Article details: 2019-0147	
Title	Improving compliance and emergency access to ASA and nitroglycerin: development and validation of the SMHeartCard®
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Reviewer 1	Dr. Laird Forrest, Professor
Institution	Pharmaceutical Chemistry Faculty, School of Pharmacy, The University of Kansas, Lawrence, KS
General comments (author response in bold)	**Thank you for reviewing this paper, Dr. Forrest.** 1. In text, indicate what RT (room temperature) generally was. E.g. 20+-2C **This has been done. (Page 6, line 157)** 2. Fig. 1, would be nice to also include actual color photo of device **Color photographs have now been included as Figure 2. (Page 14 (Figure 2))** 3. Fig. 2, subscript the 2 on N2, as indicate what the number of samplers were and give error bands on the measurements. **The subscript has been done. However, as each point represents an individual temperature extreme noted during a 24 hour observation period across varying weather conditions, each point is independent of each other point and not amenable to error bars. (Page 15 (Figure 3))** 4. Fig. 4, why SEM for such a small sample size. Suggest changing to SD. **We chose to represent SEM as our primary concern was not to identify variation within the individual pill performance (which SD more accurately reflects) but rather to show how precisely the data define the mean tablet performance, for which SEM is preferred. The formal statistical analysis of the curves is the F2 analysis, which includes all points on the curve, not just one time point. (N/A)** 5. Fig. 5, why SEM. Also, please use different symbols and/or lines dashes. This is not accessible to color blind persons. (same for Fig. 6) **We chose to represent SEM as our primary concern was not to identify variation within the individual pill performance (which SD more accurately reflects) but rather to show how precisely the data define the mean tablet performance, for which SEM is preferred. The formal statistical analysis of the curves is the F2 analysis, which includes all points on the curve, not just one time point.** **We have recoloured figure 5 to address the color blind issues, and added markers where feasible; ironically, one of the authors is colour-blind. (Page 16 (Figure 4), Page 17 (Figure 5), Page 18 (Figure 6))**
Reviewer 2	Dr. Casey Sayre
Institution	College of Pharmacy, Roseman University of Health Sciences, Henderson, NV; Pharmaceutical Chemistry, The University of Utah, Salt Lake City, UT
General comments (author response in bold)	Summary: The manuscript presents the development of a portable carrying device for the storage of nitroglycerin and aspirin tablets. Clinical treatment guidelines recommend that patients with coronary artery disease carry these medications at all times. This device purports to make adherence to this recommendation easier for patients. The manuscript describes the chemical stability of these drugs under a range or temperature and time storage conditions.

	General comments: The manuscript features language which is well written and easy to understand. There are no significant faults in grammar and arrangement that would preclude understanding. The product is an important innovation that addresses real time limitations in the proper storage conditions of life-saving medications. **We thank the reviewer for this assessment.** 1. Page 5 Line 36: Please define the abbreviation "iv." **This is a list using lower case Roman numerals indicating 4. (N/A)** 2. Page 6 Line 28: End of sentence should include "coated." **The cap liners were solid polyethylene and were not coated. (N/A)** 3. Page 6 Line 29: It wasn't clear whether both the borosilicate glass container and the experimental PTFE container were tested under N2 or atmospheric air. **This has been reworded to eliminate ambiguity. (Page 6, lines 161-162)** 4. Page 6 Line 33: An explanation of why only one time point was tested under -20 degrees celsius should be added.' **The literature suggests that high temperature, not low temperatures, degrade nitroglycerin pills. This was simply to confirm that short term storage at freezing temperatures did not impair pill performance, an important consideration for Canadian patients. (N/A)** 5. The authors acknowledge that they did not test stability at the 6 month time point. However, a statement explaining why it was not tested at that time, or if there are future plans to do so, should be added to the manuscript. **We tested at the 24 week time point, which we did not consider to be meaningfully different from a 6 month time point. (N/A)**
Reviewer 3	Dr. Praveen Nekkar Rao
Institution	School of Pharmacy, University of Waterloo, Kitchener, Ont.
General comments (author response in bold)	**Thank you for reviewing our paper, Dr. Rao.** This study reports the development and stability testing of a smart container containing aspirin and nitroglycerin tablets as carry on to mitigate and treat patients with coronary artery disease by providing a convenient emergency access. Study authors have used real-world conditions including carrying the container in wallets and pockets at various temperature (-20 C to 60 C) range and time periods (up to 24 weeks). The stability of nitroglycerin was the main focus of this study as it is known to be volatile and prone to degradation. In vitro release study and HPLC were used to determine nitroglycerin release and stability. The results suggest that the smart card container is a valuable and addition in treating patients from MI in emergency conditions which can be used. This work is acceptable for publication in CMAJ after addressing the concerns listed below: 1) Authors should provide HPLC trace of nitroglycerin peaks obtained after storing 0.3 mg Nitrostat tablets in the original borosilicate glass packaging (control) and in PTFE insert, PTFE cap at RT and at 35 C (Figure 5). This information will provide concrete evidence on the stability and concentration of nitroglycerin under these conditions. This can be provided as supporting document/supplementary content.

	The requested representative HPLC trace data is now included as supplementary figure 1. (Page 7, lines 193-194, Supplementary Figure 1) 2) Figure 5: Interesting to see that nitroglycerin underwent significant degradation at 35 C (glass insert, PTFE cap and PTFE insert, PE cap) which shows that dose will be reduced drastically over a period of 6-months. Even the PTFE insert, PTFE cap at 35 C (green trace) did not show 100% release indicating potential degradation and dose reduction of nitroglycerin. This suggests that the product may not be stable under these conditions for 6-months. These observations should be discussed under the "Interpretation section" on page 12. Authors have indicated follow-up studies. It is very clear that there should be an expiry date on these smart cards which could be less than 6-months. There should be a mechanism to refill. These observations also require the authors to change the wording under Results section of the abstract - Line 5 "(PTFE) performed similarly to those stored in the ....." Should be modified as" performed close to those...." to reflect their stability at RT as per Fig 6. **The SMHeartCard has an expiry date indicated on the back of the card (see new Figure 2C). Refills for the card are clearly mentioned on the packaging and in the accompanying directions sheet, and the product webpages.** **The wording has been changed as suggested to "performed close to". (Page 8, line 219, Page 14 (Figure 2C))** 3) Authors should include additional references on the stability of nitroglycerin tablets and are encouraged to read this paper Am J Cardiol. 2018 Dec 15;122(12):2151-2156. doi: 10.1016/j.amjcard.2018.08.048. Epub 2018 Sep 13 which has many important aspects relevant to this work **Thank you! This very informative and highly relevant paper has been read and is now referenced in the manuscript. We were previously unaware of this work. (Page 4, lines 99-101)** 4) With on-body carriage, only 4-individuals were used. Was there any particular reason for not recruiting more to increase the sample size? **To address this concern, three additional persons were recruited to study temperature extremes over winter conditions, and these data are now included to increase the sample size to 7 individuals. We did not seek higher numbers as we chose laboratory test temperature ranges that greatly exceeded the observed temperature extremes. (Page 6, line 141, Page 15, line 373 (Figure 3))** 5) At many places, while typing "0.3mg or 0.6mg or 35C or N=6" space is missing in-between. Should be "0.3 mg". Check the manuscript thoroughly to fix this. **These changes have been made. (--)** 6) Figure 4: X-axis range - limit to 60 min **This has been changed as suggested throughout. (Page 16 (Figure 4), Page 17 (Figure 5), Page 18 (Figure 6))**