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COMPARATIVE EVALUATION OF DIRECT COMPRESSION AMPICILLIN FORMULATIONS

S. Niazi[1], R.M. El-Rashidy and F. El-Khwas

[1]Department of Pharmacy

College of Pharmacy

University of Illinois at the Medical Center

Chicago, Illinois 60612

Department of Inudstrial Pharmacy

Faculty of Pharmacy

Alexandria University

Alexandria, Egypt

ABSTRACT

Direct compression formulations were developed for ampicillin using methyl vinyl ether/maleic anhydride copolymer (I) and vinyl acetate/crotonic acid copolymer (II) as binders. A comparison was made between these formulations and wet granulation method using gelatin as binder regarding the chemical stability of ampicillin as a function of relative humidity (55 to 90%) and

[1]To whom enquiries should be directed.

temperature (40 to 75°C). Polymer I showed least moisture uptake followed by polymer II and gelatin. The mechanism suggested here involves moisture uptake and dissolution followed by chemical decomposition. The temperature had lesser effect on stability because of low activation energies but an Arrhenius relationship was established for three formulations studied. It was concluded that formulation using polymer I gives the most ideal combination of physiochemical properties for the direct compression of ampicillin in solid dosage forms.

INTRODUCTION

The complex nature of drug stability in solid state (1-14) makes the kinetic evaluations of drug decomposition reactions less reliable (3,4). Ampicillin, a semi-synthetic penicillin, undergoes several decomposition reactions in solution state (15-19), mainly due to the sensitive nature of its β-lactam ring to moisture and pH. The solid state stability of ampicillin has, however, been little investigated (20,21). The purposes of this paper were to report solid state stability profiles of ampicillin dosage forms prepared by directly compressing formulations containing optimum concentrations of polymers, methyl vinyl ether/maleic anhydride copolymer (I), vinyl acetate/crotonic acid

copolymer (II) and by wet granulation using gelatin solution (22). The stability properties of ampicillin as a function of moisture and temperature in these formulations provide information on the mechanism of decomposition and the choice of the best formulation for the direct compression of ampicillin in compressed dosage form.

EXPERIMENTAL

Materials: Ampicillin monohydrate[1], methyl vinyl ether/maleic anhydride copolymer[2], vinyl acetate/crotonic acid copolymer[3], gelatin[4], magnesium stearate[5], hydroxylamine hydrochloride[6], anhydrous sodium acetate[7], ferric ammonium sulfate[8], and sodium hydroxide[9] were obtained from commercial sources.

Apparatus: Spectrophotometer[10], single punch tabletting machine[11], and constant temperature incubator[12] were used.

Tablet Formulations: Three formulations of ampicillin monohydrate were prepared as shown in Table I and

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[1]Wyeth Laboratories, Philadelphia, PA
[2]GAF Corporation, N.Y., N.Y.
[3]Ciba Corporation, Basle, Switzerland
[4-9,12]Fisher Scientific Co., Chicago, IL
[10]Carl-Zeiss, Jene, Germany
[11]Erweka, Frankfurt, Germany

Table I

Direct Compression Formulations of Ampicillin

Component	I	II	III
Ampicillin monohydrate	125.0	125.0	125.0
Starch	65.0	59.0	60.0
Tale: Magnesium Stearate (9:1)	6.0	6.0	6.0
Polymer I (Methyl Vinyl ether/maleic anhydride copolymer)	4.0	—	—
Polymer II (Vinyl acetate/crotonic acid copolymer)	—	10.0	—
Gelatin solution (5%)	—	—	q.s.
Total Tablet Weight	200 mg	200 mg	200 mg

tablets prepared by direct compression in single punch tabletting machine using polymer I and II and by wet granulation using gelatin solution.

Storage Tests: Sets of 20 tablets were kept at 40°C and at four different relative humidities of 40, 55, 75 and 90% and at 55% relative humidity at three different temperatures of 40°, 55°, and 70°C in a dessicator. The desired humidity in the dessicator was maintained

by adjusting the concentration of sodium hydroxide solutions placed in the dessicator and monitored by a hygrometer. The tablets were periodically analyzed for their ampicillin content and change in weight due to moisture uptake.

