DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 14(7), 953-975 (1988)

CHARACTERIZATION OF HYDRATION /SOLVATION CHARACTERISTICS OF AZELASTINE HYDROCHLORIDE

A.K. Mitra* and S.A. Gordziel

Wallace Laboratories, Division of Carter-Wallace, Inc.,

Cranbury, NJ 08512

ABSTRACT

Azelastine hydrochloride, an investigational drug, was observed to form a hydrate or solvates upon recrystallization. X-ray diffraction and thermal analytical studies indicate that the hydrate or solvates exist in crystalline forms different from that of the parent material. Thermal analytical techniques confirmed that azelastine forms hydrate or solvates as opposed to a polymorph. The enthalpies and entropies of transitions were determined. A difference in dissolution rate of unrecrystallized and recrystallized azelastine was found.

*Present Address: 3M Co, 3M Center, Bldg. 270-4S-02, St. Paul, MN 55144; To whom inquiries should be directed

INTRODUCTION

The physicochemical properties of solid drug substances are of considerable importance in pharmaceutical product development due to the impact of these properties on processing of dosage forms and their bioavailability. Different crystalline forms can be prepared by appropriate modification of crystallization conditions. The nature of the solvent (its polarity and solvent power), temperature, and rate of cooling are important factors related to the resulting crystalline forms of polymorphs or hydrates/solvates obtained by recrystallization techniques (1). Azelastine hydrochloride (4-(4-chlorobenzyl)-2-(N-methyl-hexahydro-azepin-4-yl)-1-2H-phthalazinone hydrochloride), an investigational compound originally developed by Asta Werke, Bielfeld (Degussa Pharma) and being further developed by Wallace Laboratories, was investigated for polymorphism and hydrate/solvate formation. The formation of polymorphs or hydrates/solvates can have an impact on stability, solubility, physicochemical, and bioavailability characteristics of tablet or capsule products made with this material (2-5). This paper describes the studies conducted to determine whether polymorphs or hydrates/solvates are produced after recrystallization of azelastine hydrochloride from several solvents, and presents the dissolution properties of recrystallized and unrecrystallized material.

MATERIALS AND METHODS

1. Materials: Azelastine hydrochloride, henceforth referred to as azelastine, was used as received.[1] The chemical purity was determined to be 99% or greater using a stability indicating HPLC assay.

2. Recrystallization: Azelastine was recrystallized from deionized water, SDA-3A alcohol, methanol, chloroform and methylene chloride. A super saturated solution was prepared by the addition of azelastine to constantly stirred solvent heated to boiling. At the saturation point the solution was vacuum filtered, covered, and cooled in an ice bath. Crystals produced on cooling were vacuum filtered and dried under vacuum at room temperature for 3 days.

3. Characterization of Crystal Form:

   a. Scanning electron microscopy: Scanning electron photomicrographs[2] were obtained by coating solid samples with thin gold films while maintaining them under a vacuum of 1×10^{-5} mm. An exciting voltage of 21kv was used for the study.

   b. X-ray powder diffraction pattern: X-ray diffraction patterns were obtained using a diffractometer[3] equipped

with nickel filtered Cukα radiation and a scintillation counter detector. Recorded beam intensitites as a function of the angle 2θ, at a scanning rate of 1 degree/minute were obtained.

c. Thermal analyses: The calorimetric changes accompanying thermal transitions were measured by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA)[4]. The studies were conducted using approximately 5 mg of powdered sample at a heating rate of 10^{o}C/minute and a nitrogen purge of 50ml/minute.

d. Melting point determination: Melting points were determined using a melting point apparatus[5], and an open capillary. Samples in the capillary were heated from 25^{o}C to 250^{o}C at several heating rates, and melting points were determined.

e. Total water content determination: Karl Fischer titrimetry[6] was used to determine the water content.

f. Powder dissolution: Powder dissolution studies were conducted on unrecrystallized and recrystallized azelastine. Samples were passed through a #40 mesh screen and only 40-200 mesh size samples were used in the study in

order to minimize the variability in dissolution results contributed by particle size differences. The particle size ranges were confirmed by using a HIAC particle size analyzer.[7]

Approximately twice the quantity of the solute needed to form a saturated solution was used. The dissolution medium was kept at 37°C throughout the experiment. The flask containing the solute and the dissolution medium was shaken at 200 strokes per minute using a wrist shaker.[8] Samples were withdrawn periodically, filtered immediately through 0.45 um Zetapor (Nylon 66) membrane filters, diluted with water and analyzed spectrophotometrically.

