Impact of Multiple Freeze-Thaw Cycles on Sufentanil: A Pilot Study

Surg Cdr J Lowe[1,2,3,4,5], Surg Cdr D McConnell[1] and Surg Capt E Barnard[1,5]

[1]Academic Department of Military Emergency Medicine, Royal Centre for Defence Medicine, Birmingham, UK, [2]Medical Squadron, Commando Logistics Regiment, Barnstaple, UK, [3]Brain Sciences, Faculty of Medicine, Imperial College London, London, UK, [4]British Antarctic Survey Medical Unit, Plymouth, UK, [5]Emergency and Urgent Care Research in Cambridge (EUReCa), PACE Section, Department of Medicine, Cambridge University, Cambridge, UK

Introduction

Planning for large-scale combat operations (LSCO) has renewed interest in the delivery of care during mass-casualty events and in austere environments. Extreme cold weather presents a particular challenge for medication storage and delivery, especially where temperature-controlled storage cannot be maintained.

Injectable medicines may be vulnerable to freezing, with potential loss of container integrity or delivery-system function. Sufentanil sublingual microtablets (Dzuveo®) provide a non-parenteral analgesic option with favourable characteristics for remote and austere care. However, the effects of sustained extreme cold exposure and repeated freeze–thaw cycling on the formulation and delivery system had not previously been independently evaluated.

Aim: To assess whether the chemical stability, physical integrity and delivery-system function of Dzuveo® are maintained following sustained freezing and repeated freeze–thaw exposure.

Materials and Methods

A blinded laboratory study assessed sufentanil sublingual microtablets containing 30 µg of active pharmaceutical ingredient. Sixty tablets from two production batches were allocated across six experimental groups:

Room-temperature control 1: n=10
Room-temperature control 2: n=10
−20°C static freeze: n=10
−20°C freeze–thaw: n=10
−80°C static freeze: n=10
−80°C freeze–thaw: n=10

Control tablets were stored at 18–20°C. Freeze–thaw groups were removed from their respective freezers on alternate weekdays over 19 days, with each thaw period lasting approximately 4–8 hours. The protocol produced eight freeze–thaw cycles while ensuring that each freezing period lasted at least 24 hours. It was designed to simulate intermittent carriage by a dismounted medical professional operating without temperature-controlled storage.

Applicators were manually assessed for satisfactory function, and microtablets were visually inspected for colour, uniformity, friability and structural integrity.

Sufentanil mass and concentration were measured using liquid chromatography/heated electrospray ionisation high-resolution accurate mass spectrometry. Treatment groups were compared using one-way analysis of variance.

References

1. McConnell D, Manners H, Sutton P, Gawman N, Parham T, Lowe J. Stability of sufentanil sublingual microtablets (Dzuveo) in extreme cold weather conditions: an experimental study. BMJ Mil Health. 2026 May 6:military-2026-003278. doi: 10.1136/military-2026-003278.

Acknowledgements

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Results

All 60 tablets were analysed. One tablet-weight outlier, attributed to recording error, was excluded from concentration-based analysis, leaving 59 samples. There was no evidence of a difference in sufentanil mass between the six treatment groups:

F(5,54)=0.80, p=0.56

There was also no evidence of a difference in sufentanil concentration:

F(5,53)=0.85, p=0.52

Mean sufentanil recovery ranged from **99.45% to 103.65%** across all treatment groups. Mean concentrations ranged from **4.09 to 4.26 µg/mg per tablet**. Visual inspection identified no evidence of changes in colour, uniformity, friability or structural integrity. All applicators operated normally across the tested exposure conditions.

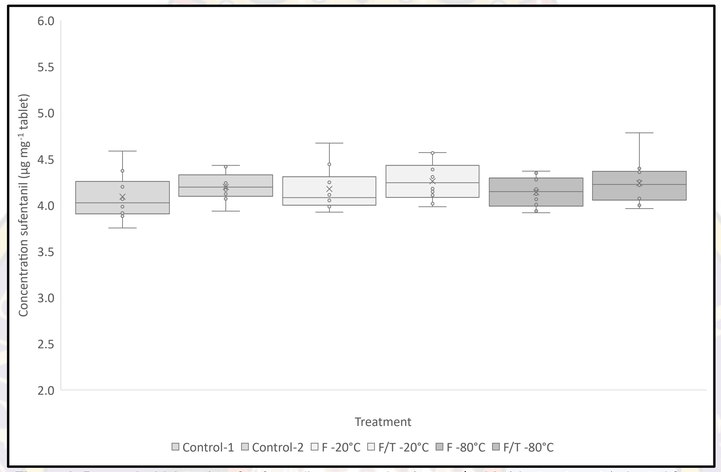

Figure 1: Box and whisker plot of sufentanil concentration (µg mg^{-1} tablet) by treatment (adapted from McConnell *et al*, BMJ Military Health, 2026. doi:10.1136/military-2026-003278)[1]

