Title:

Improving compliance and emergency access to ASA and nitroglycerin: development and validation of the SMHeartCard®

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ABSTRACT (max 250 word): 236

Background: Guidelines for coronary artery disease (CAD) recommend carrying and immediately using acetylsalicylic acid (ASA) and sublingual nitroglycerin at the onset of chest pain. However, compliance with these recommendations is poor. A recent Canadian survey of people with established CAD found only 20% of patients carried nitroglycerin and none carried ASA. We designed and tested a compact on-person carrying system for these medications.

Methods: We designed an airtight, lightproof and chemically inert container designed to carry four ASA 81mg tablets and three NitroStat® 0.3mg sublingual nitroglycerin tablets. After establishing the temperatures ranges in wallets and pockets, we performance tested (time course of nitroglycerin dissolution and release) stored Nitrostat® tablets across a range of relevant temperatures and a variety of pill enclosure systems.

Results: Nitroglycerin tablets were stable at temperatures ranging from -20°C to 60°C for one week as shown by microcalorimeter thermal conduction studies and dissolution and release testing. In testing up to 24 weeks, Nitrostat® 0.3mg completely enclosed in polytetrafluoroethylene (PTFE) performed similarly to those stored in the manufacturer's packaging across a wide range of temperatures relevant to on-person carriage. Real-world on-person testing after 24 weeks confirmed these results. Non-PTFE enclosures performed poorly.

Interpretation: The PTFE enclosure system maintains long-term performance of Nitrostat® 0.3mg tablets under laboratory and real-world conditions. This ASA and PTFE-enclosed nitroglycerin tablet storage system is now commercially available as SMHeartCard® to improve compliance and provide immediate access to emergency cardiac medications.

TEXT: WORDS 2477 (MAXIMUM 2500)

INTRODUCTION

Acetylsalicylic acid (ASA) is a potent inhibitor of platelet aggregation and clotting. Nitroglycerin is a vasodilatory drug used to alleviate cardiac chest pain due to inadequate blood supply to the myocardium. The American Heart Association Guidelines (1) recommend patients with coronary artery disease (CAD) carry and use both ASA and nitroglycerin at the onset of chest pain. Specifically, patients with known or suspected CAD who develop chest pain should immediately chew and swallow ASA at doses from 162mg to 325 mg, and take an initial dose of a nitroglycerin preparation (1). If pain is not relieved, emergency medical services should be activated.

Early administration of ASA and nitroglycerin is beneficial in acute coronary syndromes. Immediate ASA lowers mortality from myocardial infarction (MI), with a clear association between the onset of MI symptoms and time to ASA (2). In observational studies, pre-hospital administration of sublingual nitroglycerin significantly reduces chest pain (3) and is safe to use, with the only noted adverse effect being non-clinically significant hypotension in 0.7 – 3.2 % of patients (3, 4). Pre-hospital administration of nitroglycerin by emergency response teams is associated with improved survival (5) and a Cochrane meta-analysis of in-hospital nitrates in acute coronary syndromes found an initial improvement in survival when administered within the first 24 hours (6).

Storing ASA requires only a low humidity environment. In contrast, nitroglycerin has physical properties complicating storage. In its pure form, nitroglycerin is volatile, reacts with oxygen, and degrades with light. Furthermore, nitroglycerin adsorbs to most plastics and desiccants used to store and distribute tablets. While nitroglycerin sprays are the primary way to carry and administer nitroglycerin in Canada, these are inconvenient to carry, and freeze at low temperatures. In a prospective Canadian case series of 38 consecutive patients with CAD attending a primary care clinic, only 7 of 38 (18%) of patients prescribed nitroglycerin sprays carried the medication. Among men, the rate was 12% (2 of 17). The inconvenience of carrying nitroglycerin spray was the most frequent explanation for lack of compliance (7).

To improve compliance and provide immediate access to ASA and nitroglycerin, we designed a small, convenient pill holder to fit in wallets, pockets, and purses. We included clear instructions on the pill holder as people having chest pain may forget how to use their medications. In this

study, we evaluated this case with a series of nitroglycerin enclosures under a range of laboratory conditions simulating on-person carriage, as well as a full 24-week “real-world” evaluation of on-person carriage. We hypothesized that Nitrostat® 0.3mg tablets stored within the emergency medication holder would not degrade significantly faster than those stored in original borosilicate glass packaging at room temperature.

