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A COMPUTERISED METHOD FOR CONTROLLING THE TEMPERATURE OF A PHARMACEUTICAL CREAM DURING PILOT-SCALE MANUFACTURE

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ABSTRACT

A microcomputer-based system has been developed to control the rate of cooling of a cream in a commercial pilot-scale turboemulsifier. Control is achieved by opening a valve in the cooling circuit for a calculated time during any control period, allowing water to circulate in the vessel jacket. The length of time for which the valve is open is calculated from the discrete form of the Proportional-Integral-Derivative (PID) control equation. This equation contains three constants which must be optimised for any given system. These will depend on factors such as the temperature and flow-rate of the cooling water, the heat input from the homogeniser and the heat transfer characteristics of the processing vessel.

The theory behind PID control is discussed briefly. The development of the system, including methods for obtaining the control constants is also discussed. Control of the temperature of a cream to within ± 1°C of a target temperature profile has been achieved routinely with the present system.

THEORETICAL

The control method used is based on feedback control; the cooling action is calculated from the difference between the actual and required temperatures. The simplest form of feedback control is given by the proportional-only controller :

$$P(t) = K\,E(t) \tag{1}$$

where P(t) is the controller output at time t, and E(t) is the error at that time. K is a constant known as the controller gain. This equation is most readily understood when applied to the control of a heater. In this case, P(t) is the heater power output, and E(t) is the difference between the required and actual temperatures at time t. Some limitations of equation (1) may now be considered.

The equation can only be applied over a limited range of power outputs. There will be a maximum and minimum (usually zero) power output from any given heater. The system therefore cannot apply any cooling should the required temperature be exceeded, and may not be able to provide sufficient heat to overcome a drop in temperature as quickly as may be desired. These limitations will apply to any system. A controller will work best when working within its linear range, where these conditions do not apply.

A controller working from equation (1) will run at a steady-state offset from the required temperature. This arises because no heat is supplied when there is no temperature error. The system will therefore cool to a temperature at which the heater again operates.

For high values of the gain K, the system will tend to oscillate about the set point, in much the same way as a thermostat operates. The heater will overshoot the required temperature and switch off until the temperature falls below the set-point again.

The proportional controller may be improved by adding further terms to equation (1). The full Proportional-Integral-Derivative controller is given by the equation

$$P(t) = K \left[E(t) + 1/T_i \int E(t)dt + T_d \, dE(t)/dt \right] \quad (2)$$

where T_i and T_d are the integral and derivative time constants respectively. The integral term in equation 2 results in the removal of the offset error discussed above. The derivative term enables the PID controller to respond more rapidly to sudden changes in temperature. A fuller discussion of the theory of PID control may be found in references 1 to 4.

For implementation on a computer, a discrete form of equation (2) may be derived :

$$P(t) = P(t-1) + A\,E(t) + B\,E(t-1) + C\,E(t-2) \quad (3)$$

where E(t-1) and E(t-2) are the errors for the previous two control cycles, and A, B and C are constants. These constants may be obtained from the gain and time constants discussed above. The way in which the controller responds to temperature changes will depend on the values of the constants. The process of optimising the controller performance by selecting the best values for these constants is known as tuning the controller.

One way of tuning the controller is Reaction Curve Analysis[5]. In this technique, the curve resulting from a step change in the controller output is examined. From this, values for the three constants may be obtained. An example of a

