



Microwave Freeze-thaw Technique for Injectable Drugs:

A REVIEW UPDATED FROM 1980 TO 2021



Abstract

The objective of this review was to collect information and results about the method of the microwave freeze-thaw treatment of injectable drugs and whether the method can support the development of Centralized Intravenous Admixtures Services. A systematic review of the scientific literature about injectable drug stability studies was performed. The data are presented in a table, which describes the name of the drug, producer, final concentration, temperature and time of freezing storage, type of microwave oven, thawing power, method of dosage, and the results after treatment or final long-term storage at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$. From 1980 to 2021, 60 drugs were studied by the microwave freeze-thaw treatment, and the results were presented in 49 publications. Forty papers were presented by 8 teams (2 to 18 by team). The temperatures of freezing storage varied from -70°C to -10°C , the time storage from 4 hours to 12 months, and the thaw from low to full power. Drug concentrations were mainly determined by high-performance liquid chromatography. Most of the 59 drugs were stable during and after treatment. Only three teams tested the long-term stability after the microwave freeze-thaw treatment, the first for ganciclovir after 7 days, the second for ceftizoxime after 30 days, and the third for 20 drugs after 11 to 70 days. This review can help Centralized Intravenous Additive Services take charge of the productions of ready-to-use injectable drugs.

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In hospitals, a major part of the drugs is administrated intravenously,¹ and the majority of the reconstitutions of injectable drugs is carried out directly before the administration to the patient by the nursing staff. The risks and errors related to the preparation and the administration of the injectable drugs are numerous. The standardization, the centralization of the preparations, and reconstitution by the hospital pharmacy make it possible to reduce these various risks and errors. Currently, the preparation of mixtures for parenteral nutrition has a very narrow application because there are many ready-to-use formulations provided by pharmaceutical companies. The only residual interest is for some children and for neonates. In addition to the preparation of doses of anti-cancer chemotherapy, Centralized Intravenous Additive Services (CIVAS) can take charge of many other treatments, such as antibiotics, antiemetics, and pain treatments. This development started in different hospitals during the 1990s.

One of the problems of the production of ready-to-use injectable drugs is the long-term stability after reconstitution. In European countries, the development starts by batch production of seven- or ten-day stability drugs.²

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To enhance the number of drugs that CIVAS can take charge of, it is necessary to increase the long-term stability of ready-to-use drugs, and freezing seems to be an easy method. But the thawing of frozen solution takes more time. Therefore, it is necessary to accelerate the thawing process. During our study, different processes were purposed and tested:

- at room temperature,
- in a laminar airflow; this process required a substantial circulation of air volume,³
- in a water bath at 30°C; this process was crippled by the risk of microbiological contamination,³
- in a microwave oven,⁴ and
- in a fan-assisted oven set.⁵

In a 2015 manuscript by Hecq et al, results of a survey conducted from 1980 to 2014 on the microwave freeze-thaw technique of injectable drugs was presented.⁶ This current article presents an update which includes the years of 2015 to the end of 2021.

Microwave Freeze-thaw Treatment and Literature Survey

In 1979, Kleinberg et al⁷ described the interest of the use of a microwave oven to redissolve crystals in ampules of mannitol 25%. In 1980, Tomecko et al⁸ decided to use a microwave oven to thaw polyvinyl chloride (PVC) bags containing frozen solutions of cefazolin. Some other authors developed the concept of microwave treatment and applied this to different drugs.

A systematic review of the scientific literature about drug stability studies was carried out in this study. The results are presented in Table 1, which provides information about:

- the name of the product,
- the name of the manufacturer,
- the concentration,
- the type and volume of solution,
- the nature and type of the container,
- the temperature of storage during freezing,
- the time of storage,
- the brand of oven used for the microwave thawing and its characteristics,
- the thawing cycle,
- the stability and the method of dosage,
- the long-term stability, and
- the temperature of final storage.

Results

From 1980 to 2021, 46 studies were published and 60 drugs were studied.⁶⁻¹⁷ Table 2 provides a breakdown of the

results of these studies based on the Anatomical Therapeutic Chemical (ATC) Classification System from the World Health Organization (WHO).¹⁸

Four containers (syringe, glass, PVC, and polyolefin containers) were used. Four oven types are discussed: 1) fixed plate, 2) rotating plate, 3) rotating carousel, and (4) tumbling drum. Twenty-one different models of ovens (including 3 non-specified models), distributed by 11 providers (or more) were discussed. Eleven different methods and seven temperatures of storage (-10°C, -15°C, -20°C, -22°C, -27°C, -30°C, and -70°C) were described.

Again, the results are summarized in Table 1 and are very interesting for the majority of the drugs, the concentration remaining superior to 90% of the initial concentration before freezing.



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TABLE 1.**MICROWAVE FREEZE-THAW TREATMENT: SYSTEMATIC REVIEW OF LITERATURE ABOUT DRUG STABILITY STUDIES FOR THE PERIOD OF 1980-2021.**

DRUG NAME	MFG.	MG/ML	SOLUTION	VOLUME (ML)	CONTAINER	T°	TIME	OVEN
Acyclovir	GSK	5.00	s	100	Polyolefin	-20°C	21 Days	Panasonic NND998C
Acyclovir	HOS	5.00	s	100	Polyolefin	-20°C	21 Days	Panasonic NND998C
Alizapride Hydrochloride	Not Specified	0.50	s	100	PVC	-20°C	150 Days	Faure 56-45
Alizapride Hydrochloride	Not Specified	.00	s	100	PVC	-20°C	150 Days	Faure 56-45
Amikacin	Not Specified	20.00	D5	50	PVC	-20°C	30 Days	Sharp 9450
Amoxicillin + Clavulanic Acid	Not Specified	12.00	WFI	100	PVC	-20°C	4 Hrs	Not Specified
Ampicillin Sodium	Not Specified	20.00	d5	50	PVC	-20°C	30 Days	Sharp SKR-6705
Ampicillin Sodium	WYE	20.00	s	50	PVC	-30°C	30 Days	Sharp 9750 Modified
Ampicillin Sodium	WYE	20.00	s	50	PVC	-70°C	30 Days	Sharp 9750 Modified
Ampicillin Sodium	WYE	20.00	d5	50	PVC	-70°C	30 Days	Sharp 9750 Modified
Ampicillin Sodium	WYE	20.00	d5	50	PVC	-30°C	30 Days	Sharp 9750 Modified
Ampicillin Sodium	WYE	20.00	s	50	PVC	-20°C	30 Days	Sharp 9750 Modified
Ampicillin Sodium	WYE	20.00	s	50	PVC	-30°C	30 Days	Sharp 9750 Modified
Ampicillin Sodium	WYE	20.00	s	50	PVC	-70°C	30 Days	Sharp 9750 Modified
Azlocillin Sodium	BAY	50.0	s	100	PVC	-20°C	7 Days	?
Azlocillin Sodium	BAY	50.0	s	100	PVC	-20°C	30 Days	?
Azlocillin Sodium	BAY	50.0	s	100	PVC	-20°C	90 Days	?
Azlocillin Sodium	BAY	50.0	s	100	PVC	-20°C	180 Days	?
Carbenicillin Sodium	Not Specified	10.00	d5	100	PVC	-20°C	30 Days	Sharp SKR-6705
Carbenicillin Sodium	Not Specified	10.00	d5 - s	25	Glass Bottle 125 mL	-20°C	180 Days	Hitachi MR 6060
Carbenicillin Sodium	Not Specified	40.00	d5 - s	25	Glass Bottle 125 mL	-20°C	180 Days	Hitachi MR 6060
Cefamandole Sodium	Not Specified	0.40	d5 - s	50	PVC	-20°C	35 Days	Domestic oven 600 W
Cefamandole Sodium	Not Specified	20.00	d5	50	PVC	-20°C	30 Days	Sharp SKR-6705
Cefamandole Sodium	Not Specified	20.00	d5 - s	50	VC	-20°C	35 Days	Domestic oven 600 W
Cefazolin Sodium	Not Specified	10.00	d5	100	PVC	-20°C	30 Days	Sharp SKR-6705