METHODS

Materials:

0.3 mg and 0.6mg Nitrostat® tablets (Pfizer Canada Inc.) were purchased from McKesson Canada (Saint-Laurent, MTL, Canada). Durapore® membrane filter, 0.45 µm pore size hydrophobic polyvinylidene difluoride (PVDF), 13 mm membrane were obtained from Millipore Sigma (Etobicoke, ON, Canada). High-performance liquid chromatography (HPLC) grade methanol and octanol was purchased from Fischer Scientific (Ottawa, ON, Canada). Water used for release tests and HPLC analysis was purified by Elgastat Maxima UF and an Elgastat Option 3B water purifier by ELGA Laboratories Ltd. (Mississauga, ON, Canada).

Product Design:

We designed a product that: i) was small and thin enough to fit in a wallet, ii) cradled a chemically inert insert to hold three nitroglycerin tablets, iii) permitted a cap system to completely enclose nitroglycerin in a chemically inert chamber without exposure to air, moisture or light, and iv) had clear directions for medication use. The disassembled system is shown schematically in Figure 1A, showing: 1) the nitroglycerin cap; 2) the nitroglycerin cap liner; 3) three nitroglycerin tablets; 4) the chemically inert nitroglycerin insert with three individual wells to hold individual doses of nitroglycerin, minimizing the atmospheric exposure and physical mobility of the nitroglycerin tablets; 5) the base; 6) grooves to place tamper-resistant tape; 7) instructions for medication use on the card; 8) the nitroglycerin insert holder; 9) the ASA well; 10) ASA tablets; 11) the ASA cap liner; 12) the ASA cap; and 13) the cap bridge forcing the proper orientation of the NTG and ASA cap. The back surface of the card also carries a label with instructions for use and expiration date. Figure 1B demonstrates the assembled product.

Temperature and Humidity Excursions with On-Body Carriage:

Minimum and maximum pocket temperature was measured with a ThermPro -TP50 Digital LCD Indoor Thermometer Hygrometer Humidity Meter. Four individuals carried this instrument in shirt

or pants pockets continuously over 24 hours periods in both summer and winter conditions, with humidity and temperature readings taken every 10 seconds.

Heat Flow (Calorimeter Experiments):

A thermal activity monitor III (TAM III; TA instruments, USA) measured 0.3 mg Nitrostat® tablets' heat flow to identify thermal chemical degradation. Six tablets were added into a stainless steel microcalorimeter ampoule and experiments were performed at various conditions (45°C with nitrogen, and 45°C, 50°C, and 60°C in atmospheric oxygen), for one week.

Storage Conditions:

We sought to identify the appropriate materials in which to enclose nitroglycerin tablets, and to establish whether N_2 gas packaging would improve nitroglycerin tablet stability. As a control for all packaging experiments, Nitrostat® tablets were stored at room temperature (approximately 22°C), in their original Pfizer borosilicate glass screw top vial with a plastic lined metal screw cap. The case was tested with either of two inserts made from polytetrafluoroethylene (PTFE; a synthetic fluoropolymer), or borosilicate glass. Cap liners were either PTFE coated or polyethylene (PE). Tablets were also stored with and without N_2 gas to replace atmospheric oxygen. Laboratory temperatures tested were 4°C, room temperature (RT), and 35°C. Tablets were stored for 1, 2, 4, 8, 12 and 24 weeks before being subjected to release tests to evaluate their performance. Additional studies were performed at -20°C at 4 weeks. After demonstrating the stability of the SMHeartCard® PTFE insert and PTFE cap liner system at 4°C, RT and 35°C, an independent "real-world" evaluation was performed. In these experiments 0.3mg and 0.6mg Nitrostat® tablets were kept either in their original manufacturing packaging at RT (control), or within a SMHeartCard® case containing PTFE inserts and cap, and kept on-person within wallets, pockets, backpacks, and purses for 24 weeks.

