Role of an Isomorphic Desolvate in Dissolution Failures of an Erythromycin Tablet Formulation

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Abstract □ The investigation of dissolution failures for erythromycin dihydrate tablet formulation over a 12-month period using a near-infrared spectroscopy technique revealed the role of a desolvated dihydrate in the retardation of dissolution. Near infrared spectroscopy (NIR) indicated a dehydrated dihydrate of erythromycin is produced during formulation and gradually binds with $Mg(OH)_2$. The binding delays the process of dissolution. NIR was used to successfully predict that humidifying the tablets would reverse the binding and increase the dissolution rate.

Introduction

The occurrence of a variety of crystal forms for many pharmaceuticals has been well established and investigated.[1−11] The first recognition of this phenomenon of polymorphism may have been as early as the 18th century.[12] The fact that pharmaceuticals can exist as various polymorphs and/or solvates can be problematic in terms of stability, processing, and solubility since the different crystal forms and solvates of a drug can differ in these physical properties. In fact, the different polymorphs of a compound can be as different in these properties as are individual compounds from each other.

The established analytical techniques used to demonstrate that a compound exists in various crystal forms include X-ray powder diffraction (XRD), differential scanning calorimetry (DSC), solid-state C-13 nuclear magnetic resonance (SS NMR), polarized light microscopy (PLM), and near- and mid-infrared (NIR and IR) spectroscopy.

For several years the pharmaceutical literature reported various crystal forms and hydrates of erythromycin including an anhydrate, a monohydrate, and a dihydrate. In an earlier work[13] we proposed that the crystal form of erythromycin dihydrate as determined by X-ray powder diffraction was unchanged when the water was removed, indicating minimal if any difference in the crystal structure in the presence or absence of water. As a result of readily available channels or tunnels within the crystal lattice,[14] water is readily transported into and out of the crystal lattice depending on the environmental conditions. Pfeiffer et al.[15] has referred to molecules of this kind as pseudopolymorphs, and Stephenson et al.[16] note that the desolvated state or isomorphic desolvate is of higher energy than the solvated form and that there is a driving force to fill the void created when the solvent is removed. In this paper we will present an example of this tendency to fill the void created when the water is removed from erythromycin dihydrate, its resultant effect on tablet behavior, and the use of NIR spectroscopy to investigate the problem.

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Experimental Section

Materials—Several formulations of erythromycin dihydrate containing no magnesium hydroxide as well as the primary formulation which contained magnesium hydroxide were investigated. All formulations were manufactured at Abbott Laboratories and used erythromycin dihydrate USP grade. The USP grade erythromycin dihydrate was also manufactured at Abbott Laboratories through a fermentation process followed by a series of aqueous and organic extractions. This material was dried at less than 95 °C. All bulk lots met Abbott specifications.

Microscopy was performed using a Nikon Microphot-FXA polarized light microscope and a Leica Stereo Microscope Model MZAPO. X-ray powder diffraction was performed with a Nicolet I2 X-ray powder diffractometer fitted with a diffracted beam monochromator tuned for copper radiation at 1.54180 Å. All samples were ground to similar particle size immediately prior to X-ray analysis. Thermal gravimetric analysis (TGA) was performed using a TA Instruments Model 2950 TGA module with a Model 3100 Thermal Analyst, at a heating rate of 5 °C/min, and a sample weight of about 15−20 mg. A Nicolet Magna-IR Spectrometer Model 750 bench with a Nicolet SabIR near-infrared (NIR) diffuse reflectance fiber optic probe accessory were used to obtain NIR spectra at a resolution of 8 cm^{-1} with 16 scans. Intact tablets were place directly on the probe tip whereas bulk material was put into a clear glass one dram vial and then placed on the probe tip. The NIR spectrum of a bulk material was an average spectrum of four spectra acquired after manually mixing the sample for about 15 s followed by manual tapping to remove air gaps. Dynamic moisture sorption gravimetry (DMSG) was performed on a VTI Corp. Model MB300G sorption microbalance using vacuum to control the relative humidity (RH). The Automated system controlled the RH and temperature to which the sample was exposed, while continually recording sample weight changes. Sample weights were typically about 5−10 mg. Sorption and desorption isotherms were performed at 25 ± 0.1 °C with 5 ± 1% RH step intervals from 0 to 95% RH. Samples were dried under vacuum for up to 240 min (approximate RH = 0−1% RH) before each experiment. The weight loss observed during the drying period was used to estimate how tightly each sample held water. After the drying period, sorption isotherms started at 5% RH. A weight equilibrium criteria of less than 3 μg weight change over three 7 min periods was used to move to the next RH step. When the equilibrium conditions were achieved for the 95% RH step, the desorption step started. Typical sample run times were between about 24 and 48 h. Dissolution testing of tablets was performed using a single tablet in a dissolution medium of 0.05 M phosphate buffer pH 6.8 ± 0.05 at 60 °C. Quantitation was performed by UV absorbance at 236 nm versus a reference standard of erythromycin dihydrate. Intrinsic dissolution of bulk drug samples was performed at 37 °C with the same dissolution media. Quantitation was accomplished by HPLC versus a reference standard at 205 nm using an octadecylsilyl column at 50 °C and an eluent of 35% acetonitrile/65% 0.06 M phosphate buffer (pH 6.6).