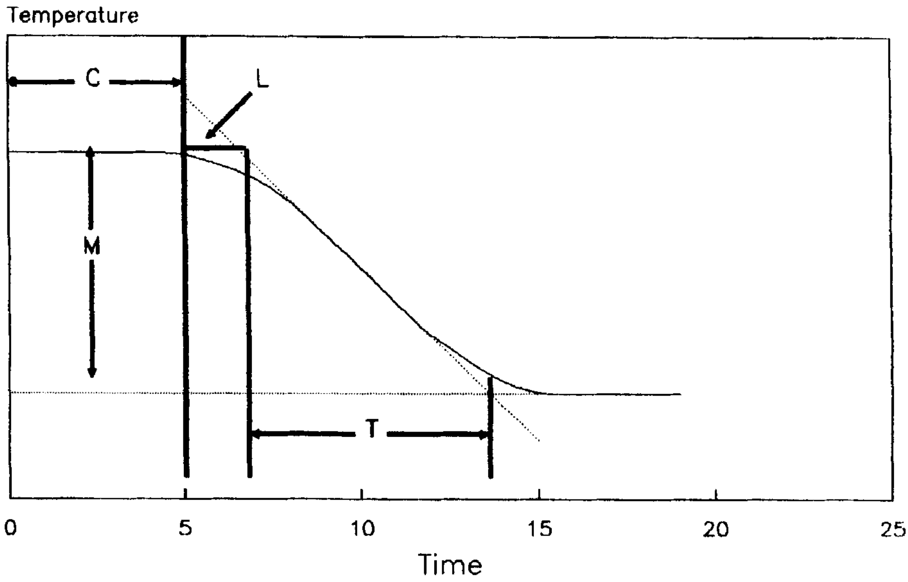

FIGURE 1
Reaction Curve Analysis
C = Cooling Time
M = Overall Temperature Change
L = Lag Time
T = Overall Reaction Time

reaction curve is shown in figure 1. A short burst of cooling water is admitted to the system at time zero. The length of this burst is denoted by C. From the resulting curve, three parameters are obtained. These are the overall change in temperature (M), the lag time before any temperature change becomes apparent (L) and the overall time for which the system reacts to the cooling burst (T). From these parameters, the gain, and the integral and derivative time constants may be derived by a method known as Cohen-Coon tuning. This method is described in the following equations. The constants in these equations were derived in order to give a good compromise in the controller between a rapid response and minimal overshoot.

The process gain, Kp is given by

$$Kp = M/C \quad (4)$$

The gradient is given by

$$R = M / T.C \quad (5)$$

An index of self-regulation, m, is obtained as

$$m = L\ (R/K) \quad (6)$$

The time constants are then calculated by Cohen-Coon tuning as

$$T_i = L\ (1 + m/5)/(0.4(1+3m/5)) \quad (7)$$

$$T_d = 11L/(30(1+m/5)) \quad (8)$$

The controller gain is given by

$$K = 1.35\ (1+m/5)\ L.R \quad (9)$$

The constants A, B and C are then obtained as

$$A = K\ (1+T/T_i) \ + (T_d/T_s)) \quad (10)$$

$$B = -K\ (1+2T_d/T_s) \quad (11)$$

$$C = K\ \ (T_d/T_s) \quad (12)$$

where T_s is the sampling time.

EQUIPMENT

The objective of this work was to develop a control system for a pilot-scale turboemulsifier (Model TE3 VR-10, Pressindustria Chemical Equipment SPA, Milan). This consists of a high-speed, high-shear mixer in a 10 litre stainless steel jacketed vessel, with anchor paddles to ensure good mixing of the product. The control system is based on an Apple][e microcomputer (Apple Computer Inc., California) fitted with an ADALAB card (Interactive Microware Inc., Pennsylvania). This card provides analogue and digital input and output facilities.

The temperature is monitored by a digital thermometer (Model 6110, Comark Electronics Ltd., W.Sussex) equipped with a Type K thermocouple. The voltage output from the thermometer is fed into the ADALAB card.

The cooling water flow rate is controlled by a set of needle valves and variable cross-section flow meters. Computer control of the flow is achieved by on/off solenoid valves (part 342-023,RS Components, Ltd. Corby, Northants.) in the cooling circuit. To obtain the required 12V output to drive these valves, the digital output from the ADALAB card is amplified by a suitable circuit, designed and built in-house. The system is able to operate up to four solenoid valves in any combination; only a single valve was used in any one experiment in the present work.

A block diagram of the system is shown in figure 2.

For small-scale experiments, the temperature in a 2 litre aluminium jacketed vessel was controlled. In this case, there was no valve to control the coolant flow rate, but in other respects the system was equivalent to that described above.

The computer program was written in Applesoft BASIC, using the QUICKI/O software to transfer information between the program and the ADALAB card. The QUICKI/O software was supplied with the card.

The main elements of the program are described in the following paragraphs.

