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Apparatus for accelerated temperature cycling

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An automatic control unit, activating electrically operated solenoid valves, is used to regulate the flow of "hot" and "cold" water from two thermostated baths to the jacket of a reaction vessel so that the temperature of a liquid sample within the vessel follows a highly reproducible programmed cycle. A comparison is made of the temperature hysteresis between 23–33° during a 16 min cycle, when the flow rates to the vessel are changed and when the valves are operated manually. The adjustment of temperature hysteresis to effect the accelerated storage testing of liquid preparations is described.

IN recent years the method of choice for the accelerated storage testing of pharmaceutical preparations has been the exposure of several different samples of the same preparation to one of a number of elevated temperatures (Garrett, 1962). This technique is applicable to chemical degradation only and produced mathematically satisfactory results on the basis of the Arrhenius equation. Nevertheless, protracted shelf storage tests under ambient conditions were still necessary to ensure that the experimental results correlated with shelf storage conditions.

The physical degradation of a product is more likely to occur under temperature oscillation than at a static elevated temperature. Thus, high frequency, reproducible temperature cycling is desirable for producing the accelerated physical degradation.

Several designs of temperature controller were investigated, but none was entirely suitable in producing the rapid temperature cycling of liquid preparations (Brandt & Brown, 1955; Barnes, 1956; Beament & Machin, 1959; Boer, 1963; Scott, Min, Campbell & Anderson, 1964; Van Outryve, 1965; Cole, Dickinson, Guczi, Hill & Tyrrell, 1965; Borgars, 1966).

We now report a design which, because of good heat transfer properties, permits a relatively high frequency of temperature cycling and the examination of one sample of the preparation over very short periods. Thus, it is possible to produce physical changes in the preparation by the variation of the time factor alone without recourse to large numbers of samples, elevated temperatures (which may alter the mechanism of degradation) or bulky apparatus.

APPARATUS

The basic apparatus is a stainless steel, jacketed reaction vessel connected to two thermostated baths supplying "hot" and "cold" water (Carless & Foster, 1966).

Water circuitry. The suspension to be studied is placed in the vessel and the temperature cycling is induced by the passage through the vessel jacket of "hot" water and "cold" water alternately, each supplied from a thermostatic bath fitted with an external pump (Circotherm II*). Suitable

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* Shandon Co., Ltd. London.

adjustment of the temperature and flow rates from each bath permits the temperature cycle to conform to the preselected programme, e.g. 23–33–23° during times 0–8–16 min. Bypasses are provided, so that, when the "hot" water is flowing through the vessel the "cold" water is being pumped through the bypass, and vice versa. By this means, it is possible to maintain a constant pumping rate for each bath through the temperature cycle. Fig. 1 illustrates the water circuitry to effect these conditions and shows the suspension being heated. V_1 to V_6 inclusive are solenoid-operated water valves, which may be either in the open or closed position. Valves V_1, V_2 and V_3 are open when the suspension is being heated, whereas V_4, V_5 and V_6 are open when the suspension is being cooled.

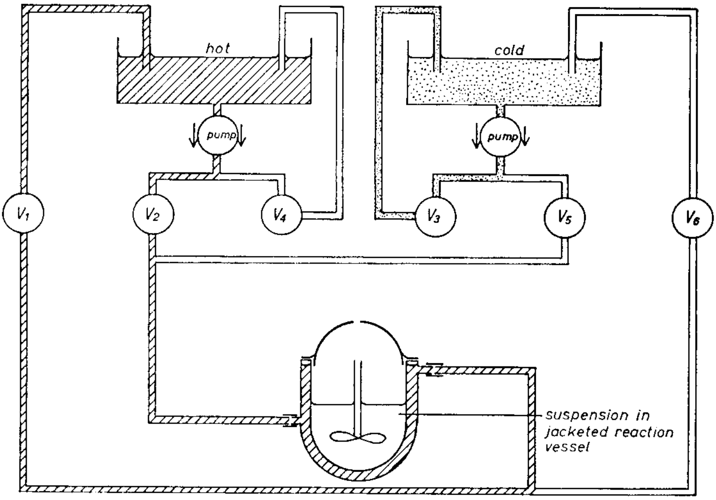

FIG. 1. Flow of hot water through reaction vessel.