DRUG NAME	CHARACTERISTICS	THAWING CYCLE	REM.	STABILITY	LONG-TERM STABILITY	REF.
Acyclovir	Rotating carousel	13 min + 7 min at 270 W	Optim	Yes, by HPLC	21 Days	10
Acyclovir	Rotating carousel	13 min + 7 min at 270 W	Optim	Yes, by HPLC	21 Days	10
Alizapride Hydrochloride	Rotating carousel	Position 6, 9 min for 6 bags	-	Stable d1, by HPLC: + 1.6%	Not Done	6
Alizapride Hydrochloride	Rotating carousel	Position 6, 9 min for 6 bags	-	Yes, by HPLC: + 1.6%	Not Done	6
Amikacin	Rotating carousel	1.5 min full power for 1 × 50 mL + 30 sec by additional bag	-	Yes, by microbiological assay	24 Hrs at room temperature	6
Amoxicillin + Clavulanic Acid	-	-	-	INCOMP	Not Done	6
Ampicillin Sodium	Carousel rotatif	1.5 min full power for 1 × 50 mL + 30 sec by additional bag	-	INCOMP, by microbiological assay	Not Done	6
Ampicillin Sodium	Rotating carousel	1.5 min full power for 1 × 50 mL + 30 sec by additional bag	-	Yes, by microbiological assay	8 Hrs at room temperature: -8.6%	6
Ampicillin Sodium	Rotating carousel	1.5 min full power for 1 × 50 mL + 30 sec by additional bag	-	Yes, by microbiological assay	8 Hrs, at room temperature: -10.3%	6
Ampicillin Sodium	Rotating carousel	1.5 min full power for 1 × 50 mL + 30 sec by additional bag	-	Yes, by microbiological assay: -7.6%	Not Done	6
Ampicillin Sodium	Rotating carousel	1.5 min full power for 1 × 50 mL + 30 sec by additional bag	-	INCOMP, by microbiological assay: -71.7%	Not Done	6
Ampicillin Sodium	Rotating carousel	1.5 min full power for 1 × 50 mL + 30 sec by additional bag	-	INCOMP, by microbiological assay: -28.8%	Not Done	6
Ampicillin Sodium	Rotating carousel	1.5 min full power for 1 × 50 mL + 30 sec by additional bag	-	Yes, by microbiological assay: -3.4%	Not Done	6
Ampicillin Sodium	Rotating carousel	1.5 min full power for 1 × 50 mL + 30 sec by additional bag	-	Yes, by microbiological assay: -3.5%	Not Done	6
Azlocillin Sodium	Tumbling drum	Erythromycin ?	-	Yes, by HPLC: -2.2%	Not Done	6
Azlocillin Sodium	Tumbling drum	Erythromycin ?	-	Yes, by HPLC: -1.1%	Not Done	6
Azlocillin Sodium	Tumbling drum	Erythromycin ?	-	Yes, by HPLC: -2.1%	Not Done	6
Azlocillin Sodium	Tumbling drum	Erythromycin ?	-	Yes, by HPLC: -1.1%	Not Done	6
Carbenicillin Sodium	Rotating carousel	2.5 min full power for 1 × 100 mL + 1 min for additional bag	-	Yes, by microbiological assay	24 Hrs at room temperature	6
Carbenicillin Sodium	Rotating plate	1.5 min	-	Yes, by HPLC and microbiological assay	Not Done	6
Carbenicillin Sodium	Rotating plate	1.5 min	-	Yes, by HPLC and microbiological assay	Not Done	6
Cefamandole Sodium	Rotating carousel	4.5 min "defrost" bybag + 15 min for 5 bags	-	Yes, by HPLC	Not Done	6
Cefamandole Sodium	Rotating carousel	1.5 min full power for 1 × 50 mL + 30 sec by additional bag	-	Yes, by microbiological assay	24 Hrs at room temperature	6
Cefamandole Sodium	Rotating carousel	4.5 min "defrost" bybag + 15 min for 5 bags	-	Yes, by HPLC	Not Done	6
Cefazolin Sodium	Rotating carousel	2.5 min full power for 1 × 100 mL + 1 min for additional bag	-	Yes, by microbiological assay	24 Hrs at room temperature	6

TABLE 1 CONTINUED.

MICROWAVE FREEZE-THAW TREATMENT: SYSTEMATIC REVIEW OF LITERATURE ABOUT DRUG STABILITY STUDIES FOR THE PERIOD OF 1980-2021 CONTINUED.

DRUG NAME	MFG.	MG/ML	SOLUTION	VOLUME (ML)	CONTAINER	T°	TIME	OVEN
Cefazolin Sodium	Not Specified	10.00	d5 - s	100	PVC	-20°C	48 Hrs	Amana Radarange RR9
Cefepime	BMS	20.00			PVC	-20°C	30 Days	Panasonic NND998C
Cefoperazone Sodium	Not Specified	40.00	d5 - s	100	Glass Bottle	-10°C	96 Days	Samsung RE 515 D
Cefotetan Disodium	Not Specified	20.00	d5 - s	50	PVC	-10°C	60 Days	Samsung RE 515 D
Cefoxitin Sodium	Not Specified	10.00	d5 - s	100	PVC	-20°C	72 Hrs	Toshiba ER 899 BT1
Cefoxitin Sodium	Not Specified	20.00	d5	50	PVC	-20°C	30 Days s	Sharp SKR-6705
Cefoxitin Sodium	Not Specified	20.00	d5 - s	100	PVC	-20°C	72 Hrs	Toshiba ER 899 BT1
Cefsulodin Sodium	Not Specified	1.00	d5 - s	?	PVC	-10°C	60 Days	Amana Radarange MR-3
Ceftazidime Sodium	Not Specified	0.80	d5 - s	50	PVC	-20°C	35 Days	Domestic oven 600 W
Ceftazidime Sodium	Not Specified	20.00	d5 - s	50	PVC	-20°C	35 Days	Domestic oven 600 W
Ceftazidime Sodium	Not Specified	40.00	d5 - s	100	Glass Bottle	-10°C	90 Days	Samsung RE 515 D
Ceftizoxime Sodium	Not Specified	20.00	d5 - s	50	PVC	-20°C	90 Days	Frigidaire FM 892-1
Ceftizoxime Sodium	Not Specified	20.00	d5 - s	50	PVC	-20°C	90 Days	Frigidaire FM 892-1
Ceftriaxone	ROC	20.00		100	Polyolefin	-20°C	98 Days	Panasonic NND998C
Ceftriaxone	ROC	20.00		100	Polyolefin	-20°C	98 Days	Panasonic NND998C
Ceftriaxone Sodium	ROC	10.00	d5 - s	25	Glass Bottle 125 mL	-22°C	182 Days	Hitachi MR 6060
Ceftriaxone Sodium	ROC	50.00	d5 - s	25	Glass Bottle 125 mL	-22°C	182 Days	Hitachi MR 6060
Cefuroxime Sodium	GSK	15.00	d5	100	PVC	-20°C	90 Days	Panasonic NND998C
Cefuroxime Sodium	GSK	15.00	d5	100	Polyolefin	-20°C	98 Days	Panasonic NND998C
Cefuroxime Sodium	GSK	15.00	d5	100	Polyolefin	-20°C	98 Days	Panasonic NND998C
Cefuroxime Sodium	GSK	15.00	d5	100	Polyolefin	-20°C	98 Days	Panasonic NND998C
Cefuroxime Sodium	GSK	15.00	d5	100	Polyolefin	-20°C	98 Days	Panasonic NND998C
Cefuroxime Sodium	Not Specified	1.10	d5 - s	50	PVC	-20°C	35 Days	Domestic oven 600 W
Cefuroxime Sodium	GLA	5.00	d5 - s	100	Glass Bottle	-10°C	30 Days	Samsung RE 515 D
Cefuroxime Sodium	Not Specified	10.00	d5 - s	100	Glass Bottle	-10°C	30 Days	Samsung RE 515 D
Cefuroxime Sodium	Not Specified	15.00	d5 - s	50	PVC	-20°C	35 Days	Domestic oven 600 W