Background

Twelve-month stability samples for a lot (lot 15, Table 1) of Erythromycin dihydrate, 250 mg tablets, were found

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Table 1—Correlation of Moisture Content (TGA) with XRD and NIR Spectroscopy for Various Erythromycin Tablet Lots

lot number	relative (crystallinity)	TGA	NIR (OH)
1	high	4.69	high
2	moderate	3.63	moderate
3	moderate	3.43	moderate
4	moderate	3.91	moderate
5	low	3.28	low
6	low	2.76	low
7	low	2.54	low
8	moderate	3.85	moderate
9	low	2.25	low
10	low	2.88	low
11	moderate	2.86	low
12	low	3.11	low
13	low	2.68	low
14	moderate	3.02	low
15	low	2.73	low
16	low	1.70	low
17	low	2.50	low
18	high	4.33	high

to fail the dissolution specification at the 60 min interval but pass at the 90 min interval. Historically, sporadic tablets of this formulation (lots 3, 6, 13 Table 1) had failed dissolution; however, this lot, which had very good initial dissolution of greater than 99%, released at 60 min failed uniformly at the 12-month time point with an average of 71% released at 60 min. Other lots of this same formulation (lots 1, 18, Table 1) had maintained very high dissolution for periods greater than 12 months. Material which had acceptable dissolution over the 12-month period will be referred to as passing while those with decreased dissolution will be designated as failing. One of these former lots (lot 1, Table 1) was used as a reference for passing tablets. The manufacturing process for erythromycin tablets involves milling and drying, and these factors have historically been shown to affect crystallinity and, as would be expected, water content. Initial work concentrated on these properties as well as examination of the tablet coating.

Results and Discussion

X-ray powder diffraction was performed on the erythromycin dihydrate tablets using computer subtraction of a placebo diffraction pattern to examine the consistency of the crystal form of erythromycin in the tablet. Figure 1 shows two representative diffraction patterns. Pattern A is that of the passing tablet, and pattern B represents a failing tablet. Both tablets give the characteristic spectrum of erythromycin dihydrate; however, resolution differences were observed, which most likely reflect a difference in crystallinity. In addition, significant changes in the relative intensities of the X-ray peaks can be observed between passing and failing lots. As previously reported,[13] crystalline erythromycin can vary in water content over a large range (50−200%) of dihydrate theory without affecting the X-ray pattern. TGA of these samples showed two weight losses, indicating the presence of a small amount of surface water as well as interstitial water. The most highly crystalline lot shows a continuous weight loss approximately equal to the dihydrate stoichiometry of 4.7%. In addition, NIR spectroscopy[17] was used to further evaluate their water content by examining the hydroxyl peak (water combination band) at approximately 1.95 μm, which reflects hydroxyl contributions from erythromycin as well as from water. Table 1 shows a compilation of XRD patterns in terms of resolution, amount of water from TGA weight loss,

