Development of self-care textile wearables with thermally stimulated drug delivery function via biological and physical investigations

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Abstract

Previous studies have examined and verified the drug loading and releasing functionality from the interior channels of hollow fibers. An integrated design for self-care textile wearables with a thermally stimulated drug delivery function was proposed. To progress the in-depth development of the proposed self-care wearables, physical and biological investigations, including i) liquid release with thermal stimulation and ii) drug release upon thermal stimulation, were conducted. Physical investigation revealed that the concentration of dyes released from the heated specimens increased with higher temperature during the initial first hour of delivery. Moreover, higher cytotoxic effect could be induced with drugs delivered through heated specimens under higher thermal stimulated energy through biological examination. These results set up milestones for demonstrating the influence of thermal energy on different therapeutic requirements, such as rapid-onset transdermal medication.

Keywords: textiles, hollow fibers, drug delivery, thermal stimulation, self-care wearables, medical and healthcare applications

Introduction

In the era of rapid technological development, advanced textile technology has been placed in a focal position in various areas. Numerous research studies have focused on textile and material technology in applications in the medical domain. Hollow fibers, already known as promising fibers in medical and healthcare applications, have been studied for their drug loading and releasing abilities.[1–8] We reported on a new conceptual idea of designing transdermal self-care textile-based wearable system with thermally stimulated drug delivery function using hollow fibers in our previous studies.[7–8] Thermal stimulation involves the supply of heat energy by utilizing heat-releasing objects with designated thermal conductivity. The principle of thermodynamics plays an important role in thermal stimulation. Heat is the transitional thermal energy that passes through the margins of a medium due to the temperature difference between that medium and its surroundings. It is generally acknowledged that thermal stimulation can trigger the molecular movement of particles, and results from propagation of the kinetic energy of vibrating molecules and the resulting increasing internal energy.[9–13] This phenomenon is believed to support various medical therapies. In past decades, thermal stimulation has been utilized directly for the medical treatments in pain relief, skin inflammation, edema, musculoskeletal injuries, soft tissue

injuries, and pediatric swallowing disorders.[14–17] Through technological advancements, thermally sensitive technology has been explored for different delivery systems. Thermoresponsive materials such as shape memory and self-folding polymers have been developed in smart delivery systems. The shape memory performance of electro-active shape memory polymer, which is filled with conductive components, can be triggered by thermal stimulation through an electric current in order to heat the material to above the glass transition temperature or melting point. Thermoresponsive self-folding polymers consist of multilayers with various thermal expansion coefficients to induce folding performance. A self-folding oral delivery device has been developed to promote the protection of drugs, targeted delivery, and bioadhesion.[18] Additionally, thermosensitive self-heating technology has been used to control the release of payload from highly dissipative hydrogel matrix and thermo-sensitive nanoparticles.[19] Targeted drug delivery to tumors could be assisted by using thermally responsive polymers with hyperthermic targeting.[20] Due to the effectiveness of thermal stimulation in current medical delivery systems, a novel development would be to interconnect the structural features of hollow fibers and thermosensitive technology to implement controllable and wearable transdermal textile-based drug delivery. In previous studies, a conceptual idea of designing a self-care textile wearable with a long-term transdermal thermally stimulated drug delivery function was proposed. The textile wearable would be produced with three main layers, which include the inner drug delivery layer (i.e., made of drug-loaded hollow fibers), the middle thermal conductive e-fabric layer (i.e., with the embedding of silver-coated conductive yarns), and an outer cover layer. A designated level of heat energy could be transferred to the drug delivery level through thermodynamics for a specific medical requirement of drug release. The stability of electrical conductivity was studied, and the thermal distribution of the thermally conductive layer at specific temperature intervals was measured. It is believed that efficient delivery of drugs to skin under optimum conditions could be achieved by a self-heating system in a controllable catalyzed manner with defined delivery strategies through a combination of hollow fibers and thermosensitive technology.[7–8] To further progress the development of wearable self-care textiles, both physical and biological studies of the release system with thermal stimulation were performed. For physical testing, liquid release upon thermal stimulation was investigated by heating dye-loaded specimens at a specific temperature and measuring the corresponding visible absorbance of the dyes released from the specimens. For biological testing, the relationship between temperature and the drug releasing ability from heated non-woven fabrics (i.e., drug loading layer) was investigated via anti-breast-cancer analysis. These studies provide important milestones in our understanding of the utilization of different heating temperatures with respect to different medical requirements of the body. In

addition, thermal stimulation could also play a crucial role in optimizing the speed of drug release, the release profile, and therapeutic performance (Figure 1).