***In vitro Release Test*:**

In vitro release studies were done using Franz glass diffusion cells to determine the cumulative percentage drug release. Receptor media was double distilled water filled between 12 to 13 mL in the receptor chamber of each cell. Receptor chambers were maintained at 37.4 ± 0.5 °C using a circulating water bath (Haake D8, Germany). A magnetic stirring bar was used to stir the receptor media in each diffusion cell at 600 rpm (IKA, USA). A 0.45 µm synthetic hydrophobic (PVDF) membrane was briefly soaked in octanol to create a partition replicating a mucosal membrane. The membrane was assembled between the donor and receptor compartments of

the Franz cell. A Nitrostat® pill was added on top of the membrane and 1 mL of double distilled water was added to dissolve the sample. 100 µL of samples were collected through a sampling port with a needle at 2, 5, 10, 20, 30, and 60 minute time points. The same volume withdrawn was replaced with double distilled water. Samples were analyzed using HPLC as described below.

***Analytical Method*:**

HPLC methods were adapted from the United States Pharmacopoeia (USP) standard with slight modifications. Analysis was carried out using a Shimadzu system equipped with two LC-10AD VP pumps, SIL-HTC autosampler, and a SPD-10AV UV-Vis detector. Chromatographic separation was achieved using a Genesis C18 column (100 x 3.0 mm, 4 µm), at room temperature. An isocratic mobile phase of methanol in water 45:55 with a flow rate of 0.75 mL/min. Samples were injected at 50 µL with UV detector's wavelength set at 210 nm.

Statistical analysis of release curves:

DDSolver, a Microsoft Excel add-in, was used to analyze the release profiles of Nitrostat® tablets. As recommended by the FDA (8), F2 values were calculated to compare the mean cumulative percent release of nitroglycerin from the original borosilicate glass enclosed packaging (control) at RT, and the different storage conditions. F2 is a similarity factor used to measure the closeness between two release profiles. F2 values above 50 indicate that two release profiles are statistically similar and acceptable to the FDA as showing clinically acceptable performance.

RESULTS

Pocket temperature ranges for nitroglycerin storage.

In order to determine on-body temperature ranges typical for Canadians, the pocket temperature extremes of four individuals was monitored using a thermometer hygrometer humidity meter. On-person carriage of this instrument in shirt and pant pockets during both winter and summer conditions demonstrated temperatures ranging from 17.2°C to 32.4°C (Figure 2). We consequently tested various enclosure systems at long-term temperatures ranging from 4ºC to 35ºC, representing real world nitroglycerin carriage conditions, and short-term temperature extremes.

Nitroglycerin tablets are chemically stable at temperatures between 45ºC to 60ºC.

Due to the probability of nitroglycerin tablets stored within the SMHeartCard® being subjected to short-term, high temperatures, such as those experienced in a hot vehicle, we evaluated the thermal chemical degradation of 0.3mg Nitrostat® tablets at elevated temperatures. We performed a series of heat flow experiments in which six 0.3mg Nitrostat® tablets were placed inside a stainless steel microcalorimeter ampoule and monitored with a TAM III thermal activity monitor for one week. By this method, we measured the heat flow of the nitroglycerin tablets at 45°C with or without N_2 packing, 50°C, and 60°C. Nitroglycerin tablets (6 at each condition) were found to chemically stable for one week at 45°C, 50°C, 60°C, and N_2 packaging did not improve their stability (Figure 3). We also subjected tablets stored under these conditions to *in vitro* release tests to determine their cumulative nitroglycerin release profile. One week exposure to high temperatures without N_2 packaging did not trigger nitroglycerin degradation or impairment (Figure 4). Thus, short-term exposure of Nitrostat® tablets to high temperatures does not appear to significantly affect drug stability.

Nitroglycerine tablets stored in PTFE enclosed conditions perform similarly to those stored in original packaging in nitroglycerin release tests.