DRUG NAME	CHARACTERISTICS	THAWING CYCLE	REM.	STABILITY	LONG-TERM STABILITY	REF.
Cefazolin Sodium	Fixed plate	Position "warm"; 50 sec for 50 mL, 95 sec for 100 mL, 220 sec for 250 mL	a	Yes, by microbiological assay	4 Hrs	6
Cefepime	Rotating carousel	13 min + 7 min at 270 W	-	Yes, by HPLC	11 Days	6
Cefoperazone Sodium	?	1.5 min	-	Yes, by HPLC	Not Done	6
Cefotetan Disodium	?	90 sec	-	Yes, by HPLC	Not Done	6
Cefoxitin Sodium	Fixed plate	2.5 min full power pour 1 x 100 mL + 1 min par poche supplément-aire	-	Yes, by HPLC	6 Hrs at room temperature	6
Cefoxitin Sodium	Rotating carousel	1.5 min full power pour 1 x 50 mL + 30 sec par viaflex supplément-aire	-	Yes, by microbiological assay	24 Hrs at room temperature	6
Cefoxitin Sodium	Fixed plate	86% of power (576 watts) in the center of the oven, 69 sec for 50 mL, 114 sec for 100 mL	-	Yes, by HPLC	6 Hrs at room temperature	6
Cefsulodin Sodium	?	90 sec	-	Yes, by HPLC, no loss	Not Done	6
Ceftazidime Sodium	Rotating carousel	4.5 min "defrost" by bag + 15 min for 5 bags	-	Yes, by HPLC	Not Done	6
Ceftazidime Sodium	Rotating carousel	4.5 min "defrost" by bag + 15 min for 5 bags	-	Yes, by HPLC	Not Done	6
Ceftazidime Sodium	?	1.5 min	-	Yes, by HPLC	Not Done	6
Ceftizoxime Sodium	Fixed plate, 120 V 60 HZ 1300 W	Auto defrost, the bags are shaken each 2 or 3 min during 10 min	-	Yes, by HPLC	30 Days at 4°C	6
Ceftizoxime Sodium	Fixed plate, 120 V 60 HZ 1300 W	Auto-defrost 10 min., setting 0.5 min, shaking of the bags each 2 of 3 min	-	Yes, by HPLC	30 Days at 4°C	6
Ceftriaxone	Rotating carousel	13 min + 7 min at 270 W	Optim-	Yes, by HPLC	44 Days	6
Ceftriaxone	Rotating carousel	5 min at 800 W	Optim	Yes, by HPLC	56 Days	6
Ceftriaxone Sodium	Rotating plate	1.5 min	b	Yes, by HPLC	Not Done	6
Ceftriaxone Sodium	Rotating plate	1.5 min	b	Yes, by HPLC	Not Done	6
Cefuroxime Sodium	Rotating carousel	13 min + 7 min at 270 W	-	Yes, by HPLC	15 Days	6
Cefuroxime Sodium	Rotating carousel	13 min + 7 min at 270 W	Optim	Yes, by HPLC	23 Days	6
Cefuroxime Sodium	Rotating carousel	5 min at 800 W	Optim	Yes, by HPLC	21 Days	6
Cefuroxime Sodium	Rotating carousel	13 min + 7 min at 270 W	Minim	Yes, by HPLC	21 Days	6
Cefuroxime Sodium	Rotating carousel	5 min at 800 W	Minim	Yes, by HPLC	18 Days	6
Cefuroxime Sodium	Rotating carousel	4.5 min "defrost" by bag + 15 min for 5 bags	-	Yes, by HPLC	Not Done	6
Cefuroxime Sodium	?	1 min	-	INCOMP	Not Done	6
Cefuroxime Sodium	?	1 min	-	INCOMP	Not Done	6
Cefuroxime Sodium	Rotating carousel	4.5 min "defrost" by bag + 15 min for 5 bags	-	Yes, by HPLC	Not Done	6

TABLE 1 CONTINUED.

MICROWAVE FREEZE-THAW TREATMENT: SYSTEMATIC REVIEW OF LITERATURE ABOUT DRUG STABILITY STUDIES FOR THE PERIOD OF 1980-2021 CONTINUED.

