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G16H 20/10 (2006.01)(72) Inventors: **Muhammad Mustafa HUSSAIN, Austin, TX (US); Abdurrahman GUMUS, Istanbul (TR); Wedyan BABATAIN, Thuwal (SA)**(52) **U.S. Cl.**
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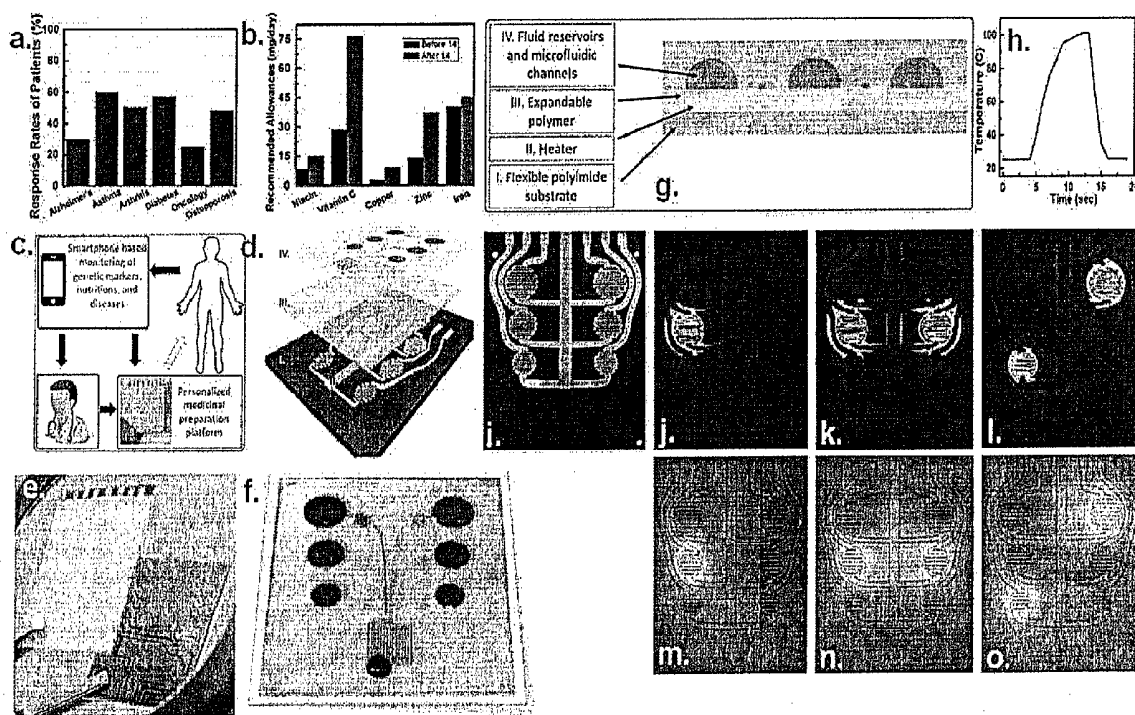
§ 371 (c)(1),

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(57) **ABSTRACT**

An apparatus for personal health maintenance has a sensor attached at least indirectly to a carrier member in turn attachable to a user or subject and configured for measurement of at least one physiological parameter of the user. A reservoir contains a preselected composition. An electronic processor is operatively connected to the sensor for receiving a signal therefrom encoding a measurement of the physiological parameter, the processor being configured for determining a divergence of the physiological parameter from a predetermined magnitude, the processor being operatively connected to a dispensing mechanism for ejecting, from the reservoir, an amount of the composition to be administered to the user to reduce divergence of the physiological parameter from the predetermined magnitude. The dispensing mechanism includes an expandable polymer composite layer with gas-filled micro-bubbles or micro-spheres expandable by operation of a heating element.



