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Characterisation of a frozen storage-microwave thawing system for intravenous infusions

G.J. Sewell [1], A.J. Palmer [2] and P.J. Tidy [2]

[1] *FORCE Cancer Research Centre, University of Exeter and* [2] *Department of Pharmacy, Royal Devon & Exeter Hospital, Exeter EX2 5DW (U.K.)*

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Summary

Many hospital pharmacy departments now undertake the centralised preparation of intravenous admixtures. The use of frozen storage-microwave thawing systems to facilitate the batch-scale production of frequently required infusions has received considerable interest. Caution in the use of freeze-thaw systems has also been expressed and it is recommended that in addition to infusion stability studies, the freeze-thaw system should be characterised and routinely monitored. Freezing and thawing conditions for each infusion should be pre-determined. We report a frozen storage-microwave thaw system for infusions incorporating a novel 'tumbling drum' microwave thawing mechanism originally designed for thawing blood products. Freezing and thawing profiles of various infusions were established and the effect of infusion volume, infusion load size and microwave power output on rate of thawing and on thawed infusion temperature were determined. An infrared thermometer for routine monitoring of thawed infusion temperature was also assessed. Frozen infusions of 100–550 ml volume were thawed evenly and reproducibly without overheating. Linear relationships were demonstrated for microwave power output and rate of thawing, and for infusion load size and thawing time. These relationships enable pre-determination of microwave thawing times and will facilitate stability studies on a range of infusions. The freezing and thawing characteristics determined in this study provide a basis for subsequent performance monitoring of the freezer and microwave thawing system.

Introduction

The majority of intravenous (i.v.) infusions prepared by hospital pharmacy-based centralised i.v. additive service (CIVAS) centres are aseptically dispensed for individual patients as and when required. In the case of those infusions required on a regular basis, batch-scale production is an attractive alternative. Centralised batch production of i.v. infusions reduces the risk of microbial contamination and compounding errors, provides a CIVAS service outside of normal hours and enables the application of prospective quality control (Brown et al., 1986). Batch preparation may also reduce drug wastage and reduce staff costs (Hilleman et al., 1984). Unfortunately this approach, which requires long-term storage (1–12

Correspondence: G.J. Sewell, Department of Pharmacy, Royal Devon & Exeter Hospital, Barrack Road, Exeter EX2 5DW, U.K.

months) of prepared infusions, is often precluded by drug stability considerations. In an attempt to overcome these difficulties the frozen storage and subsequent thawing of i.v. infusions has received considerable interest (Dinel et al., 1977; Holmes et al., 1982).

Efforts to reduce the lengthy thawing times of frozen infusions at ambient temperature have focused on the use of microwave ovens (Tomecko et al., 1980). This approach facilitates rapid thawing (a few minutes) but is more difficult to control (Williamson and Luce, 1987). Uneven thawing of infusions may result in overheating and drug decomposition (Thomas et al., 1984; Tabor and Norton, 1985). Various rotating carousel systems have been used to achieve homogenous microwave thawing of infusions (Tredree, 1982; Thomas et al., 1984). Alternative approaches have involved periodic removal and physical agitation of infusions during the microwave thawing cycle (Kirk et al., 1984).

We describe a microwave thawing system in which the approach of rotating the infusion in the microwave field is combined with agitation of the thawed solution. This system comprises a tumbling drum mechanism rotating in a vertical plane about an axis located on a carousel which simultaneously rotates in a horizontal plane. Frozen infusions positioned against the inner wall of the drum receive uniform exposure to microwave irradiation and sufficient agitation to ensure mixing of frozen and liquid components during thawing.

The frozen storage and microwave thawing of infusions are influenced by many variables including infusion volume and the number of infusion containers subjected to the process (Tabor and Norton, 1985; Williamson and Luce, 1987). Before the freeze-thaw process is introduced into practice the operating conditions must be determined for each infusion load of interest (Stiles, 1981; Stolk, 1987). Characterisation of the freezer and microwave thawing equipment also provides base-line data for subsequent performance monitoring programmes.

We report the assessment and characterisation of a frozen storage/microwave thawing system for intravenous infusions using a novel microwave oven with a 'tumbling drum' mechanism. Guidelines for performance monitoring of this system are discussed and non-destructive quality assurance procedures are evaluated. Detailed sterility studies with i.v. infusions subjected to the freeze-thaw process described in this report are the subject of a further study (Sewell and Palmer, 1990).