RESULTS AND DISCUSSION

1. Scanning Electron Microscopy: No significant differences in crystal form were observed between unrecrystallized and recrystallized azelastine at 1000 and 2000X magnifications (Figures 1 and 2).
   All samples were observed to be present predominantly as broken plates. Azelastine recrystallized from water was observed to be finer than unrecrystallized material.

2. X-ray Diffraction Pattern: A typical diffraction pattern of azelastine is shown in Figure 3. Major peaks for

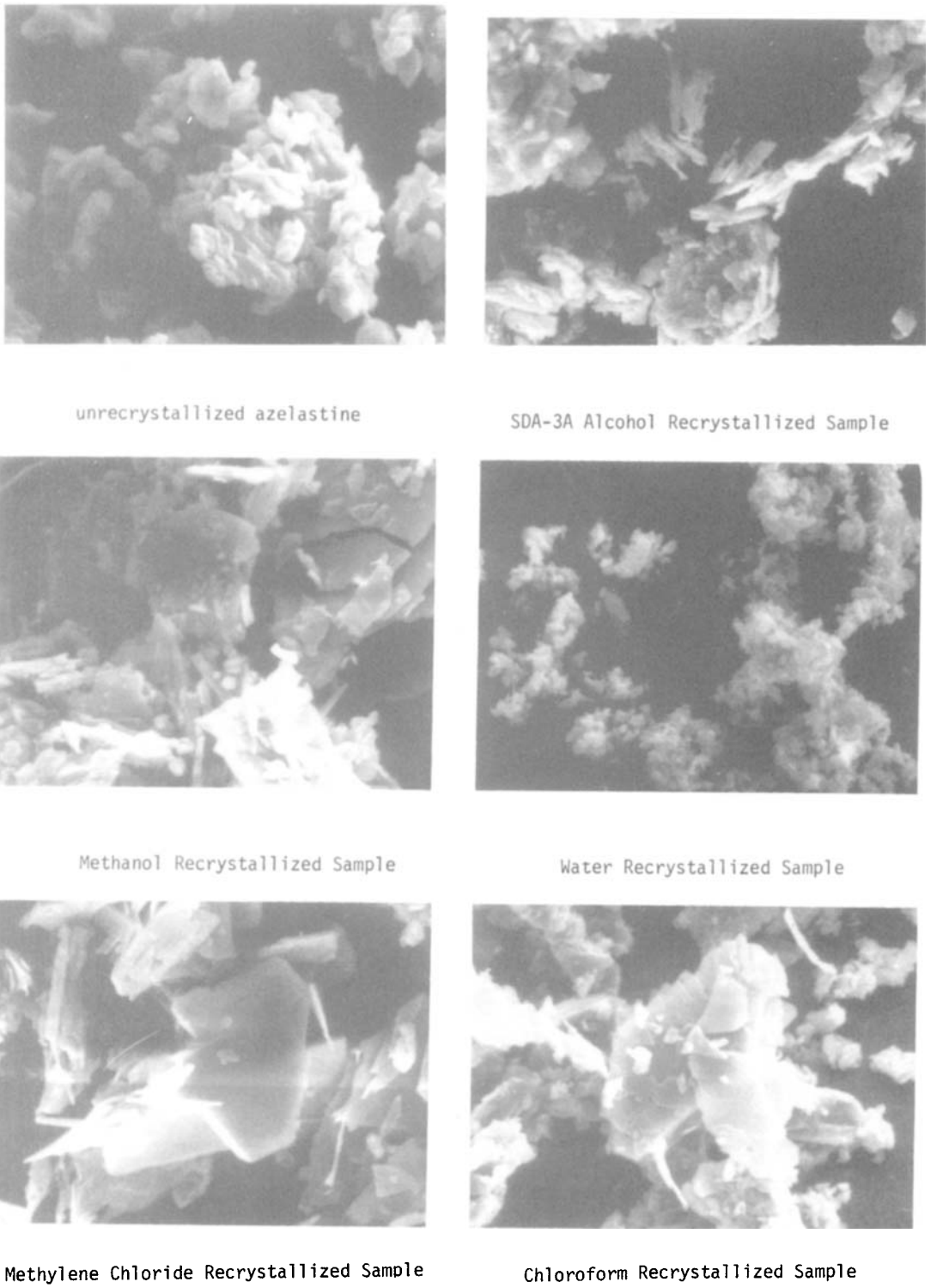

Figure 1: Scanning Electron Photomicrographs, Original Magnification 1000X, for Drug Substance