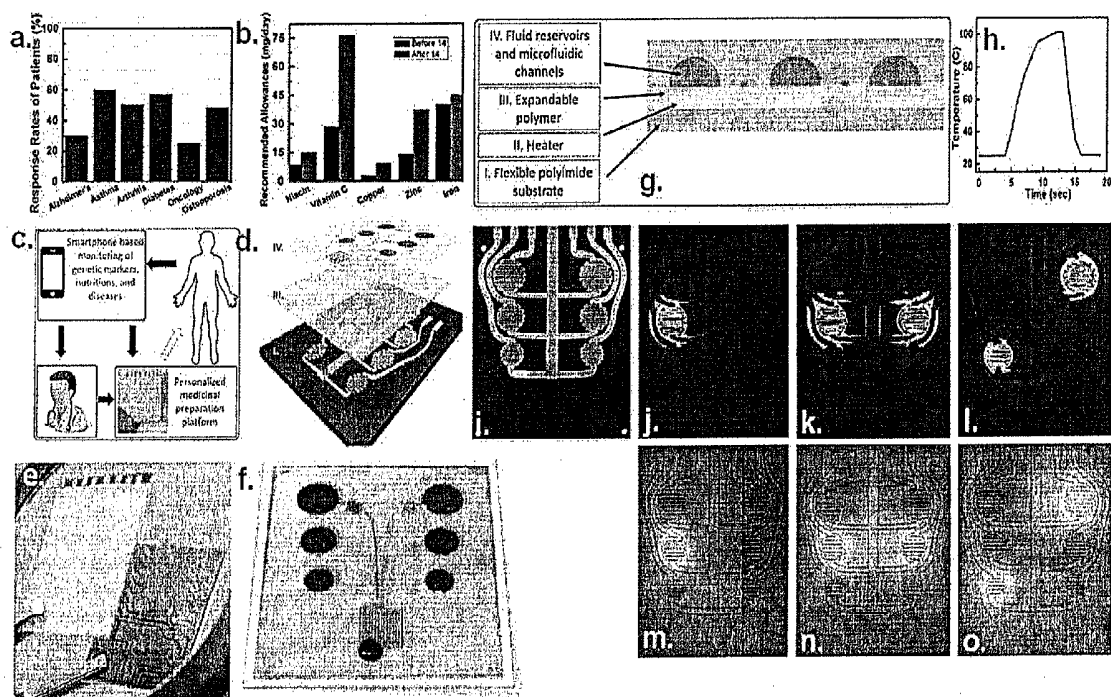


FIG. 1

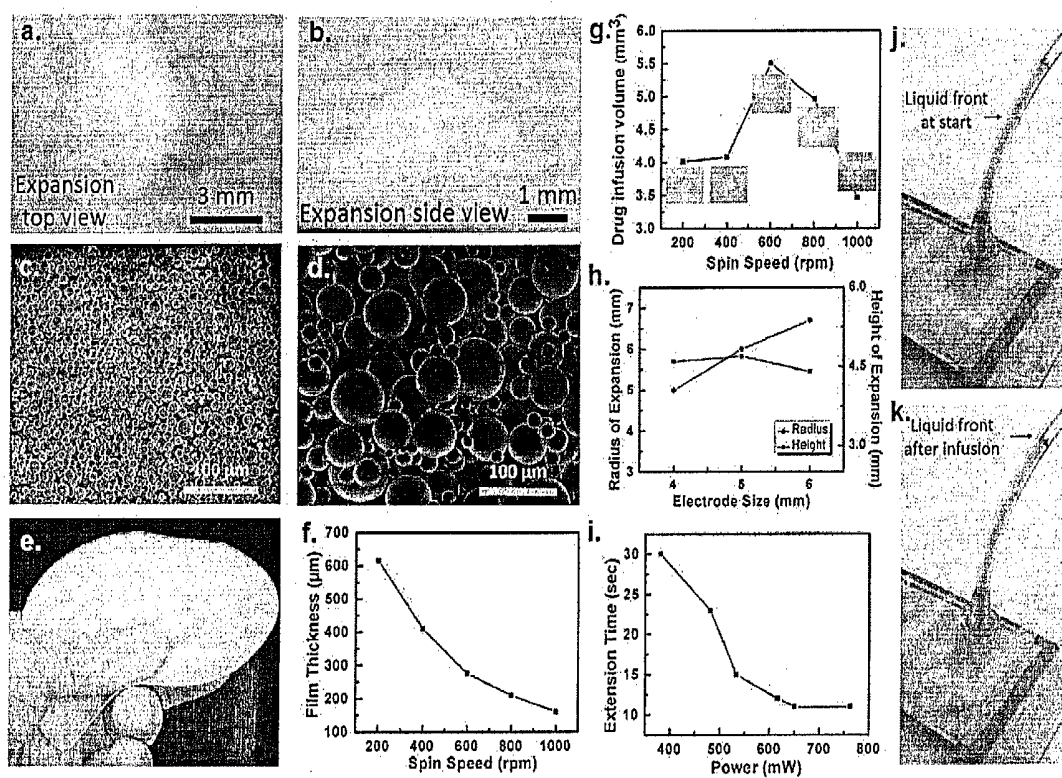


FIG. 2

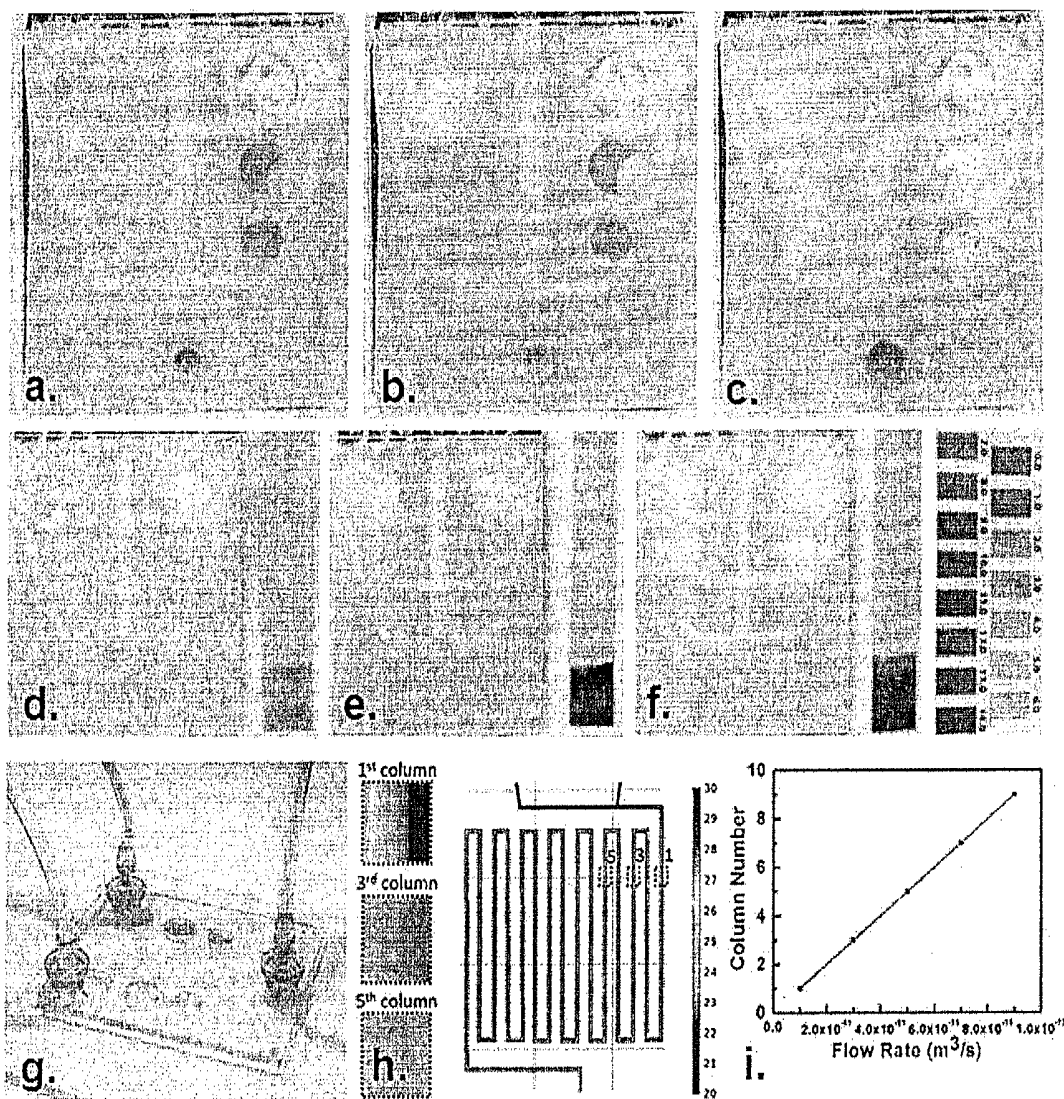


FIG. 3

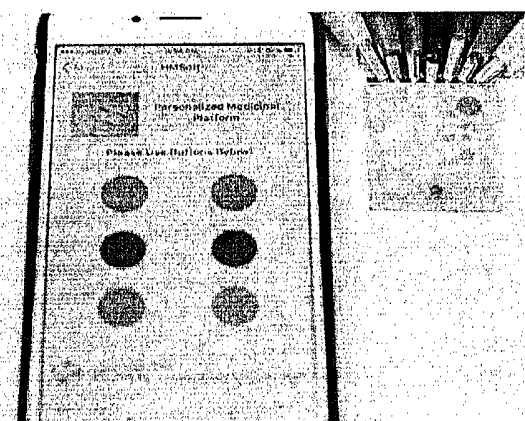
