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HYGROSCOPICITY OF CELIPROLOL HYDROCHLORIDE POLYMORPHS

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ABSTRACT

The moisture absorption of two crystalline forms (form I and form II) of celiprolol hydrochloride was investigated at different relative humidities. Celiprolol hydrochloride form I was found to be less hygroscopic than celiprolol hydrochloride form II. It was also found that the high melting form I undergoes a transition to a low melting form II at high relative humidity.

INTRODUCTION

Since different polymorphs have different physical properties, it is often advantageous to choose the proper polymorph for the desired pharmaceutical application. Haleblian and McCrone[1] have reviewed several examples of application of polymorphism in the pharmaceutical industry. Simmons et al.[2] showed that the tolbutamide Form B which is platelike causes powder bridging in the hopper and a capping problem during tableting, whereas Form A which is not platelike, showed no such problems during tableting. Methylprednisolone crystallizes in two forms.

One form is stable while the other is reactive when exposed to high humidity.[3]

Celiprolol hydrochloride is known to exist in two forms. Form I (m.p. 193°C) crystallizes out from organic solvents, whereas Form II (m.p. 145°C) crystallizes from water. This paper describes the moisture pick-up tendencies of the two polymorphic forms which may have implications in processing and stability of solid dosage forms.

EXPERIMENTAL SECTION

Materials: Celiprolol hydrochloride (lot #M31722, Chemie Linz AG, Austria) was used as received. The material was confirmed to be Form I by differential scanning calorimetry (DSC), hot stage microscopy and infrared spectroscopy (IR). Form II was prepared by dissolving 100 grams of Form I in 100 mL of distilled water; the resultant clear solution was evaporated to dryness by vacuum distillation at 60°C. It was further dried in powdered form under vacuum at 50°C. The formation of Form II was confirmed by DSC, hot stage microscopy and IR spectroscopy.

A Quantasorb surface analyzer model Q5-10 was used for the determination of specific surface areas of Form I and Form II.

Differential Scanning Calorimetry (DSC) was carried out in a DuPont 990 Thermal Analyzer. The material (3-5 mg) was heated in hermetically sealed aluminum pans at different rates and the thermograms were recorded at appropriate sensitivities.

Thermogravimetric Analysis (TGA) was performed in a DuPont 951 Thermogravimetric Analyzer module plugged into a 990 Thermal Analyzer.

The material was heated at a rate of 10°C/minute in an atmosphere of dry nitrogen.

A Mettler FP5 hot stage microscope was used for the determination of the melting point. The melting points of celiprolol hydrochloride Form I and Form II were determined using a heating rate of 1°C/minute.

Infrared spectra were recorded on a Perkin Elmer 283B infrared spectrophotometer using a KBr disc.

Hygroscopicity Studies

Approximately 10 grams of celiprolol hydrochloride powder was placed in desiccators containing various concentrations of aqueous sulfuric acid yielding relative humidities of 37, 58, 80 and 100% at 25°C. These relative humidities were checked prior to and at the end of experiments by using standard gauges.

RESULTS AND DISCUSSION

The DSC (Figure 1) and IR spectroscopy (Figures 2, 3) of celiprolol hydrochloride were used for distinguishing Form I and Form II. The results in Figure 1 indicate that celiprolol hydrochloride Form I melts at around 193°C with an endothermic peak at 206°C whereas celiprolol hydrochloride Form II melts at 145°C with an endothermic peak at 155°C. These results were further confirmed by visual observation of their melting behavior under the hot stage microscope.

The DSC results as shown in Figure 1 also indicate that there is no melting of celiprolol hydrochloride (either Form I or Form II) until