DRUG NAME	MFG.	MG/ML	SOLUTION	VOLUME (ML)	CONTAINER	T°	TIME	OVEN
Cephalothin Sodium	Not Specified	10.00	d5	100	PVC	-20°C	30 Days	Sharp SKR-6705
Cephapirin Sodium	Not Specified	10.00	d5 - s	100	PVC	-15°C	14 Days	General Electric Jet 110-OV1
Cephapirin Sodium	Not Specified	40.00	d5 - s	100	PVC	-15°C	14 Days	General Electric Jet 110-OV1
Cimetidine Hydrochloride	Not Specified	3.00	d5	100	PVC	-10°C	28 Days	General Electric Jet 870 V 3
Cimetidine Hydrochloride	Not Specified	6.00	d5	100	PVC	-10°C	28 Days	General Electric Jet 870 V 3
Clindamycin Phosphate	Not Specified	1.50	d5 - s	50	PVC	-20°C	35 Days	Domestic oven 600 W
Clindamycin Phosphate	Not Specified	6.00	d5	50	PVC	-20°C	30 Days	Sharp 9750 Modified
Clindamycin Phosphate	Not Specified	20.00	d5 - s	50	PVC	-20°C	35 Days	Domestic oven 600 W
Cloxacillin Sodium	Not Specified	20.00	d5 - s	50	PVC	-27°C	90 Days	Westinghouse PM 600 R
Cyclophosphamide	Not Specified	4.00	s	100	PVC	-20°C	28 Days	Sharp R-9410 E
Cyclophosphamide	Not Specified	4.00	e	50	Syringe Polypro-pylene	-20°C	28 Days	Sharp R-9410 E
Cyclophosphamide	Not Specified	20.00	-	100	Glass Bottle	-20°C	28 Days	Shar R-9410-E
Cytarabine Hydrochloride	Not Specified	0.02	s	53	PVC COR	-30°C	11 Days	?
Diclofenac	EG	75 mg + 42 mg Sodium Bicarbonate	d5	100	Polyolefin	-20°C	60 Days	Panasonic NND998C
Ondansetron + Dexamethasone	ORG + GLA	0.10 + 0.08	d5	100	Polyolefin	-20°C	90 Days	Panasonic NND998C
Doxorubicin Hydrochloride	Not Specified	1.00	s	50	PVC	-20°C	14 Days	Philips AKB 117
Doxorubicin Hydrochloride	Not Specified	1.40	s	50	PVC	-20°C	30 Days	Sharp R 6950-E
Epirubicin Hydrochloride	Not Specified	1.00	s	50	PVC	-20°C	28 Days	Philips AKB 117
Erythromycin Lactobionate	ABB	4.54	s	110	PVC	-20°C	12 Mos	Sharp R 4560
Erythromycin Lactobionate	ABB	4.54	s	110	PVC	-20°C	6 Mos	Sharp R 4560
Erythromycin Lactobionate	ABB	4.54	s	110	PVC	-20°C	3 Mos	Sharp R 4560
Flucloxacillin Sodium	Not Specified	20.00	d5 - s	50	PVC	-27°C	90 Days	Westinghouse PM 600 R
Esomeprazole	AZ	0.40	d5	100	Polyolefin	-20°C	30 Days	Panasonic NN-D998W
Esomeprazole	AZ	0.80	d5	100	Polyolefin	-20°C	30 Days	Panasonic NND998W
Fluorouracil	TV	8.0	s	100	PVC	-20°C	79 Days	Panasonic NND998C
Folate Sodium	TV	3.20	d5		Polyolefin	-20°C	90 Days	Panasonic NND998C
Fusidic Acid	LEO	0.90	s	550	PVC	-20°C	12 Mos	Sharp R 4560
Fusidic Acid	LEO	0.90	s	550	PVC	-20°C	6 Mos	Sharp R 4560

DRUG NAME	CHARACTERISTICS	THAWING CYCLE	REM.	STABILITY	LONG-TERM STABILITY	REF.
Cephalothin Sodium	Rotating carousel	2.5 min full power for 1 × 100 mL + 1 min by additional bag	-	Yes, by microbiological assay	24 Hrs at room temperature	6
Cephapirin Sodium	?	2.5 min full power (875 watts)	c	Yes, by spectrophotometry	24 Hrs at room temperature	6
Cephapirin Sodium	?	2.5 min full power (875 watts)	c	Yes, by spectrophotometry	24 Hrs at room temperature	6
Cimetidine Hydrochloride	Fixed plate	Full power, 50 sec for 50 mL, 55 sec for 100 mL, 1 bag one by one, in the center of the oven	-	Yes, by HPLC	Not Done	6
Cimetidine Hydrochloride	Fixed plate	Full power, 50 sec for 50 mL, 55 sec for 100 mL, 1 bag one by one, in the center of the oven	-	Yes, by HPLC	Not Done	6
Clindamycin Phosphate	Rotating carousel	4.5 min "defrost" by bag + 15 min for 5 bags	-	Yes, by HPLC	Not Done	6
Clindamycin Phosphate	Rotating carousel	1.5 min full power pour 1 × 50 mL + 30 sec for additional bag	-	Yes, by microbiological assay	24 Hrs at room temperature	6
Clindamycin Phosphate	Rotating carousel	4.5 min "defrost" by bag + 15 min for 5 bags	-	Yes, by HPLC	Not Done	6
Cloxacillin Sodium	?	2.5 min	-	Yes, by HPLC	24 Hrs at 4°C	6
Cyclophos-phamide	?	60 sec full power, 30 sec of shaking and return to the oven, 6 times.	d	Yes, by HPLC	Not Done	6
Cyclophos-phamide	?	80 sec full power, and shake vigorously	e	Yes, by HPLC	Not Done	6
Cyclophosphamide	?	20 sec full power	-	Yes, by HPLC	Not Done	6
Cytarabine Hydrochloride	Rotating plate	120 sec at 450 watts	-	Yes, by HPLC	Not Done	6
Diclofenac	Rotating carousel	13 min + 7 min at 270 W	Optim	Yes, by HPLC	60 Days	6
Ondansetron + Dexamethasone	Rotating carousel	13 min + 7 min at 270 W	Optim	Yes, by HPLC	30 Days	6
Doxorubicin Hydrochloride	Fixed plate	180 sec full power	a	Yes, by HPLC and TLC	Not Done	6
Doxorubicin Hydrochloride	?	2 min	f	Yes, by HPLC	Not Done	6
Epirubicin Hydrochloride	Fixed plate	180 sec full power	a	Yes, by HPLC and TLC	Not Done	6
Erythromycin Lactobionate	Tumbling drum	4 min full power	-	Yes, by HPLC: -0.4 %	Not Done	6
Erythromycin Lactobionate	Tumbling drum	4 min full power	-	Yes, by HPLC: +1.6%	Not Done	6
Erythromycin Lactobionate	Tumbling drum	4 min full power	-	Yes, by HPLC: +1.8%	Not Done	6
Flucloxacillin Sodium	?	2.5 min	-	Yes, by HPLC	24 Hrs at 4°C	6
Esomeprazole	Rotating carousel	13 min + 7 min at 270 W	Optim	Yes, by HPLC	20 Days at 5°C ± 3°C	11
Esomeprazole	Rotating carousel	13 min + 7 min at 270 W	Optim	Yes, by HPLC	29 Days at 5°C ± 3°C	11
Fluorouracil	Rotating carousel	13 min + 7 min at 270 W	Optim	Yes, by HPLC	28 Days	6
Folate Sodium	Rotating carousel	13 min + 7 min at 270 W	Optim	Yes, by HPLC	30 Days	6
Fusidic Acid	Tumbling drum	8.5 min full power	-	Yes, by HPLC: No loss	Not Done	6
Fusidic Acid	Tumbling drum	8.5 min full power	-	Yes, by HPLC: +1.1%	Not Done	6

TABLE 1 CONTINUED.

MICROWAVE FREEZE-THAW TREATMENT: SYSTEMATIC REVIEW OF LITERATURE ABOUT DRUG STABILITY STUDIES FOR THE PERIOD OF 1980-2021 CONTINUED.

