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Cetiedil Citrate Injection, Resolve Instability: Case Study

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Abstract

Cetiedil Citrate Injection, containing 5 mg/mL cetiedil citrate, sodium chloride, and Water for Injection in Type I glass ampules, having an unadjusted pH of 3.3 to 3.7 was insufficiently stable if stored at controlled room temperature (20° to 25°). Shelf life predictions indicated a 1.66 to 1.8 year expiry period. A solution kinetics study showed maximum stability at pH between 3.5 and 3.8. No advantage was observed in the stabilities when the concentration was increased 10-fold, or one of three buffers (citrate-phosphate, acetate, or succinate) were used. The only alternative was storage at refrigeration or Controlled Cold Storage, 2° to 8°.

Arrhenius plots were used to estimate the rate constants at the higher extremes of Controlled Cold (8°) and Controlled Room Temperatures (25°). Eight degrees showed the best promise for satisfactory expiry dating. The experimental and derived temperatures and rate constants were applied to 2 process models that defined all of the steps in the manufacture, testing, release, packaging, transportation and storage, tracking the hypothetical stability in terms of % cetiedil remaining after each step in the process. The models were identical except that one included refrigeration storage and the other did not. The refrigerated solution met stability criteria longer than the non-refrigerated product. However, several processing steps including autoclaving and transportation demanded the application of higher temperatures for a short duration and affected the stability of the product. The data from this study indicate that a 3 year expiry date should be applied.

INTRODUCTION

Cetiedil Citrate, 2-(azepan-1-yl)ethyl-2-cyclohexyl-2-thiophen-3-ylacetate; 2-hydroxypropane-1,2,3-tricarboxylic acid salt (Figure 1). Cetiedil Citrate Injection was an in licensed product under development for the treatment of sickle cell crises. Cetiedil at a dose of 0.4 mg/kg was found to be significantly superior to placebo in reducing the number of painful sites present on all four treatment days and in shortening the total time in crisis [1].

The formulation contained cetiedil citrate 5 mg/mL expressed as the free base, sodium chloride, and Water for Injection in 10 mL Type I glass ampules. The solution was isotonic, contained no other ingredients and was sterilized by terminal sterilization in an autoclave at 120º/14 psi for 20 minutes. The pH was in the range 3.3 to 3.7 (its native pH). Clinical supply batches were on stability testing in 40°, 30°, and 25° chambers with protocols for appropriate testing at monthly intervals for 6 months, quarterly until 18 months, and semiannually up to 48 months.

An early assessment of the stability of the clinical supplies after 3 months storage (Table 1) indicated that solution stability was becoming a problem. The accelerated 3 month 40° samples had 96.2% remaining. The 30° samples had 98.5% and the 25° or Controlled Room Temperature samples had 99.0%. The shelf life specification was not less than 95.0% remaining. The stability problem was confirmed at 6 months, with 93.0% at 40°, 97.3% at 30°, and 98.0% at 25°. The data indicated a shorter than 2 year expiry dating or shelf life which would be problematic both in the clinical development program and eventual commercialization.

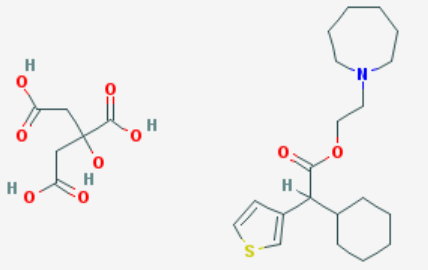

Figure 1 Cetiedil Citrate.

Table 1: Cetiedil Citrate Injection, 5 mg/mL, 10 mL ampules, Clinical Supplies Stability Data.