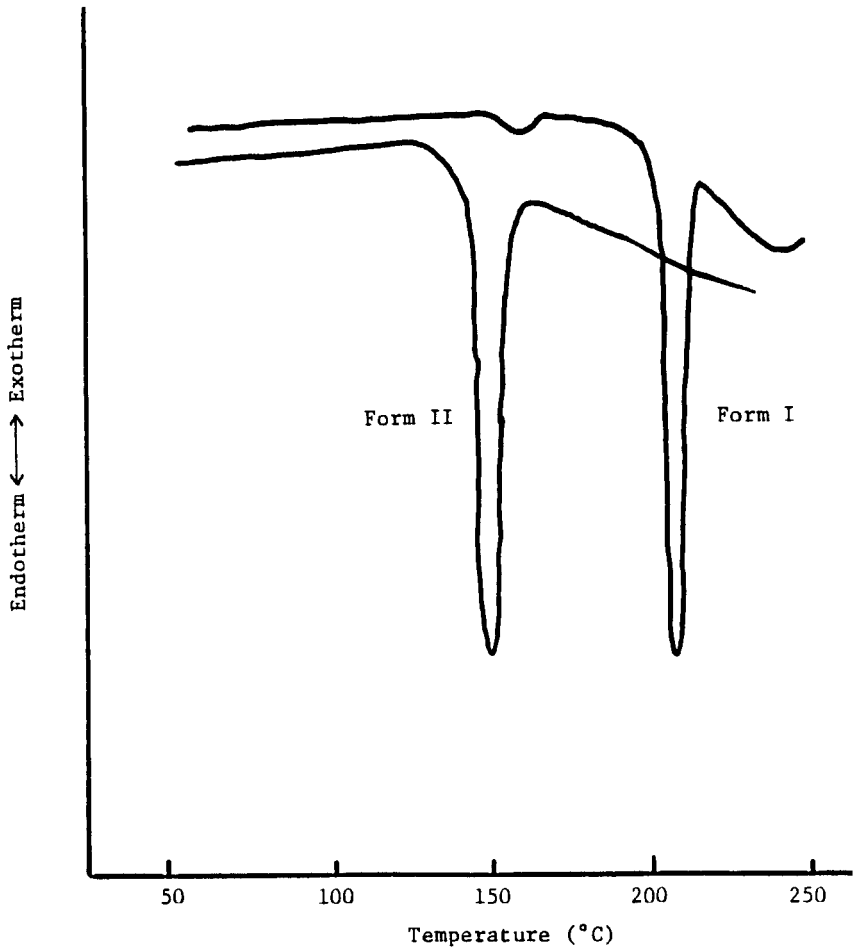

Figure 1 DSC thermograms of two polymorphic forms of celiprolol hydrochloride (sample size 3 mg, 5°C/minute)

145°C. The TGA results as shown in Figure 4 indicate initial weight loss for Form II only between 50 to 100°C. These results are an indication of the absence of any hydrate or solvate.

For a meaningful comparison of hygroscopicity studies, it is desirable that the compounds have approximate equal specific surface areas. The specific surface area as determined by a single point BET method of Form