Analysis of Ampicillin: One tablet was ground and dissolved in 100 ml distilled water and the solution filtered. The filtrate was diluted 1:20 and to 1 ml portion, 3 ml of neutralized hydroxylamine solution were added followed by 1 ml of ferric ammonium sulfate solution, three minutes later. The absorbance was read at 550 nm. This method allows the quantitation of intact ampicillin in the presence of its decomposition products. The details of this method were reported elsewhere (18, 19).

RESULTS AND DISCUSSION

The purpose of this investigation was to study the stability of ampicillin in solid dosage forms prepared by direct compression. The formulations of ampicillin containing polymer I and II (Table I) represent the optimum concentration of these polymers required to give desired tablet properties, such as friability, disintegration and dissolution as reported earlier (22). The use of 5% aqueous gelatin solution was made to

prepare tablets by wet granulation method for comparative purposes.

Moisture Uptake: It has often been suggested (1) that the decomposition of drugs in solid state precedes by moisture uptake resulting in the localized dissolution of the drugs. The rate and the extent of water uptake was studied for the three formulations listed in Table I as a function of relative humidity and temperature. Although it has been demonstrated (23) that ampicillin itself does not abosrb any moisture, the uptake of moisture was significant by the three formulations studied. As shown in Figs. 1 and 2 the moisture uptake was both a function of temperature and relative humidity. In all instances the maximum moisture uptake took 40-50 days. Formulation I showed the least uptake of moisture and the increase in the uptake was gradual as the temperature or humidity increased compared to formulation II.

The major factor responsible for the differences in the moisture uptake between the three formulations studied is the binder used to prepare the tablets (Table I). Formulation I contained 2% of polymer I which has often been used as a coating material for its desirable film forming properties. It seems likely that this property might play an important role

in the lower moisture uptake by the formulation containing this polymer. Formulation II containing 5% of polymer II absorbed higher moisture possible due to its hygroscopic properties and/or to the higher concentration of the polymer used to obtain desirable tablet properties. Formulation III contained 5% aqueous gelatin solution as binder and was included here for comparative purposes as an example of wet granulation method. As can be expected, addition of gelatin resulted in significant increase in the moisture uptake making this formulation less desirable than the other two.

It should be pointed out that the comparison between polymer I and II is made based on their concentration providing most desirable tablet properties and in this evaluation formulation I seems to be preferably over formulation II. Another aspect that need attention is that the moisture uptake is an apparent property only and may not reflect the true values since the weight change does not account for the possible loss of any volatile components; thus formlation showing higher uptake will involve greater underestimation since the rates of reaction resulting in possible volatile components will be directly dependent on the moisture uptake. The data presented

here, therefore, provide more conservative yet still valid comparisons between formulations.

Some insight into the mechanism of moisture uptake can be derived from Figs. 1 and 2. In general, the maximum moisture uptake was only slightly increased as the relative humidity increased from 55 to 75% but further increase in humidity resulted in proportionately much larger increase in the moisture uptake by all the formulations studied. It is possible that at higher humidity an apparent saturation of the sites responsible for diffusional resistance occurs facilitating the diffusion process. A similar argument can be presented for the effect of temperature on formulations II and III (Fig.2), where temperature above 55°C apparently results in a significant decrease in diffusional resistance. The effect of temperature on moisture uptake by formulation I was almost linear over the range studied possibly due to lack of appreciable affinity of the binder to moisture.