Materials and Methods

PVC bags containing 100 and 500 ml volumes of sodium chloride injection (0.9% w/v) were obtained from Baxter Laboratories Ltd, Thetford, U.K. Ampoules of Water for Injection BP (20 ml volume) were obtained from Antigen Ltd, Roscrea, Ireland. Erythromycin lactobionate (Erythrocin 1 g) vials were obtained from Abbott Laboratories Ltd, Queensborough, U.K., and fusidic acid (Fucidin 0.5 g + diluent) vials were obtained from Leo Laboratories, Aylesbury, U.K. Cardboard cartons (used to support PVC containers during frozen storage and thawing) in sizes of $110 \times 110 \times 30$ and $250 \times 105 \times 50$ mm for 100 and 500 ml infusion, respectively, were purchased from Leeds Pharmaceutical Packaging, Leeds, U.K. A cut-out window was provided in each carton to enable visual inspection of the infusion and the infusion label. Disposable temperature monitors comprising Lab Temp 20 and Lab Temp 40 monitors (range 1–21 and 19–41 °C, respectively) and Stafreeze indicators (indicate if frozen product exceeds −20 °C for > 1.5 h) were obtained from Camlab Ltd, Cambridge, U.K. Model ST-505 digital thermometers (range −50 to 800 °C) with stainless-steel probes were supplied by Solex Ltd, Luton, U.K. An Infratrace 800 infrared temperature monitor was obtained from Kane and May Ltd, Welwyn Garden City, U.K. This instrument was mounted on a lightweight steel rig to maintain a distance of 1 m (recommended by the manufacturer) between the face of the instrument and the object under assessment. Infusions were stored in a Sanyo MDF-330 upright medical freezer with five drawer type compartments and a minimum operating temperature of −30 °C. This freezer was fitted with visual and audible alarms and was supplied by Gallenkamp Ltd, Loughborough, U.K.

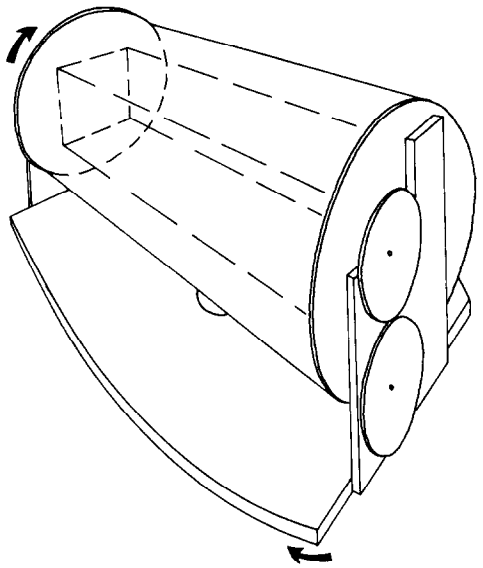

Fig. 1. Rotating carousel/tumbling drum mechanism used for microwave thawing of frozen infusions.

A model R4560 Carousel microwave oven, delivering a maximum power of 650 W, was obtained from Sharp Electronics Ltd, Manchester, U.K. Four microwave power outputs (100, 70, 50, 30% of maximum) were available. The carousel/tumbling drum mechanism was based on a design by the Blood Transfusion Service, Cardiff, U.K., for the thawing of plasma and is shown in Fig. 1. This mechanism was constructed in perspex (4.5 mm thickness) to give loading capacities of 2–8 100 ml infusions and 1–4 500 ml infusions. One end of the drum was detachable to permit loading of cartons containing infusions between the drum insert and drum wall. The turntable was designed to engage the microwave drive mechanism and rotation of the turntable in the horizontal plane resulted in rotation of the drum in the vertical plane through two drive wheels.

Freezing profiles of infusions

Freezing profiles of 20×100 ml sodium chloride infusions in PVC bags were determined on each of the five freezer shelves. The infusions were packaged in cardboard cartons, placed in a freezer drawer and frozen on each shelf in turn. A thermocouple probe was inserted into a container at the centre of the load and the temperature was recorded at intervals over a period of 10 h.

