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COMMUNICATION

Moist-Heat Sterilization and the Chemical Stability of Heat-Labile Parenteral Solutions

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ABSTRACT

The impact of moist-heat sterilization (autoclaving) on the chemical stability of parenteral solutions was examined using two heat-labile products, clindamycin phosphate and succinylcholine chloride injections, as examples. A nonisothermal kinetic model was used to predict the extent of product degradation during autoclaving. The predicted results were found to be in close agreement with the experimental data. For the same peak temperature, a greater loss of product was shown by using a cycle with a higher F_0. On the other hand, a higher peak-temperature cycle resulted in less product degradation for the same F_0 value. The benefit of a high-temperature cycle was further illustrated by the fact that less chemical degradation for both products was produced by a 122°C cycle with an F_0 of 11 as compared to that which occurred during a 116.5°C cycle with an F_0 of 8.

Although clindamycin phosphate was found to be highly unstable during a conventional autoclaving process, predicted data indicate that a UHT (Ultra-High Temperature) process may be used to sterilize this product with acceptable degradation.

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INTRODUCTION

Moist-heat sterilization is the most commonly used terminal sterilization method for parenteral solutions. The effectiveness of such a process can be quantified by its microbial inactivation capability, which is measured by the F_0 value achieved by that process. An F_0 value is defined as an equivalent sterilizing time (in minutes) of product exposure to a saturated steam environment of 121.11°C. Mathematically, F_0 is calculated by integrating temperatures during various phases of the process and equating these integrated values to time at 121.11°C as shown by the following equation.

$$F_0 = \int_{t_0}^{t_1} 10^{(T(t)-121.11)/Z}\, dt \qquad (1)$$

where $T(t)$ is the mean temperature (°C) between process time t_0 and t_1, and Z is the temperature difference which causes a 10-fold change in the D value of microorganisms. The D value is a measure of the resistance of a population of microorganisms to sterilization. A Z value of 10°C is assumed for an F_0 calculation.

In industrial sterilization, the same value of F_0 can be attained by using sterilization cycles with different temperature–time profiles which are characterized by the peak temperature and the peak dwell-time of the process. The extent of chemical degradation of a drug in solution during moist-heat sterilization can be described by the following equation (1).

$$C_n = C_0 \prod_{I=1}^{n} e^{[Ae^{-Ea/RTi}]\Delta t_i} \qquad (2)$$

where C_0 is the initial drug concentration, C_n is the remaining drug concentration at the completion of the sterilization cycle, A is the frequency factor, Ea is the activation energy, and T_i is the average cycle temperature for each time interval Δt_i.

The impact of the frequency factor, activation energy, and the sterilization cycle on the extent of chemical degradation of a drug has been discussed in detail from the theoretical point of view (1). It was concluded that for a given F_0 value, less chemical degradation occurs during a high peak-temperature and short dwell-time cycle. In this study, the extent of chemical degradation of two heat-sensitive drug solutions, succinylcholine hydrochloride [Ea = 17.2 Kcal/mole and $A = 1.14 \times 10^6$ min^{-1}(2)] and clindamycin phosphate [Ea = 32.4 Kcal/mole and $A = 2.32 \times 10^{16}$ min^{-1}(3)], as a function of the sterilization cycle were experimentally determined and compared with the predicted values as calculated using Eq. (2). Succinylcholine hydrochloride represents drugs with a relatively low activation energy and frequency factor, while clindamycin phosphate represents drugs with a high activation energy and frequency factor. Both of them have been shown to theoretically benefit from a high peak-temperature and short dwell-time cycle.

Ultra-high temperature (UHT) processing and aseptic packaging of liquids have been used for producing sterile dairy-food products (4). A UHT processing system is a continuous-flow operation whereby the product is subjected to axial dispersion and a range of temperatures well above 121°C at any given cross-section and throughout the total process. Though the exposure of the solution to these extreme temperatures is very brief, adequate microbial inactivation can be obtained while unacceptable chemical degradation may be avoided. This is because the activation energies associated with bacterial spore destruction (65–80 Kcal/mole) are much higher than those for chemical reactions (10–25 Kcal/mole). Thus, chemical reactions are less sensitive to changes in temperatures and more dependent on total process time at the elevated temperatures used in a UHT process (5). The feasibility of such a process for sterilization of parenteral solutions was theoretically examined in terms of F_0 value generated and the extent of chemical degradation using clindamycin phosphate as the model drug.