DRUG NAME	MFG.	MG/ML	SOLUTION	VOLUME (ML)	CONTAINER	T°	TIME	OVEN
Fusidic Acid	LEO	0.90	s	550	PVC	-20°C	3 Mos	Sharp R 4560
Ganciclovir Sodium	STX	0.28	s	250	PVC	-20°C	364 Days	Hitachi MR 6060
Ganciclovir Sodium	STX	1.40	s	250	PVC	-20°C	364 Days	Hitach MR 6060
Ganciclovir Sodium	STX	1.40	s	50	Syringe polypropylene	-20°C	364 Days	Hitachi MR 6060
Ganciclovir Sodium	STX	4.00	s	50	Syringe polypropylene	-20°C	364 Days	Hitachi MR 6060
Ganciclovir Sodium	STX	7.00	s	50	Syringe polypropylene	-20°C	364 Days	Hitachi MR 60-60
Gentamicin Sulfate	Not Specified	0.80	d5	100	PVC	-20°C	30 Days	Sharp SKR-6705
Ketorolac	ROC	0.10	d5	100	Polyolefin	-20°C	15 Days	Panasonic NND998C
Ketorolac	ROC	0.10	d5	100	Polyolefin	-20°C	15 Days	Panasonic NND998C
Ketorolac	ROC	0.20	d5	100	Polyolefin	-20°C	90 Days	Panasonic NND998C
Ketorolac	ROC	0.30	d5	100	Polyolefin	-20°C	15 Days	Panasonic NND998C
Ketorolac	ROC	0.30	d5	100	Polyolefin	-20°C	15 Days	Panasonic NND998C
Levofolinate Calcium	WYE	1.60	d5	250	Polyolefin	-20°C	95 Days	Panasonic NND998C
Levobupivacaine + Sufentanil	AZ + JAN	1.25 + 0.00012	d5	500	PVC	-20°C	120 Days	Panasonic NND998C
Mesna	Not Specified	4.00	d5	?	PVC	-20°C	90 Days	Faure 56-45
Mesna	Not Specified	8.00	d5	?	PVC	-20°C	90 Days	Faure 56-45
Methotrexate Sodium	Not Specified	0.10	s	50	PVC	-20°C	90 Days	Sharp R 6750-E
Methotrexate Sodium	Not Specified	0.50	d5	100	PVC	-20°C	30 Days	Sharp R 6950-E
Methotrexate Sodium	Not Specified	1.00	s	50	PVC	-20°C	90 Days	Sharp R 6750-E
Methotrexate Sodium	Not Specified	20.00	s	50	PVC	-20°C	90 Days	Sharp R 6750-E
Methylprednisolone Sodium Succinate	UPJ	4.62	s	108	PVC	-20°C	12 Mos	Sharp R 4560
Methylprednisolone Sodium Succinate	UPJ	4.62	s	108	PVC	-20°C	6 Mos	Sharp R 4560
Methylprednisolone Sodium Succinate	UPJ	4.62	s	108	PVC	-20°C	1 Mos	Sharp R 4560
Metoclopramide Hydrochloride	Not Specified	0.30	s	100	PVC	-20°C	150 Days	Faure 56-45
Metoclopramide Hydrochloride	Not Specified	1.00	s	100	PVC	-20°C	150 Days	Faure 56-45
Mitomycin C	BMS	0.06	s	50	PVC	-20°C	28 Days	Philips AKB 117
Mitomycin C	BMS	0.06	tampon	50	PVC	-20°C	28 Days	Philips AKB 117
Mitomycin C	BMS	0.06	s	50	PVC	-30°C	28 Days	Philips AKB 117
Mitomycin C	BMS	0.06	tampon	50	PVC	-30°C	28 Days	Philips AKB 117
Mitomycin C	LAM	0.06	s	50	PVC	-20°C	28 Days	Philips AKB 117
Mitomycin C	LAM	0.06	s	50	PVC	-20°C	28 Days	Philips AKB 117

DRUG NAME	CHARACTERISTICS	THAWING CYCLE	REM.	STABILITY	LONG-TERM STABILITY	REF.
Fusidic Acid	Tumbling drum	8.5 min full power	-	Yes, by HPLC: -1.2%	Not Done	6
Ganciclovir Sodium	Rotating carousel	Moderate power	-	Yes, by HPLC	7 Days at room temperature: -2%	6
Ganciclovir Sodium	Carousel rotatif	Moderate power	-	Yes, by HPLC	7 Days at room temperature: -2%	6
Ganciclovir Sodium	Rotating carousel	Moderate power	-	Yes, by HPLC	7 Days at room temperature: -3.4%	6
Ganciclovir Sodium	Rotating carousel	Moderate power	-	Yes, by HPLC	Not Done	6
Ganciclovir Sodium	Carousel rotatif	Moderate power	-	Yes, by HPLC	7 Days at room temperature : -2 %	6
Gentamicin Sulfate	Rotating carousel	2.5 min full power for 1 × 100 mL + 1 min for additional bag	-	Yes, by microbiological assay	24 Hrs at room temperature	6
Ketorolac	Rotating carousel	13 min + 7 min at 270 W	Optim	Yes, by HPLC	35 Days	6
Ketorolac	Rotating carousel	5 min at 800 W	Optim	Yes, by HPLC	35 Days	6
Ketorolac	Rotating carousel	13 min + 7 min at 270 W	Optim	Yes, by HPLC	60 Days	6
Ketorolac	Rotating carousel	13 min + 7 min at 270 W	Optim	Yes, by HPLC	30 Days	6
Ketorolac	Rotating carousel	5 min at 800 W	Optim	Yes, by HPLC	35 Days	6
Levofolinate Calcium	Rotating carousel	13 min + 7 min at 270 W	Optim	Yes, by HPLC	30 Days	6
Levobupivacaine + Sufentanil	Rotating carousel	15 min + 15 min at 270 W	Optim	Yes, by HPLC	70 Days	6
Mesna	Rotating carousel	Position 6, 9 min for 6 bags	-	Yes, by colorimetric assay	Not Done	6
Mesna	Rotating carousel	Position 6, 9 min for 6 bags	-	Stable, by colorimetric assay	Not Done	6
Methotrexate Sodium	?	Between "simmer" et "defrost"	-	Yes, by HPLC	Not Done	6
Methotrexate Sodium	?	2 min	g	Yes, by HPLC	Not Done	6
Methotrexate Sodium	?	Between "simmer" et "defrost"	-	Yes, by HPLC	Not Done	6
Methotrexate Sodium	?	Between "simmer" et "defrost"	-	Yes, by HPLC	Not Done	6
Methylprednisolone Sodium Succinate	Tumbling drum	4 min full power	-	Yes, by HPLC: +1.86%	Not Done	6
Methylprednisolone Sodium Succinate	Tumbling drum	4 min full power	-	Yes, by HPLC: +2.34%	Not Done	6
Methylprednisolone Sodium Succinate	Tumbling drum	4 min full power	-	Yes, by HPLC: No Loss	Not Done	6
Metoclopramide Hydrochloride	Rotating carousel	Position 6, 9 min for 6 bags	-	Yes, by HPLC: -0.53%	Not Done	6
Metoclopramide Hydrochloride	Rotating carousel	Position 6, 9 min for 6 bags	-	Yes, by HPLC: -0.9%	Not Done	6
Mitomycin C	Fixed plate	180 sec full power	a	Yes, by HPLC: -6.5%	Not Done	6
Mitomycin C	Fixed plate	180 sec full power	a	INCOMP : -46.3%	Not Done	6
Mitomycin C	Fixed plate	180 sec full power	a	Yes, by HPLC: -1.1%	Not Done	6
Mitomycin C	Fixed plate	180 sec full power	a	Yes, by HPLC: -1.5%	Not Done	6
Mitomycin C	Fixed plate	180 sec full power	a	Yes, by HPLC: -0.6%	Not Done	6
Mitomycin C	Fixed plate	180 sec full power	a	Yes, by HPLC: -0.4%	Not Done	6

TABLE 1 CONTINUED.