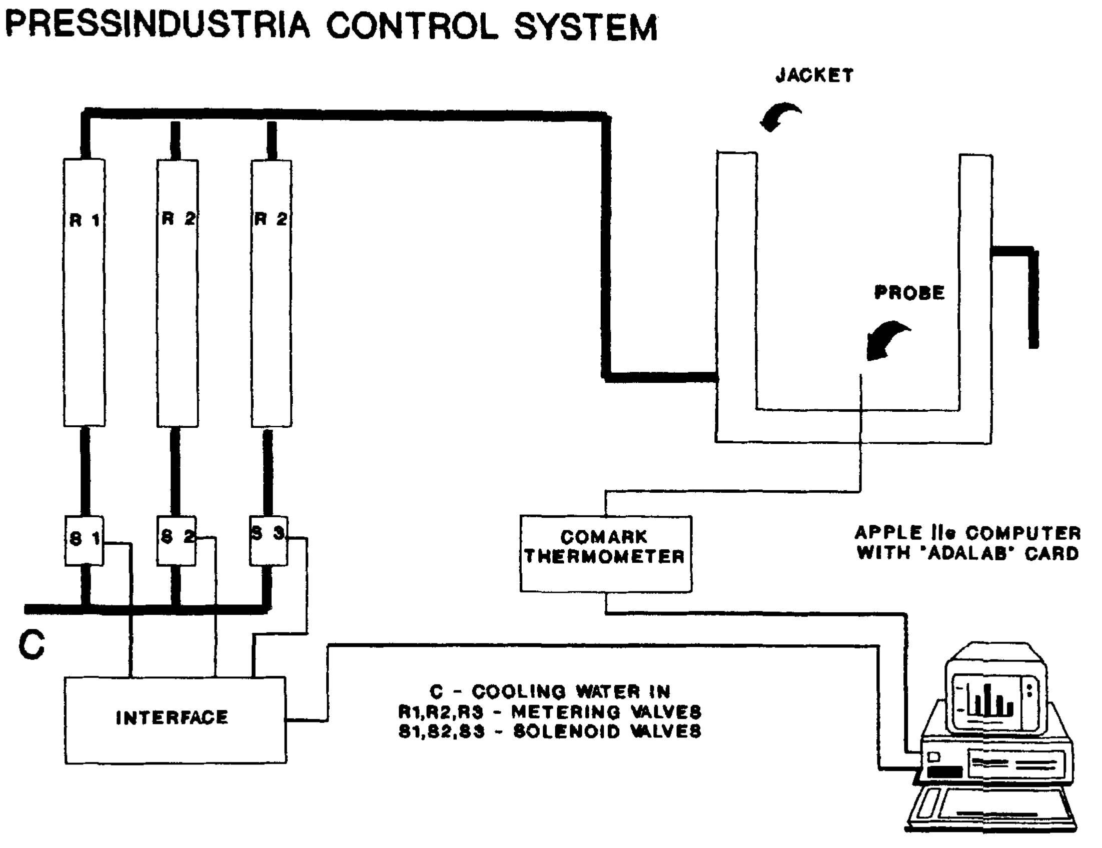

FIGURE 2
Block Diagram for Control System

The initialisation routine is used to enter the A, B and C constants, the reading interval and the temperature control curve. This curve consists of an initial holding phase at a constant temperature, followed by a linear decrease of temperature with time.

The calibration routine calibrates the temperature and output voltage from the digital thermometer.

In the control routine, a set of ten readings are taken at 50 ms intervals at the start of each control cycle. These are averaged, and the mean compared with the current required temperature, as calculated from the control curve. Equation (3) is then applied to calculate the valve open time for that cycle. Boundary conditions are applied to the result of this equation, so that P(t) is never less than zero, nor greater than the control interval. The valve is opened for the calculated time, then closed for the remainder of that cycle. If P(t) is at its maximum value, the valve is not closed at the end of the control cycle, enabling the maximum uninterrupted cooling to be given when required. While the control routine is running, the required and actual temperature are displayed on the monitor, with the valve status and calculated valve open time. This enables the operator to follow the control of the process.

The final routine will either print the actual and required temperatures for the process, or store these on disk for later analysis. This enables a record of the cooling of the cream to be kept as part of a batch record.

MATERIALS AND METHODS

The cream used in these studies was a formulation containing Cetomacrogol BP, Stearyl Alchol, Liquid Paraffin BP and distilled water, together with an active ingredient and a preservative. The required process is to melt and mix the non-aqueous ingredients at 65°C, add the drug and preservative and homogenise, add pre-heated water at 65°C, homogenise at this temperature for 10 minutes, then cool under vacuum with homogenisation to 35°C, and cool to ambient with no further homogenisation. The advantage of the control system is that the time for homogenisation and cooling, as well as the temperature range, may be controlled. A cooling rate of 1°C min^{-1} was specified;

cooling from 65°C to 25°C therefore occurs over a period of 40 minutes.