V_3 and V_4 are open when both water supplies are allowed to bypass the reaction vessel. This condition permits the baths to acquire their working temperatures before a cycling run is commenced.

The Cyclothermostat. In the initial work (Carless & Foster, 1966) using the water circuitry described, the valves V_1 to V_6 were operated manually every 8 min. This did not permit easy operation, particularly over protracted periods, so the valve operation was automated by the introduction of the "Cyclothermostat", the circuitry of which is shown in Fig. 2. S_1 to S_6 inclusive represent a six-pole, three-way switch and the three positions used are, as indicated on the figure, OFF/BYPASS/RUN.

In the position OFF the power is essentially disconnected. For BYPASS power is supplied to valves V_3 and V_4 (neons P_8 and P_7); also by operation of the relay A/2 (contacts A_1 and A_2), power is supplied to the thermostatically controlled heaters and pumps. In the BYPASS position the thermostatic baths are allowed to attain their working temperatures.

On RUN, the motor, M, starts to turn and the neon lamp, P_2, indicates that power is being supplied to the motor. The microswitch, S_8, is positioned so that it operates valves V_4, V_5 and V_6 (neons P_7, P_5 and P_6). The counter operates and a visual record of the number of the cycle is registered. S_7 is an "autoreset" microswitch, which actuates the counter during a cycling run and which is also used to switch off the motor at the end of a run. Since the same motor, is used for microswitch, S_8, the "autoreset" switch always switches off the valve control at the same point in the cycle, when a run is completed. Thus, at the beginning of a run, S_8 is always in the position shown and valves V_4, V_5 and V_6 are open.

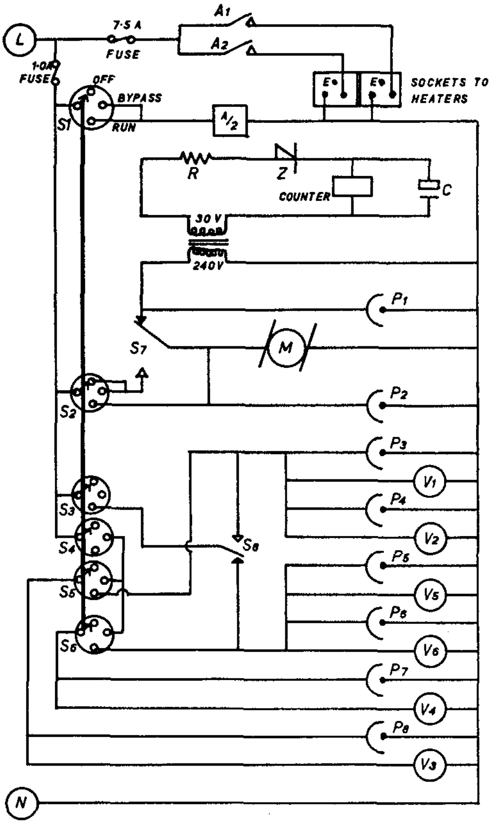

FIG. 2. Circuit diagram of the cyclothermostat. Components: P_1 to P_8, neon indicator lamps 712D (Bulgin). V_1 to V_6, Alcon ACO2 solenoid-operated valves (Alexander Controls) (numbered as in Fig. 1). S_1 to S_6, six-pole, three-way switch S438 (Bulgin). S_7, microswitch S511 (Bulgin). S_8, microswitch S511/RSS (Bulgin). M, Sangamo Weston motor, 12 r.p.h. (M. R. Supplies) (Gearing, 20:64). Counter, P.O. Counter, 24 v, S375 (H. Franks). Transformer, 240 v/30 v a.c. C, 25 mfd, 50 v wkg (Radiospares). R, 20 ohm Hystab (Radiospares). Z, REC 50A (Radiospares). A/2, Relay Type 12, 5A contacts (Radiospares).