Time	Cetiedil Remaining, %		
Days	**40° C**	**30° C**	**25°**
Initial	99.5	99.5	99.5
30	98.3	99.2	Not tested
60	97.5	99.0	Not Tested
90	96.2	98.5	99.0
180	93.0	97.3	98.0

[a] *Specifications: Release: 98 to 102%, Shelf Life: NLT 95.0 % remaining*

The intended release specifications are 98 to 102%, and a shelf life of not less than 95.0 % remaining. A minimum shelf life of 2 years would be acceptable; however, 3 years or more would be preferred.

Preformulation testing of cetiedil citrate drug substance had been initiated and was ongoing at the time of discovery of the stability problem. Cetiedil has a pK_a = 9.56 [2]. Cetiedil citrate has usable solubility within the range pH 1 to 5. The solution kinetics were under investigation in the pH 1 to 5 range at a concentration of 0.2 mg/mL in 0.1 N hydrochloric acid, pH 2, 3, 4 and 5 citrate-phosphate buffers at constant ionic strength, μ = 0.5 M, water with and without ionic strength adjustment at temperatures of 80º, 60º, 40º and 30º. The effect of cetiedil concentration at 10-fold the 0.2 mg/mL concentration, and buffers were added after discovery of the stability problem with the formulation on stability testing.

Arrhenius plots were created from data collected from two pH values to obtain estimates of the rate constants at 25° and 8°. These temperatures represent the upper temperature limits of the USP/NF defined Controlled Room Temperature (20° to 25°) and Controlled Cold Temperature (2° to 8°) [3]. The USP/NF further states *a refrigerator is a cold place in which the temperature is maintained thermostatically between 2° and 8°.*

The stability and degradation of a hypothetical batch of cetiedil citrate ampules carried through the manufacturing, packaging, warehouse storage and delivery to a pharmacy was evaluated assuming the absence of refrigeration storage and the inclusion of refrigeration storage to demonstrate the advantages of using refrigeration and validate the selection of using refrigeration for storage and transport of Cetiedil Citrate Injection by the manufacturer.

MATERIALS AND METHODS

Kinetics

Cetiedil citrate solutions containing 0.2 mg/mL were prepared at pHs of 1, 2, 3, 4 and 5 using 0.1 N hydrochloric acid (pH 1), McIlveen's Citrate-Phosphate pH 2, 3, 4 and 5 Buffers and adjusted to constant ionic strength, μ = 0.5 M [4] and water with and without ionic strength adjustment for use in the pH Stability Profile determination. The pH range was limited to pH 1 to 5 because the solubility of cetiedil citrate was less 0.2 mg/mL at pH 6 and higher. Additional 0.2 mg/mL solutions were prepared using acetate [5], succinate [6] and the citrate phosphate buffers adjusted to pH 3.7, and cetiedil citrate in water at a 10-fold concentration of 2.0 mg/mL.

The cetiedil concentrations remaining (%) vs. time (days) for each solution were plotted on semi-logarithmic graph paper. The rate constant (k) was determined by fitting the concentration vs. time data to the following non-linear model equations for first-order kinetics using a kinetics variation of the NONLIN program developed by Niebergall et al [7].

Non-linear first-order kinetics model

$$A_t = A_0\, e^{-kt}$$

where:

A_t = concentration (%) remaining at time, t (days)

A_0 = an initial concentration

k = rate constant ($days^{-1}$)

t = time in days

The time in which a solution stored at the same temperature reaches 95.0%, (t_{95}) can be calculated from its rate constant (k).

$$t_{95} = \ln (0.95)/k$$

$$= - 0.05129/k$$

Arrhenius plots

The rate constants from 80° and 60° storage of the initial 0.2 mg/mL 0.1 N hydrochloric acid, citrate-phosphate buffer solutions, and water with and without ionic strength adjustment were used to create a pH-Stability Profile. The rate constants for 80°, 60°, 40° and 30° for pH 3.7 (water) and 5.0 (citrate-phosphate) were used to create graphical plots of the Arrhenius Equation as described below to obtain estimates for the degradation rates at 25° and 8° by extrapolation.