Chemical Stability: Ampicillin, like other penicillins, undergoes hydrolysis due to the strained (10-20 Kcal/mole) four membered β-lactam ring resulting in penicillaldehyde, pencillamine and carbon dioxide (16,23). This reaction has been demonstrated to follow an apparent first order kinetics (16). Some insight into the

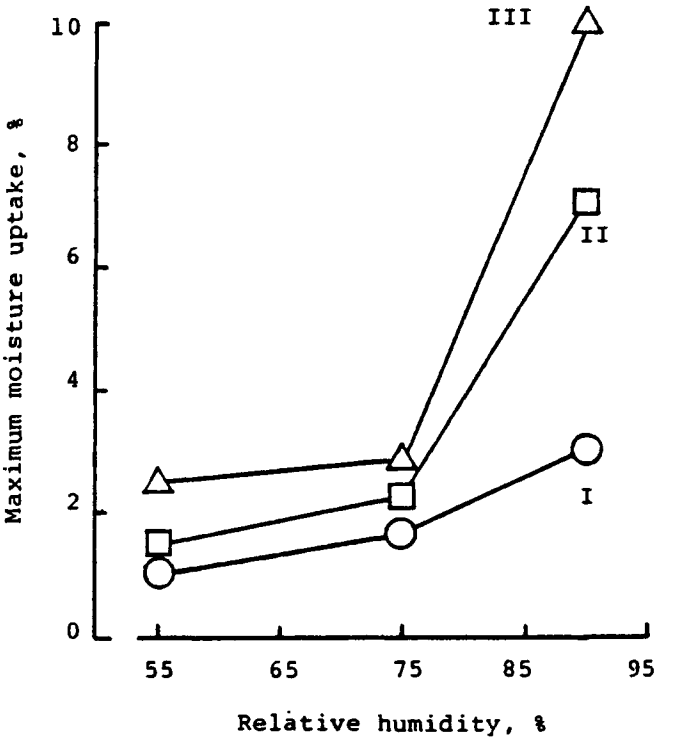

FIGURE 1

Maximum moisture uptake as a function of relative humidity at 40°C.

mechanism of reaction in the formulation studied can be derived from the data presented in Fig.3. An apparent log-linear relationship exists between the ampicillin content remaining as a function of time for formulation I. Similar plots were obtained for the other two formulations. The half lives of decomposition at 40°C are reported in Table II.

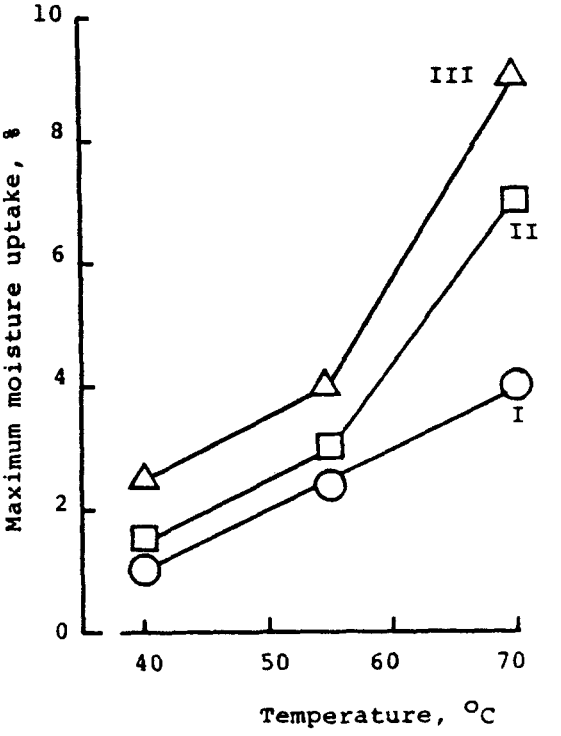

FIGURE 2

Maximum moisture uptake as a funciton of temperature at 55% relative humidity.

An interesting observation was the presence of lag time at lower relative humidity values for all formulations. Such observations have previously been reported for other drugs (24) and were attributed to the access of moisture to the drug and the solution process. At high relative humidity the lag time seems to disappear (24) due to the higher access of moisture to the formulations studied (Fig.3).