The "autoreset" switch is so positioned that, within 15 sec of switching to "RUN", S_8 changes, V_1 V_2 and V_3 (neons P_3, P_4 and P_8) are opened and a heating phase starts. This position corresponds to a time of 15¾ min in Fig. 3.

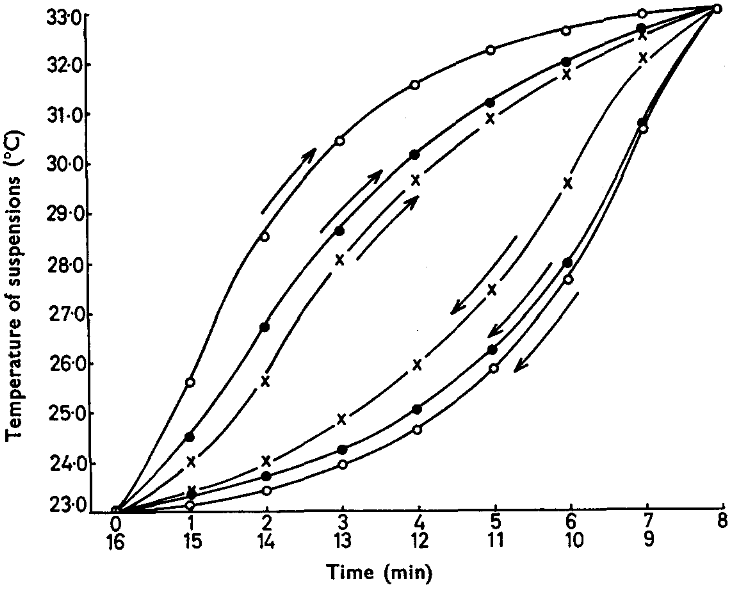

FIG. 3. Suspension temperature during cycling. ○ = 740 ml/min, ● = manual, X = 320 ml/min.

Neon lamp, P_1, is connected through S_7 so that it lights as the micro-switch is tripped, giving a visual signal 15 sec before a heating phase is about to commence. During this time the temperature of the solution or suspension in the reaction vessel is approaching 23° and a sample may be removed with a pipette.

The supply sockets for the thermostatically-controlled heaters are included in the wiring diagram of the Cyclothermostat so that they are switched on at the same time as the valves and counter, thus the Circotherm pumps do not pump against closed valves.

SOME RESULTS

The effect of passing "hot" water and "cold" water through the vessel jacket is to produce a temperature hysteresis in *the bulk of the suspension.* Fig. 3 illustrates the temperature hysteresis observed and each curve represents results from duplicate experiments. The variation between duplicate results was always less than 0·05°.

All three sets of curves conform to the preselected programme of 23–33–23° in a 16 min cycle, divided into an 8 min heating phase and an 8 min cooling phase. The curves annotated "manual" were obtained using the manual version of the instrument (Carless & Foster, 1966).

The other two sets of curves were obtained from Cyclothermostat controlled experiments with vehicle flow rates of 320 ml and 740 ml/min.

The relative and actual flow rates of the "hot" and "cold" vehicle were adjusted by introducing suitable lengths of capillary tubing into each side of the water circuitry. By manipulation, it was possible to obtain a temperature hysteresis identical with manual operation results (not illustrated).

Other factors which may influence the hysteresis are (a) the volume of sample, (b) relative and actual times of each phase of the cycle, (c) sample stirring rate and the degree of agitation within the reaction vessel jacket, (d) ambient laboratory temperature, insulation of the reaction vessel and the temperature range chosen.

Most of the control of the hysteresis is readily achieved by altering the temperature settings in the thermostatically controlled baths, altering vehicle flow rates and interchanging the motor and cam mechanism.

Improvement in thermostat control may be achieved by the method of Finch (1963) and an automatic-thermostat-warming-up-device may be employed to permit the baths to attain their working temperatures more quickly (Jervis, 1955).

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