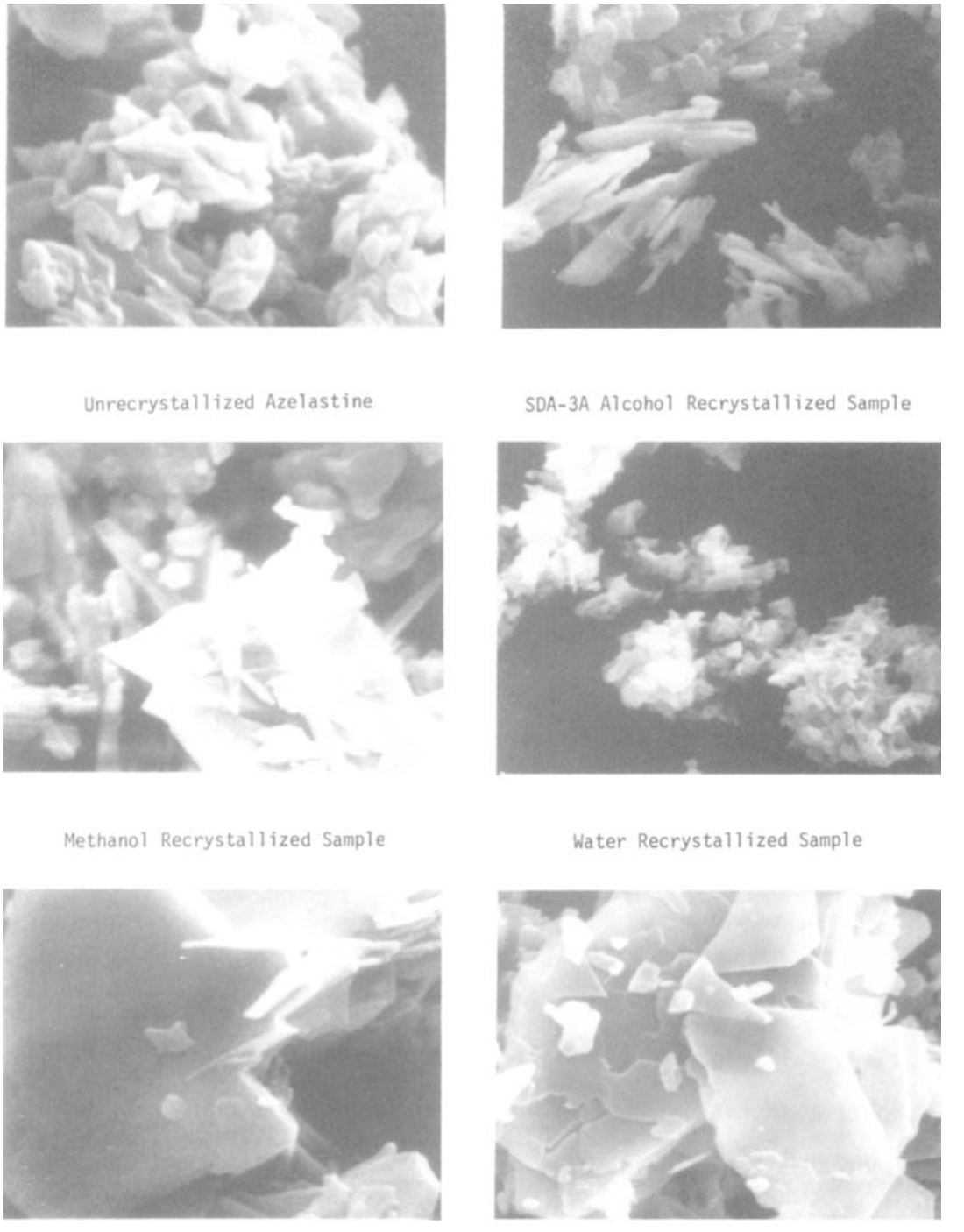

FIGURE 2: SCANNING ELECTRON PHOTOMICROGRAPHS, ORIGINAL MAGNIFICATION 2000X, FOR DRUG SUBSTANCE

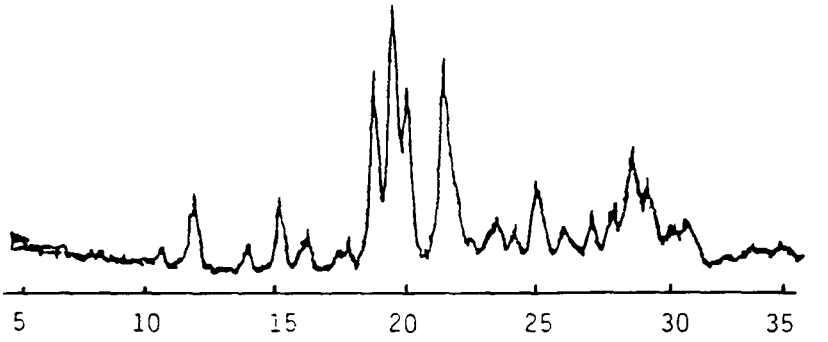

FIGURE 3

X-ray diffraction pattern of unrecrystallized azelastine.