Arrhenius Plots

$$k = Ae^{-Ea/RT}$$

where

k = rate constant at a given temperature and pH,

A = pre-exponential factor

Ea = Activation energy

R = Gas Constant

T = Absolute temperature, K (degrees Kelvin)

and

$$\ln(k) = \ln (A) - (Ea/R)\,(1/T)$$

The linear version, ln(k) = ln(A) –(Ea/R)(1/T), was evaluated using linear regression because there was insufficient data at each pH to fit the Arrhenius equation to a non-linear model. Reasonable estimates for the values of A and Ea were not available.

Process models

A list of the processes, lengths of time and upper temperature limits starting at mix, fill and finish stage up to dispensing to a patient was created assuming no storage at temperatures less than ambient room temperature (25°). A second similar list was

created assuming that refrigerated storage (2° to 8°) was available during the life of the product and its initial transportation from the manufacturing facility. The upper limits of the temperature ranges and duration of each steep were used to calculate the concentrations of cetiedil remaining after each step in the proposed life of the product.

RESULTS

Kinetics

Semi-logarithmic plots of cetiedil % remaining vs. time for all of the solutions indicated that cetiedil degradation followed a pseudo first-order model with respect to cetiedil concentration. Plots representing the kinetics at pH 3.7 and 5.0 are presented in Figure 2**.** Non-linear regression analyses of the data provided rate constant values supporting pseudo first order degradation dependent upon the concentration of cetiedil in all of the test solutions. The pH-Stability Profile created using the rate constants at 80º and 60º is presented as Figure 3: Cetiedil pH Stability Profile, 80° and 60°.

Maximum rates of degradation were observed at the extremes, pH 1 and pH 5, with minimal degradation in range pH 3.3 to 3.8, which happens to be the pH range of the 5 mg/mL injection formulation. The optimal pH range is the existing pH range of the formulated product.

The degradation rate was not affected by a 10 fold increase in cetiedil concentration, 0.2 to 2 mg/mL. Stability could not be increased or improved by changes in pH, ionic strength, adding buffers such as citrate-phosphate, acetate, or succinate.

Arrhenius Plots

The Arrhenius plots for pH 3.7 and 5.0 are presented in Figure 4 The rate constants used to create Figure 4 and the extrapolated rate constants are presented in Table II also lists the t_{95} for pH 3.7 and 5.0 at 8° as 11.4 and 2.9 years respectively. The t_{95} at 25º and pH 3.7 is 1.8 years.

Process Models

The t_{95} value for pH 3.7 and storage at 8° suggests incredible stability, 11.4 years. However, other processes and activities, and the temperatures and durations must be considered to guarantee satisfactory prediction of stability gained by the use of 8º storage. The maximum duration for a process, analyses, inspections, transportation, packaging and storage were applied with the maximum temperature and its respective rate constant to demonstrate the stability or lack of sufficient stability to meet a preferred 3 year shelf life, i.e. at least 3 years expiry dating after manufacture. Shorter times and lower temperatures might have been sufficient for some of the procedures. However, if a shorter time period could not be guaranteed, the model would not be as dependable and predictive. Then the model would be inadequate to predict an expiry date. Procedures such as Warehouse and Pharmacy storage were automatically assigned 180 days duration because that is what happens at these locations, waiting to be ordered and shipped, or waiting to be needed and dispensed.

The hypothetical solutions are assumed to have a concentration equal to 100% after formulation and 1% degradation due to sterilization under autoclave conditions. Laboratory and storage experiences were assigned a 25º temperature. Shipping was assigned a 40° temperature because it is equivalent to 104°F, a temperature that might be encountered during the summer in the northeast and central US. The calculations were made using the non-linear equation $A = A_0e^{-kt}$. The value of A_0 for each process was the value of A, the % remaining at the end of the last procedure. The tables list the procedures, durations and cumulative durations, the assigned temperatures and rate constants, the ratios of A/A_0, percentage remaining and cumulative time in years.