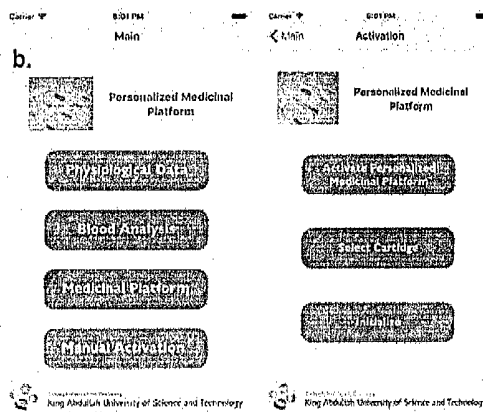
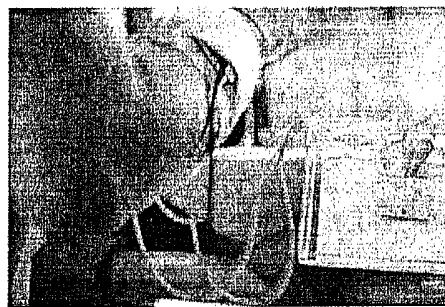
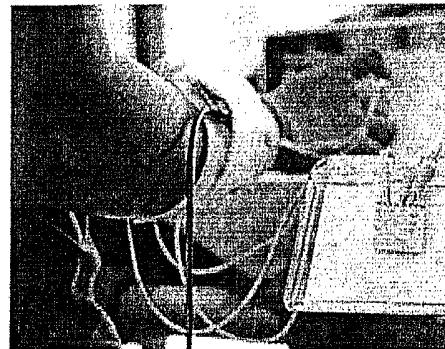
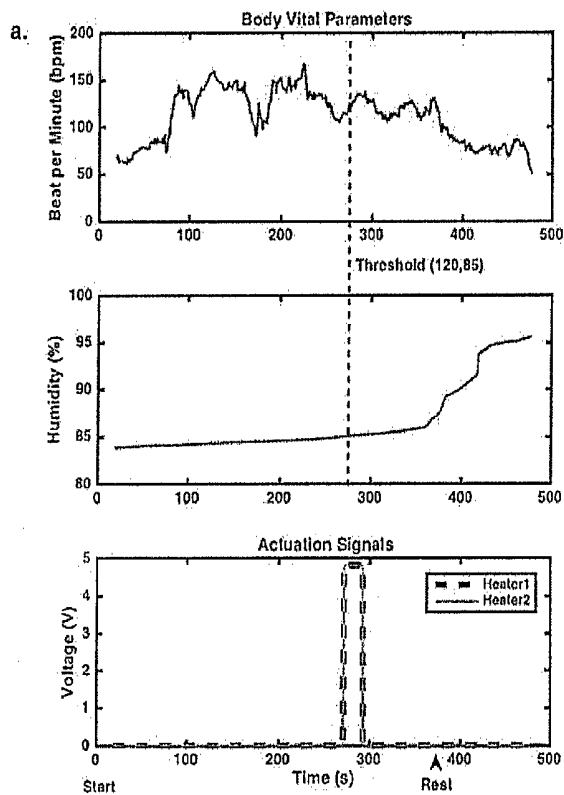