Freezing profiles of fusidic acid infusion (500 mg in 550 ml sodium chloride infusion) and erythromycin infusion (500 mg in 110 ml sodium chloride infusion) were obtained for loads of 10 and 20 PVC containers, respectively. In both cases, freezing profiles were obtained on the 3rd (middle) freezer shelf, since in the previous experiment infusions on this shelf had exhibited the slowest rate of freezing to $-20\,^{\circ}C$. Temperatures of infusions at the centre of the load were recorded in duplicate at intervals over 10 h (erythromycin infusion) or 18 h (fusidic acid infusion).

Accuracy of infrared thermometer and disposable temperature monitors

Temperature measurements of sodium chloride infusion (100 ml) in PVC containers were recorded at six different temperatures ranging from 0 to $40\,^{\circ}C$ using the infrared thermometer, disposable temperature monitors and the digital thermometer with thermocouple.

Characterisation of microwave thawing system

The thawing rate of frozen ($-20\,^{\circ}C$) sodium chloride infusion (100 ml) in PVC containers was determined at four different microwave power outputs (100, 70, 50 and 30% of maximum). A load comprising two infusions, previously weighed, was thawed at each output energy in turn. At intervals during the thawing cycle infusions were removed from the microwave oven and thawed liquid was aspirated with a syringe and needle. The infusions were then rapidly re-weighed before thawing was continued. The fraction of infusion thawed at each sample time was calculated from the weight loss after aspiration of the thawed liquid.

The microwave exposure times required to achieve complete thawing of various load sizes (2, 4 or 8×100 sodium chloride infusion) were determined at each microwave power output. Complete thawing of infusions was confirmed by visual inspection. The temperature of each infusion was determined immediately after thawing using the infrared thermometer. The mean thawed temperature and the temperature spread of each load size

were calculated for thawing cycles at each microwave power output.

The variation in thawed infusion temperature between identical microwave loads subjected to replicate thawing was determined for two drug infusions of different volumes. Using the infrared thermometer the temperatures of five replicate loads of 2 × erythromycin infusions (110 ml) and six replicate loads of 1 × fusidic acid infusion (550 ml) were measured after pre-determined thawing times of 4.0 and 9.5 min, respectively, at 100% energy output.

Results

Freezing profile of infusions

Freezing profiles for infusion loads (20 × 100 ml sodium chloride 0.9% w/v) on each freezer shelf are shown in Fig. 2. Similar profiles for fusidic acid infusion (500 mg in 550 ml) and erythromycin infusion (500 mg in 110 ml) are presented in Fig. 3.

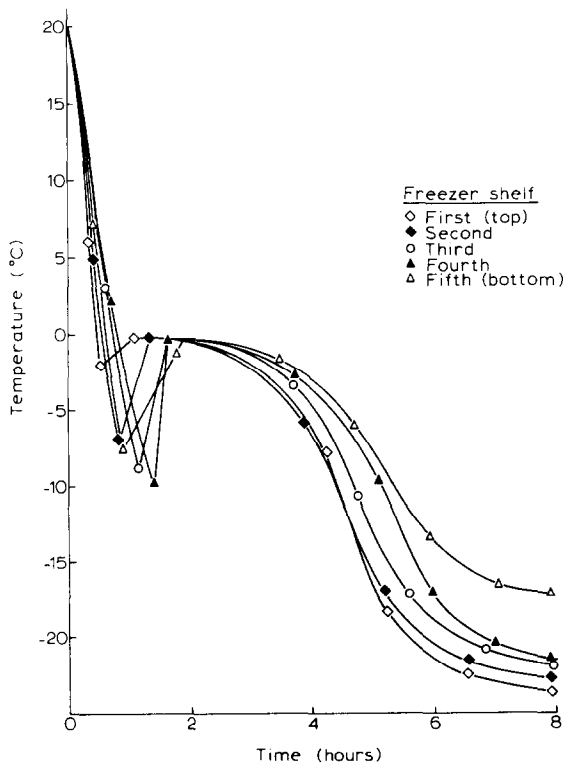

Fig. 2. Freezing profiles of loads comprising 20 × 100 ml sodium chloride (0.9%) infusion on each freezer shelf.