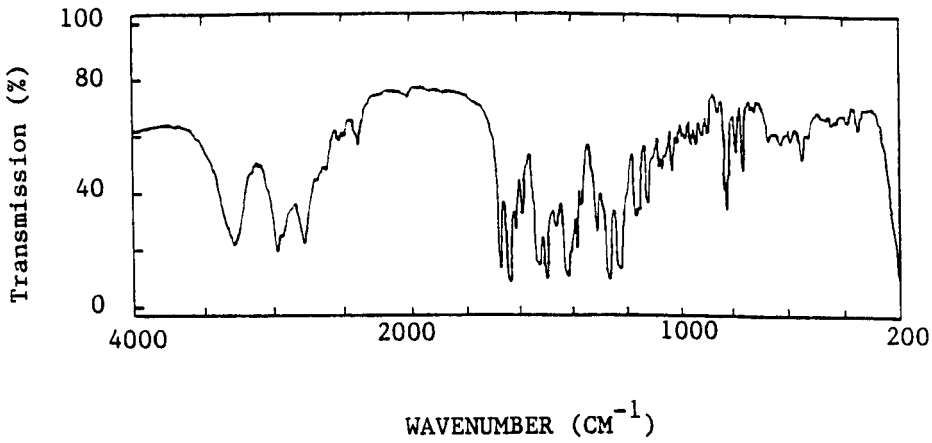

Figure 2 Infrared Spectrum of Celiprolol Hydrochloride Form I

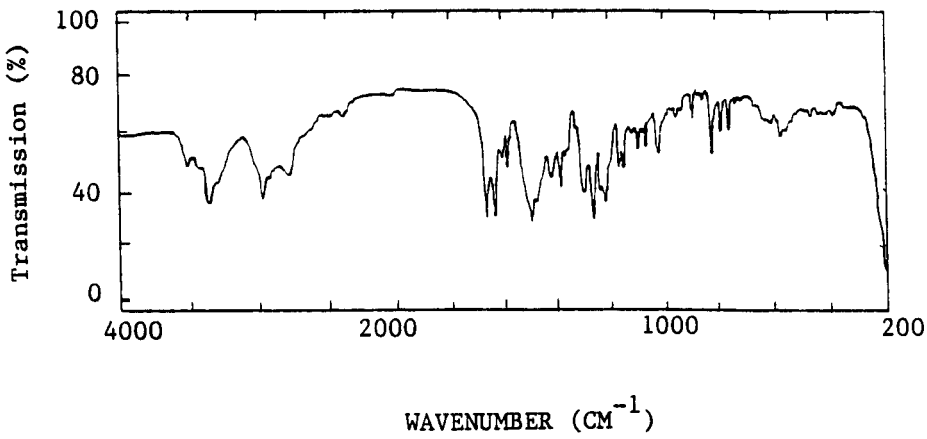

Figure 3 Infrared Spectrum of Celiprolol Hydrochloride Form II

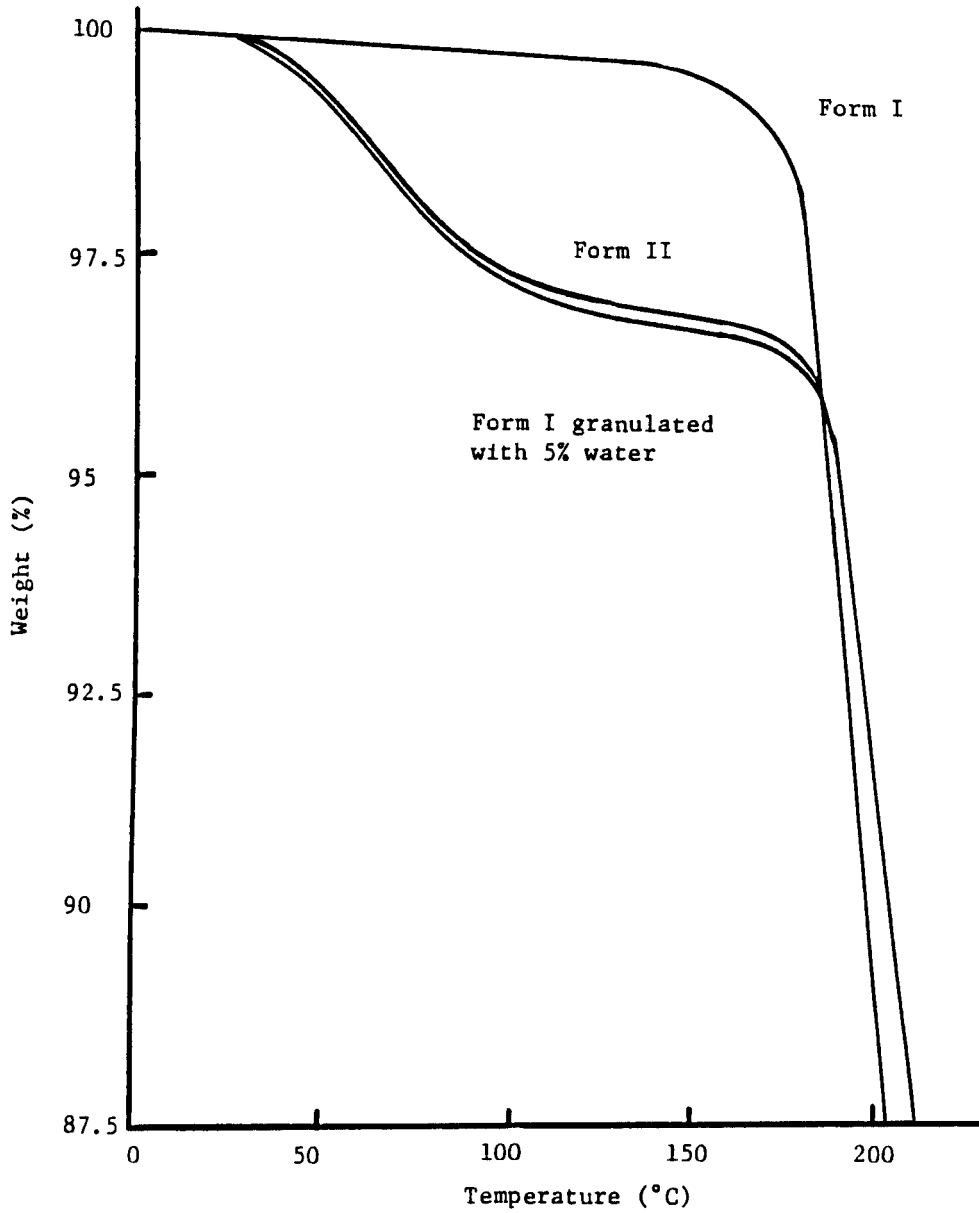

Figure 4 TGA of celiprolol hydrochloride, Form I and Form II (sample size 30 mg, 10°C/minute)