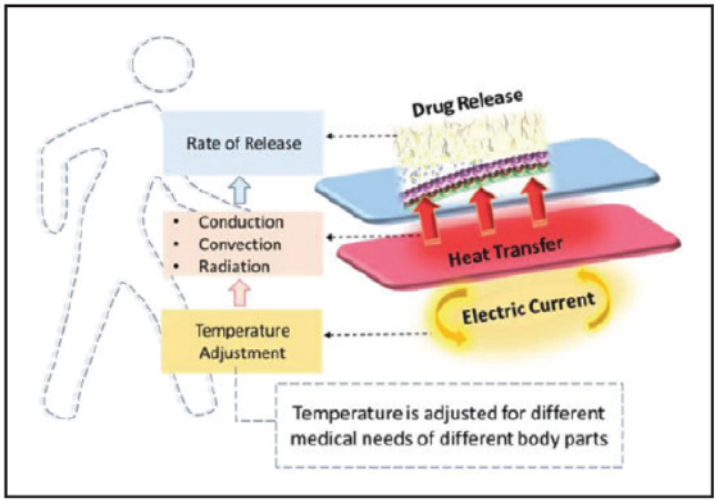


Figure 1. Schematic diagram of thermally stimulated drug delivery system.

Experimentation and Development

Preparation of specimens

The staple crimped hollow fibers used in previous studies were also the major materials of these proposed studies. Melt spun hollow fibers with crimps were inserted during the process of relaxation. Non-woven fabrics prepared by the needle-punching method were used as samples for the subsequent physical and biological investigations.

Method of drug loading

The drug delivery layers (non-woven fabrics) were submerged into a tube of drug solution. The tube containing the specimens was sealed inside a Büchner flask. The flask was then subjected to a water circulating vacuum machine under pressure of 0.05–0.06 mPa for 20 min. The exported drug delivery layers were then airdried (Figure 2).[7–8]

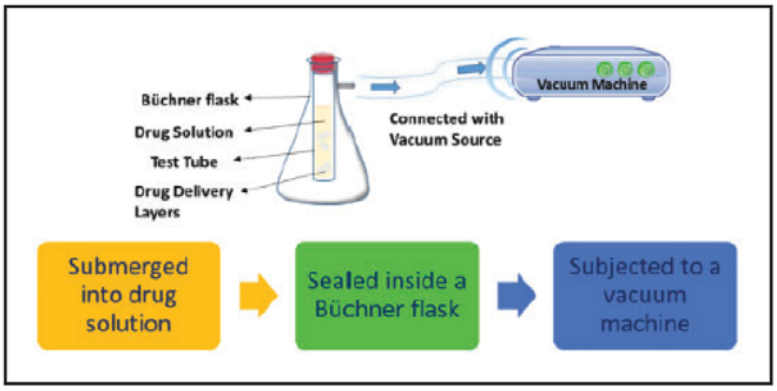
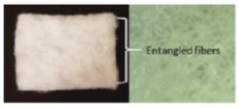
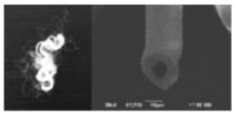


Figure 2. Schematic representation of the drug loading method by vacuum.

Method of the physical investigation of liquid release with thermal stimulation

Loading agent, 1% blue dye, was diluted to specific concentrations (1:5, 1:25, and 1:125) for calibration and comparison. The dye-loaded specimens (i.e., non-woven fabrics) were placed in sealed centrifuge tubes containing 1ml deionized water. The specimens were then placed in a digital block heater (genius dry bath incubator, Major Science) at a specific temperature (25℃, 37℃, 40℃, and 43℃). After 1 h of thermal stimulation, 0.3 ml of solution was taken from the centrifuge tube. Visible absorbance was measured using a microplate reader (synergy H1 microplate reader, Bio-Tek) at a specific wavelength (Table 1 and Figure 3).