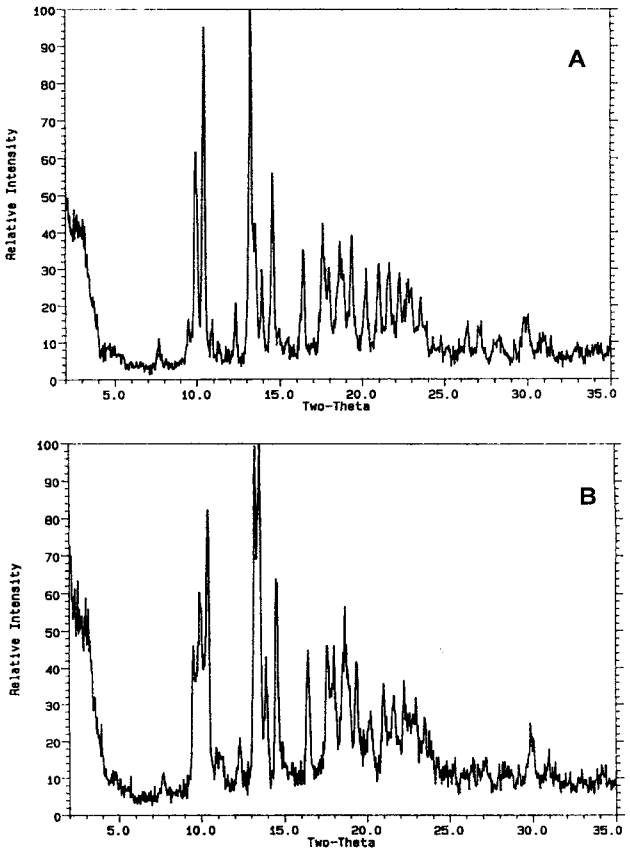

Figure 1—XRD of passing and failing Erythromycin tablet lots. (A) Passing tablets. (B) Failing tablets.

and the relative amount of hydroxyl content by NIR. The data indicate that the samples with low water content relative to the theoretical dihydrate stoichiometry also show broader, less-resolved peaks in the X-ray pattern. The NIR hydroxyl content also follows the same trend, i.e., lower hydroxyl content corresponds to broader X-ray peaks. Samples with less than 3.3% weight loss up to 136 °C show the lowest crystallinity and hydroxyl content compared to lot 1 which is the stoichiometric dihydrate. NIR spectroscopy was used in the remainder of the study to evaluate the water content of the tablets nondestructively on individual tablets, thereby allowing further testing on the same tablet by dissolution to investigate the correlation shown in Table 1.

While selecting a sample of amorphous erythromycin to characterize by NIR and XRD, a mesomorphic form or mesophase of erythromycin was identified which has not been previously reported. This material has a well-defined crystal habit and shows birefringence when examined by PLM but as shown in Figure 3 appears mostly amorphous by XRD showing only either a strong broad single line or multiple lines near 2 θ values of 9.4−9.6. The XRD and PLM data are consistent with a solid phase having 2-D order but lacking 3-D order. Amorphous erythromycin was produced separately by freeze-drying an aqueous solution of erythromycin. Examination of the XRD data described above suggests a possible transformation of the pattern for crystalline erythromycin dihydrate over time in the 250 mg formulation to a pattern representing a mixture of erythromycin dihydrate and the mesophase. However, since erythromycin dihydrate can produce an isomorphic dehydrated dihydrate, these XRD patterns could also represent a conversion to mesophase plus dehydrated dihydrate. This latter explanation is consistent with the parallel decrease in water content.

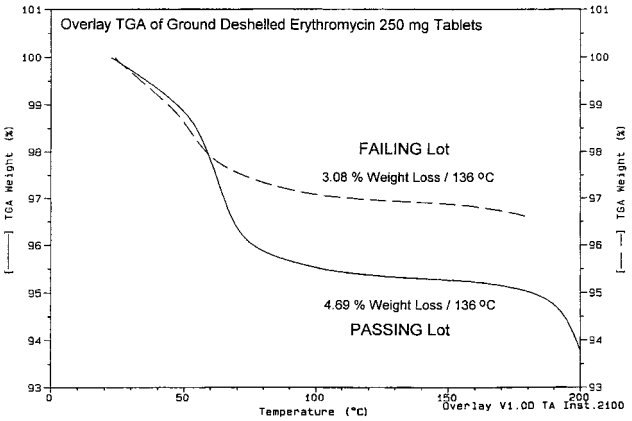

Figure 2—Overlay TGA of passing and failing lots of deshelled 250 mg erythromycin tablets.