FIG. 4

FIG. 5

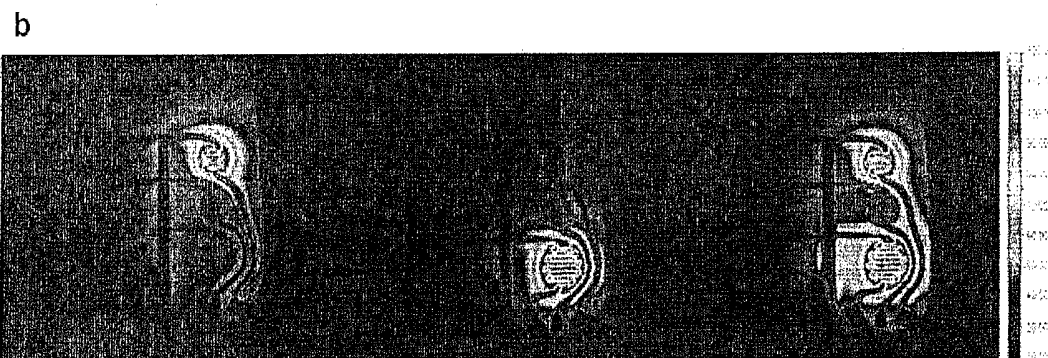
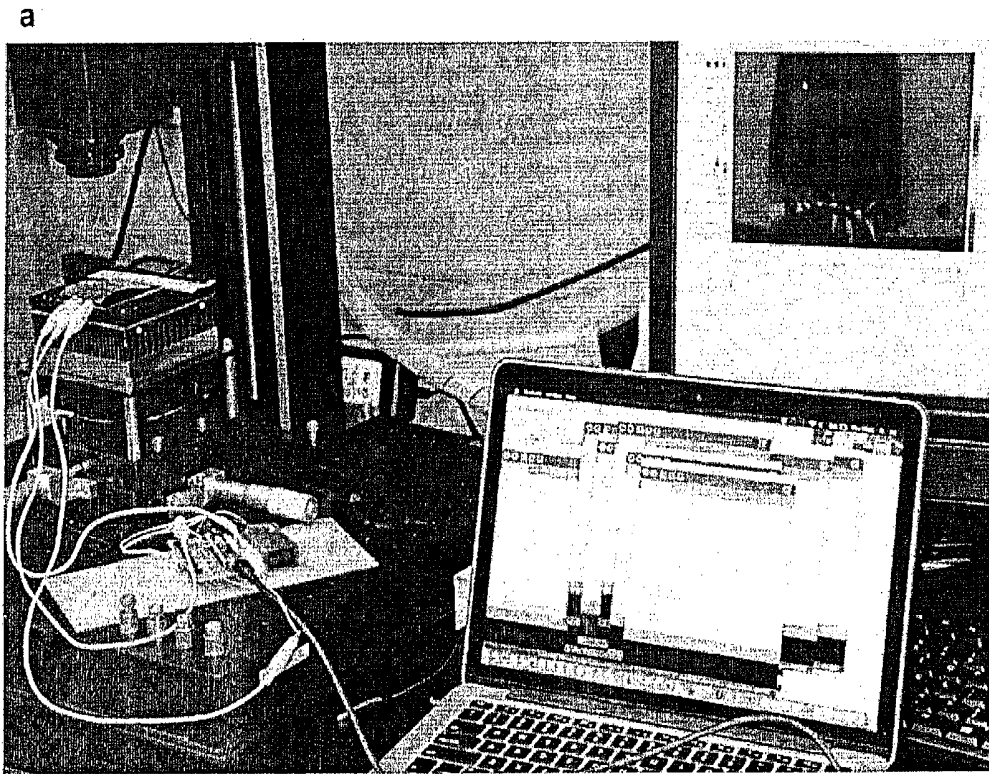


FIG. 6

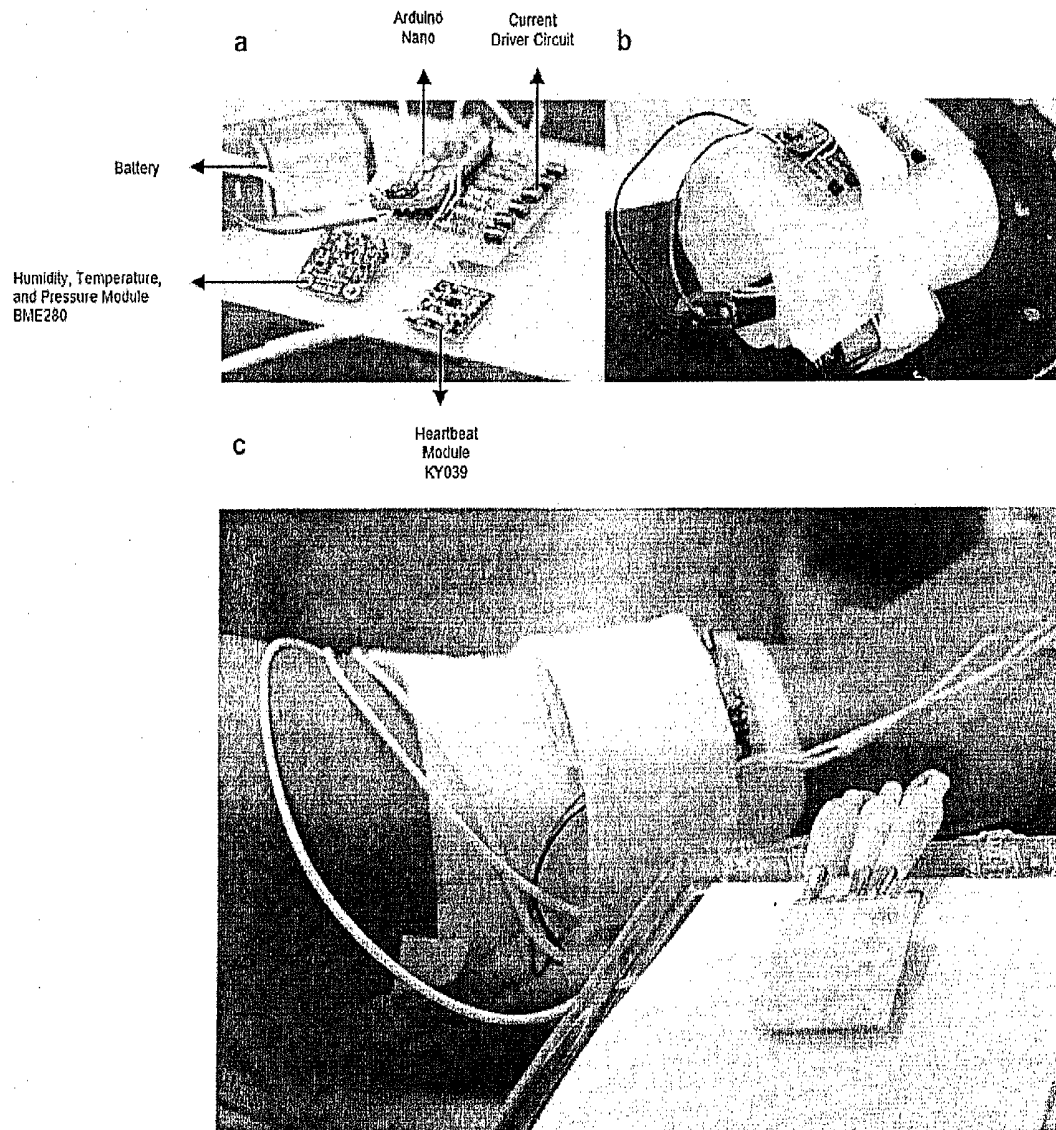


FIG. 7

WEARABLE PERSONALIZED MEDICINAL PLATFORM

[0001] The present invention is directed to a wearable apparatus for personal health maintenance. The present invention may be embodied as a wearable personalized medicinal platform.