Table 1. Experimental Elements of Liquid Release with Thermal Stimulation.

	Fluid delivery layer	Instruments for thermal stimulation
Name of elements	Synthetic (nylon–polyester) staple crimped hollow fibers[8]  Nonwovens made of hollow fibers 	Digital block heater 
Specifications of hollow fibers	Fiber fineness: 1.5D Fiber length: 38 mm Internal diameter of hollow: ~8–10 μm Overall diameter of fiber: ~20 μm	
Specifications of nonwovens	Non-woven GSM: ~375 g/m^2 Thickness: ~3 mm Production process: A spun-bonded web was made by interlocking the fibers with the use of barbed felting needles.	

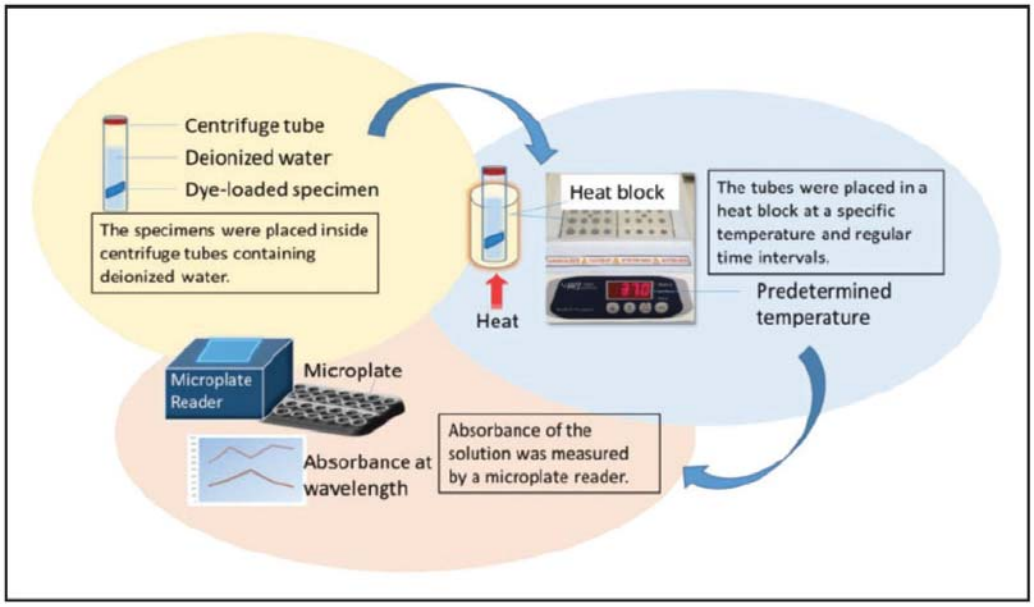


Figure 3. Schematic diagram of liquid release with thermal stimulation under physical investigation. A centrifuge tube containing dye-loaded specimens and water was placed in a digital block heater at a specific temperature. A specific amount of solution was taken from the centrifuge tube. Absorbance was measured at a specific wavelength.

Method of biological investigation of drug release with thermal stimulation

To further study implementation of the hollow fiber–drug delivery system with thermal stimulation, the drug delivery layers (i.e., non-woven fabrics), which were under thermal heating from a digital block heater, were investigated. Each sample was placed inside a tube of cell culture medium. Each tube was heated at a specific temperature (i.e., 37C, and 42C). After 1 h, the solution was centrifuged at 8000 rpm for 2 min. The supernatant was collected from each tube and added to a well of breast cancer cells (Figure 4). The effect of thermal heating on the drug release function from the crimped hollow fiber structure, and the relationship between temperature and the effects of drug release kinetics from the non-woven fabrics were examined.