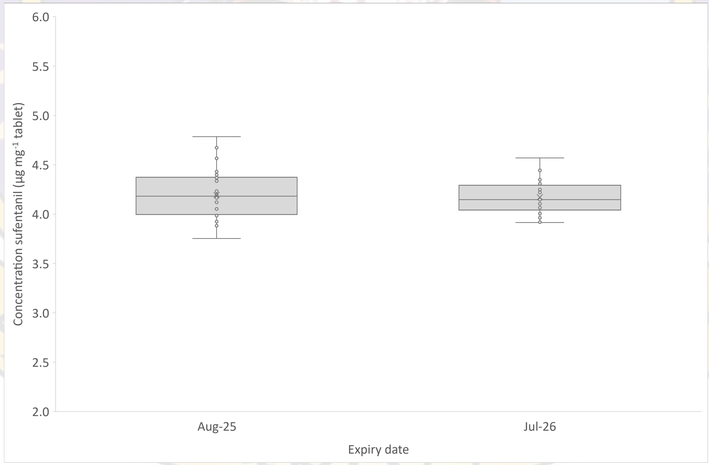

Figure 2: Box and whisker plot of sufentanil concentrations (µg mg^{-1} tablet) from tablets with different expiry dates. (adapted from McConnell *et al*, BMJ Military Health, 2026. doi:10.1136/military-2026-003278)[1]

Discussion

Sustained freezing and repeated freeze–thaw cycling at −20°C and −80°C were not associated with detectable differences in sufentanil mass or concentration. No evidence of physical microtablet degradation or applicator dysfunction was identified. The absence of variation in parent-compound mass, together with the absence of additional mono-isotopic mass peaks, suggested that sufentanil did not undergo detectable fragmentation, isomerisation, precipitation or cryo-concentration under the tested conditions.

This study used lower temperatures than previously reported medication-stability investigations. The combination of molecular analysis and functional assessment also provided a broader evaluation than visual inspection alone. The findings should nevertheless be interpreted cautiously. This was a small laboratory pilot study involving a single drug and solid formulation. It was not powered to exclude small differences between groups and did not assess clinical effectiveness. The results may not be generalisable to liquid, suspended, injectable or pre-drawn formulations, which may have different thermal vulnerabilities.

Impact for LSCO

During LSCO, medical materiel may be dispersed, cached or carried forward for prolonged periods without reliable temperature control. Repeated movement between heated shelters, vehicles and exposed environments may produce multiple freeze–thaw cycles before a medicine is required.

Although prevention of freezing should remain an operational priority, complete avoidance may be unrealistic during dynamic and dispersed operations. Evidence that selected medicines tolerate freezing could: increase confidence in forward-carried and cached medical materiel; reduce unnecessary disposal following suspected cold exposure; improve logistical resilience where resupply is delayed or contested; support prolonged field care and opportunistic casualty evacuation; reduce dependence on parenteral analgesia and temperature-sensitive delivery systems; and inform evidence-based cold-weather storage and controlled-drug governance policies.

The validated experimental method may also provide a framework for evaluating other operationally essential medicines, particularly liquid formulations, pre-drawn drugs and associated thermoplastic delivery systems.

Conclusions

Sufentanil sublingual microtablets and their single-dose delivery system maintained chemical stability, physical integrity and satisfactory function following sustained freezing and repeated freeze–thaw exposure at temperatures down to −80°C.

These findings provide reassurance regarding the resilience of this solid formulation under extreme cold weather conditions and suggest potential utility for forward medical logistics during LSCO.

Further research should assess other operationally important medicines, particularly liquid, injectable and pre-prepared formulations, and determine whether laboratory stability translates into maintained clinical effectiveness.