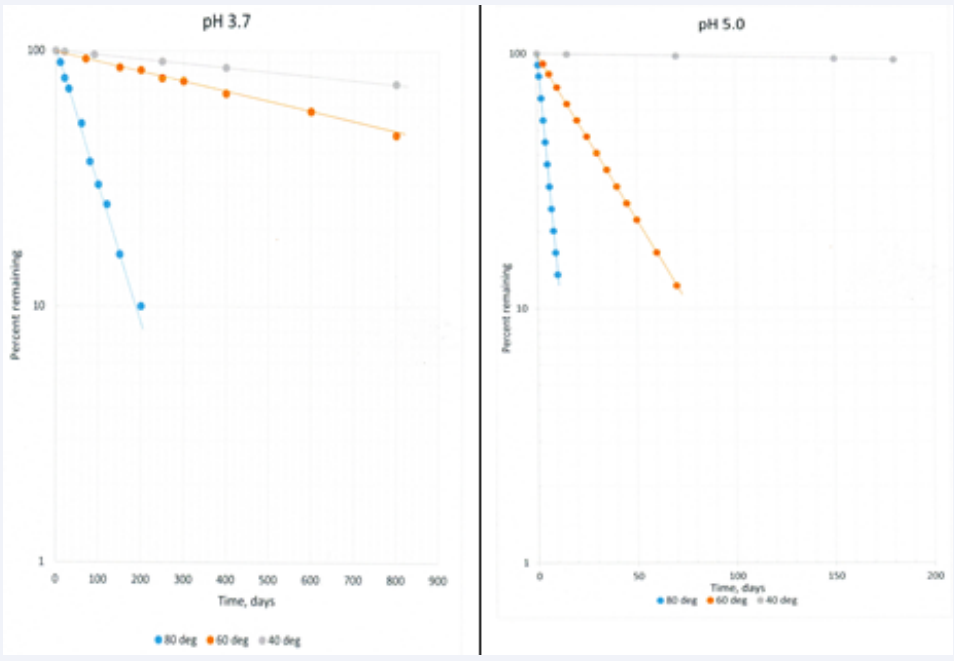

Figure 2 Cetiedil Solution Kinetics pH 3.7 and 5.0 at 80º, 60º, and 40º.

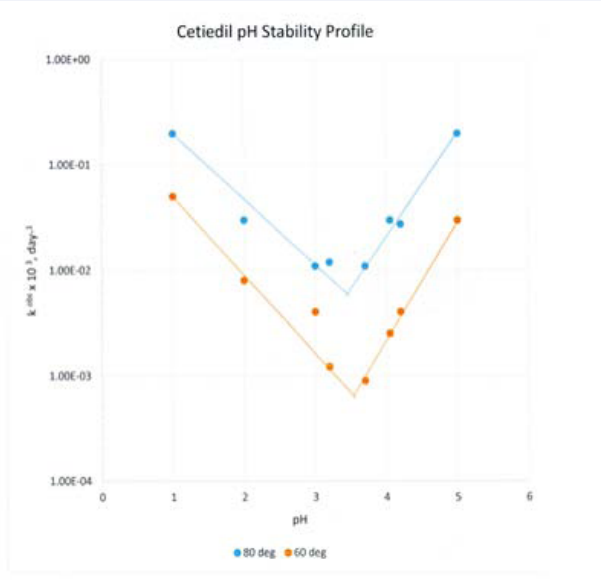

Figure 3 Cetiedil pH Stability Profile, 80º and 60º.