MICROWAVE FREEZE-THAW TREATMENT: SYSTEMATIC REVIEW OF LITERATURE ABOUT DRUG STABILITY STUDIES FOR THE PERIOD OF 1980-2021 CONTINUED.

DRUG NAME	MFG.	MG/ML	SOLUTION	VOLUME (ML)	CONTAINER	T°	TIME	OVEN
Morphine Hydrochloride	STP	1.0	s	100	Polyolefin	-20°C	58 Days	Panasonic NND998C
Nafcillin Sodium	Not Specified	20.00	d5	50	PVC	-20°C	30 Days	Sharp 9750 modified
Ondansetron Hydrochloride	GLA	0.08	s	100	PVC	-20°C	120 Days	Faure 56-54
Ondansetron + Dexamethasone	GLA + ORG	0.08 + 0.10	d5	100	Polyolefin	-20°C	90 Days	Panasonic NND998C
Oxacillin Sodium	Not Specified	10.00	d5	100	PVC	-20°C	30 Days	Sharp SKR-6705
Penicillin G Potassium	Not Specified	10,000 u/mL	d5	100	PVC	-20°C	30 Days	Sharp SKR-6705
Piperacillin + Tazobactam	CYN	80 + 10	d5 - s	50	PVC	-15°C	30 Days	?
Piperacillin + Tazobactam	AHP	40 + 0.5	d5	100	PVC	-20°C	90 Days	Panasonic NND998C
Piperacillin + Tazobactam	SDZ	40 + 0.5	d5	100	Polyolefin	-20°C	90 Days	Panasonic NND998C
Piperacillin + Tazobactam	PFI	40 + 0.5	d5	100	PVC	-20°C	90 Days	Panasonic NND998C
Piperacillin Sodium	Not Specified	10.00	d5 - s	100	PVC	-10°C	71 Days	Amana Radarrange MR-3
Procaine	FED	0.20	Cardioplegic solution	500	PVC	-30°C	120 Days	Panasonic NND998C
Sufentanil + Levobupivacaine	JAN + AZ	0.00012 + 1.25	d5	500	PVC	-20°C	120 Days	Panasonic NND998C
Temocillin	Eumed	20.00	d5	100	Polyolefin	-20°C	30 Days	Panasonic
Temocillin	Eumed	20.00	s	100	Polyolefin	-20°C	30 Days	Panasonic NND998C
Ticarcillin Disodium	Not Specified	30.00	d5 - s	50	PVC	-27°C	270 Days	Westinghouse PM 600 R
Ticarcillin Disodium	Not Specified	60.00	d5	50	PVC	-20°C	30 Days	Sharp 9750 Modified
Tobramycin Sulfate	Not Specified	0.20	d5 - s	50	PVC	-20°C	35 Days	Domestic oven 600 W
Tobramycin Sulfate	Not Specified	0.60	d5 - s	50	PVC	-20°C	35 Days	Domestic oven 600 W
Tobramycin Sulfate	Not Specified	3.20	d5	50	PVC	-20°C	30 Days	Sharp 9750 Modified
Tramadol	GRU	1	d5	100	PVC	-20°C	120 Days	Panasonic NND998C
Tropisetron Hydrochloride	SDZ	0.05	s	100	PVC	-20°C	90 Days	Faure 56-45
Tropisetron Hydrochloride	SDZ	0.05	d5	100	PVC	-20°C	90 Days	Faure 56-45
Tropisetron Hydrochloride	SDZ	0.05	s	100	Polyolefin	-20°C	90 Days	Faure 56-45
Tropisetron Hydrochloride	SDZ	0.05	d5	100	Polyolefin	-20°C	90 Days	Faure 56-45
Vancomycin	ELI	5	d5	100	Polyolefin	-20°C	105 Days	Panasonic NND998C

a = Determination of the temperature in several sections of the oven: the central section was warmless and used.

b = 1 bottle at "12 hrs" on the shelf.

c = The temperature in the bag is 26.3°C ± 3.7°C.

d = During the thawing of the solution at 20 mg/mL, a precipitate appears and is eliminated eliminated by a vigorous shake. There nevertheless exists the possibility that particulate cyclophosphamide may be administered to the patient.

e = The syringes were damaged during the storage at -20°C, representing a risk of microbiological contamination and leakage.

f = Stability after 4 freeze-thaw treatments.

g = Same stability at -20°C and at 4°C.

DRUG NAME	CHARACTERISTICS	THAWING CYCLE	REM.	STABILITY	LONG-TERM STABILITY	REF.
Morphine Hydrochloride	Rotating carousel	13 min + 7 min at 270 W	Optim	Yes, by HPLC	58 Days	6
Nafcillin Sodium	Rotating carousel	1.5 min full power for 1 × 50 mL + 30 sec for additional bag	-	Yes, by microbiological assay	24 Hrs at room temperature	6
Ondansetron Hydrochloride	?	?	-	Yes, by HPLC	Not Done	6
Ondansetron + Dexamethasone	Rotating carousel	13 min + 7 min at 270 W	Optim	Yes, by HPLC	30 Days	6
Oxacillin Sodium	Rotating carousel	2.5 min full power for 1 × 100 mL + 1 min for additional bag	-	Yes, by microbiological assay	24 Hrs at room temperature	6
Penicillin G Potassium	Rotating carousel	2.5 min full power for 1 × 100 mL + 1 min for additional bag	-	Yes, by microbiological assay	24 Hrs at room temperature	6
Piperacillin + Tazobactam	?	45 sec	-	Yes, by HPLC: No Loss	Not Done	6
Piperacillin + Tazobactam	Rotating carousel	13 min + 7 min at 270 W	Optim	Yes, by HPLC	35 Days	6
Piperacillin + Tazobactam	Rotating carousel	13 min + 7 min at 270 W	Optim	Yes, by HPLC	58 Days at 5°C ± 3°C	9
Piperacillin + Tazobactam	Rotating carousel	13 min + 7 min at 270 W	Optim	Yes, by HPLC	58 Days at 5°C ± 3°C	9
Piperacillin Sodium	?	2 × 2 min	-	Yes, by HPLC	Not Done	6
Procaïne	Rotating carousel	13 min + 13 min at 270 W	Optim	Yes, by HPLC	9 Days at 5°C ± 3°C	6
Sufentanil + Levobupivacaine	Rotating carousel	15 min + 15 min at 270 W	Optim	Yes, by HPLC	70 Days	6
Temocillin	Rotating carousel	13 min + 7 min at 270 W	Optim	Yes	14 Days	6
Temocillin	Rotating carousel	13 min + 7 min at 270 W	Optim	Yes	11 Days	6
Ticarcillin Disodium	?	2.5 min	-	Yes, by HPLC	24 Hrs at 4°C	6
Ticarcillin Disodium	Rotating carousel	1.5 min full power pour 1 × 50 mL + 30 sec for additional bag	-	Yes, by microbiological assay	24 Hrs at room temperature	6
Tobramycin Sulfate	Rotating carousel	4.5 min by bag and 15 min for 5 bags	-	Yes, by HPLC	Not Done	6
Tobramycin Sulfate	Rotating carousel	4.5 min by bag and 15 min for 5 bags	-	Yes, by HPLC	Not Done	6
Tobramycin Sulfate	Rotating carousel	1.5 min full power pour 1 × 50 mL + 30 sec for additional bag	-	Yes, by microbiological assay	24 Hrs at room temperature	6
Tramadol	Rotating carousel	13 min + 7 min at 270 W	Optim	Yes, by HPLC	60 Days at 5°C ± 3°C	6
Tropisetron Hydrochloride	Rotating carousel	Position 6, 9 min for 6 bags	-	Yes, by HPLC: -1.4%	Not Done	6
Tropisetron Hydrochloride	Rotating carousel	Position 6, 9 min for 6 bags	-	Yes, by HPLC: No Loss	Not Done	6
Tropisetron Hydrochloride	Rotating carousel	Position 6, 9 min for 6 bags	-	Yes, by HPLC: - 0.9%	Not Done	6
Tropisetron Hydrochloride	Rotating carousel	Position 6, 9 min for 6 bags	-	Yes, by HPLC: No Loss	Not Done	6
Vancomycin	Rotating carousel	13 min + 7 min at 270 W	Optim	Yes, by HPLC	56 Days at 5°C ± 3°C	6