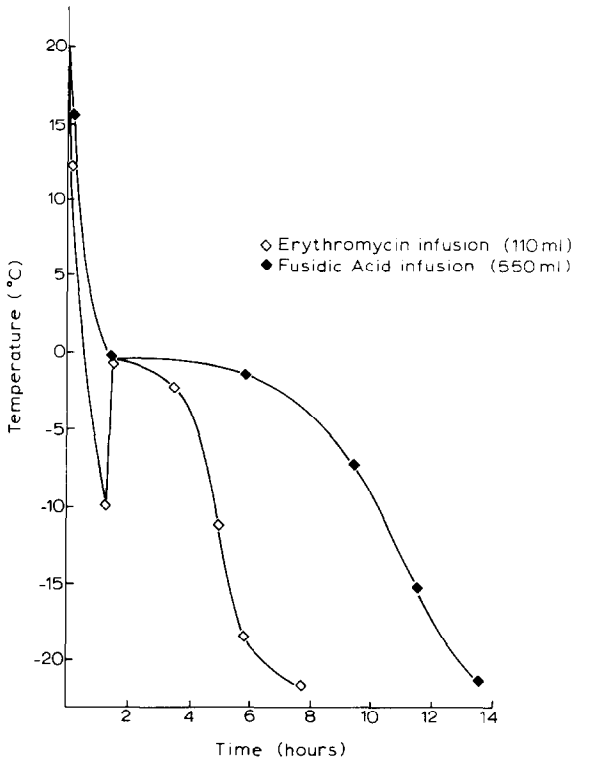

Fig. 3. Freezing profiles of loads comprising (a) 20 × erythromycin infusions (500 mg in 110 ml sodium chloride 0.9%) and (b) 10 × fusidic acid infusions (500 mg in 550 ml sodium chloride 0.9%). Freezing profiles were obtained on the 3rd freezer shelf.

Accuracy of infrared thermometer and disposable temperature monitors

Fig. 4 shows a plot of infusion temperatures recorded with the digital thermometer (abscissae) against infusion temperatures obtained with (a) the infrared thermometer and (b) disposable monitors.

Characterisation of microwave thawing system

Fig. 5 shows the rate of thawing for microwave loads comprising frozen (−20 °C) sodium chloride infusions (2 × 100 ml in PVC containers) at each microwave power output (100, 70, 50 and 30% of maximum). In each case the rate of thaw-

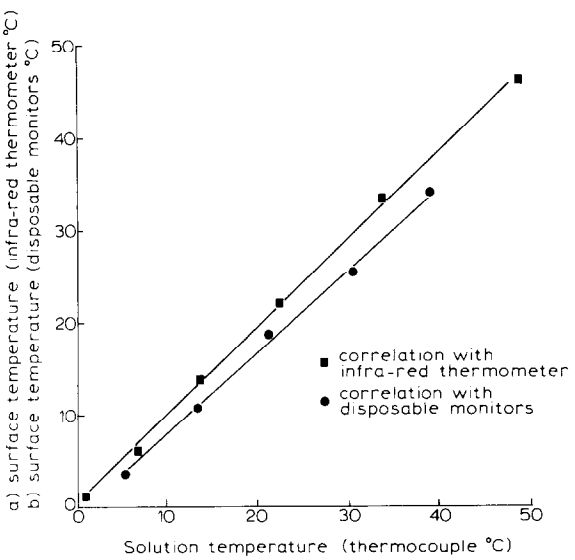

Fig. 4. Relationship between infusion temperature, measured with a thermocouple and surface temperature measured with (a) infrared thermometer and (b) disposable monitors.