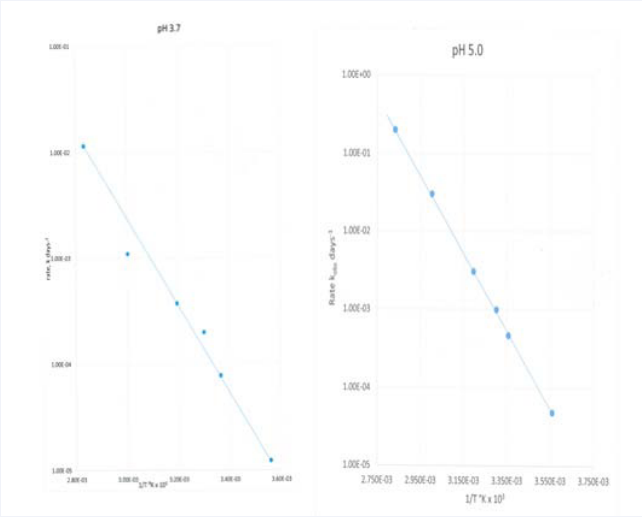

Figure 4 Arrhenius Plots, rate constant k vs. 1/TºK for pH 3.7 and 5.0.

In the absence of storage and transportation under refrigerated conditions the data in Table 2 demonstrate that the hypothetical batch is at 95.1% after 1.66 years, although the calculation from its rate constant at 25° was 1.8 years, a difference of 55 days, showing that expiry dating calculated with only one temperature such as ambient room, i.e. ~ 25° may overestimate the expiry date.

A review of the results of this study lead to a decision to provide refrigerated storage and transportation of the product by the manufacturing organization, and require refrigerated storage for the product, with allowable excursions during transport. The specification that the product could only be stored in the Cold could be enforced at warehousing and in the pharmacy inventories. However, requiring refrigeration for transport from the packaging or wholesaler organizations would be difficult to enforce. Table 4 describes the processes, duration, assigned temperature and rate constant, the ratio and percentage of cetiedil remaining when cold storage/refrigeration is used. After 1.66 years, the time for 95.1% remaining in the previous model, the hypothetical product would contain 97.7% intact cetiedil. Because a Cold Place is required for all storage, time spent in the warehouses and pharmacy is interchangeable. Table 4 contains 8 entries listed as Pharmacy / WWH indicating the equivalence. The Ship to Pharmacy Truck captures the effect of the last transportation of the product and could appear at a different time in the history of the product. However, its existence is captured at 425 days or 1.16 years, although it could occur at any time up to 1865 days or 5.11 years and 96.2% of the cetiedil would have remained in this hypothetical example. Table 3 and Table 4 show that for a parenteral product such as cetiedil citrate, it takes about 58 days or about 2 months to manufacture and have available for distribution to wholesalers and pharmacies. This should be included in any consideration of establishing an expiry date.

CONCLUSION

The data in this study demonstrated that the native pH range of the existing formulation provided maximum stability for the product. Changes in pH, ionic strength, and buffer did not improve the stability of Cetiedil Injection. The only viable alternative for improving stability is storage in a Cold Storage environment. The data in Table 3 and Table 4 show the advantages of lower temperature storage in a Cold Place. A corporate decision was made that storage under refrigeration would be provided by corporate at the manufacturing and warehouse facilities and corporate trucks for delivery to the packaging facility.

The data in Table IV demonstrate that only about 3% degradation occurs after 3 years. Had the initial batch contained only 98.0%, which is within the release rate criteria, the cetiedil percent remaining would approach 95.0% at 3 years. The shelf-life specification for this product is 95.0%. The data in this study support a 3 year maximum expiry dating.

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Table 2: Cetiedil degradation rates ($days^{-1}$) at pH 3.7 and 5.0 vs. temperatures and t_{95} at 8º.

Temperature, °C	pH 3.7	pH 5.0
80	1.15E-02	2.00E-01
60	9.00E-04	3.00E-02
40	3.75E-04	3.11E-03
30	1.00E-04	9.95E-04
25	7.81E-05*	4.50E-04*
8	1.23E-05*	4.85E-05*
8, t_{95}	11.4 years*	2.9 years*

*By extrapolation

Table 3: Calculated Stability for Cetiedil Citrate Injection *vs.* manufacturing, testing, release, distribution, and storage processes with no refrigeration.