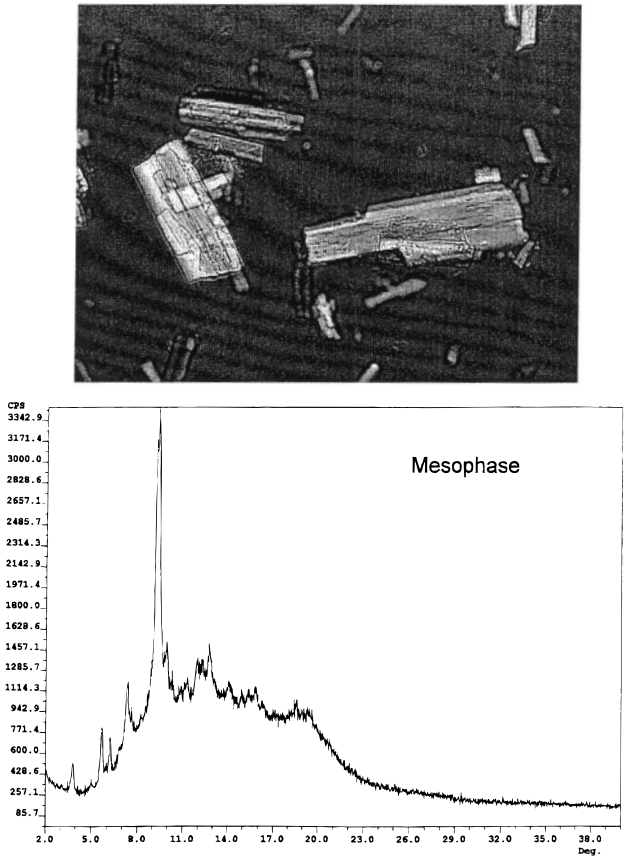

Figure 3—Characterization of erythromycin mesophase by PLM and XRD.

Table 2—Intrinsic Dissolution Data for Erythromycin Crystal Forms in Aqueous Solution (pH = 5.96)

form	amount dissolved in 60 min, mg
dihydrate	0.8
amorphous	2.8
mesophase	5.0

A basic tenet of solubility states that higher energy level crystal forms as well as amorphous material should have high intrinsic solubility compared to the more stable forms. The data presented in Table 2 show the intrinsic solubility relationship of mesophase, amorphous, and dihydrate forms of erythromycin. These data indicate that conversion to mesophase alone should not result in dissolution failure.

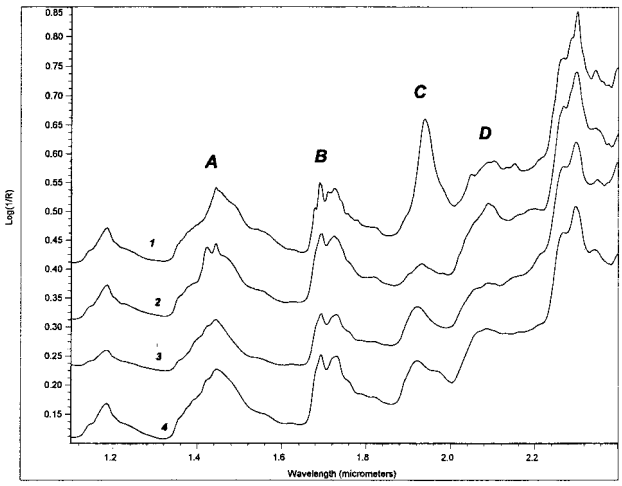

Figure 4—NIR spectra of (1) erythromycin dihydrate, (2) dehydrated erythromycin dihydrate, (3) erythromycin amorphous, and (4) erythromycin mesophase.