unrecrystallized and recrystallized azelastine are given in Table I. X-ray diffraction patterns of recrystallized azelastine samples are different from that of unrecrystallized material. The results indicate a change in crystal form as a result of recrystallization.

In order to determine whether a hydrate is formed during recrystallization of azelastine from water, the water recrystallized material was tested for water content by a Karl Fischer titration. The Karl Fischer water content of 6.6% indicated that the recrystallized material contained one and one half molecules of water per molecule of azelastine calculated on the basis of an azelastine molecular weight of 418.

TABLE I:

Major X-ray Diffraction Peaks for Unrecrystallized and Recrystallized Azelastine

Major 2θ Peaks (Degrees)	Drying Conditons and Recrystallization Solvent
12.0, 15.2, 19.0, 19.8, 20.3, 21.8, 25.0, and 28.6	1. Dried at 110°C under vacuum a. None b. Chloroform c. Methanol d. SDA-3A alcohol e. Deionized water f. Methylene Chloride
6.1, 10.1, 13.5, 18.2, , 19.4, 20.2, 21.5, 27.2	2. Dried at ambient temperature and vacuum a. chloroform
6.6, 10.2, 14.0, 17.8 19.5, 21.5, 22.6, 23.2 26.0	3. Dried at ambient temperature and vacuum a. SDA-3A alcohol b. Methanol c. Methylene chloride d. Deionized water

In another experiment, water recrystallized azelastine was exposed to drying conditions of 110°C and vacuum overnight, or 80°C overnight. The Karl Fischer water content for the 110°C and vacuum dried sample was observed to be less than 0.5%; whereas, a water content of 2% was found in the 80°C dried sample. The later value is equivalent to one molecule of water to two molecules of azelastine.

The X-ray diffraction pattern of the 110°C vacuum dried sample is similar to that of the unrecrystallized material; whereas, the X-ray diffraction pattern of the 80°C dried sample showed a diffraction pattern similar to that of the room temperature vacuum dried material recrystallized from water. All other recrystallized samples dried at 110°C under vacuum also showed similar X-ray diffraction patterns to that of the azelastine raw material (Table I). These results indicate that upon recrystallization azelastine forms a hydrate/solvate and when the solvent of recrystallization is removed by an exposure to accelerated temperatures and vacuum, azelastine converts from its hydrated/solvated form to the parent material.

3. Thermal Analysis: Unrecrystallized, and recrystallized and 110°C vacuum dried azelastine samples were observed to show only one endotherm at approximately 225°C in DSC runs with the sample in a crimped or open pan (Figure 4). This may indicate

