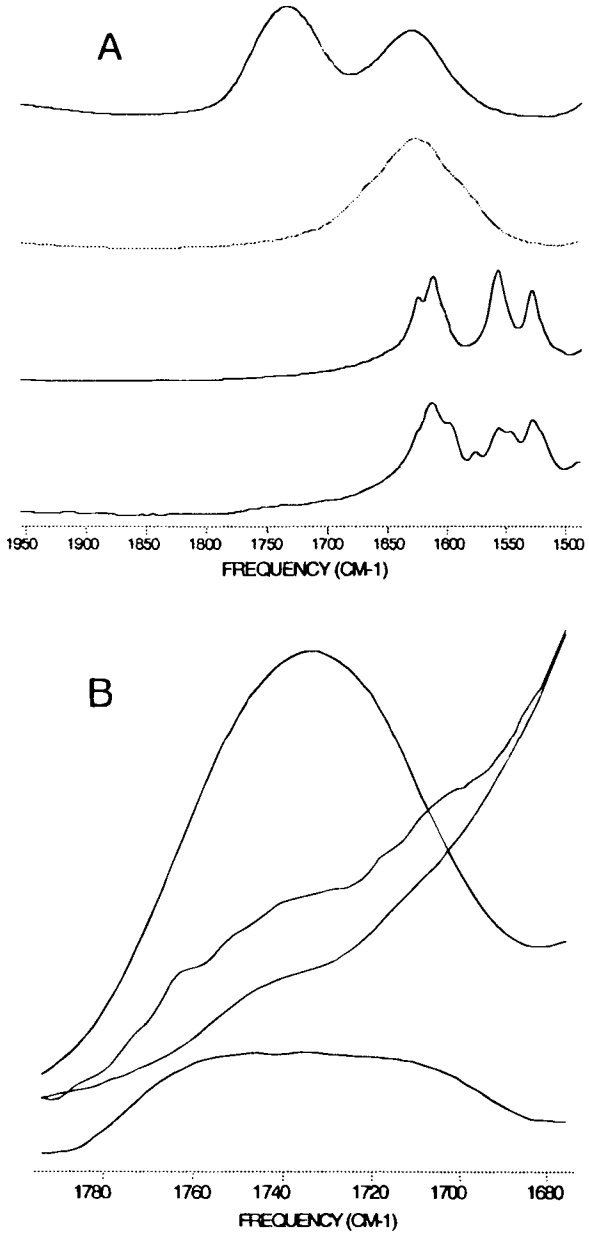

Fig. 8. IR spectra of (top to bottom) (A) croscarmellose sodium isolated at pH 2.0, croscarmellose sodium isolated at pH 8.9, delavirdine mesylate tablet, and tablet exposed for two weeks to 40°C/75%RH, (B) expansion of 1680–1800 cm^{-1} region for acidified croscarmellose, stressed tablet, initial tablet, and difference between stressed and initial tablet spectra

DISCUSSION

Solid State Reaction

Both SSNMR and IR spectroscopies provide evidence that delavirdine mesylate converts to free base within the tablet matrix upon exposure to high humidity. As a consequence of that conversion, methanesulfonic acid (CH_3SO_3H) is liberated. The disintegrant, croscarmellose sodium, is a cross-linked form of carboxymethylcellulose sodium (NaCMC). The carboxyl group on NaCMC has a pKa of 4.3, (12) whereas methanesulfonic acid has a pKa of −1.20. (13) If the acid is mobile within the NaCMC, an acid/base reaction should occur resulting in protonation of the carboxyl sites on the disintegrant. The IR difference spectrum in Fig. 8B provides evidence that protonation does indeed take place. The resultant chemical equation is:

$$DLVH^+ \cdot CH_3SO_3- + NaCMC \rightleftharpoons$$

$$DLV + HCMC + Na^+ \cdot CH_3SO_3-$$

where $DLVH^+ \cdot CH_3SO_3-$ is delavirdine mesylate, DLV is the free base form of delavirdine and HCMC is the protonated form of the croscarmellose disintegrant.