[0002] Healthcare today is focused largely on “one size fits all” treatments. Patients with similar medical issues can be given the same medication and dosage, but the treatment might not be effective for all of them¹⁻³. There is an emerging field called as personalized medicine, which can be considered as going beyond the traditional approaches to understand and treat diseases. Personalization of the medication gives physicians the ability to use the patient’s mainly genetic information to guide selection of certain drugs or treatments for individuals, which can increase the possibility of a more effective and low cost approach for clinical care^{1,2}. Recently, researchers developed a compact, reconfigurable manufacturing platform which can produce pharmaceuticals on-demand, continuously for small quantities with shorter processing times which could be helpful to produce personalized medicines in the future more easily⁴.

[0003] Technological advances such as lab-on-a-chip technologies have enabled the deployment of easy to use, disposable, and informative diagnostic tests directly to the consumer allowing them to take control of their own health⁵⁻⁷. There are also wearable sensor technologies developed to pursue personalized clinical investigations through real-time continuous physiological monitoring of an individual⁸⁻¹¹.

[0004] Smartphone technology is rapidly being more accessible and a potentially transformative opportunity for the deployment of these health monitoring technologies with its communication and computational capabilities⁶. Since most consumers already own a test reader/instrument in the form of a smart phone, integration of existing rapid diagnostic test strips or wearable health sensors to smartphones is an emerging research field^{5,7,12}. On the other hand, more complex devices are being developed for the analysis of blood which can give a wealth of information ranging from general molecular markers of infectious diseases, to cancer diagnostics, genetic analysis, vitamins and micronutrient deficiencies¹³. This can increase the awareness through physiological feedback by enabling rapid detection of body vitals and molecular signs which could potentially decrease many health problems. Wearable sensor technologies will record the data for certain intervals and be integrated with smart phones where they can remind the user about his/her condition. Alternatively, a smart phone can send results to the doctor which can save time and effort for both doctors and patients.

[0005] This also enables doctors to intervene remotely through drug delivery devices or schedule an appointment with a patient. These medical monitoring and drug delivery devices⁷⁻¹⁰ decrease the cost of healthcare and increase the quality of life of patients. Significant work has been done previously using similar device structures to the system presented here to apply different dosages of a drug¹⁴, applying single dosage of different drugs¹⁵, or microfluidic platform that can integrate active dosing¹⁶. Still using these devices for the personalization of medicine and incorporating them for appropriate applications is yet to be done.

SUMMARY OF THE INVENTION

[0006] To complement as well as to significantly advance the earlier works, here we show a wearable personalized medicinal platform that has the capability to prepare (vary and mix multiple constituents) drugs, vitamins, and minerals on demand or depending on the needs of the individual using integrated wearable health sensors. By integrating with advance complementary metal oxide semiconductor (CMOS) electronics and technology, we present this microfluidics-based wearable medicinal preparation platform to pursue the goal of the in-situ personalization of medicine preparation which offers a unique impact on global healthcare. Instead of “one size fits all” treatment approaches for healthcare issues, the demonstrated system can prepare the drugs, vitamins and minerals instantly and in-situ depending on the needs of a person at any given time.

[0007] The system developed here has the capability of mixing two (can be scaled up further in straight forward manner) different drugs with different dosages on demand or with external stimuli through wearable body sensors when it is tested on a human subject.

[0008] Adaptive drug preparation is critical to personalize healthcare and immediate application areas are energy drinks and multi-vitamins for everyone and specially soldiers, athletes, patients and blue collar personnel.

[0009] An apparatus for personal health maintenance comprises, in accordance with the present invention, a carrier member, at least one sensor attached at least indirectly to the carrier member and configured for measurement of at least one physiological parameter of a user, an attachment device connected to the carrier member for maintaining the sensor in operative proximity with the user, at least one reservoir provided on the carrier member and containing a preselected composition, a dispensing mechanism provided on the carrier member in operative contact with the reservoir, and an electronic processor mounted to or carried by the carrier member and operatively connected to the sensor for receiving a signal therefrom encoding a measurement of the physiological parameter. The processor is configured for determining a divergence of the physiological parameter from a predetermined magnitude and is operatively connected to the dispensing mechanism for operating the same to eject, from the reservoir, an amount of the composition to be administered to the user to reduce divergence of the physiological parameter from the predetermined magnitude.

[0010] The dispensing mechanism preferably includes an expandable polymer composite layer. The expandable polymer composite layer preferably includes gas-filled microbubbles or microspheres. The dispensing mechanism preferably further includes an electric circuit with at least one heating element proximate the expandable polymer composite layer.

[0011] Thus, in an apparatus in accordance with the present invention, the reservoir is part of a microfluidic circuit disposed on a substrate included in the carrier member.

[0012] The sensor is preferably configured for non-invasive detection of the physiological parameter. The physiological parameter may be body temperature, blood pressure, pulse rate, skin hydration, perspiration state, respiration rate, glucose level, and oxygen content. When multiple sensors are provided, each may measure a different one of these physiological parameters. Concomitantly, the

sensor may be a temperature sensor, an electrical conductivity or electrical resistance detector, a pressure sensor, a moisture sensor, etc.

[0013] The physiological parameter may be a level of an analyte such as calcium, potassium, magnesium, and glucose or a pharmaceutical analyte. Alternatively, the physiological parameter may be a physiological abnormality such as acute myocardial infarction, subarachnoid bleed, and fluid accumulation around the heart.