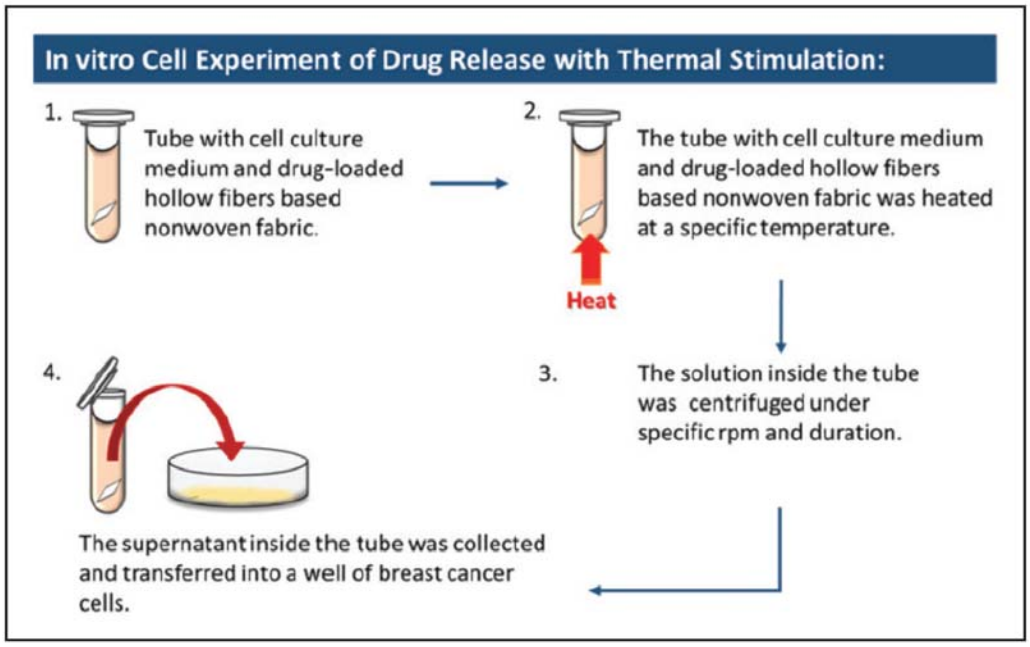


Figure 4. Flow chart of in vitro cell experiment of drug release with thermal stimulation. Drug-loaded hollow-fiber-based non-woven fabrics were heated with the medium at specific temperature. The supernatant collected was then transported into a well of breast cancer cells for further investigation.

Results and Discussion

The results and discussion are categorized into two main sections: i) physical investigation of liquid release with thermal stimulation, and ii) biological investigation of drug release with thermal stimulation. The controllable catalyzed drug delivery performance of the hollow fibers with thermosensitive technology was examined via these two investigations in order to provide a comprehensive and quantitative study of the thermal-stimuli drug delivery function of the proposed textile-based wearable system.

Liquid release with thermal stimulation under physical investigation

To measure the visible absorbance (i.e., optical density (O.D.)) of the liquid dye released from heated specimens, wavelength of maximum dye absorption at 595nm was chosen. A linear relationship between O.D. and concentration of dye released was observed (Figure 5). The measurement of O.D. at wavelength with maximum absorbance increased with increasing concentration of dye solution and vice versa.[21] To compare the result of visible absorbance, a summary was outlined as follows: after a 1-h release, the O.D. of specimen 1 (control, 25℃) was lowest, the O.D. of specimen 3 (heated, 40℃) was a little higher than that of specimen 2 (heated, 37℃), and the O.D.

of specimen 4 (heated, 43℃) was highest. The higher the temperature applied for thermal stimulation, the higher the concentration of dye released (Table 2 and Figure 6). This may be because the given thermal energy had accelerated the rate of dye release from specimens 2, 3, and 4, respectively, at the initial stage; thus, a higher amount of encapsulated dyes was released during the first hour for the specimens with thermal stimulation. The dye molecules could be excited and move more vigorously from the lumens of the hollow fibers when being heated up. The kinetic energy of the moving dye molecules could be increased by the thermal energy. The higher the temperature applied, the less viscous the dye solution, and the faster the releasing movement of the dye solution. As a result, a higher concentration of dye released was obtained with increasing temperature via thermal stimulation.[9,13,22]

Time to onset of action is defined as the time taken for drugs to take effect at the target site. Rapid onset of transdermal medication would be important for relieving symptoms caused by inflammation and dermatitis. Besides, it could also help for emerging modes of superficial wound healing or acute pain relief such as postsurgical mastalgia and lumbar spine pain.[23] Our results show that the promotion of release under thermal stimulation will facilitate short duration transdermal medication for treating acute symptoms.