To assess the performance of 0.3mg Nitrostat® tablets enclosed in a variety of materials, we performed *in vitro* nitroglycerin release tests using Franz glass diffusion cells. As a control for these experiments, nitroglycerine tablets were stored in their original borosilicate glass packing at room temperature (RT). F2 values were also calculated to compare the similarity in nitroglycerin release profiles between controls and tablets stored under the test conditions described for all experiments (Table 1). 0.3mg Nitrostat® tablets stored in PTFE enclosed conditions (PTFE insert, PTFE cap) were found to perform similarly to controls across a range of temperatures (-20ºC, 4ºC, RT, and 35ºC), indicating that the storage system with a PTFE insert and PTFE-lined cap provided the best storage solution for these tablets (Figure 5). Importantly, 0.3mg Nitrostat® tablets storage with a PTFE insert and cap under real-world conditions for 24 weeks again had release profile that was similar to the borosilicate glass control, indicating that these tablets maintained their stability during on-person SMHeartCard® carriage (Figure 6). Altogether, these results demonstrate that 0.3mg Nitrostat® tablets are stable across a range of temperatures (-20°C to 35°C) when stored in PTFE enclosed conditions for up to 24 weeks.

Storage conditions that did not perform similarly to the control included the case with a borosilicate glass insert and PTFE cap, a PTFE insert and PE cap, the case with nitrogen gas

packing (PTFE insert, PTFE cap and glass insert, PTFE cap) at 35ºC, and 0.6mg Nitrostat® tablets (Table 1).

INTERPRETATION

Despite the importance of immediate access to ASA and nitroglycerin during MI, a recent Canadian survey showed only 20% of patients with established CAD could produce nitroglycerin when directly questioned, and none carried ASA (7). Furthermore, an audit of a Canadian hospital found that among patients presenting with acute coronary syndromes (myocardial infarction and unstable angina), the median time to ASA and nitroglycerin administration was more than 90 minutes after arrival at the emergency room (9). Unfortunately, approximately thirty percent of people with MI do not survive long enough to reach medical care (10), and this is more frequent in people who live and work in geographically isolated areas. To increase the convenience and improve compliance with carrying and proper use of these medications, we designed a credit card sized holder to carry nitroglycerin tablets and ASA with clear patient instructions.

We evaluated a number of configurations and components to optimize the stability of nitroglycerin tablets for long-term, on-person carriage. Among the various experimental permutations, we found that by tightly enclosing Nitrostat® 0.3 mg tablets in a PTFE insert, and covering the insert with a PTFE coated cap liner, we maintained long-term performance properties of Nitrostat® 0.3 mg tablets for 24 weeks under both laboratory and real-world conditions. Nitrogen packing provided no benefit in stabilizing Nitrostat®. The complete PTFE enclosure performed as well as storage in standard borosilicate glass vials. This product is patented (CA180764S) and trademarked as SMHeartCard®, and now marketed in Canada (www.smheartcard.ca) for on-person carriage of ASA and 0.3 mg Nitrostat® tablets.

By demonstrating that the SMHeartCard® system is an effective storage system to provide immediate access to emergency cardiac medications for a 24 week period, the product has the potential to reduce MI mortality by improving access and timeliness of treatment. The results are of potential importance to three groups. The first group is the population with established coronary artery disease (CAD) whose compliance with carrying ASA and standard nitroglycerin spray formulations is very poor (7). The second group comprises individuals with risk factors for MI but without a previous cardiac ischemic event. Canadians have a high prevalence of risk factors for coronary artery disease, including hypertension, tobacco smoking, diabetes,

hyperlipidemia, obesity, sedentary lifestyle, and age > 50 years (11). Treatment of modifiable risk factors reduces, but does not eliminate risk of MI. Additionally, while people with these kinds of cardiovascular risk factors are sometimes recommended to take daily low dose ASA as prophylaxis, new evidence suggests that for older individuals, the risks of daily ASA use outweighs the benefits (12). Additionally, first responders may wish to carry SMHeartCard® and permit first-aid trained individuals to provide immediate treatment to those with heart attack symptoms.

We acknowledge we have not tested SMHeartCard® for periods exceeding the manufacturer's recommendations of 6 month stability. Formal demonstration that on-person compliance with SMHeartCard® exceeds that of nitroglycerin sublingual spray preparations is planned in an prospective clinical trial.

In summary, we designed and validated a new medication storage system, now marketed as SMHeartCard®, to permit on-person carriage and immediate treatment of symptoms of MI and angina. Given that time to initial treatment is an important determinant of survival in MI, and that a substantial proportion of MIs are fatal before the patient reaches hospital, this system has the potential to improve outcomes in people with established and previously undiagnosed coronary artery disease.