[0014] In one embodiment of the invention, the dispensing mechanism includes a nozzle to dispense the amount of the composition into or onto an ingestible substance. The user may be alerted to the recommended supplement by operation of an alert signal generator operatively connected to the processor for prompting the user to take action to ingest the amount of the composition.

[0015] The composition in the reservoir may include one or more vitamins.

[0016] It is to be noted that multiple reservoirs may be provided in the apparatus, each containing a predetermined amount of a preselected composition. A respective, dedicated heating element for each such reservoir is included in the electrical circuit.

[0017] The multiple reservoir may contain different compositions, thus enabling mixing of different composite compositions depending on the needs of the user as determined by multiple sensor readings and the pre-programmed processor.

[0018] A microfluidic dispensing assembly in accordance with the present invention comprises a substrate, at least one reservoir provided on the substrate and containing a preselected composition, and a dispensing mechanism provided in juxtaposition to the at least one reservoir, where the dispensing mechanism includes an expandable polymer composite layer. The microfluidic dispensing assembly further comprises an electronic processor operatively connected to the dispensing mechanism for operating the same to eject, from the reservoir, an amount of the composition.

[0019] Pursuant to one feature of the present invention, the expandable polymer composite layer includes gas-filled micro-bubbles or microspheres. The dispensing mechanism further includes an electric circuit with at least one heating element proximate the expandable polymer composite layer, the processor being operatively connected to the electric circuit.

[0020] The reservoir is part of a microfluidic circuit disposed on the substrate.

[0021] A sensor may operatively connected to the processor and attachment means for maintaining the sensor in operative engagement with a user. In that case, the processor is configured for receiving a signal from the sensor encoding a measurement of a physiological parameter, the processor being further configured for determining a divergence of the physiological parameter from a predetermined magnitude. The processor is operatively connected to the dispensing mechanism for operating the same to eject, from the reservoir, an amount of the composition to be administered to the user to reduce divergence of the physiological parameter from the predetermined magnitude.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] FIG. 1a is a graph showing response rates of patients to medications for different diseases2.

[0023] FIG. 1b is a graph showing different vitamin and mineral needs of people below and after 14 years age¹⁷⁻¹⁹.

[0024] FIG. 1c is a diagram illustrating operation principle of a web integrated wearable personalized medical system in accordance with the present invention.

[0025] FIG. 1d is a schematic exploded perspective view of selected parts of a wearable personalized medical system in accordance with the present invention, including, top to bottom, a microfluidic system, an expandable polymer composite layer and electric heaters.

[0026] FIG. 1e is a photograph showing components of an advanced version of a wearable personalized medical system pursuant to the present invention, with flexible silicon CMOS chip sets (25 μm thick, 1 mm² with 256 fan-outs in a spider-web) on the back (imaged using a mirror).

[0027] FIG. 1f is a schematic isometric top and front view of a fully functional medicinal platform in accordance with the present invention, with two different liquids (red and green colored in a color version of the figure) contained in different sizes of reservoir.

[0028] FIG. 1g is a schematic cross-sectional view of a wearable personalized medical system pursuant to the present invention.

[0029] FIG. 1h is a photograph showing an electric circuit and reservoirs of a wearable personalized medical system in accordance with the invention, showing experimental results of electrode temperature increase and decrease profiles.

[0030] FIGS. 1i through 1l are infrared photographs of an electric circuit of a wearable personalized medical system in accordance with the invention, depicting thermal actuator electrodes powered up sequentially and infrared (IR) images were collected to observe the temperature profiles and distributions.

[0031] FIG. 1m through 1o are infrared photographs of an electric circuit of a wearable personalized medical system in accordance with the invention showing an investigation of temperature profiles with Finite Element Analysis (FEA).

[0032] FIGS. 2a and 2b are photographs of an expandable polymer layer of a wearable personalized medical system in accordance with the invention, after expansion thereof.

[0033] FIGS. 2c and 2d are SEM images of expandable polymer particles composite incorporated into a wearable personalized medical system in accordance with the invention.

[0034] FIG. 2e is a photograph of an expandable polymer layer after release from a 4-inch wafer.

[0035] FIG. 2f is a graph of film thickness as a function of spin speed in the manufacture of an expandable polymer composite layer for incorporation in a wearable personalized medical system in accordance with the invention.

[0036] FIG. 2g is a graph of drug infusion volume as a function of spin coating speed in the manufacture of an expandable polymer composite layer for incorporation in a wearable personalized medical system in accordance with the invention.

[0037] FIG. 2h is a graph of radius and height of expansion of gas-filled microspheres as functions of different electrode size, in a wearable personalized medical system in accordance with the invention.

[0038] FIG. 2i is a graph of extension time as a function of power input to the electrodes.

[0039] FIGS. 2j and 2k are photographs of a drug infusion test setup showing liquid places marked before and after infusion.

[0040] FIG. 3a through 3f are optical images of a set of reservoirs of a wearable personalized medical system in accordance with the invention, showing selective triggering or personalized medicinal preparation platform where reservoirs filled with water solutions (different colors and different pH values) to get a desired output mixture.

[0041] FIG. 3g is a photograph an experimental set-up in validation of microfluidic mixing capability of a wearable personalized medical system in accordance with the invention (yellow and blue liquid mixture yielding a green colored liquid).

[0042] FIG. 3h is a 3D FEA to observe the simultaneous flow of liquids through a micromixer channel structure in accordance with the invention.

[0043] FIG. 3i is a graph of column number as a function of flow rate of solution mixing using FAE.

[0044] FIG. 4a is a set of three graphs of physiological parameters detectable via skin sensors, pulse rate, humidity, and electric potential medicinal platform by triggering the device after detecting physical fatigue from wearable sensors. FIG. 4a also includes two photographs of an experimental wearable personalized medical system attached to an arm of a test subject.

[0045] FIG. 4b are Web screenshots of a developed App from an iPhone display (left) and a smartphone-based wireless operation of medicinal platform (right).

[0046] FIG. 5 is a circuit diagram of a control circuit and heating electrodes included in a wearable medicinal platform integrated system in accordance with the present invention, showing an interface between a micro-controller, sensors, and current driver circuitry.