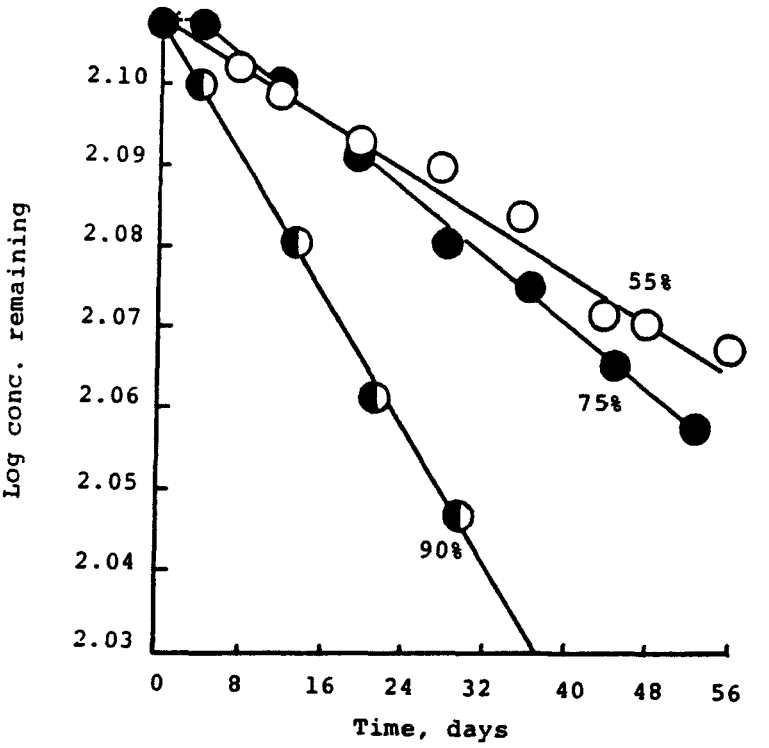

FIGURE 3

Decomposition of ampicillin in formulation I at 40°C and different relative humidities.

The effect of moisture uptake on the decomposition rate can be discerned from Table II. An interesting correlation can be derived from Fig.4 where the half lives of ampicillin are plotted as a function of moisture uptake. Although moisture uptake upto approximately 3% seems to increase the decomposition rate, much higher uptake had lesser effect. Referring back to Fig.2, it can be concluded that an increase in lower

Table II

Half Lives (days) of Ampicillin at 40°C in Three Formulations as a Function of Relative Humidity.

Relative Humidity %	Formulation		
	I	II	III
55	336	239	201
75	182	150	118
90	150	108	70

relative humidity affects the decomposition rate more than increases in high relative humidity.

The data presented here can be explained in terms of a theory proposed earlier (15) that low ampicillin concentration results in increased half life of decomposition. It is possible that higher moisture content results in the dilution of ampicillin resulting in much lower increase in its decomposition. This contention is further substantiated by the fact that an all instances the decomposition half lives were much longer than the time needed for the maximum saturation of the formulation. This would mean that the solution formation is not the rate limiting step

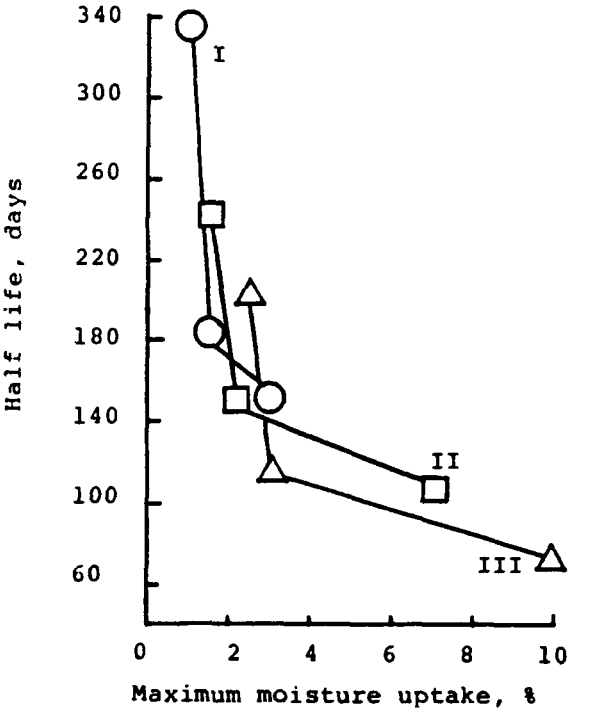

FIGURE 4

Decomposition half lives of ampicillin formulation as a function of maximum moisture uptake at 40°C.

in the deterioration of the formulations rather the solution composition resulting due to the moisture uptake.