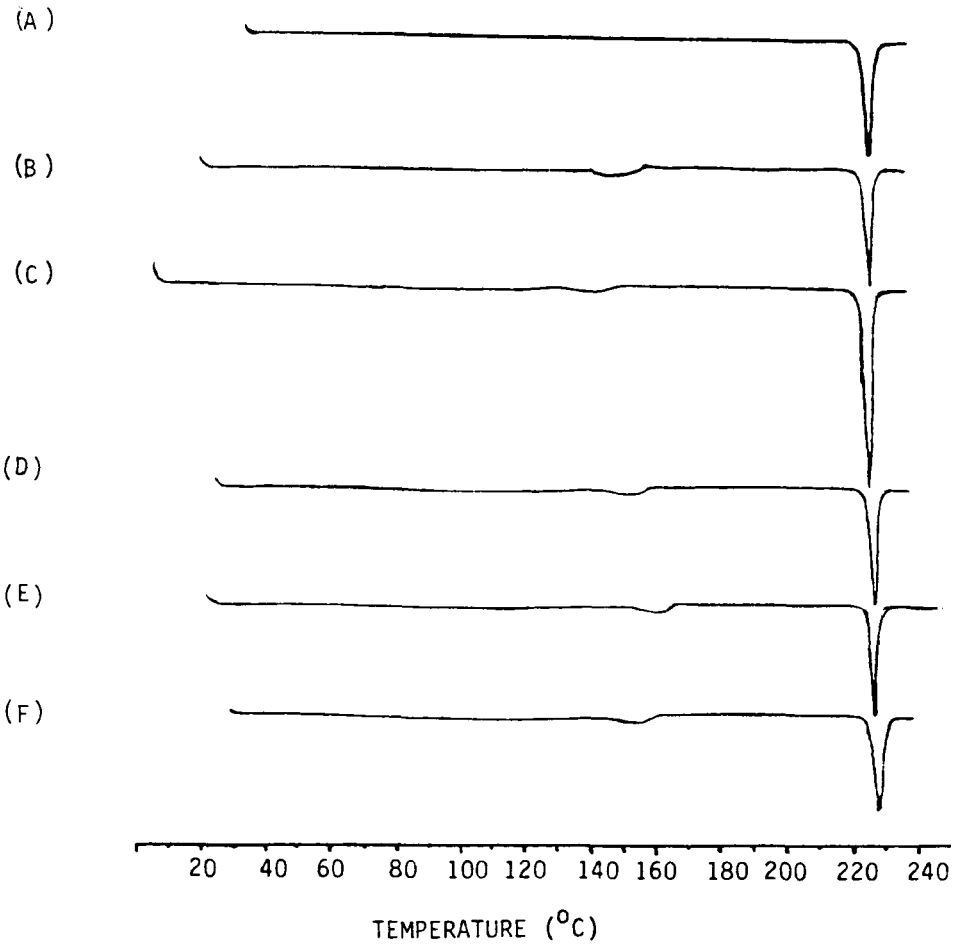

FIGURE 4

DSC thermograms of unrecrystallized and recrystallized azelastine at a heating rate of 10°C/minute.

A - unrecrystallized, and recrystallized azelastine dried under vacuum at 110°C overnight, open or closed pan; B - SDA-3A alcohol recrystallized sample, crimped pan; C - methanol recrystallized sample, crimped pan; D - chloroform recrystallized sample, crimped pan; E - methylene chloride recrystallized sample, crimped pan; F - water recrystallized.

the same crystal form for the sample. However, in a similar experiment using recrystallized azelastine samples dried at ambient conditions and the crimped pan, two melting endotherms-one between 132° and 152°C and another between 224° and 225°C were found (Figure 4). All recrystallized materials, when dried at 110°C overnight, showed only one endotherm at approximately 224°C.

In the open pan experiments with water recrystallized material, three endotherms and one exotherm were found in the DSC thermogram (Figure 5). A broad endotherm was found at approximately 78°C- probably due to the loss of water. The other thermal transitions were: an endotherm at approximately 164°C- probably due to the melting of the hydrated form, an exotherm at 171°C- probably due to the recrystallization of the melt, and an endotherm at 225°C- probably due to melting of the azelastine raw material. In a recycling experiment with the sample in an open pan, water recrystallized material was heated from 25°C to 185°C, cooled to 25°C and reheated to 250°C. Only one endotherm at approximately 225°C was found after reheating. This result indicates complete conversion of the recrystallized azelastine to the original form.

The heat of transition values were calculated by using equation 1.

$\Delta H = K(A)/m$ ---------- equation 1

Where ΔH is the enthalpy of transition, K is a calibration coefficient which is a function of temperature, A is the area of the transition peak and m is the mass. Entropy value associated with the transition were obtained by dividing the