TABLE I

MOISTURE ABSORPTION PROFILE OF CELIPROLOL HYDROCHLORIDE FORM I AND FORM II AT VARIOUS RELATIVE HUMIDITIES AT 25°C

	Form I	Form II
100% R.H.		
1 day	2.2%	6.5%
3 days	4.5%	10.5%
1 week	6.4%	15.2%
1 month	18.3%	40.1%
2 months	24.0%	60.0%
80% R.H.		
1 day	0.3%	3.3%
3 days	0.3%	3.3%
1 week	0.3%	3.3%
1 month	0.5%	3.5%
2 months	0.7%	3.5%
58% R.H.		
1 day	0.3%	3.0%
3 days	0.3%	3.0%
1 week	0.3%	3.1%
1 month	0.4%	3.2%
2 months	0.4%	3.2%

I (0.35 m^2/g) was close to that of Form II (0.32m^2/g). The moisture absorption results on Table I shows the moisture pick-up behavior of Form I and Form II at various relative humdities. It is apparent that Form II is more hygroscopic than Form I. There was no significant moisture gain for Form I up to 80% R.H. However, at 100% R.H., a

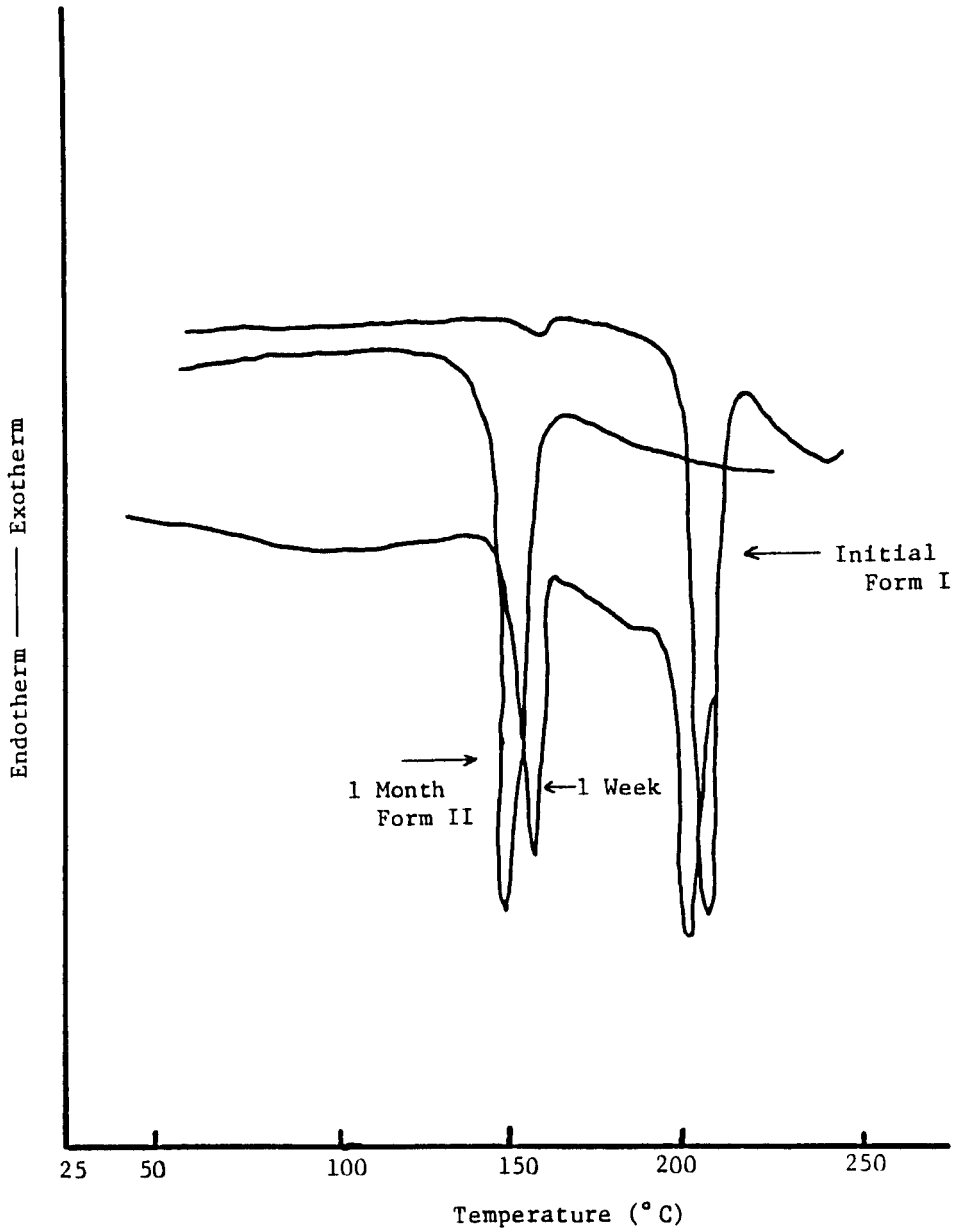

Figure 5 DSC thermograms of celiprolol hydrochloride Form I subjected to 100% relative humidity at various intervals