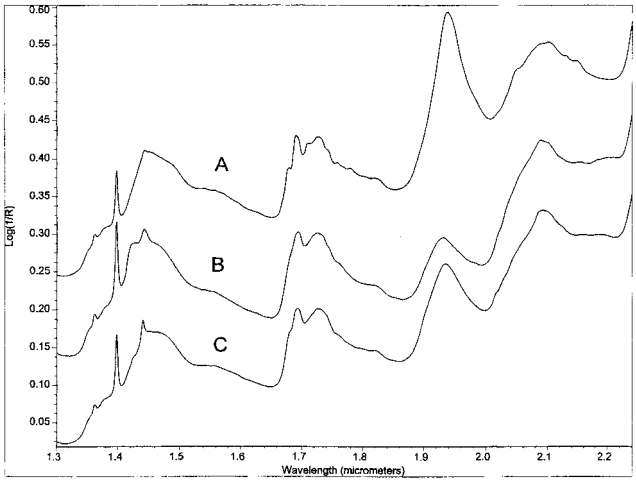

Figure 5—NIR spectra of (A) passing tablets, (B) dehydrated dihydrate, and (C) failing tablets.

Although erythromycin maintains its crystallographic order when dried, the local chemical environment is significantly influenced by the loss of water. When the dehydrated dihydrate is formed, this higher energy crystal form of erythromycin is more reactive and hygroscopic. Close examination of the NIR data (Figure 4) of bulk erythromycin dihydrate, isomorphic dehydrate, mesophase, and amorphous erythromycin indicates that each of the forms have distinguishing characteristics in the NIR spectral areas 1.45, 1.7, 1.95, and 2.1 μm (regions A, B, C, and D in Figure 4). Comparison of the NIR spectra of the passing lot, failing lot, and a dried passing lot (Figure 5) shows that the spectra of the samples are different particularly in the 1.4−1.5 μm region. These comparisons indicate that the majority of the erythromycin form in the failing lot is not dihydrate, isomorphic dehydrate, mesophase, or amorphous material.

Erythromycin tablets with greater drug load (333 and 500 mg) are prepared with corn starch and drug as the two predominant ingredients. The 250 mg tablets contain mainly drug, corn starch, and magnesium hydroxide. All other components are common to all formulations and are present in the same small quantities in all formulations. These include colorants and coatings. Samples of the higher dosage formulation were found to contain the same low (i.e., 3.3% or less) levels of water; however, no dissolution failures were observed after storage. If the reduced dis-

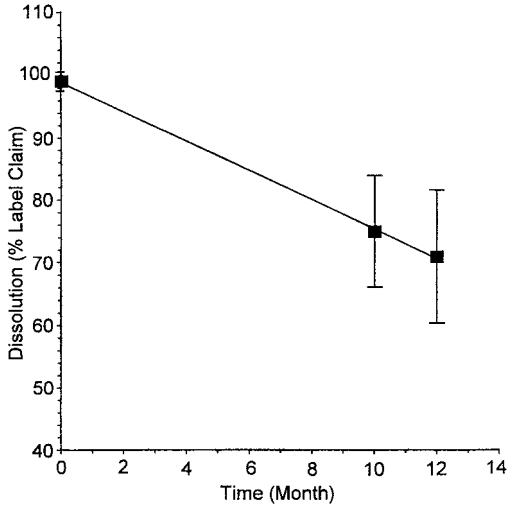

Figure 6—Comparison of failing lot 15 dissolution (% label claim) versus time.

solution rate were a result of changes in the excipients over time, for example, dehydration, the same dissolution failures would be expected with the higher dosage formulation. TGA and DMSG studies on the bulk drug and excipients indicate that the water in the formulation is preferentially lost from erythromycin upon heating rather than from the excipients.

Since the performance of the 250 mg tablet is different than that of the 333 and 500 mg tablets, an interaction with an excipient unique to the 250 mg tablet formulation was suspected. The only excipient unique to the 250 mg formulation is magnesium hydroxide, and the lack of dissolution failures in the higher dosage formulation even with low water content indicates that in the absence of this ingredient, changes in the other excipients over time do not result in dissolution failures. This could only explain part of the phenomenon, however, since only random tablets and one individual lot exhibited dissolution failures.