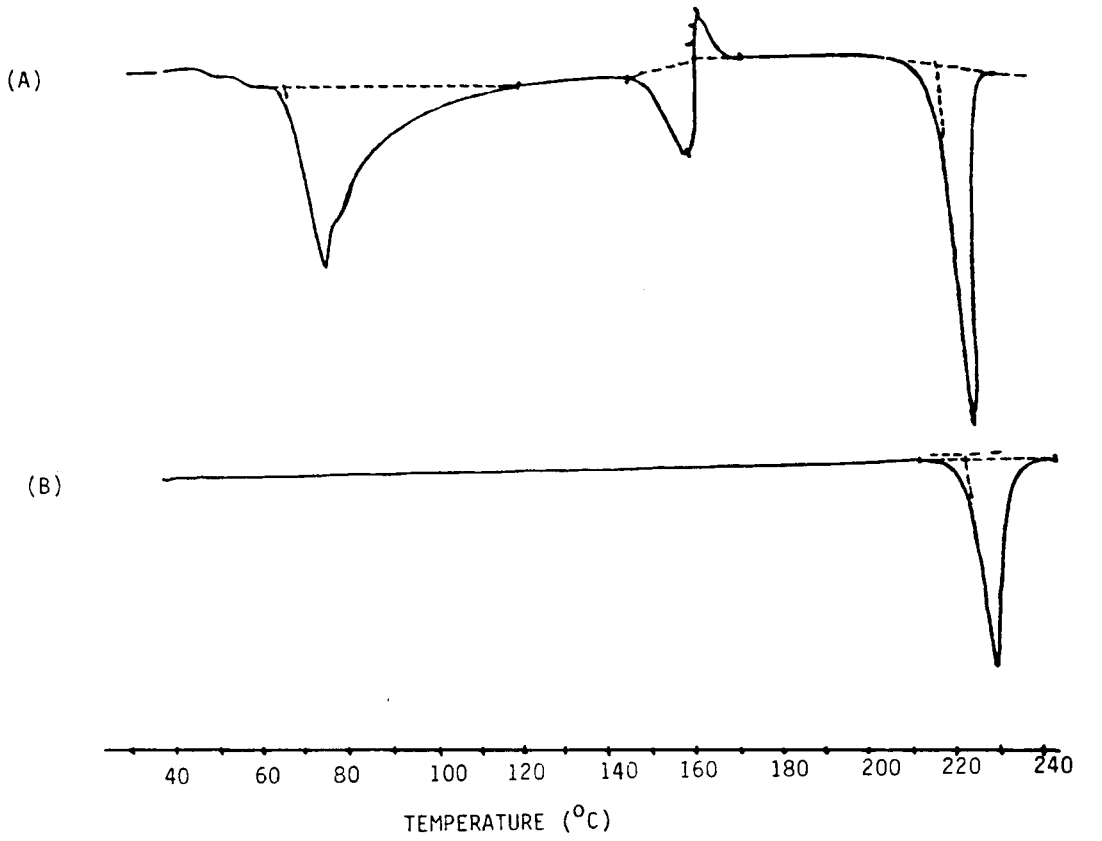

FIGURE 5

DSC thermograms of water, recrystallized azelastine, at a heating rate of 10°C per minute.

A - room temperature dried material, open pan; B - sample heated from 25°C to 185°C, cooled to 25°C and reheated to 250°C.

transition enthalpy by the degrees in Kelvin. No significant difference in the enthalpies of transition was observed between unrecrystallized and recrystallized azelastine at 225°C, indicating complete conversion of the hydrate/solvates to the original material at 225°C. However, all the recrystallized materials showed two melting transitions: one between 132-152° and the other at approximately 225°C, the melting point for the drug substance. The enthalpies and entropies of transitions for the recrystallized materials at two different transitions are given in Table II. The difference in the enthalpies of transition, between 132-152°C, could be attributed to the difference in energy needed to melt the various recrystallized materials or to the different rates of evaporation of the solvent which contributes to the effective mass during melting. The enthalpies of transition for the first melting was similar for water, SDA-3A alcohol and methylene chloride recrystallized materials; whereas, chloroform and methanol recrystallized materials had similar enthalpies of transition.

Thermogravimetric analysis thermograms were obtained and show weight losses of 4.13% to 5.28% before melting, for all recrystallized materials. In contrast, no weight loss was observed for unrecrystallized azelastine. The number of solvent molecules per azelastine molecule in the

TABLE II:

Thermodynamic Data for Unrecrystallized and Recrystallized Azelastine

Materials	Enthalpic Transition Type: Endothermic (first) Temp(°C)[1]	ΔH(KCal/mole)[1]	ΔS(eu)[1]	Endothermic (second) Temp(°C)[1]	ΔH(KCal/mole)[1]	ΔS(eu)[1]
Azelastine				222.10±3.61	11.32±1.44	22.35±2.81
Water recrystallized azelastine	145.16±1.19	2.04±0.55	4.87±0.33	225.06±4.15	9.27±1.11	18.63±1.51
Chloroform recrystallized azelastine	144.31±1.95	1.59±0.15	3.83±0.12	225.24±2.01	9.29±0.22	18.64±0.29
Methylene Chloride recrystallized azelastine	151.07±1.53	2.25±0.30	5.31±0.25	224.70±2.83	8.78±1.21	17.64±1.51
SDA-3A alcohol recrystallized azelastine	140.09±1.95	2.31±0.43	5.44±0.19	224.68±1.91	9.75±1.49	19.60±0.23
Methanol recrystallized azelastine	133.36±0.31	1.20±0.85	2.95±0.18	224.31±2.57	9.13±1.45	19.50±0.31

[1]Mean and standard deviation.

recrystallized materials was calculated and is given in Table III. No weight loss was detected for the recrystallized samples dried overnight at 110°C under vacuum.