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TABLES

Table 1. F2 values comparing the release profile of Nitrostat® tablets stored in original borosilicate glass packaging at room temperature to that of Nitrostat® tablets stored within the cardiac medication holder at various temperatures and test conditions.

	Experimental storage condition	Week 1		Week 2		Week 4		Week 8		Week 12		Week 24	
		F2	S/NS	F2	S/NS	F2	S/NS	F2	S/NS	F2	S/NS	F2	S/NS
Control: Original borosilicate glass packaging, RT	PTFE insert, PTFE cap, RT	64.6	S	69.4	S	84.6	S	86.6	S	87.6	S	52.4	S
	Glass insert, PTFE cap, RT	46.9	NS	59.8	S	66.1	S	69.5	S	85.8	S	58.7	S
	PTFE insert, PTFE cap, 4°C	68.5	S	76.1	S	67.4	S	68.9	S	80.1	S	58.6	S
	Glass insert, PTFE cap, 4°C	53.2	S	59.6	S	75.6	S	85.0	S	73.5	S	62.9	S
	PTFE insert, PTFE cap, 35°C	62.3	S	78.2	S	71.1	S	95.1	S	64.8	S	61.8	S
	Glass insert, PTFE cap, 35°C	46.7	NS	71.4	S	64.1	S	82.2	S	58.1	S	26.4	NS
	PTFE insert, PE cap, 35°C	77.4	S	82.3	S	44.3	NS	46.3	NS	45.0	NS	30.2	NS
	PTFE insert, PTFE cap, 35°C, N_2 packed	58.8	S	78.7	S	65.1	S	75.7	S	84.2	S	37.1	NS
	Glass insert, PTFE cap, 35°C, N_2 packed	55.0	S	61.2	S	75.8	S	62.0	S	77.1	S	31.1	NS
	PTFE insert, PTFE cap, -20°C					60.1	S						
	PTFE insert, PTFE cap, 0.3 mg NitroStat, RWC											56.0	S
	PTFE insert, PTFE cap, 0.6 mg NitroStat, RWC											49.9	NS

Glass = borosilicate glass, F2 = similarity factor, S/NS = similar/ not similar, PTFE = polytetrafluoroethylene, PE = Polyethelene, N_2 = nitrogen gas packed, RT = room temperature, RWC = real world conditions. Red letters indicate results for the marketed product components and configuration of SMHeartCard®. N = 6 mean ± SEM. F2 values over 50 indicate statistical similarity.

FIGURES

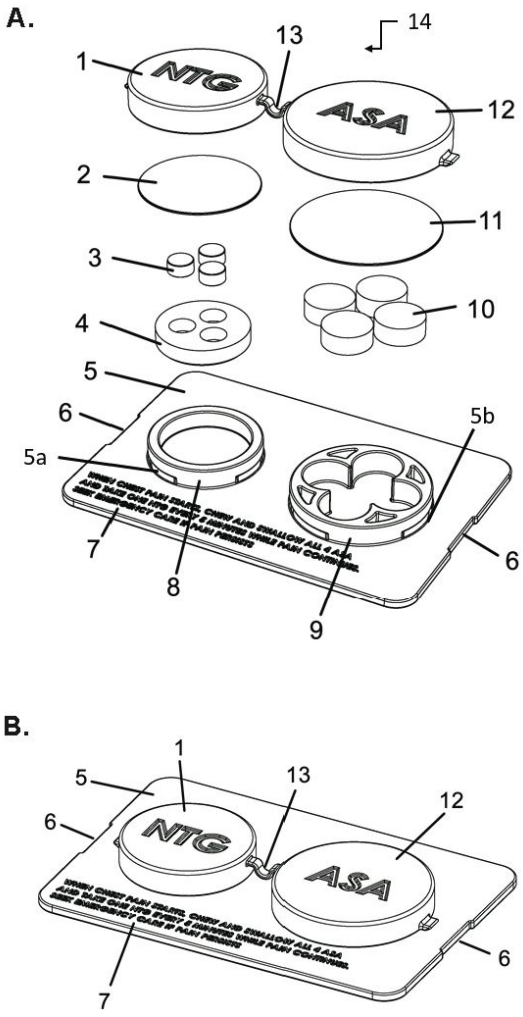

Figure 1. Cardiac medication holder design. Diagram of the disassembled (**A**), and assembled (**B**), cardiac medication holder demonstrating: 1) the nitroglycerin cap; 2) the NTG cap liner; 3) three NTG tablets; 4) the NTG insert; 5) the base; 6) grooves; 7) instructions; 8) the NTG insert holder; 9) the ASA well; 10) ASA tablets; 11) the ASA cap liner; 12) the ASA cap; 13) the cap bridge.