Dissolution of failing lot 15 was monitored over a 12-month period and analyzed at the initial and 10- and 12-month time points (Figure 6). Although only three points were obtained, there was very good linear correlation between the decrease in dissolution (% label claim) and time, with a correlation coefficient of greater than 0.99. Over the same period of time, moisture content by LOD of the coated tablets was 2.6, 2.1, and 2.4% (initial and 10- and 12-month, respectively). However, by comparison the typical passing lot 1 gave LOD values of 3.8, 3.7, and 3.8% (initial and 10- and 12-month, respectively). The decrease in dissolution can be associated with the constant low level of water in the coated tablets over time. This constant low level of water in the coated tablets prevents rehydration of the dehydrated erythromycin dihydrate and maintains erythromycin in the activated state.

When erythromycin dihydrate dehydrates to form a desolvated dihydrate, it reduces the number of hydrogen bonds in the structure dramatically from three to zero. This results in a void in the lattice which has a high hydrogen bonding potential. As noted by Stephenson et al.[16] over time the tunnels slowly relax unless either water is reabsorbed or an alternate ligand is obtained. The 250 mg tablet formulation contains $Mg(OH)_2$, a hydroxyl-rich material, as one of the excipients. Interaction of the activated dehydrated dihydrate of erythromycin with $Mg(OH)_2$ is a possible mechanism for filling the void created in the crystal lattice as a result of overdrying. This interaction in the solid state requires a finite period of time and would correlate well with the slow onset of dissolution failures in the 250 mg formulation over time.

Figure 7 shows schematically a process whereby overdrying could create dehydrated dihydrate in the tablet fill. As a result of the granulation and compaction of the tablet, the $Mg(OH)_2$ could then become associated with the same sites in the dehydrated dihydrate which tend to interact or bind with water in the dihydrate. Over time the association of $Mg(OH)_2$ with dehydrated erythromycin dihydrate could strengthen to a degree where the reversing of the binding interaction necessary for the dissolution of erythromycin becomes a progressively slower process. The extent of this binding would depend on time and the amount of overdrying. Therefore, it would account for both whole lot failure as well as isolated individual tablet failures. Close examination of the NIR spectra in the region of the $Mg(OH)_2$ peak shows discernible differences between passing lots and failing lots of the 250 mg tablets (Figure 8) and supports the model of $Mg(OH)_2$ interacting with the dehydrated dihydrate.

The extent of erythromycin/magnesium hydroxide binding in the tablets was estimated from dissolution data. Figure 6 displays the relationship between the dissolution of the tablet and time. A good linear relationship was observed. Hence, the rate of dissolution retardation in the coated tablet, lot 15, can be estimated at 2.4% per month.

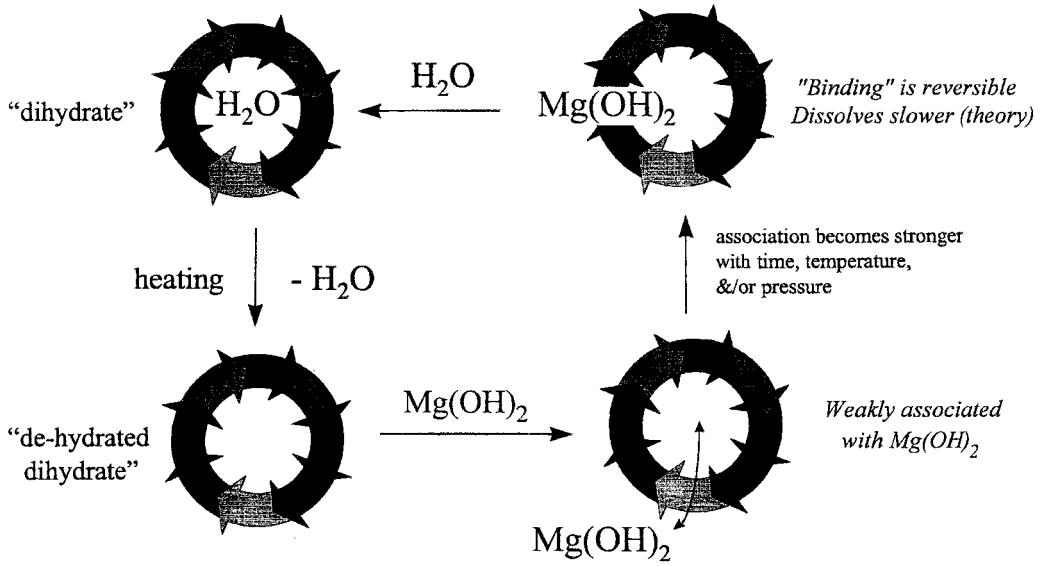

Figure 7—Schematic representation of reversible binding in erythromycin tablets.