d5 = dextrose 5%; HPLC = high-performance liquid chromatography; MFG. = Manufacturer; Minim = minimal conditions of freeze-thaw treatment (40); Optim = optimal conditions of freeze-thaw treatment (40); s = NaCl 0.9%; TLC = thin layer chromatography; WFI = Water for Injection

Identification of pharmaceutical manufacturers shown as abbreviations within Table 1:

ABB = Abbott; AHP = American Home Products; AZ = Astra-Zeneca; BAY = Bayer; BMS = Bristol Myers Squibb; CYN = Cyanamid; EUMED = Eumed; EG = Eurogenerics; ELI = Eli Lilly; FED = Federa; GLA = Glaxo; GRU = Grunenthal; GSK = Glaxo Smith Kline; HOS = Hospira; JAN = Janssen Pharmaceutica; LAM = Lameris; LEO = Leo Pharmaceuticals; ORG = Organon; PFI = Pfizer; REM = Remarks; ROC = Roche; SDZ = Sandoz; STP = Sterop; STX = Synthex; TV = Teva; UPJ = Upjohn; WYE = Wyeth

TABLE 2.

SUPPLIER INFORMATION FOR EQUIPMENT USED WITHIN THIS REVIEW.

NAME AND MODEL OF EQUIPMENT	NAME OF SUPPLIER	CITY OF SUPPLIER	STATE OF SUPPLIER
Amana Radarage	Amana Corporation	Benton Harbor	Michigan
Domestic Oven	Not Specified		
Faure 56-45	Electrolux	Senlis	France
Frigidaire FM 892-1	Electrolux Home Products	Mississauga	Ontario, Canada
General Electric Jet 110-OVI	General Electric Company	Boston	Massachusetts
General Electric Jet 870 V 3	General Electric Company	Boston	Massachusetts
Hitachi MR 6060	Hitachi	Issy-les-Moulineaux	France
Panasonic NND998C	Panasonic	Saint-Denis	France
Philips AKB 117	Philips	Eindhoven	The Netherlands
Samsung RE 515 D	Samsung	Séoul	South Korea
Sharp 9450	Sharp Electronics Corporation	Montvale	New Jersey
Sharp SKR-6705	Sharp Electronics Corporation	Montvale	New Jersey
Toshiba ER 899 BT1	Toshiba American Inc.	New York	New York
Westinghouse PM 600 R	Westinghouse	Tokyo	Japan

Note: This list provides information on equipment that may not have been identified within the text of this review.



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Discussion

Several drugs may be frozen and a lot are commercially produced in frozen premix by the pharmaceutical industry.¹⁹ It appeared from the literature survey that many drugs were not degraded by the microwave freeze-thaw treatment, as shown in the following discussion.

- Amoxicillin and clavulanic acid were unstable.
- Ampicillin needed a temperature of storage from -30°C to -70°C, not currently obtained with a majority of freezers.
- Cefuroxime needed to be stored at a temperature equal or inferior to -20°C.
- Cyclophosphamide, at a concentration of 20 mg/mL, was found to precipitate out of solution, but it was possible to redissolve the solid material by vigorous shaking for a five-minute period. This phenomenon of precipitation did not occur at concentrations below 8 mg/mL.
- Polypropylene syringe plungers exhibited a marked contraction during cooling. This resulted in seepage of hazardous fluid past the plunger out onto the inner surface of the barrel, with a potential risk of microbiological contamination of the solution. This phenomenon was not discussed by Phaypradith et al²⁰ in his 1992 study.
- Mitomycin C was stable at -30°C but not at -20°C.

Following the ATC drug classification system,¹⁸ the most studied molecular groups were anti-infectives for systemic use (J), antineoplastic agents (L01), and drugs for alimentary tract metabolism (A).

Penicillins

For the penicillins with extended spectrum (J01CA), as stated previously, amoxicillin and clavulanic acid were unstable. Ampicillin needed a temperature of storage from -30°C to -70°C, temperatures

Several drugs may be frozen and a lot are commercially produced in frozen premix by the pharmaceutical industry. It appeared from the literature survey that many drugs were not degraded by the microwave freeze-thaw treatment...

which are not currently obtained with a majority of freezers. Azlocillin, carbenicillin, piperacillin, temocillin, and ticarcillin, supported microvascular free tissue transfer (MFTT). Stability for storage after thawing was evaluated for ampicillin, carbenicillin, and ticarcillin. For beta-lactamase sensitive penicillins (J01CE), penicillin G supported MFTT, and stability for storage after thawing was evaluated. It was also the case for beta-lactamase resistant penicillins (e.g., cloxacillin, flucloxacillin, nafcillin, oxacillin). The stability for storage after thawing was evaluated. Combinations of penicillins and beta-lactamases (J01CR: e.g., piperacillin + tazobactam) were submitted with success to MFTT and, therefore, can be stored after thawing, whether for the original form⁶ or the generic form.⁹

Cephalosporins

FIRST GENERATION OF CEPHALOSPORINS

In the first generation of cephalosporins (J01DB), cefazolin, cephalothin, and cephapirin remained chemically stable during MFTT and, therefore, can be stored after thawing.

SECOND GENERATION OF CEPHALOSPORINS

In the second generation of cephalosporins (J01DC: e.g., cefamandole, cefotetan, cefoxitin, cefuroxime), cefamandole, cefoxitin, and cefuroxime can be stored after thawing. Cefotetan was not studied.