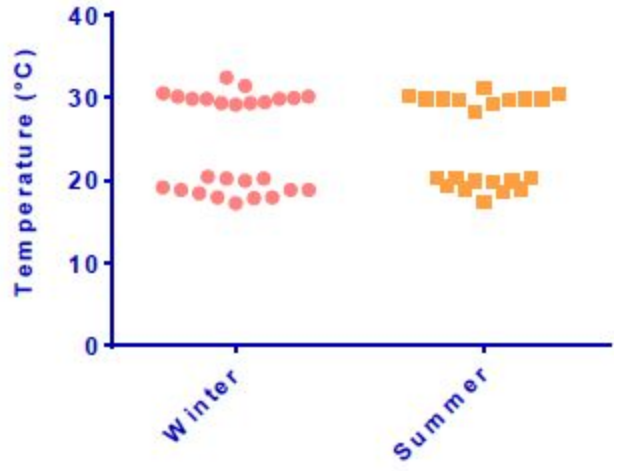

Figure 2. Minimum and maximum 24hr pocket temperature excursions of four individuals measured using a ThermPro - TP50 Digital LCD Indoor Thermometer Hygrometer Humidity Meter in both summer and winter conditions.

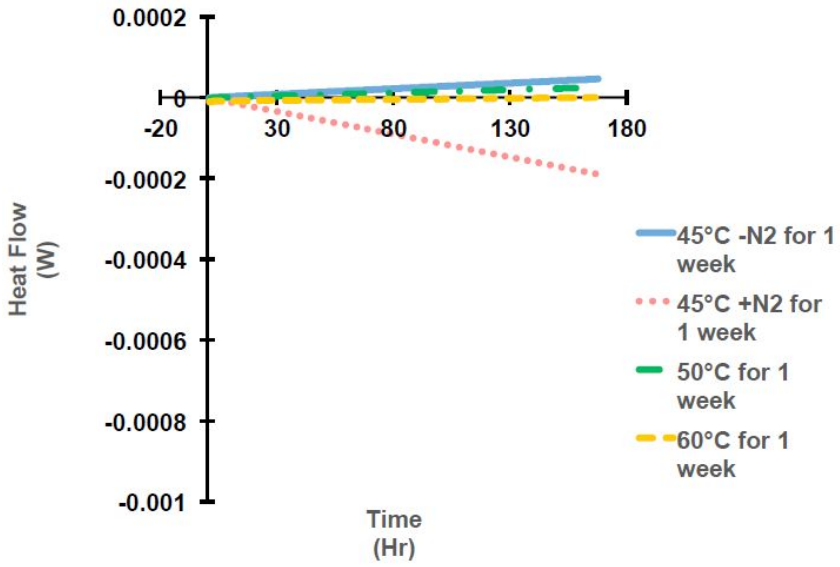

Figure 3. Heat flow of 0.3mg Nitrostat® tablets stored for 1 week at high temperatures (45ºC to 60ºC) measured using a microcalorimeter. ±N2 = with/without nitrogen packaging.