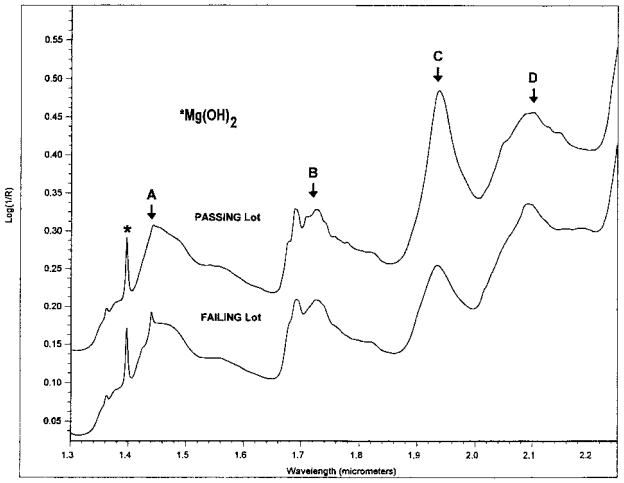

Figure 8—Four spectral regions of difference in the NIR spectra of passing and failing lots of deshelled erythromycin tablets.

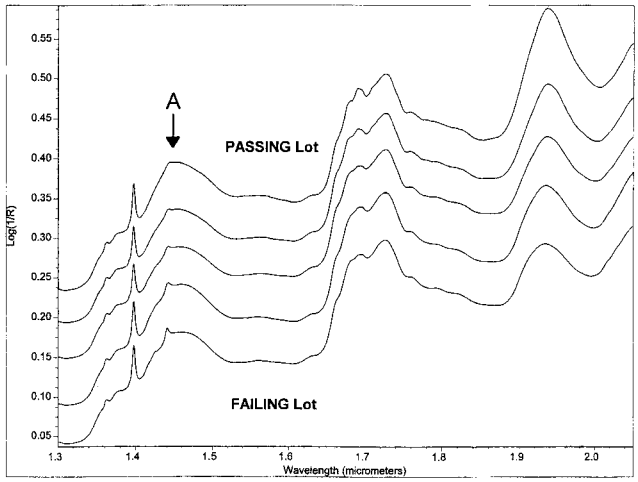

Figure 9—Series of NIR spectra of erythromycin tablets showing progression from passing to failing lot.

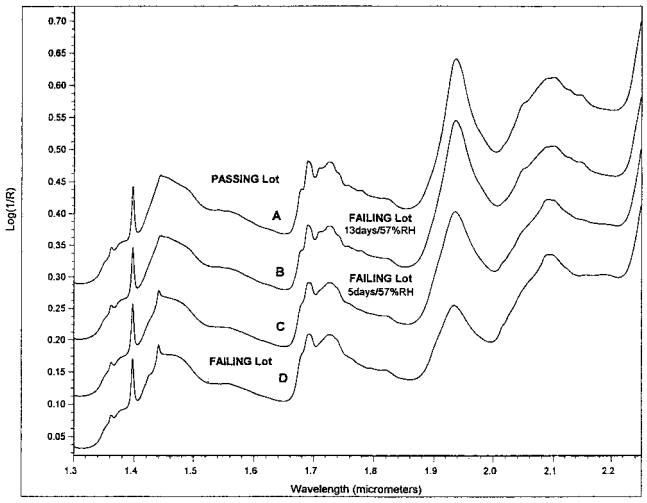

Figure 10—NIR spectra of (A) deshelled passing lot, (B) failing lot after exposure to high humidity for 5 days, (C) failing lot after exposure to high humidity for 13 days, and (D) failing lot.