Manufacturing	Days		Temp	Rate, k	A/Ao		Cumulative
Procedures	Process	Cumulative	° C	days^{-1}	ratio	%	years
Mix, Fill and Finish	2		30	1.000E-04	1.000	100.0%	
Autoclave	1	1	120/14psi		0.990	99.0%	0.00
Inspection (100%)	7	8	25	7.807E-05	0.989	98.9%	0.02
Analysis/Quarantine	21	29	25	7.807E-05	0.988	98.8%	0.08
QA Review & Release	5	34	25	7.807E-05	0.987	98.7%	0.09
Ship to Packaging	5	39	40	3.750E-04	0.986	98.6%	0.11
Packaging Site	14	53	25	7.807E-05	0.985	98.5%	0.15
Ship to Our Warehouse (OWH)	5	58	40	3.750E-04	0.983	98.3%	0.16
Store OWH 6 mon	180	238	25	7.807E-05	0.969	96.9%	0.65
Ship to Wholesaler's Warehouse (WWH)	5	243	40	3.750E-04	0.967	96.7%	0.67
Store WWH 6mon	180	423	25	7.807E-05	0.954	95.4%	1.16
Ship to Pharmacy	2	425	40	3.750E-04	0.953	95.3%	1.16
Pharmacy 6 mon	180	605	25	1.233E-05	0.951	95.1%	1.66
Pharmacy 6 mon	180	785	25	1.233E-05	0.949	94.9%	2.15

Table 4: Calculated Stability for Cetiedil Citrate Injection vs. manufacturing, testing, release, packaging, storage, and distribution processes that include Cold Storage.

Manufacturing	Days		Temp	Rate, k	A/Ao		Age/years
Procedures	Process	Cumulative	° C	days^{-1}	ratio	%	Cumulative
Mix, Fill and Finish	2		25	7.81eE-05	1.000	100.0%	
Autoclave	1	1	120/14 psi		0.990	99.0%	0.00
Inspection (100%)	7	8	25	7.807E-05	0.989	98.9%	0.02
Analysis/Quarantine	21	29	8	1.233E-05	0.989	98.9%	0.08
QA Review & Release	5	34	8	1.233E-05	0.989	98.9%	0.09
Ship to Packaging	5	39	8	1.233E-05	0.989	98.9%	0.11
Packaging Site	14	53	25	7.807E-05	0.988	98.8%	0.15
Ship to Our Warehouse (OWH)	5	58	40	3.750E-04	0.986	98.6%	0.16
Store OWH 6 mon	180	238	8	1.233E-05	0.984	98.4%	0.65
Ship to Wholesaler Warehouse (WWH)	5	243	40	3.750E-04	0.982	98.2%	0.67
WWH 6 mon storage	180	423	8	1.233E-05	0.980	98.0%	1.16
Ship to Pharmacy Truck	2	425	40	3.750E-04	0.979	97.9%	1.16
Pharmacy / WWH	180	605	8	1.233E-05	0.977	97.7%	1.66
Pharmacy /WWH	180	785	8	1.233E-05	0.975	97.5%	2.15
Pharmacy / WWH	180	965	8	1.233E-05	0.973	97.3%	2.64
Pharmacy /WWH	180	1145	8	1.233E-05	0.971	97.1%	3.14
Pharmacy / WWH	180	1325	8	1.233E-05	0.968	96.8%	3.63
Pharmacy / WWH	180	1505	8	1.233E-05	0.966	96.6%	4.12
Pharmacy / WWH	180	1685	8	1.233E-05	0.964	96.4%	4.62
Pharmacy / WWH	180	1865	8	1.233E-05	0.962	96.2%	5.11

Irwin Gibbs for suggesting consideration of including processing conditions and their effects on stability.

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