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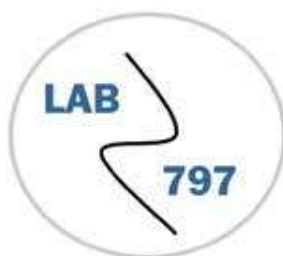
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THIRD GENERATION OF CEPHALOSPORINS

Among the third generation of cephalosporins (J01DD), cefoperazone, cefsulodin, ceftazidime, ceftizoxime, and ceftriaxone supported MFTT. Ceftizoxime and ceftriaxone were studied for storage after microwave thawing.

FOURTH GENERATION OF CEPHALOSPORINS

In the fourth generation of cephalosporins, only cefepime was studied with good results. Aztreonam (a monobactam; J01DF) can be stored during 6 months in the freezer. MFTT was not applied. Contrariwise, doripenem, ertapenem, and meropenem (carbapenems; J01DH) did not support freezing. Imipenem was not tested but met probably the same characteristics. For macrolides (J01FA), erythromycin supported MFTT, as did clindamycin (a lincosamide; J01FF).

AMINOGLYCIDES

Among the aminoglycosides, amikacin, gentamicin, and tobramycin presented good results against MFTT, and amikacin, gentamicin, and tobramycin for later storage. Vancomycin (gly-

copeptide; J01XA) supported MFTT and later storage, as did fusidic acid (steroid antibacterial; J01CX), but later storage was not tested.⁶ Acyclovir (antiviral for systemic use; J05) was also tested and was stable.¹⁰

ANTINEOPLASTIC AGENTS

For the antineoplastic agents, cyclophosphamide, cytarabine, doxorubicin, epirubicin, fluorouracil, methotrexate, and mitomycin were chemically stable after MFTT. Later storage was also studied for fluorouracil.



CYTOTOXIC DRUGS

As reported in a previous review, six studies described the stability of seven cytotoxic drugs (cytarabine, daunorubicin, doxorubicin, epirubicin, fluorouracil, methotrexate, and mitomycin) after one to 11 thawing/refreezing cycles (with conventional or microwave thawing). At the studied concentrations, the drugs presented a chemical loss below 10%.⁶

ATC A CLASS MOLECULES

With regard to the molecules of the ATC A class (alimentary tract and metabolism), drugs for acid-related disorders (cimetidine and esomeprazole; A02), drugs for functional gastrointestinal disorders (alzapride and metoclopramide; A03), and antiemetics and antinauseants drugs (ondansetron, tropisetron; A04) were chemically stable after MFTT. One association of ondansetron + dexamethasone was also tested with success.⁶

The other molecular group contains 1 to 3 drugs and are used for the concomitant treatment of cancer diseases. The result of the 12 other drugs are also described in Table 1.

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A characteristic of these studies was, nevertheless, the length of the period of study after thawing; mainly one day and no more, which was the case in 31 drugs described in 22 papers. The stability for a period of at least 24 hours was described for 17 drugs in 8 papers. Indeed, only 3 teams have tested the long-term stability after MFTT: the first for ganciclovir after 7 days; the second for ceftizoxime after 30 days; and the third for 20 drugs after 11 days to 70 days described in 20 papers.^{6,11,15}

In two studies conducted by Hecq and colleagues,¹²⁻¹³ the drugs were selected by the importance of their utilization in the hospital. After reconstitution under a laminar airflow hood, drugs were frozen in a “freezing” freezer (Comfort GS5203 520 L; Freezer Liebherr, Lienz, Austria) during the first 24 hours, then stored in a “storage” freezer (Comfort GS5203 520 L; Freezer Liebherr) to eliminate the phenomenon of freezing and surfusion for frozen solutions, as previously described.¹⁴ Indeed, the authors highlighted a number of temperature oscillations during the freezing process, up to approximately 10°C. These oscillations were due to the liberation of heat during the process. This liberation of heat may have interacted with the frozen bags previously stored in the same freezer.

Freezing temperature of storage was registered by a Val Probe temperature logger (Kaye, a SPIRENT company). Preliminary tests were made with recent microwave ovens because the oven described in the literature was no longer available. Two cycles of thawing were selected and tested, 1) one light cycle (270 W) and 2) one hard cycle (800 W). The cycles were described in a previous publication¹⁵ comparing light cycle and hard cycle of defrosting on the same drug, cefuroxime, in dextrose 5% infusion polyolefin bags. Ten bags were frozen individually in one drawer, and ten bags were frozen with 40 other polyolefin bags in another drawer. The bags were thawed in a microwave oven (Panasonic NND998C/W 230 volts, 800 W, 2450 MHZ; Saint Denis, France) equipped with a carousel, using 2 validated cycles at 1) 270 W (light cycle) and 2) 800 W (hard cycle).

During the light cycle (270 watts), the bags were thawed for 13 minutes, removed, mixed by inversion for a few seconds, and replaced for a second period of 7 minutes, allowing researchers to obtain a remaining ice volume between 1 cm³ and 8 cm³. During the hard cycle (800 W), the bags were thawed over 5 minutes. Solutions were finally stored in a refrigerator for an unknown number of days. Analyses were made by HPLC, freezing by package, and thawing with a high wattage, decreasing the stability of the solution. The optimal conditions to conserve the solution could be freezing of individual containers followed by a light cycle. Conditions of storage in the freezer are important for the long-term stability of cefuroxime, and these observations confirm the observations of McDonald.¹⁴

Following these findings, the optimal conditions of storage and the 270 light defrosting cycle for the following studies were selected.¹¹⁻¹⁵

Although some of the drugs described in this review present a good chemical stability after microwave treatment, it must be noticed that some studies were carried out many years ago in microwave ovens which are no longer available. It is consequently imprudent to transpose these studies in the currently available ovens. A validated process of freezing and standardizing of the method of defrosting according to the volume of the bag, and the number of bags to be defrosted¹⁶ must be developed in order to avoid the degradation of the molecules by overheating during the non-suitable thawing cycles.¹⁷



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The growing range of molecules tested can lead to the conclusion that the objective of the reviewed studies was realized.

On the other hand, the number of long-term stability studies is increasing every day. The introduction of public procurement has led generic drug companies to prove the chemical stability of their products for a longer period of days or weeks, while initial firms continue to deliver 24-hour stability data.

Finally, the new molecules on the market are monoclonal antibodies, for which stability studies indicate, initially, a stability of 24 hours, while research teams demonstrate periods of much higher chemical stability at 4°C and/or 25°C.^{21,22}

Conclusion

In an operating CIVAS, the increase in the production activities is required to find solutions that make it possible to lengthen the periods of validity of ready-to-use intravenous medications. The majority of the molecules described in this review present a good chemical stability after microwave freeze-thaw treatment, and some drugs even resisted several freezing and defrosting methods. The conditions of storage must be optimized: freezer of freezing, freezers of storage, quantities reduced by drawer of freezer. Defrosting by microwave oven, if controlled well, makes it possible to raise a major hurdle of this technique — namely defrosting time. Microwaves act by warming the ice. Considering their length (12.2 cm), they do not interfere with the molecular structure of the active ingredient. The power of warming used should not degrade the active ingredient. It must be recognized that some studies were carried out many years ago in microwave ovens that are no longer available.

To transpose these studies in the daily practice, it is necessary to develop a validated process of freezing and to standardize the methods of defrosting according to the volume of the bag and the number of bags to be defrosted in order to avoid degradation of the molecules by overheating during the use of non-suitable defrosting cycles. The

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