MATERIALS

Succinylcholine chloride injection (20 mg/ml, 10 ml, Abbott Laboratories, North Chicago, IL, Lot 73-225-DK), clindamycin phosphate injection (150 mg/ml, 6 ml, Abbott Laboratories, Lot 73-298-DK), and clindamycin phosphate in 5% dextrose solution were used.

METHODS

Analytical Methods

Succinylcholine Chloride

A Shimadzu RPLC system (LC-6A) equipped with an autosampler (SIL-9A) was used to determine the concentration of succinylcholine chloride in the product before and after autoclaving. A 4 mm × 30 cm micro Porasil column (Waters®, P/N 27477) was the stationary phase. The mobile phase consisted of 1 N tetraethylammonium chloride and methanol (1:9) and the

flow rate was 0.8 ml/min. A UV detector (SPD-6A) was set at 214 nm and 0.1 AUFS. A standard solution of succinylcholine chloride was used to calculate the drug concentration in samples by comparing the peak height of these two solutions. Three samples were assayed with duplicate injections.

Clindamycin Phosphate

The same RPLC system as described above was used to determine the concentration of clindamycin phosphate in the products before and after autoclaving. A 3.9 mm × 30 cm C18 reverse-phase column (Waters Microbondapak®) was the stationary phase. The mobile phase consisted of 23% v/v of acetonitrile in 0.01 M potassium phosphate monobasic buffer containing 0.005 M heptanesulfonic acid sodium salt. The flow rate was 2 ml/min. The UV detector was set at 214 nm with 0.08 AUFS. The drug concentration in the sample was calculated by means of a calibration curve which was prepared from a series of clindamycin phosphate standard solutions. Three samples were assayed with duplicate injections.

Autoclaving Cycles

Samples were autoclaved in a laboratory autoclave (the chamber is 24 in. in diameter and 18 in. in depth) using six different cycles (spray-water-air-overpressure cycle) with the peak temperatures ranging from 122.1°C to 112.8°C and the resultant F_0 values ranging from 20.7 to 8.4. The pressure was 30 psig and the samples were placed in flat, perforated racks. Two thermocouples were used to monitor the temperature of the autoclave chamber at two separate locations. The temperature of the product was monitored by using two thermocouples in two product containers. Figure 1 depicts the temperature–time profiles for the three cycles with the higher F_0 values. These profiles were constructed using the average of the temperature output from the two product thermocouples.

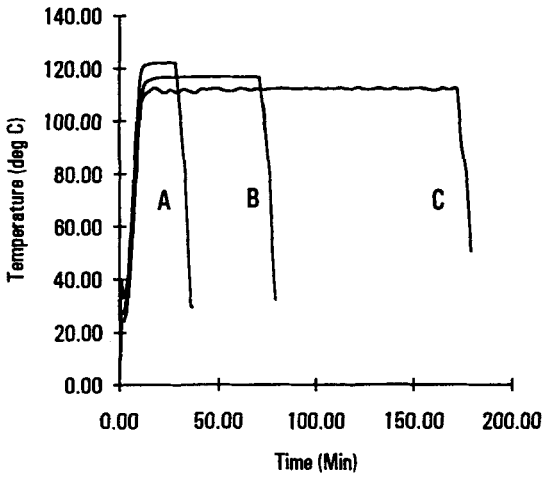

Figure 1. Three autoclaving cycles. A: 122.1°C, F_0 = 20.5, B: 116.7°C, F_0 = 20.7, and C: 112.8°C, F_0 = 20.5.

RESULTS AND DISCUSSION

The theoretical remaining potencies for clindamycin phosphate and succinylcholine chloride after autoclaving via the six different cycles are calculated using Eq. (2) with the time interval set for 1 sec. The predicted and actual remaining potencies for these two injections after autoclaving are presented in Table 1. In spite of a comparatively higher actual loss of the drug than that predicted using Eq. (2), both sets of data are in reasonably good agreement. The discrepancies may be attributed to the deviations from the Arrhenius relationship for reactions occurring at high temperatures (i.e., above 100°C). Both the experimental and predicted data indicate that a greater extent of drug degradation occurs during autoclaving cycles with lower peak temperatures but longer times in achieving the same F_0 value. Although this phenomenon is present in both the cases of clindamycin phosphate and succinylcholine chloride, the impact of the autoclave cycle on clindamycin phosphate is much more pronounced than that observed on succinylcholine chloride. This can be explained by the relatively fast degradation rate (a high frequency factor) associated with clindamycin phosphate.