Effect of temperature: The rates of the chemical decomposition of ampicillin were studied at 40°C, 55°C and 70°C and as shown in Fig.5, an Arrhenius type relationship exists for the three formulations studied. Interestingly, the activation energies were almost

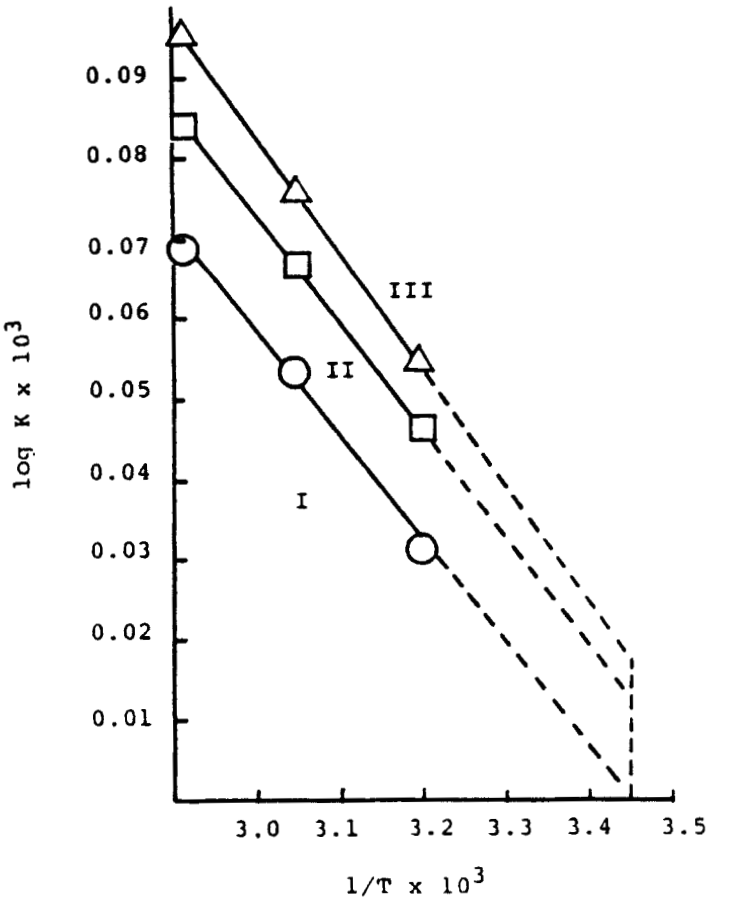

FIGURE 5

Arrhenius plot of ampicillin in three formulations at 55% relative humidity extrapolated to room temperature.

identical ranging from 6.02 to 6.77 Kcal/mole. As discussed earlier, the dissolution of the drug precedes decomposition and a change in temperature will affect the rate of reaction by increasing the diffusion of water vapors through the formulation,

increasing the dissolution and thus increasing the rate of decomposition. It can, therefore, be inferred that relatively similar mechanisms exist for the decomposition of ampicillin in the three formulations studied with similar temperature dependency.

The activation energy valued reported here are, however, lower than reported previously for ampicillin decomposition (16). This observation can be explained on the basis of possible contribution of formulation factors in facilitating the decomposition reaction.

From the data presented above it can be concluded that the formulation containing polymer I exhibits the most ideal stability properties for direct compression formulations of ampicillin. The mechanism of the decomposition of ampicillin in directly compressed dosage forms involves moisture uptake which significantly affects the stability of the drug in the formulation. The temperature effect was less significant because of low activation energies involved.

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