Based on the above findings, it can be concluded that azelastine forms solvates and hydrates instead of polymorphs during recrystallization from various solvents, including water. The bound solvent or water molecules can be removed by drying recrystallized materials at 110°C overnight under vacuum.

4. Powder Dissolution: Powder dissolution studies were conducted on azelastine and azelastine recrystallized from deionized water in 0.1 N hydrochloric acid and deionized water (Figure 6). Both materials were observed to have similar initial dissolution rate profiles in water. In water, the equilibrium solubility value was reached in 7 days and was similar for both azelastine and water recrystallized azelastine.

In 0.1 N hydrochloric acid, a higher dissolution rate for azelastine compared to the recrystallized azelastine was observed. A maximum solution concentration of azelastine was achieved in 2 minutes followed by a slow decrease in concentration with time until the solubility equilibrium was reached after one day. In similar studies with recrystallized

TABLE III:

Summary of TGA Results

Material	% Weight Loss (mean ± standard deviation)	Loss in number of molecules per molecule of azelastine (calculated from the mean % weight loss)
Azelastine SDA-3A alcohol recrystallized azelastine	4.51 ± 0.20	0.41
Methanol recrystallized azelastine	4.47 ± 0.18	0.58
Chloroform recrystallized azelastine	4.28 ± 0.15	0.15
Methylene Chloride recrystallized azelastine	4.13 ± 0.19	0.2
Water recrystallized azelastine	6.00 ± 0.14	1.4

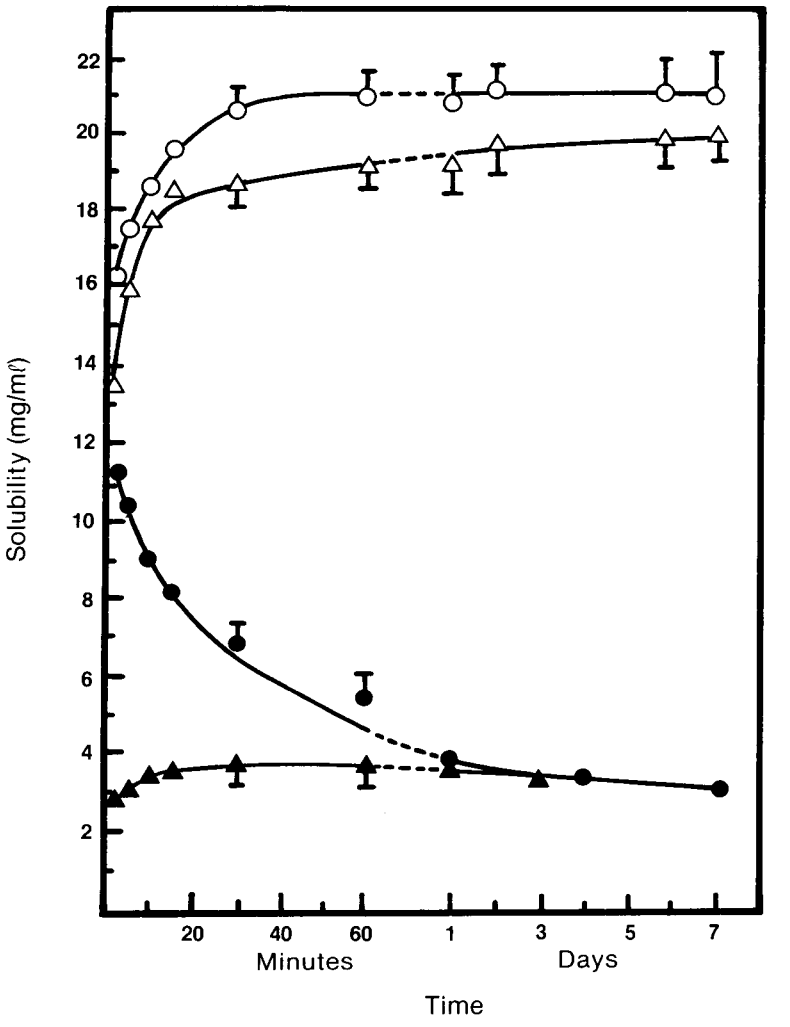

Figure 6

Dissolution profiles of azelastine and recrystallized azelastine in two different dissolution media at 37°C.