[0047] FIG. 6a is a photograph of an integrated system testing environment with a thermal image microscope for real-time temperature analysis of medicinal platform heaters pursuant to the invention.

[0048] FIG. 6b is an infrared photograph of temperature profiles showing the results of automatically actuated sequential heating (left and middle) and simultaneous heating (right).

[0049] FIG. 7a is a photograph of an integrated system for wearable medicinal platform.

[0050] FIG. 6b is a photograph of the integrated system of FIG. 7a placed onto a 3D-printed sleeve.

[0051] FIG. 7c is a photograph of the wearable system of FIG. 7b on a wrist of a test subject with connections to a medicinal platform in accordance with the present invention, for the real-time fatigue detection test.

DETAILED DESCRIPTION

[0052] As can be seen from FIGS. 1a-1b, for some of the most common diseases, drugs on the market work only for a percentage (at the most 60%) of the population² and for multi-vitamins—personalization can be more effective¹⁷⁻¹⁹, respectively. Patients continue to switch from one drug to another until they find an effective therapy. This increases the cost of the medical treatment while compromising the quality of life and life expectancy of the patients¹. Rather than trial-and-error prescriptions, technological developments have enabled us to understand human genetics and its influence on disease and treatment, allowing physicians to select the optimal therapy during early stages of treatment³. As portable personal genome sequencers are imminent, by incorporating personal genome sequencers with smartphones' computation and communication capabilities, we

have the ability to do not just one time analysis of genetic markers, but continuous tracking of the changes on our genetic signatures throughout our life. By combining this genetic information with other physiological data acquired by wearable sensors, it is possible to evaluate a person's susceptibility to diseases and health condition continuously and address it accordingly. Personalized medicinal platform will play an increasingly critical role with the ability of preparing different drugs at different dosages autonomously or on demand precisely and safely (FIG. 1c). This also creates a new opportunity for the personalization of vitamin and mineral supplements where each person gets the amount of nutrient one needs, which can vary with multitude of variables (FIG. 1b).

[0053] FIGS. 1d-1g show the details of the device structure and the system itself with varying degrees of maturity. Laser-patterning of electrodes enabled etching the sputtered gold easily up to a resolution of 100 μm (FIG. 1i). Polyimide sheet (125 μm thick) was chosen as a substrate with low thermal conductivity (0.46 W m⁻¹ K) which can reach high temperatures (>90° C.) without thermal noise between electrodes. Using a thin polyimide sheet as a substrate also gives advantage of flexibility for flexible microfluidic applications in various versions of the medicinal platform. Each electrode is individually addressable.

[0054] FIGS. 1j-1l shows sequential activation of heating electrodes through thermal mapping collected with an IR camera. Power was delivered to the system using a coin cell battery (CR2032 Lithium Coin Cell Battery with 20 mm diameter, 0.02 lb shipping weights, 3 volts voltage and 200 mAh capacity) for joule heating over 90° C. within ~10 seconds of triggering. Temperature dissipates only around the triggered electrode avoiding any thermal cross talk between electrodes and allowing independent operation of each reservoir. After release of the trigger, temperature decreases to room temperature within four seconds (FIG. 1h). Temperature profiling results agree with Finite Element Analysis (FEA) using COMSOL™ Multiphysics (110 FIGS. 1m-o). Simulation details can be found in the Supplementary Information (SI) section below.

[0055] We preferred to use a solid microfluidic channels (PMMA) (FIG. S1) with low moisture and water absorbing capacity. The Computer Numerical Control (CNC) based direct micro-milling process to pattern microfluidic channels used here, can be easily implemented in any high-precision CNC machine without a need for a clean room facility. The LPKF™ system has an x-y resolution of $\pm 0.5 \mu\text{m}$ and is equipped with a depth delimiter that reduces the depth variation across the chip below $\pm 10 \mu\text{m}$, depending on the substrate flatness. Channels have a negligible surface roughness (~150 nm) which was validated with a profilometer. Incorporating different layers of the system using double sided tape enables an inexpensive and simple device assembly enabling the concept of Do It Yourself (DIY).

[0056] Each reservoir connects to a microfluidic mixing chamber. Infusion of the fluids into the mixing chamber from the reservoirs is initiated through expansion of the expandable polymeric material induced by joule heating of one or more underlying heating electrodes^{14-16,20}. The active layer increases its volume by thermal expansion of expandable microspheres that encapsulate hydrocarbon gas (FIGS. 2a-2d). The expandable polymer composite undergoes a rapid and irreversible change in volume around 7 times at ~80° C. (FIG. 2d), which pushes the liquid out of

the reservoirs towards microfluidic channels. For future versions of the device, it is possible to avoid water absorption of PDMS/Expancel mixture by coating with a thin (5 μm) layer of parlyene. This is helpful in applications where it might be necessary to store the drugs for long term.

[0057] Thickness of the expandable polymer layer can be altered by changing the spin coating speed (FIG. 2D, which affects the infused volume of drugs from the reservoirs. We have found an optimum thickness value around 600 rpm ($\sim 275 \mu\text{m}$), where most of the drug was discharged from the reservoirs (FIGS. 2f-2g). Thinner or thicker expandable composite layers in comparison to 600 rpm cannot eject all of the fluid. Radius of the expansion linearly changes with electrode sizes (FIG. 2h). On the other hand, height of the expanded composite does not change with electrode sizes.

[0058] Extension time of the expandable composite is another important parameter during drug infusion. We have investigated extension time for different power inputs, and found out that ideal power values are 500-600 mW to get an extension between 10 to 15 seconds (FIG. 2i). FIGS. 2j-2k show photographs of drug infusion test setup showing liquid places marked before and after infusion.