Croscarmellose represents the limiting reagent in the reaction. The extent of croscarmellose protonation can be estimated from the molar amounts of drug and disintegrant in the tablet matrix. If a higher degree of free base conversion occurs than is predicted from the number of available sites on the disintegrant, the reaction hypothesis would need revision. The formulation contains 0.362 millimoles of delavirdine mesylate per tablet. SSNMR results (Fig. 6) show that salt to free base

conversion levels off at 32% of the initial amount of salt, so 0.116 millimoles of methanesulfonic acid are released. The USP/NF methods of titration and residue on ignition (15) were used to determine the degree of sodium carboxymethyl substitution for the particular lot of disintegrant used to manufacture the tablets. The number of milliequivalents of sodium carboxymethyl sites per gram multiplied by the amount of disintegrant in the tablet yields 0.131 millimoles per tablet. If the entire amount of acid available protonated the carboxyl sites on the croscarmellose, 0.116/0.131 or 89% of the croscarmellose sodium would be converted to the acid form. The reaction hypothesis is therefore not refuted.

Water content is critical to the onset of this reaction. Figure 6 shows a direct relationship between the increase in water content in the tablet matrix and the appearance of free base. A recent review lists the possible roles of water in solid state reactions as either a reactant, a medium, or a plasticizer of amorphous regions. (14) While the role of water in this reaction needs further investigation, presumably water is not a reactant, but could function as a medium and/or a plasticizer. The first step in the reaction mechanism is likely dissolution of the delavirdine mesylate salt where water would function as a medium for solvation. Water could also act as a plasticizer of the croscarmellose sodium. Water has a significant impact on molecular mobility within amorphous regions of a material by lowering the material's glass transition temperature, T_g. (14) Acid diffusion in NaCMC is necessary for the formation of HCMC to occur within the disintegrant particles. Addition of water into croscarmellose sodium and the subsequent increase in acid mobility would allow the reaction to proceed.

Dissolution Mechanism Hypothesis

After exposure to moisture, tablet dissolution is affected in two ways, the total extent of drug released and the release profile shape as a function of agitation rate (Fig. 4A and 4B). Extent of dissolution can be limited by solubility factors. The mesylate salt of delavirdine has a high solubility. Form XI solubility has been estimated to be at least 320 mg per gram water. The free base form is much less soluble. Using the shake flask method, the saturated solubility of the free base in the dissolution medium at 37°C was determined to be 143 μg/ml. The dissolution test is performed in 900 ml of dissolution medium, so the maximum soluble dose on a free base basis is 129 mg. Using the molecular weight ratio of free base to salt (0.814), this corresponds to 158 mg on a mesylate salt basis, or 79% of the initial 200 mg dose. The extent of dissolution reaches a maximum of about 70% in one hour (Fig. 4B), so although the concentration is still below the saturation value, free base solubility likely plays a significant role in limiting the extent of dissolution.

The change in dissolution behavior as a function of agitation rate may also be related to free base formation. The dissolution process for immediate release tablets typically involves disintegration, then deaggregation of the tablet matrix. Both processes expose drug to the dissolution medium. Visual observation of delavirdine mesylate tablet dissolution revealed rapid swelling of the matrix with flocculent pieces that broke off and dispersed in the medium. At higher agitation rates, the tablets dispersed more quickly. For tablets exposed to moisture, swelling still occurred, but the tablet broke up into large pieces which did not disperse well, even at high agitation rates. This behavior points to deaggregation as a key step in drug release from the tablet matrix. A change in the ability of tablets to deaggregate should result in a corresponding dissolution profile shape change between initial and moisture treated tablets, as was observed.

One possible explanation for this behavior is that the nature of the disintegrant changes upon protonation. Although tablets swell when exposed to dissolution medium, the ability of the disintegrant to fully push apart the tablet matrix may be reduced. A more likely explanation lies in changes to the internal tablet structure. (1) Recrystallization of delavirdine and/or tablet excipients when exposed to high humidity could change the interparticle bonding within the compacted tablet matrix. This in turn would change the disintegration/deaggregation behavior, occluding drug in the aggregates that did not dispersed during testing. The extent of dissolution would then be limited perhaps not only by free base solubility, but also by the lack of drug surface exposed to the dissolution medium.

CONCLUSIONS

A decrease in dissolution occurs when 200 mg delavirdine mesylate tablets are exposed to high humidity. The amount of water within the matrix is critical for this phenomenon to occur, so the appropriate use of desiccants within the packaging system will protect tablets. Concurrently with the dissolution decrease, a conversion from the mesylate salt of delavirdine to the free base occurs within the tablet matrix. The methanesulfonic acid initially bound up in the salt form protonates the carboxyl sites on the croscarmellose sodium disintegrant. Because of the general nature of this acid/base reaction, this interaction has the potential to occur whenever the acid salt of a free base is formulated with a basic excipient.

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