During the above process, various factors will affect the temperature of the cream. The controller should minimise the deviations from the required temperature due to such causes, as well as providing a uniform rate of cooling.

There is an energy input of about 1kW from the homogeniser when working at full speed. Thus some cooling by the controller is required even during the initial holding phase. Later homogenisation is at a slower speed, therefore there is less heat to be dissipated during the cooling phase.

The controller will tend to maintain the required temperature during the addition of ingredients, even if these are not at exactly the required temperature. In this case, the heat input from the homogeniser is a positive benefit, since the mix may be heated if required.

RESULTS AND DISCUSSION

A typical cooling curve, with no feedback control, is shown in figure 3. In this case the cream was cooled from 80°C to 25°C, and the homogeniser switched off at 35°C. The graph clearly shows the change in cooling rate as the temperature decreases, and also the point at which the homogeniser was switched off. There is a sudden decrease in temperature at about 50°C, due to the cream undergoing a phase inversion. Between about 50°C and 45°C the temperature fluctuates rapidly, over about ± 2.5°C in less than a second. Because the data was recorded with a much

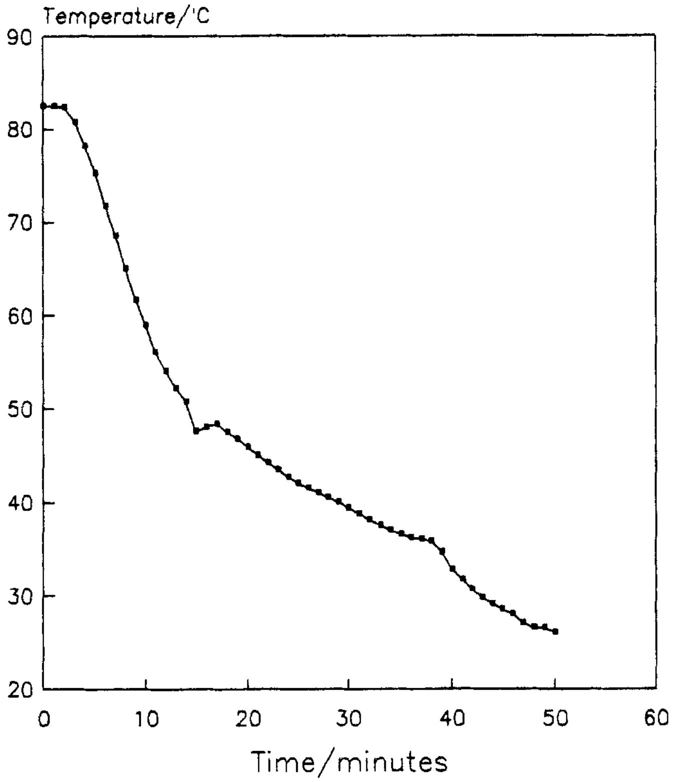

FIGURE 3
Cooling Curve with no Feedback Control
Water flow rate 650 ml min^{-1}

longer interval, this does not appear in the figure. These fluctuations tend to upset the controller. The averaging of ten temperature readings was included in the program to reduce the effect of such fluctuations on temperature control.

Figure 4 shows the cooling curve obtained when the controller is in operation, but before the control constants have been optimised. The fluctuations about the required