● - azelastine, 0.1 N hydrochloric acid; ▲ - recrystallized azelastine, 0.1 N hrdrochloric acid.
o - azelastine, deionized water; △ - recrystallized azelastine, deionized water.

TABLE IV:

Solubilities of Various Forms of Azelastine in Deionized Water or 0.1 N HCl

	Equilibrium Solubility[1] (mg/ml)	
	Deionized water	0.1 N HCl
Azelastine raw material	21.3±1.2	3.8±0.5
SDA-3A alcohol recrystallized material	19.9±1.5	4.0±0.2
Methanol recrystallized material	20.4±0.3	3.7±0.3
Methylene Chloride recrystallized material	20.0±1.4	3.8±0.2
Chloroform recrystallized material	20.9±0.4	3.8±0.4
Water recrystallized material	20.3±0.5	4.0±0.4

[1]mean and standard deviation.

azelastine, the concentration of azelastine in 0.1 N hydrochloric acid was observed to increase gradually with time until the equilibrium solubility value was reached in 60 minutes. The equilibrium solubility of azelastine and recrystallized azelastine were similar (Table IV).

The similar dissolution rates and initial solubilities of azelastine and water recrystallized azelastine in water suggest that azelastine forms a hydrate more rapidly in water than in 0.1 N hydrochloric acid, and that the equilibrium solubilities for both azelastine and recrystallized azelastine are similar because of hydrate formation in the media. The equilibrium solubility of azelastine in 0.1 N hydrochloric acid is much lower than that in deionized water due to the common ion effect.

CONCLUSION

Upon recrystallization, azelastine was found to bind varying amounts of water or organic solvents. The mechanism by which these solvents are bound may simply be absorption or mechanical entrapment, or they may be part of the crystal lattice. The data more strongly suggest that the hydrate/solvates of azelastine are part of the crystal lattice. Several techniques for characterizing the hydrated/solvated form of azelastine have been

studied. The data suggest that azelastine forms hydrates or solvates, as opposed to polymorphs on recrystallization respectively from water or organic solvents. The data also suggest that the hydrated/solvated material on drying under accelerated temperatures will lose its bound solvents, and convert to a material having properties similar to unrecrystallized azelastine. The enthalpy of transition for the first melting was similar for water, SDA-3A alcohol and methylene chloride recrystallized materials; whereas, chloroform and methanol recrystallized materials had similar enthalpies of transition. A difference in dissolution rates among the hydrated/solvated and parent materials was observed.

FUOTNOTES

1. Azelastine HCl of purity greater than 99%, via HPLC, was supplied by Degussa Pharma, Astra Werke, Bielfeld, West Germany.

2. Scanning Electron Microscope - AMR 900 SEM; Middlesex Turnpike, Burlington, MA.

3. Siemens X-ray Diffractometer; Siemens Allis, Inc., Analytical Systems, 1 Computer Drive, Cherry Hill, NJ.

4. Dupont 1090 Thermal Analyzer, E.I. Dupont De Nemours & Co., Inc.; Wilmington, DE.

5. Capillary Melting Point Apparatus; Arthur H. Thomas Co., Philadelphia, PA.

6. Fisher Automatic K-F Titrimeter System; Fisher Scientific Co., 711 Forbes Avenue, Pittsburgh, PA.

7. HIAC analyzer model PC-320; manufactured by HIAC Instruments Division, Pacific Scientific, 4719 West Brooks Street, Montclair, CA.

8. Burrel Wrist Action Shaker; Burrel Corp; Pittsburgh, PA.

REFERENCES

1. Y. Matsuda, S. Kawoguchi, H. Kobayashi and J. Nishijo J. Pharm. Sci., 73 (2), 1984

2. A.R. Ebian, M.A. Moustata, S.A. Khalil, and M.M. Motawi, J. Pharm. Pharmacol., 25, 13 (1973)

3. M.A. Moustata, S.A. Khalil, A.R. Ebian, and M.M. Motawi J. Pharm. Pharmacol., 63, 1103 (1974)

4. M.A. Moustata and J.E. Carless, J. Pharm. Pharmacol., 21, 359 (1969).

5. E.G. Shami, P.D. Bernardo, E.S. Rattic, and L.J. Ravin, J. Pharm. Sci., 61, 1318 (1972).

6. S. Miyazaki, M. Nakano, and T. Arita, Chem. Pharm. Bul., 24, 1832 (1976).