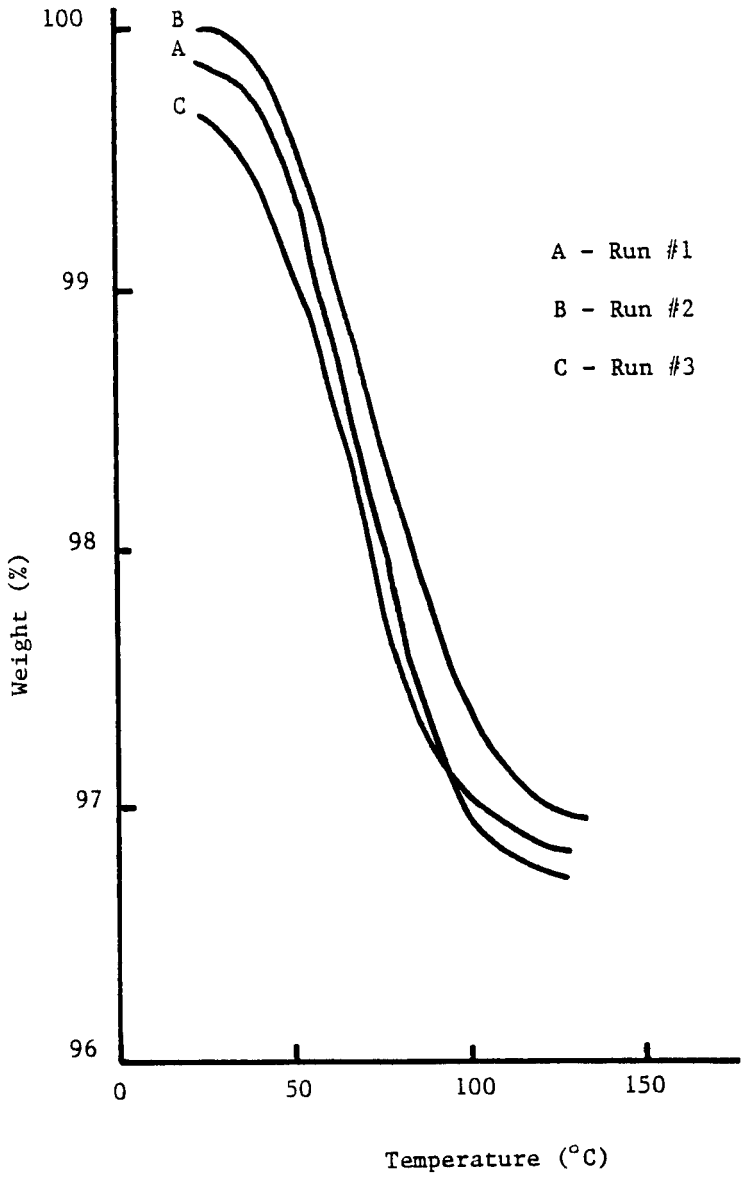

Figure 6 Repeated TGA of celiprolol Form II (sample size 30 mg, 10°C/minute)

considerable amount of moisture was picked up over a period of two months. The DSC results as shown in Figure 5 indicate that most of celiprolol hydrochloride Form I gradually converted to Form II over a period of one month. Celiprolol hydrochloride Form II absorbs about 3.0% moisture even at 37% R.H. in one hour. The TGA results as shown in Figure 6 further demonstrated the hygroscopicity of Form II. The sample, unlike form I, dried at a temperature below its melting point, reabsorbed the same amount of moisture during cooling under ambient conditions (i.e., 40% R.H.) while resting on the platinum pan used for TGA.

CONCLUSION

Celiprolol hydrochloride Form I is less hygroscopic than Form II. Conversion of Form I to Form II can be prevented by controling the relative humidity below 80% at ambient temperature. These results provide valuable information for the formulation and stability of celiprolol hydrochloride solid dosage forms.

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