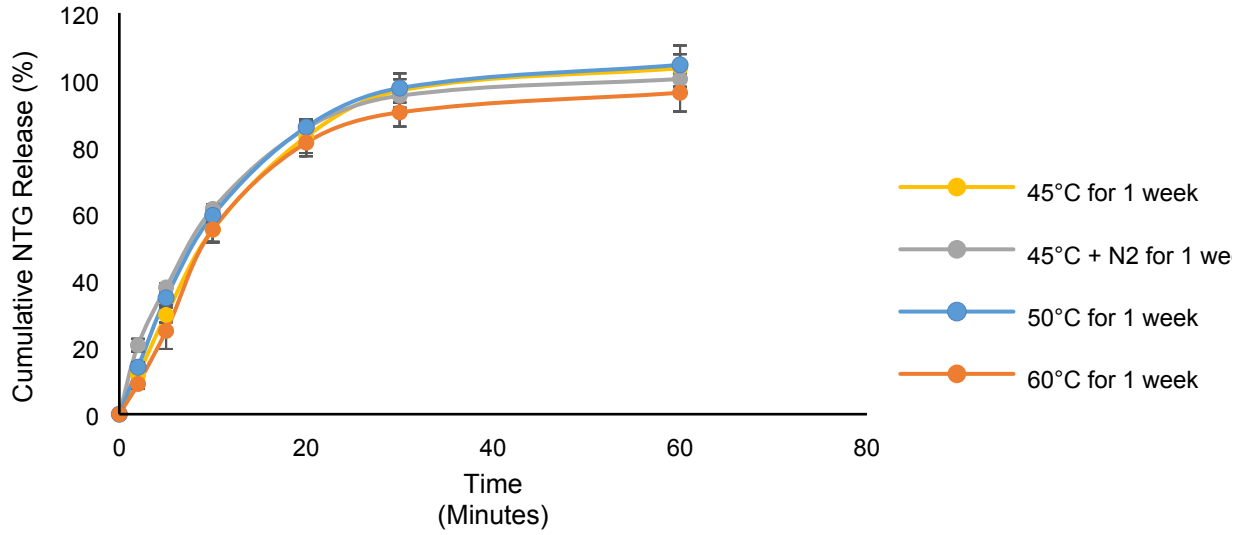

Figure 4. Cumulative nitroglycerin release profiles of 0.3mg Nitrostat® tablets stored in a microcalorimeter at high temperatures (45ºC to 60ºC) for 1 week. ±N2 = with/without N_2 packaging. N=6 mean ± SEM.