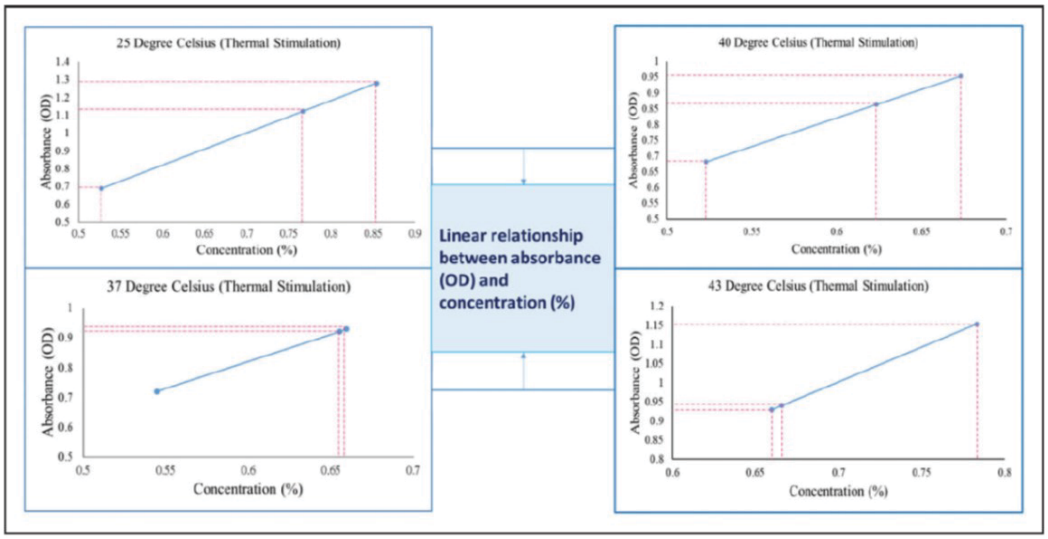


Figure 5. Linear relationship between absorbance (optical density) and concentration of released dye.

Table 2. Indications of dye-loaded specimens.

	Status	Room temperature	Thermal stimulation
Specimen 1	Control	25°C	/
Specimen 2	Heated	/	37°C
Specimen 3	Heated	/	40°C
Specimen 4	Heated	/	43°C

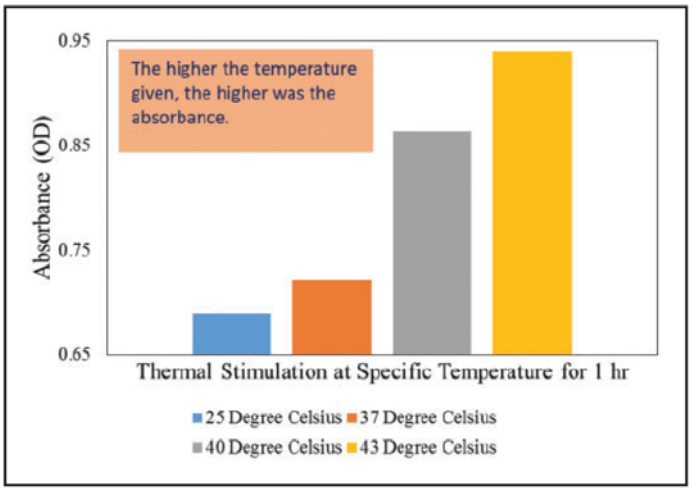


Figure 6. Visible absorbance of released dye in related to thermal stimulation at 25℃, 37℃, 40℃ and 43℃, respectively, for 1 h.

Drug release with thermal stimulation under biological investigation

In addition to the physical analysis of dye release, biological investigation of drug delivery with the integration of thermally stimulated therapeutic technology was also performed in order to conduct a comprehensive study together with both biological and physical perspectives. The drug delivery layer, which was a non-woven fabric made of staple crimped hollow fibers, was investigated with thermal stimulation to examine the effect of thermal heating on the kinetics of drug release from and within the crimped hollow structure of the fibers. Drug release from thermally stimulated drug-loaded specimens was studied at different temperatures. Temperatures of 25 ℃ (i.e., room temperature as control), 37 ℃ (i.e., body temperature) and 42 ℃ (mild heating temperature) were the target range of thermal stimulation given to the 5-FU-loaded non-woven fabric specimens (Table 3). The effectiveness of drug release at a specific heating temperature and duration was examined by calculating the viability of breast cancer cells after the released drugs were collected from the heated specimens and transferred to plates containing breast cancer cells.

