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ORIGINAL ARTICLE

suppl. Informations

Microwave freeze-thaw technique of injectable drugs. A review from 1980 to 2014

Traitement de congélation/décongélation par micro-ondes de médications injectables. Une revue de la littérature de 1980 à 2014

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KEYWORDS
Microwave freeze-thaw treatment;
Drug stability;
CIVAS;
Compounding;
Intravenous infusion;
Hospital pharmacy

Summary
Objective. — Microwave freeze-thaw treatment (MFTT) of injectable drugs can support the development of centralized intravenous admixtures services (CIVAS). The aim of the review is to collect information and results about this method.
Methods. — A systematic review of the scientific literature about injectable drug stability studies was performed. The data are presented in a table and describe name of the drug, producer, final concentration, temperature and time of freezing storage, type of microwave oven, thawing power, method of dosage and results after treatment or final long-term storage at 5 ± 3 °C.
Results. — From 1980 to 2014, 59 drugs were studied by MFTT 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 vary from −70 °C to −10 °C, the time storage from 4 hours to 12 months, the thaw from low to full power. Dosages are mainly made by high performance liquid chromatography. Most of the 59 drugs are stable during and after treatment. 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 19 drugs after 11 to 70 days.

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Conclusions. — This review can help CIVAS to take in charge the productions of ready-to-use injectable drugs.

MOTS CLÉS
Décongélation par micro-ondes ;
Stabilité des médicaments ;
Unités centrales de reconstitution d'injectables ;
Préparations médicamenteuses ;
Perfusion intraveineuse ;
Pharmacie hospitalière

Résumé
Objectif. — Le traitement de congélation/décongélation par micro-ondes (TCDM) de médications injectables peut aider au développement d'unités centrales de reconstitution d'injectables (UCRI). Le but de cette revue de littérature est de rassembler des informations et des résultats concernant ce procédé.
Méthode. — Une revue systématique de la littérature scientifique concernant les études de stabilité des médicaments injectables a été réalisée. Les résultats sont présentés dans une table et décrivent le nom de la médication, le producteur, la concentration finale, la température et la durée de stockage au congélateur, le type de four à micro-ondes, la puissance de chauffage, la méthode de dosage et les résultats après traitement ou stockage final à $5 \pm 3\,^{\circ}C$.
Résultats. — De 1980 à 2014, 59 ont été étudiés par TCDM et les résultats ont été présentés dans 49 publications. Quarante d'entre elles sont rédigées par 8 équipes (2 à 18 par équipe). Les températures de congélation varient de $-70\,^{\circ}C$ à $-10\,^{\circ}C$, la durée de stockage de 4 heures à 12 mois, la méthode de réchauffement de faible à pleine puissance. La plupart des dosages sont réalisés par chromatographie liquide à haute performance. La plupart des 59 molécules sont stables après TCDM. Seules 3 équipes ont testé la stabilité à long terme après TCDM, la première pour le ganciclovir après 7 jours, la deuxième pour la ceftizoxime après 30 jours et la dernière pour 19 médications de 11 à 70 jours.
Conclusion. — Cette revue de littérature peut aider les UCRI à prendre en charge la production d'injectables prêts à l'emploi.

Introduction

In hospitals, the major part of the drugs is administrated by intravenous way [1—9] and the majority of the reconstitutions of injectable drugs are carried out right before the administration to the patient by the nursing staff. The risks and errors related on the preparation and the administration of the injectable drugs are numerous [3—7].

The standardization, then 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 now a very narrow application because there are many ready-to-use formulation provided by pharmaceutical companies. The only residual interest is for some children and for neonates. In addition to the preparation of dosis of anti-cancer chemotherapy, many other treatments can be taken in charge, such as antibiotics, antiemetics and pain treatments. This development starts in different hospitals during the years 90 [10].

One of the problems of the production of ready-to-use injectable drug is the long-term stability after reconstitution. In European countries, the development start by batch production of seven or ten days stability drugs [11].

To enhance the number of drugs to be taken in charge, it is necessary to increase the long-term stability of ready-to-use drugs and freezing seems an easy method. But the thawing of frozen solution takes many times and can vary from 45 minutes to 5 hours, according to the volume [12—18].

It is necessary to accelerate the thawing process. Different process were purposed and tested: at room temperature [14], in a laminar airflow (LAF) [14], in a bath at 30 °C [14], microwave oven [14], fan assisted oven set [19]. The defrosting by laminar airflow need a substantial circulation of air volume [20]. The defrosting by water bath is crippled by the risk of microbiological contamination [20].

Microwave freeze-thaw treatment and literature survey

In 1979, Kleinberg et al. [21] describe the interest of the use of a microwave oven to redissolve crytals in ampuls of mannitol 25%. In 1980, Tomecko et al. [22] decide to use a microwave oven to thaw polyvinyl chloride (PVC) bags containing frozen solution of cefazolin. Some other authors develop the concept of microwave treatment and apply this to different drugs.

A systematic review of the scientific literature about drug stability studies was carried out.

The results are presented in Table S1 and mention information about the name of the product, 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

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