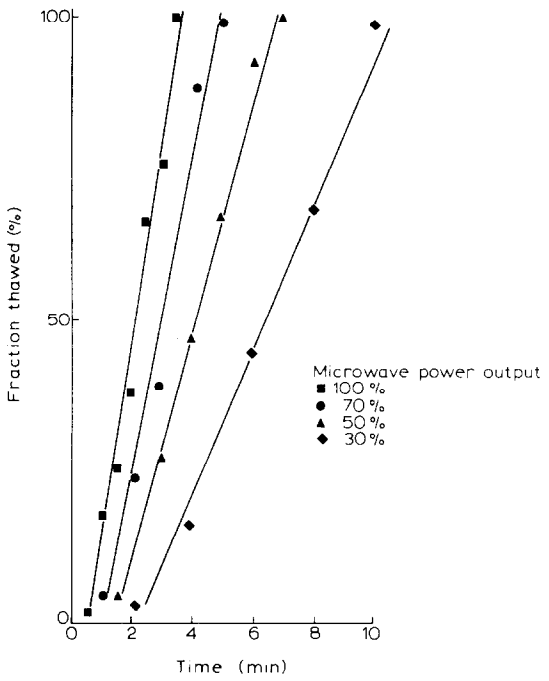

Fig. 5. Rate of thawing of 2×100 ml sodium chloride 0.9% infusions at microwave power outputs of 100, 70, 50, 30% of maximum power.

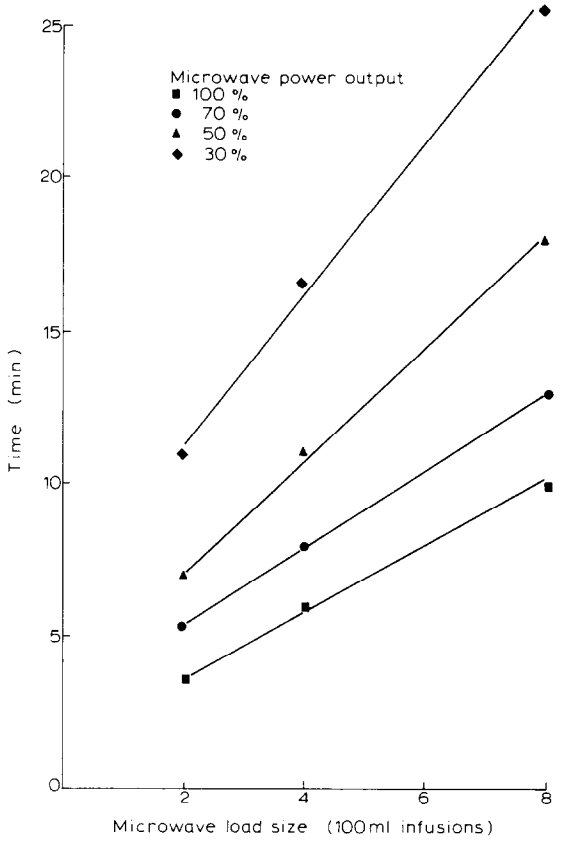

Fig. 6. Effect of microwave load size on the time required for complete thawing of infusions at each microwave power output.

ing was linear and the data were fitted to the following least-square regression equations:

100% output: $y = 32.13x - 17.76$, $r = 0.989$, $n = 7$

70% output: $y = 25.23x - 24.46$, $r = 0.976$, $n = 5$

50% output: $y = 19.64x - 29.15$, $r = 0.996$, $n = 5$

30% output: $y = 12.03x - 26.39$, $r = 0.994$, $n = 5$

TABLE 1

Mean thawed temperature (°C) and temperature range (in parentheses) of sodium chloride infusions subjected to microwave thawing in three load sizes (2, 4 and 8×100 ml) at four microwave power levels

Microwave power (% of maximum)	Microwave infusion load (×100 ml PVC bags)		
	2	4	8
100	18.0 (N/A)	18.5 (17–20)	18.0 (17–19)
70	18.5 (17–20)	17.0 (16–20)	20.0 (19–22)
50	18.0 (17–19)	17.0 (15–21)	19.0 (16–26)
30	19.0 (18–20)	22.0 (21–23)	18.0 (17–21)

Fig. 6 shows the microwave exposure time required to obtain complete thawing of frozen sodium chloride infusion (−20 °C) in different load sizes (2, 4 and 8 × 100 ml PVC containers). Data are presented for each microwave power output level.

The mean temperature of thawed sodium chloride infusions (100 ml) from the same microwave load and the thawed temperature range of the infusion load are presented in Table 1. Data were obtained for three load sizes (2, 4 and 8 × 100 ml PVC containers) at each microwave power output.

Table 2 lists thawed temperatures of five replicate microwave loads comprising 2 × PVC containers of erythromycin infusion (500 mg in 110 ml) and six replicate loads of 1 × PVC container of fusidic acid infusion (500 mg in 550 ml). The mean, standard deviation and precision of thawed temperatures were calculated and these data are also shown in Table 2.