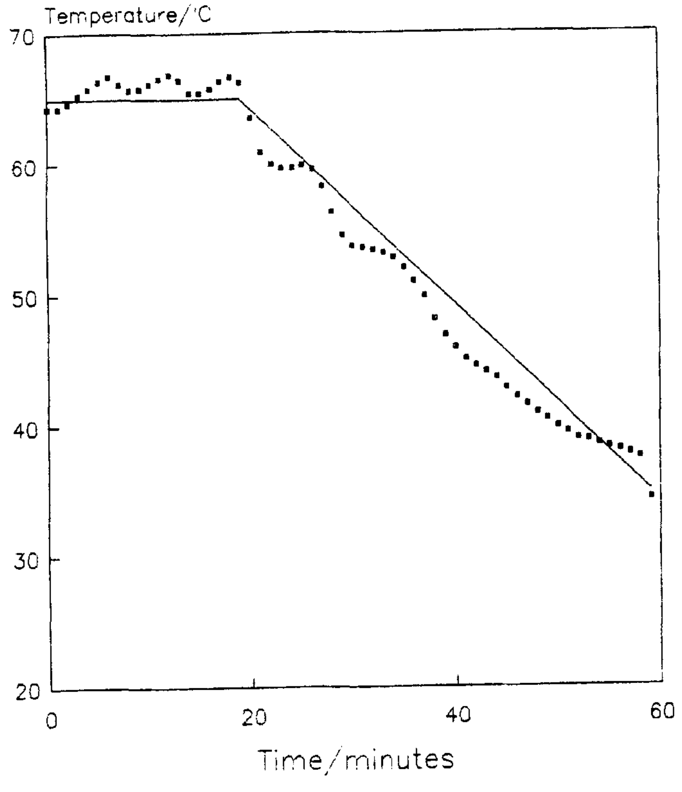

FIGURE 4
Cooling Curve with PID Control
Water flow rate 800 ml min^{-1}
Required curve is shown as a solid line.
A = 12 B = - 10 C = 0.1

line are typical of a poorly tuned system. Overcooling is followed by a delay while the required temperature catches up, and this cycle is repeated. Control below 40°C is poor; cooling water at the maximum flow-rate (800 ml min^{-1} in this case) cannot remove the heat sufficiently quickly. For this reason, no data was collected after 60 minutes. Compared to the uncontrolled cooling of figure 3, the temperature/time curve is now much closer to a straight line.

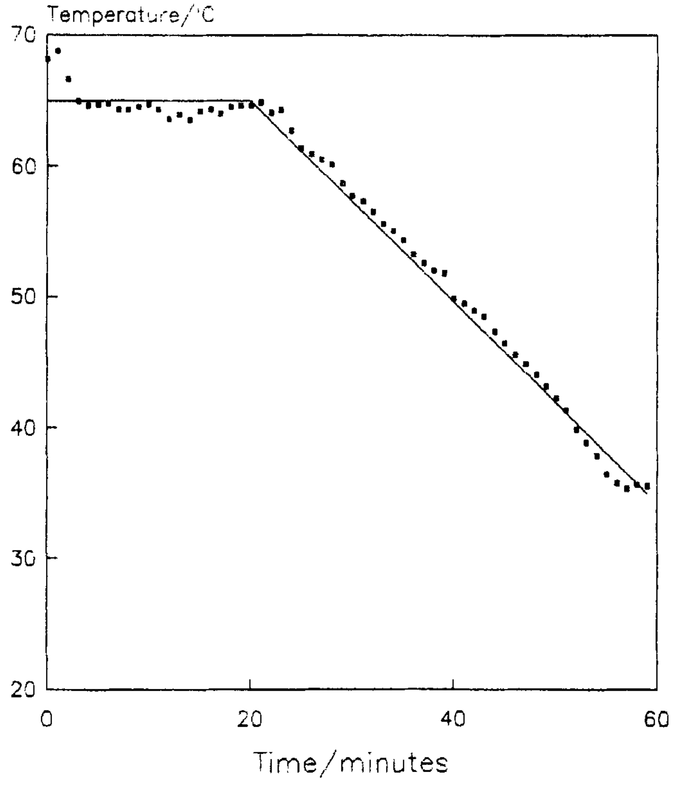

FIGURE 5
Cooling Curve with Optimised PID Control
Water flow rate 800 ml min^{-1}
Required curve is shown as a solid line
A = 120 B = -100 C = 1

When the constants are optimised, much better control is achieved, as shown in figure 5. Control is still poor below 35°C, but otherwise good control to within ± 1°C is obtained. It was thought unlikely that further optimisation of the constants would yield any significant improvement in this case.

In order to obtain better control at low temperatures, the coolant flow rate was increased to 5000 ml min^{-1}. To obtain the constants at this new flow rate, reaction curve analysis was used. The cream was heated to approximately 70°C, and allowed to come to a steady temperature. A 20s burst of cooling water was put through the system, and the resulting temperature/time curve recorded. This was repeated at approximately 10°C intervals down the cooling curve, and also with 10s and 5s bursts of cooling water. From the resulting curves, the overall temperature change, lag time and reaction time were calculated, and hence new values for the A, B and C constants. It was noted that the lag time and cooling gradient were greater at higher temperatures, as might be expected. Variation in the calculated constants reflected this, these being higher at low temperatures. The mean values of the constants were calculated, and used to control the cooling of a cream using the higher coolant flow rate.