Four spectral regions were examined at about 1.45, 1.7, 1.95, and 2.1 μm. The region of 1.45 μm represents overtones of hydroxyl and alkyl groups, the region at about 1.7 μm represents overtones of alkyl groups, the region near 1.95 μm represents combination bands of hydroxyl groups (and water content) of the sample, and the region near 2.1

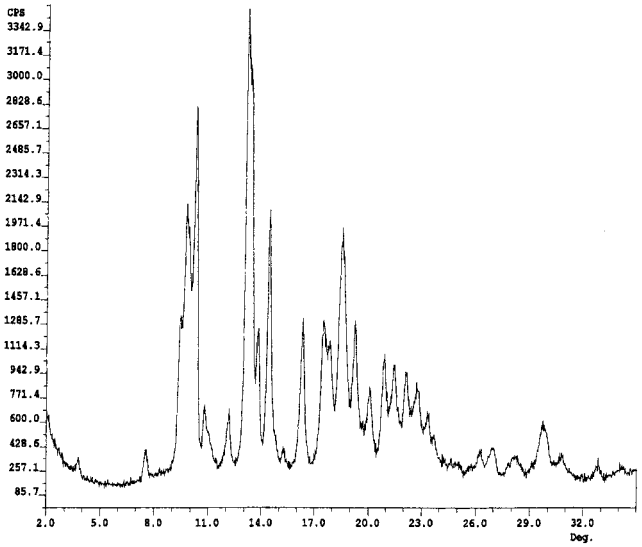

Figure 11—XRD of admixture of dehydrated dihydrate of erythromycin and magnesium hydroxide stored in a closed container for 12 months.

μm represents the first overtones of C−H stretching, and combination bands of alcohol hydroxy groups. As can be seen in Figure 8, the passing lot shows a significantly larger water peak (region C) and a broad multiplet at about 2.1 μm (region D), but not much definition in the area of 1.45 m (region A). The failing lot shows a distinct shoulder and a sharp peak in the region of 1.45 μm, a smaller peak in the water region, and a sharper and smoother peak in the 2.1 μm region. These changes indicate conformational and perhaps structural differences similar to those observed upon drying erythromycin dihydrate but more defined and sharper particularly in the 1.45 μm region. Figure 9 shows spectra of the 250 mg whole tablets for a series of lots displaying the progression (region A) from passing to failing lots.

The NIR data suggest that in the absence of water, dehydrated erythromycin dihydrate interacts with $Mg(OH)_2$ in the 250 mg tablets. This association occurs slowly over time (12 months), suggesting that it is a relatively unselective reaction. Thus, the binding process should be reversible in the presence of a more selective (or reactive) ligand. Since water forms a stable complex with erythromycin (dihydrate), it should be able to displace $Mg(OH)_2$ and reverse the complex formation.

To investigate the proposed reversibility of this phenomenon, tablets from the failing lot were exposed to high humidity (57% RH). Figure 10 shows the NIR spectra for a failing lot, the failing lot exposed to 57% RH for 5 and 13 days, and a passing lot of deshelled tablets. The NIR spectrum of the failing lot exposed to 57% RH/13 days converted to that of the passing lot after exposure to water vapor in the solid state.

Dissolution testing on these moisture-exposed tablets gave results >98% within 60 min, confirming that the binding phenomenon can be reversed.

Dried erythromycin, i.e., the dehydrated dihydrate, compressed with $Mg(OH)_2$ and stored in closed containers for a period of 12 months indicated spectral changes in the NIR spectrum similar to those detected in erythromycin tablets after 12 months. X-ray powder diffraction on the mixture showed a pattern matching that of the failing tablets (Figure 11).

Conclusion

Erythromycin dihydrate when dried is converted to an isomorphic dehydrated dihydrate which exists as an acti-

vated high energy form with a tendency to fill the void created by the loss of water. In erythromycin tablet formulations where water cannot be easily reabsorbed, this has been shown to result in binding to other hydroxyl-rich excipients such as $Mg(OH)_2$ which then adversely effects the properties of the formulation. This phenomenon can be reversed by exposing the tablets to water vapor for a relatively short period of time.

NIR spectroscopy has been shown to be a useful technique in the study of such crystal form transformation and binding. It allows a determination of such properties as drug and moisture content on individual tablets nondestructively thereby allowing further testing on the same tablet to establish a direct correlation with other properties. In addition, it has proven to be predictive of dissolution failures in erythromycin tablet formulations.

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