TABLE 2

Thawed temperatures of frozen infusion loads comprising 2× erythromycin infusion (500 mg in 110 ml) and 1×fusidic acid infusion (500 mg in 550 ml) subjected to replicate microwave thawing

Erythromycin infusion			Fusidic acid infusion	
Load	Container	Thawed temp. (°C)	Load	Thawed temp. (°C)
1	a	24	1	21
	b	22		
2	a	25	2	20
	b	23		
3	a	24	3	19
	b	24		
4	a	22	4	23
	b	24		
5	a	25	5	23
	b	22		
			6	21
x = 23.5			x = 21.2	
S.D. = 1.18			S.D. = 1.60	
C.V. = 5.0%			C.V. = 7.6%	

Discussion

It has been recognised that freezing and microwave thawing systems used in CIVAS programmes should be validated and standardised (Tabor and Norton, 1985; Sanburg et al., 1987). Characterisation of freeze-thaw systems enables the determination of standard freezing and thawing cycles for each infusion type/load size and also provides baseline data for subsequent performance monitoring of freezers and microwave equipment. Routine performance monitoring is essential to assure batch to batch reproducibility.

The infusion freezing profiles shown in Fig. 2 exhibit an initial cooling phase (where infusion temperatures reached −6 to −10 °C) followed by a rapid rise to 0 °C and then further cooling to −20 °C. These profiles indicate the existence of a supercooled liquid state from which the infusions solidify with an accompanying temperature rise. Final cooling of the frozen infusions to −20 °C required a total freezing time of 5.5–6.8 h, depending on the freezer shelf used. It is evident from Fig. 2 that an infusion load placed on the 5th (lower) shelf of the freezer would require much longer to reach the required storage temperature (−20 °C). This observation was attributed to the absence of a refrigeration element in the floor of the 5th shelf. This shelf was therefore permanently blanked-off to preclude inadvertent use.

A batch of 20 × 110 ml erythromycin infusions in PVC containers were frozen to −20 °C on the 3rd shelf of the freezer (this was the slowest of the usable shelves to cool). The infusion containing the thermocouple probe required 6.5 h to reach

$-20\,^{\circ}C$ and also exhibited a supercooling phase (Fig. 3a). The freezing profile of a batch of 10×550 ml fusidic acid infusions (Fig. 3b) did not contain a supercooling phase and required 12.8 h to reach $-20\,^{\circ}C$. These studies clearly demonstrate that infusion freezing profiles are influenced not only by infusion volume but also by solute composition.

We advocate that freezing profiles of all relevant infusions should be obtained on a routine basis as part of a performance monitoring programme. Freezing profiles of infusions should be determined for all new freezers brought into service, since the duration of the freezing phase may significantly influence infusion stability observed for the total storage period.

Temperature measurements on thawed infusions obtained with the infrared thermometer correlated closely ($r = 0.999$, $n = 6$) with infusion temperatures determined by the thermocouple method (Fig. 4a). The gradient of this plot was close to unity (least-squares regression gradient, $m = 0.97$) indicating that infusion temperatures may be accurately determined from infrared surface temperature measurements. Unlike thermocouple methods, temperature measurement with the infrared system does not compromise infusion integrity. The infrared thermometer therefore lends itself to the non-destructive quality control of infusion temperatures immediately after thawing. Monitoring of thawed infusion temperatures with this rapid technique offers a satisfactory alternative to complex thermocouple probes used to control microwave thawing processes in previous studies (Thomas et al., 1984). The readability of the Infratrace 800 thermometer to only $1\,^{\circ}C$ was not considered a practical drawback. From Fig. 4b it is evident that the disposable temperature monitors also provided a reliable indication of thawed infusion temperature ($r = 0.998$, $m = 0.93$, $n = 5$), although these were considered too costly for routine use.

The rate of thawing for sodium chloride infusions (2×100 ml) was linear at each of the four microwave power settings (Fig. 5). The constant rate of infusion thawing suggests that infusions received uniform exposure to microwave irradiation throughout the thawing cycle and that the solid (ice) and liquid components of the infusion were adequately mixed during thawing. The rate of thawing (slope from least-squares regression data in Results) was plotted against the respective microwave power output (Fig. 7). There is a linear relationship between microwave power output and thawing rate ($r = 0.993$, $n = 4$). This relationship could find utility in monitoring the power output of the microwave source.