Figure 6 shows the resulting cooling curve. Good control is achieved right down to 25°C. Control between 60°C and 50°C is slightly poorer than with the lower flow rate, but this is more than compensated for by the improved control at lower temperatures. In particular, it is no longer possible to detect the point at which the homogeniser is switched off.

The following paragraphs describe further improvements to the control system. These were carried out using a 2 litre jacketed metal vessel rather than the Pressindustria system. The coolant flowrate was 3900ml. min^{-1}. No other changes were made to the system.

Before using this small-scale system, the appropriate values of the control constants must be determined. Rather

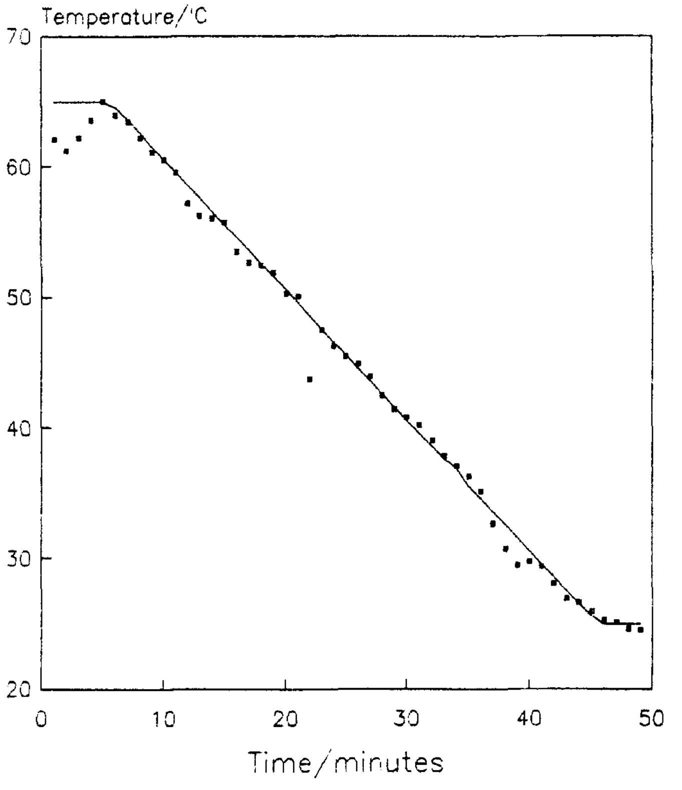

FIGURE 6
Cooling Curve with Optimised PID Control
Water flow rate 5.0 l min^{-1}
Required curve is shown as a solid line
A = 33 B = - 15 C = 0.5

than using the Cohen-Coon method, the constants were optimised by the sequential simplex method [1,6]. It had previously been noted that the system is fairly insensitive to the value of C. This was kept constant, and the A and B constants were optimised. The steps in this optimisation are shown in table 1. The initial conditions were chosen such that the simplex contracts towards the optimum. The quality of control for each set of constants was measured by

TABLE 1

Simplex Optimisation of Control Constants

Run	A	B	RMS Error	Simplex Move	Current Simplex
1	100	- 50	0.053	Initial	
2	500	- 50	0.230	Initial	
3	500	-400	0.552	Initial	
4	100	300	0.667	Reflect 3	1,2,3
5	400	-225	0.135	Contract 3	
6	0	-225	xxxx	Reflect 2	1,2,5
7	375	- 90	0.134	Contract 2	
8	75	85	0.154	Reflect 5	1,5,7
9	319	-148	0.154	Contract 5	
10	158	6	0.097	Reflect 9	1,7,9
11	-108	38	xxxx	Reflect 7	1,7,10
12	254	- 58	0.173	Contract 7	
13	190	- 32	0.077	Contract 12	
14	132.5	- 95	0.074	Reflect 10	1,10,13
15	42	-108	xxxx	Reflect 13	1,13,14
16	152	- 55	0.080	Contract 13	

xxxx = no control.

calculating the root mean square difference between the actual and required temperatures for all readings taken. The optimum constants were taken as the central coordinates of the final triangle. Repeat experiments using these constants gave rms error values between 0.07 and 0.10°C. These constants were used in the following experiments.