As shown in Figure 7a, 5-FU-loaded non-woven fabrics were placed at 25℃ as a control or heated at 37℃ for 60 min.

Reductions in viability of 6.75% and 7.45% were observed for cancer cells treated with drug released from 25℃(control) and 37℃ heated samples, respectively. Fewer cancer cells grew and survived for the heated samples compared with the control one. Figure 7b shows the results obtained with 5-FUloaded non-woven fabrics heated at 37℃ and 42℃ for 60 min. Reductions in cancer cell viability of 5.05% and 5.9% were observed for cells treated with drug released from 37℃-heated and 42℃-heated samples. respectively. Comparatively fewer cancer cells grew and survived in the 42℃-heated samples.

Given the relationship between temperature and liquid kinetics, the kinetic energy of a liquid is directly proportional to the temperature applied. An increase in the temperature of a liquid can induce a corresponding increase in the average velocity and momentum of its molecules. The movement of molecules is hence increased with the elevated kinetic energy. The increase in kinetic energy can further reduce the intermolecular forces between molecules. In accordance with the results achieved in this biological cell study, more cancer cells became unviable and died after being treated with drugs released from samples heated at higher temperatures. The cytotoxic effect was slightly more prominent when providing a mildly elevated heating temperature than when applying body temperature. Similarly, body temperature could contribute to better cytotoxic performance compared with room temperature. This may be because, as the drugs encapsulated inside the channels were heated up with thermal stimulation, the drug molecules would be excited to move with the elevation of velocity and particle momentum. As a result, the kinetic energy of the encapsulated drug solution would be increased, which may diminish the van der Waals forces existing between the drug molecules. This may tend to decrease the gathering of molecules to form large clusters. The surface tension of drug fluid would be reduced by the energy of molecular movement. The drug fluid would become less viscous with increasing temperature, which would diminish the intermolecular attraction between the drug molecules. In addition, the adhesive forces between the drug solution and the surface walls of the hollow fibers would also be reduced to a certain extent, which would promote the escape of drug solution from the hollow fibers with higher thermal stimulation. The rate of drug flow through the channels to the target site of cancer cells would thus be enhanced with decreasing resistance. [13,22,24] Furthermore, only a slight reduction in the percentage of viability was observed for the treated cancer cells. This was probably because the drug released from the specimens for 1 h was only a small portion of the

encapsulated drugs, which might not outweigh the growth of cancer cells entirely. No apparent burst effect was shown for the first hour upon placement of the drug-loaded fabrics on the cell plates. A rate-limiting effect of the drugs was believed to be encouraged with the use of staple crimped hollow fibers.[25] Accelerated yet controllable drug delivery could be balanced with the use of both staple crimped hollow fibers and thermal stimulation technology.

Table 3. Indications of drug-loaded specimens.

	Status	Room temperature	Thermal stimulation
Specimen 1	Control	25°C	/
Specimen 2	Heated	/	37°C
Specimen 3	Heated	/	42°C