Judging from the results presented in Table 1, it is apparent that succinylcholine chloride can be terminally sterilized by moist heat using an autoclave cycle with a high peak temperature and short process time. The autoclaving of clindamycin phosphate using the cycles evaluated in this study resulted in unacceptable product degradation. However, a close examination of the data (Table 1) reveals that the use of a high peak-temperature cycle with a high F_0 (121.9°C, F_0 = 11.2) resulted in less degradation than that present using a low temperature cycle with a low F_0 (113.8°C, F_0 = 8.4, and 117.8°C, F_0 = 8.8).

These results clearly indicate that a UHT process with a very brief processing time and temperatures much higher than 121°C may allow the moist-heat sterilization of clindamycin phosphate without unacceptable

Table 1

Effect of Autoclaving Cycles on the Chemical Degradation of Clindamycin Phosphate and Succinylcholine Chloride in Injectable Solutions

	Percent Potency Remaining						
	Clindamycin Phosphate				Succinylcholine Chloride		
Peak Temp.	F_0	Predicted	Actual[a]	Δ	Predicted	Actual[a]	Δ
122.1°C	20.5	64.08	60.01	4.07	99.34	98.32	1.02
116.7°C	20.7	46.53	42.79	3.74	98.53	96.34	2.19
112.8°C	20.5	27.07	21.95	5.12	97.05	92.80	4.25
113.8°C	8.4	58.69	56.59	2.10	98.76	97.58	1.18
117.8°C	8.8	71.80	69.65	2.15	99.39	98.33	1.06
121.9°C	11.2	77.34	74.86	2.48	99.60	99.37	0.23

[a]Mean of three samples.
Δ = predicted - actual.

Table 2

F_0 and the Percent Drug Remaining as a Function of Temperature (Above 121°C) and Time

	Time (sec)											
	5		10		15		20		25		30	
T (°C)	F_0	%	F_0	%	F_0	%	F_0	%	F_0	%	F_0	%
124	0.16	99.8	0.32	99.5	0.48	99.3	0.64	99.0	0.80	98.8	0.96	98.6
126	0.26	99.7	0.52	99.4	0.78	99.1	1.02	98.8	1.30	98.5	1.56	98.2
128	0.41	99.6	0.82	99.3	1.23	98.9	1.65	98.5	2.05	98.2	2.46	97.8
130	0.65	99.5	1.30	99.1	1.95	98.7	2.60	98.2	3.25	97.8	3.90	97.3
132	1.02	99.5	2.04	98.9	3.06	98.4	4.08	97.8	5.10	97.3	6.12	96.8
134	1.62	99.3	3.24	98.7	4.86	98.0	6.48	97.4	8.10	96.7	9.72	96.1
136	2.57	99.2	5.14	98.4	7.71	97.6	10.28	96.8	12.85	96.0	15.42	95.2
138	4.07	99.0	8.14	98.0	12.21	97.1	16.28	96.0	20.36	95.2	24.42	94.2
140	6.45	98.8	12.90	97.6	19.35	96.6	25.80	95.3	32.25	94.2	38.70	93.1
142	10.32	98.6	20.46	97.1	30.69	95.7	40.92	94.4	51.15	93.0	61.38	92.1

degradation. Table 2 presents the predicted F_0 [Eq. (1)] and the percent of drug remaining [Eq. (2)] after the solution is exposed to temperatures higher than 121°C for various time intervals which can be employed in a UHT process. These data further demonstrate the advantage of using higher temperatures and shorter exposure times in minimizing drug degradation. For example, at 142°C, an F_0 of 10.3 can be achieved within 5 sec with 98.6% of drug remaining, whereas at 134°C, it takes 30 sec to yield an F_0 of 9.7 but results in 96.1% of drug remaining, which represents drug degradation almost three times higher. Therefore, in theory, a UHT process can be considered for moist-heat sterilization of heat-labile drug solutions. However, it is important to realize that the use of a UHT process can only provide sterilization of the bulk solution. Since, in non-controlled manufacturing areas, contamination may occur during the subsequent filling of the sterile solution, the sterility assurance level (SAL) achieved during the UHT process cannot be assured in the final product unless other advanced sterile manufacturing processes are used. Examples of such processes are form-fill seal or barrier technology which, when coupled with the UHT process, can produce sterile product with an acceptable SAL.

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