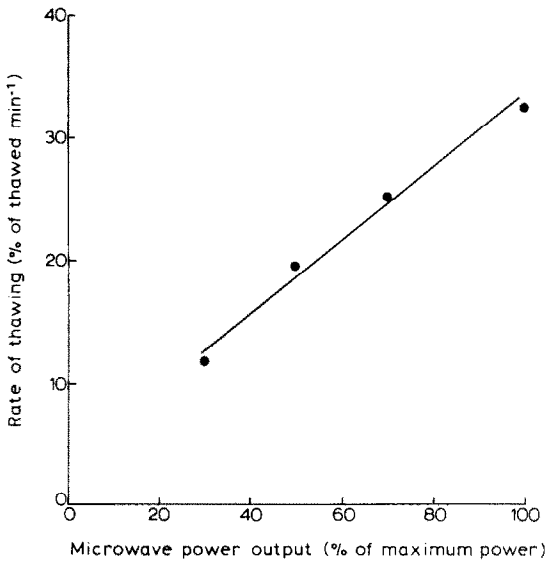

Fig. 7. Relationship between microwave power output and rate of thawing (slope from Fig. 5) of 2×100 ml sodium chloride infusions.

The infusion thawing time exhibited a linear relationship with the microwave load size at each power output (Fig. 6). From a practical point of view, thawing at the 100% microwave power output would be favoured with relatively rapid thawing times of 3.5, 6 and 10 min for loads of 2, 4 and 8×100 ml infusions, respectively.

The mean load temperature of 100 ml sodium chloride infusions thawed in three load sizes (2, 4 and 8 containers) and at different microwave power levels ranged from 17 to $22\,^{\circ}C$ (Table 1). Thawed temperatures of this order (close to ambient temperature) were encouraging since excessive heating of infusions would compromise drug stability. It was notable, however, that the greatest temperature variation between infusions from the same microwave load occurred in those infusion

loads thawed at low microwave power outputs. Only the 100% microwave power output should therefore be used for infusion thawing.

The data presented in Table 2 provide evidence for reproducible thawing of two drug-containing infusions of different volumes. The respective coefficients of variation of 5.0 and 7.6% for replicate thawing of erythromycin infusions (2×110 ml) and fusidic acid infusion (1×550 ml) were considered to be acceptable for the introduction of this system into practice, pending infusion stability studies.

This study describes a new microwave system for thawing batch-prepared i.v. infusions taken from frozen storage at $-20\,^{\circ}C$. Two types of microwave drum insert have been produced to thaw balanced loads of 2, 4 or 8×100–110 ml volume infusions or 1×500–550 ml infusion. The Infratrace 800 infrared thermometer proved to be ideal for the rapid monitoring of thawed infusion temperature. On the basis of these studies we would recommend that the following controls are applied to the use of this freeze-thaw system in practice:

(a) Infusions should be weighed before freezing and after microwave thawing. This will identify excessive transfer of water across the PVC container wall and any leaks arising due to the mechanical stress of the freeze/thaw process. Weights should be recorded and acceptable limits for weight difference should be established for each type of infusion/PVC container used.
(b) Indicators of the Stafreeze type should be attached to each container prior to frozen storage. This will indicate if the infusion temperature has exceeded $-20\,^{\circ}C$ for > 1.5 h.
(c) Freezer temperatures should be monitored with either digital thermometers which record maximum and minimum temperatures or with a continuous temperature recording chart.
(d) All microwave thawing times and power outputs should be pre-determined for each type of infusion.
(e) The thawed temperature of infusions should be determined and recorded immediately after microwave thawing. Limits for the maximum temperature of thawed infusions should be established.
(f) Infusions should be inspected visually immediately after thawing.

The characterisation data for both freezer and microwave thawing systems obtained in this study have produced baseline data for performance monitoring of this equipment. We suggest that freezing profiles and rates of microwave thawing are determined for at least one infusion of each type, on a rotational basis, at 3 monthly intervals.

The physical and chemical stability of i.v. infusions subjected to frozen storage and microwave thawing should be established under defined conditions. Stability studies on infusions subjected to the frozen storage-microwave thawing system described are the subject of a separate report (Sewell and Palmer, 1990).

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