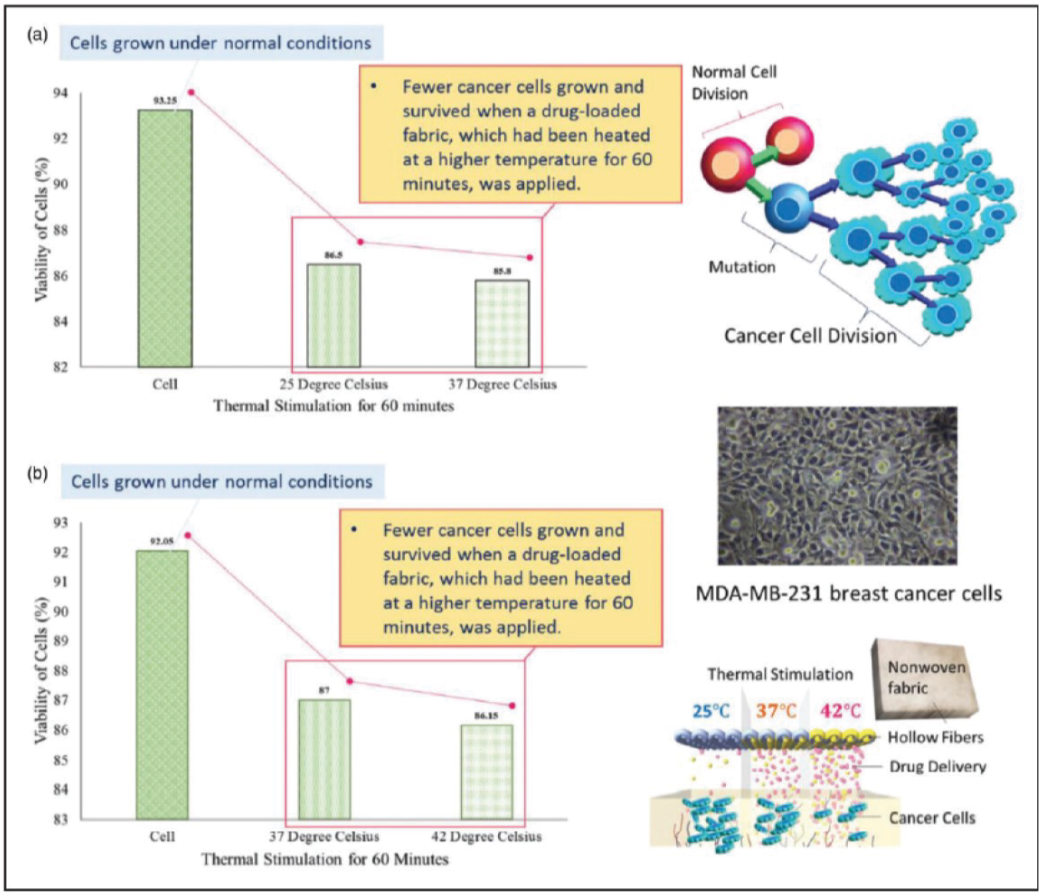


Figure 7. Viability of cells treated with thermally stimulated drug delivery samples. a) 5-FU-loaded non-woven fabrics were being placed at 25℃ as the control and heated at 37℃ for 60 minutes respectively. b) 5-FUloaded non-woven fabrics were heated at 37℃ and 42℃ for 60 minutes respectively.

Conclusion and Future Perspectives

The physical investigation performed in this study analyzed the visible absorbance of liquid release under the influence of thermal stimulation, finding a linear relationship between O.D. and the concentration of dye released. During the first hour of delivery, the higher the temperature applied, the higher the concentration of dyes released. The influence of thermal stimulation on drug delivery performance within hollow fibers was then further investigated by biological cell analysis; lower cell viability (i.e., higher cytotoxic effect) was found to be induced with drugs delivery through samples heated with higher thermal stimulated energy (i.e., higher temperature). No burst effect was apparent for the first hour of delivery. Thus, both physical and biological results implied that thermal energy could accelerate the release rate of drugs at the beginning. It was believed that the elevated rate of drug delivery could give rise to rapid onset or short duration therapeutic action. Controllable drug delivery could be triggered at the initial stage without an apparent burst release. Moreover, permeation of drugs could be further controlled by the protective cutaneous barrier.

These research findings are believed to give impetus to the development of new advanced therapeutic methods leading to wearable medical equipment for external delivery of transdermal medication. Based on functional and wearable textiles, the proposed innovative drug delivery system can be used to offer a wide range of medical and healthcare applications. Aforementioned in previous studies, an integrated design for a self-care textile wearable could be developed for postoperative cancer treatment. Moreover, bandages and wound dressings could be produced for the fast healing of the acute inflammation of wounds. Likewise, medical clothing for relieving persistent postoperative pain, and for conditions such as pressure ulcers, arthritis and fibromyalgia could be designed. Long-term, continuous, and controllable delivery of specific drugs to their target sites of action could be offered by wearing the textile-based garments and devices. A wide range of textile accessories, body care wearables and household bedclothes could be developed with the thermally stimulated drug delivery systems for patients of all ages.

Declaration of conflicting interests

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