One advantage of the feedback controller is that any type of cooling curve may be used, provided that the

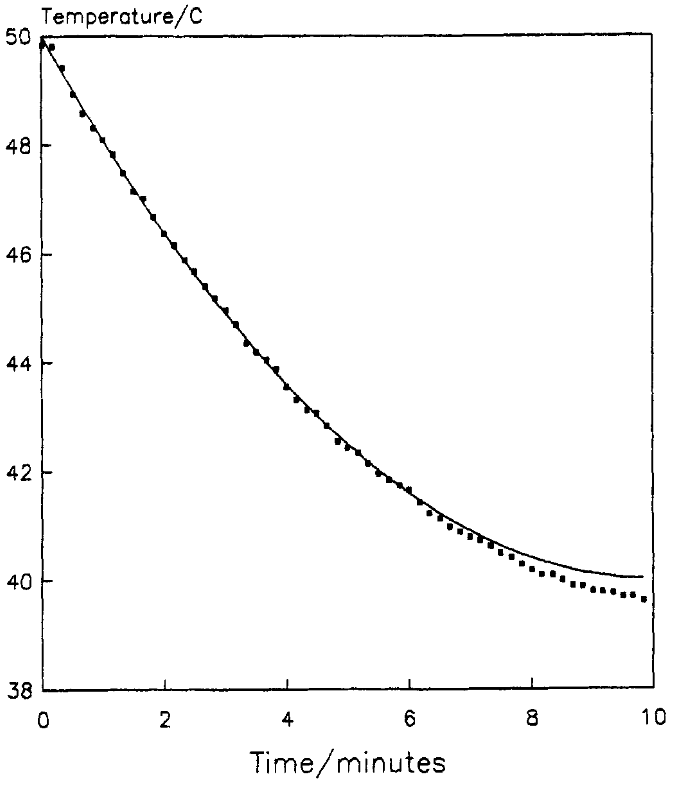

FIGURE 7
Quadratic Cooling Curve (Small scale apparatus)
Water flow rate 3.6 l min^{-1}
Required curve is shown as a solid line
A = 141 B = - 59 C = 1

required temperature at any given time can be obtained, either from a suitable equation, or by manual storage in computer memory.

An example of non-linear cooling is shown in figure 7. The cooling curve in this case is a quadratic curve, decreasing from 50°C to 40°C over 10 minutes. At the end of this time, the gradient of the curve is specified to be zero. The temperature is within ± 0.2°C of the target temperature until near the end of the experiment, when the temperature falls faster than required. This is because there is no source of heat in the system. The contents will cool faster than the required rate, even with no coolant flowing.

The theory behind the PID controller assumes that there is a linear response to the controller output. In the present case, this is not so. The cooling effect of a 10s burst of cold water will be greater at 60°C than at 20°C. In order to obtain a linear response, the controller output may be multiplied by a suitable temperature-dependant factor. The cooling effect of the circulating water is porportional to the temperature difference between the vessel contents and the coolant. The time for which the valve must be opened is therefore inversely proportional to this diference. The linearisation factor (F) may therefore be obtained from an equaton such as

$$F = (45 - Tc) / (T - Tc) \qquad (13)$$

where T is the temperature of the vessel contents and Tc is the coolant temperature. The figure 45 in this equation is the mid-point of the normal cooling range. This ensures that at this temperatures the factor is unity.

This factor should be applied before the condition that the valve open time P(t) is less than the control interval. At present this improved algorithm has only been used on the small scale vessel, with encouraging results.

CONCLUSION

The control system works well for the Pessindustria turboemulsifier. Control to within ± 1°C is seen as adequate for the production of creams on a pilot scale, and this has been achieved routinely. The development cost of the system was low, as the computer hardware was already available. The same control strategy may be used in other applications, as demonstrated by the small-scale cooling experiments. With slight modification, controlled heating could also be achieved.

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REFERENCES

1) M.A.Sharaf, D.L.Illman and B.R.Kowalski, "Chemometrics", Chapter 7, John Wiley and Sons, New York. (1986).

2) C.L.Pomernacki, Rev. Sci Instrum 48, 1420 (1977).

3) A.B.Corripo, in "AIChE Modular Instruction Series A", T.F.Edgar ed., Amercian Institute of Chemical Engineers, New York. 3, 63 (1982).

4) J.S.Smith, Laboratory Microcomputer 5, 26 (1986)

5) G.A.Coulman, in "AIChE Modular Instruction Series A", T.F.Edgar ed., American Institute of Chemical Engineers, New York. 2, 22 (1982).

6) J.A.Nelder and R.A.Mead, Comput.J. 7, 308 (1965).