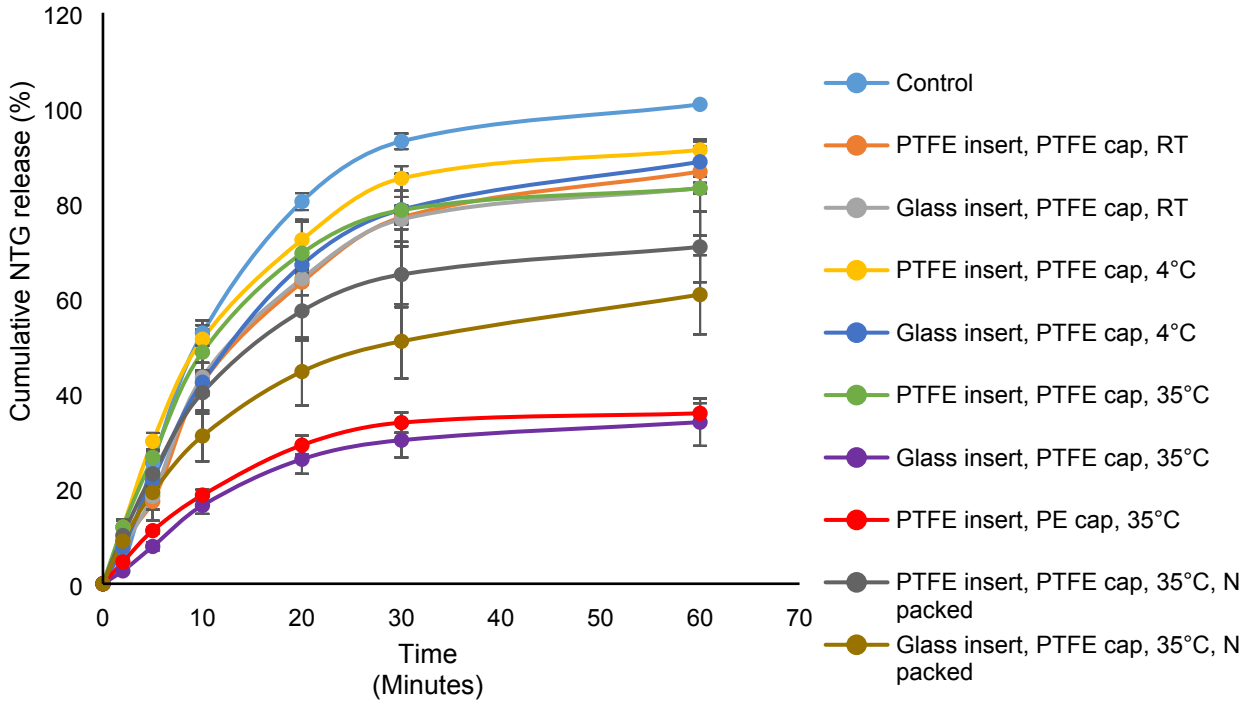

Figure 5. Cumulative nitroglycerin release profiles of 0.3mg Nitrostat® tablets stored within in original borosilicate glass packaging (control, RT), or the cardiac medication holder enclosed with polytetrafluoroethylene (PTFE), polyethelene (PE), or glass at 4°C, RT (22°C), or 35°C, with or without N_2 packaging, for 24 weeks. N=6 mean ± SEM for each timepoint.

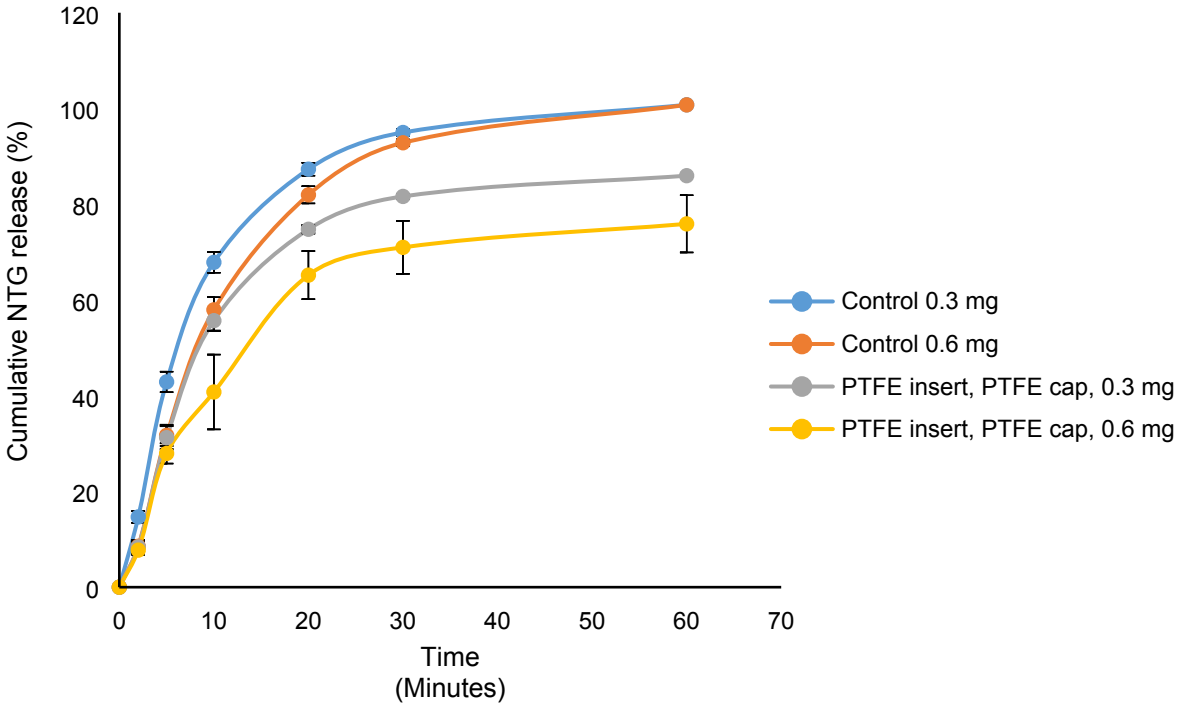

Figure 6. Nitroglycerin release profiles of 0.3mg and 0.6mg Nitrostat® tablets stored at RT in original borosilicate glass packaging (controls), compared to 0.3mg and 0.6mg Nitrostat® tablets stored in the medication holder enclosed with polytetrafluoroethylene (PTFE) for 24 weeks under real world conditions. N=6 mean ± SEM for each time point.