[0059] The device consists of different sizes of drug chambers to keep different amounts and types of drugs. For demonstration purposes, we used food dye colored water as a solution. As shown in FIGS. 3a-3c, by selectively enabling different drug reservoirs of personalized medicinal platform, we were able to eject the solution out of the device. Initially individual reservoirs were enabled to eject blue and yellow solutions separately and then mixed different colors of solutions (blue and yellow) to form a desired mixture output (green) (FIG. 3a-3c). We also investigated the system's capability with different pH value solutions and changing the output solution's pH by triggering different reservoirs (FIG. 3d-3f). The envisioned function here is the controlled release of drugs with different dosages and mixture upon the need. FIG. 3g demonstrates the mixing ability of the microfluidic channels. Blue and yellow solutions enter the personalized medicinal platform's microfluidic channels at a constant speed (5 $\mu\text{L}/\text{min}$) using a syringe pump and resulting in a green solution at the output channel.

[0060] We have also investigated the effect of viscosity change of the fluids to the mixture output through simulations, and found out viscosity changes of the solutions (up to 30%) do not affect the mixture of the drugs (data not shown). A 3D FEA was carried out to observe the simultaneous flow of liquids through the micromixer structure of the channels. The simulation result for the stationary study of the concentration plot is shown in FIG. 3h. It can be observed that the two liquids are completely mixed around 6th column of the mixer. Moreover, we have varied the flow rate at the input of the channels and observed the complete mixing of fluids at different column numbers, as shown in FIG. 3i. It can be observed that as the flow rate is increased, the complete mixing of fluids occurs at higher column numbers.

[0061] A personalized medicinal platform as described herein can operate not only by user activated schemes, but in different modes such as autonomous triggering in response to sensors measuring body vitals or smartphone based operation. We have already shown in FIG. 1c the envisioned working schematic of the system. Vital signs such as, heart rate, blood pressure, body temperature, skin hydration, sweat condition and respiration rate, give impor-

tant information about the physiological status of the human body^{8,10,21-23}. Genetic markers, nutrition and diseases can be detected using lab-on-a-chip based technologies. If there is a need for urgent medical attention, the output of the system can be broadcasted to emergency medical providers for required intervention.

[0062] FIG. 4a demonstrates an example application of the proposed medicinal platform by detecting physical fatigue via wearable sensors. Details of the integrated system can be found at in the Supplementary Information below (including FIGS. S1-S2). CMOS based heart rate and humidity sensors are interfaced with the medicinal platform 177 integrated system and applied to the subject's skin as shown in FIG. S2. In the data shown here, the subject performs an 8-minute test including constant running on a treadmill at 12 mph. As the subject's beat-per minute and skin moisture both reach a certain threshold (120 bpm, 85% RH) the system actuates the medicinal platform triggering a mixing process between two different fluid reservoirs as documented in Supplementary Video S1. The resulting liquid could then be injected to the subject; for instance, to compensate for a deficiency in certain concentration of body vitamins or minerals. This responsive medicinal platform will open up new possibilities of real-time, efficient, and low-cost drug preparation and delivery without human interaction based on physiological data and can be used in a broad range of healthcare applications. In FIG. 4b, we have demonstrated a smartphone based control of the medicinal preparation platform where individual reservoirs are triggered using an App and desired drug output achieved. This smartphone App can be further developed to achieve analysis of physiological and blood analysis data and take a required action autonomously.

[0063] One of the limitations of the above-described version of the device is to have remaining fluids inside the microfluidic channels after infusion which can get mixed with the drug coming afterwards. To overcome this challenge, more complicated microfluidic systems are provided with a self-cleaning capability where fluidic pressure, exemplarily from saline solution stored in one or more dedicated cleaning reservoirs, push the remaining fluid out of the channels and then infuse a new set of drugs. On the other hand, this is not a problem for applications where drug mixing is contemplated. One time usage of each reservoir is another disadvantage of the above-described embodiment. To overcome this challenge, more complex pumping mechanisms are incorporated to push fluids out of the reservoirs stepwise. One option is a reusable personalized medicinal platform serving as a replaceable cartridge which can be easily changed for different drug/vitamin needs. Additionally, the number of reservoirs can be increased to improve the systems capability. We also envision a DIY version of the whole system using recyclable materials for further affordability.

[0064] Methods: Fabrication of Personalized Medicinal Platform

[0065] Device design details are shown schematically in FIGS. 1d-1g. 185 nm gold was sputtered on 125 μm thick polyimide film (Good Fellows) and electrodes were patterned using 1.06 μm ytterbium-doped fiber laser (PLS6MW Multi-Wavelength Laser Platform, Universal Laser Systems) (FIG. 1h). Thermally expandable polymer (Expancel, 031 DU 40, AkzoNobel) was mixed with polydimethylsiloxane (PDMS) (2:1 ratio) and spin coated on wafer to get

a thin ($\sim 275 \mu\text{m}$) sheet of expandable polymer composite and cured in an oven at 65°C . for 2 hours. It was then peeled off from the wafer using razor blade to get a thin layer of expandable polymer composite which was then placed on heating electrodes using double sided adhesive film ($30 \mu\text{m}$ thick, ARclear, Adhesive Research). Thermal maps of activated heating electrodes were collected with an infrared (IR) camera (FIG. 1j) where the speed of heating and cooling was also analyzed (FIG. 1k). Temperature profiles were also investigated with finite element analysis using COMSOL Multiphysics (FIG. 1l). Microfluidic channels and drug reservoirs are made of 1 mm sheet of poly(methylmethacrylate) PMMA, an inexpensive material commonly used in microfluidics. Microfluidic channels ($\sim 150 \mu\text{m}$ width and $\sim 100 \mu\text{m}$ deep) and reservoirs are directly micromachined on PMMA using a printed circuit board plotter (LPCF Protomat S103). Three different reservoir sizes (6.3 mm^3 , 9.8 mm^3 , 14.1 mm^3) were fabricated to get different amounts of drug infusions. Surface roughness of the channels were measured with a profilometer (Ambios XP-200, Ambios Technology). After micromachining process, the device was brushed with soapy water, rinsed with ethanol, blown dry with compressed air and visually inspected to guarantee that no residue left from the milling process which might block the channels. Double sided tape is used to assemble the heating electrodes, expandable polymer layer, and microfluidic channels/reservoirs to each other. reservoirs were filled with water dyed with food color through predefined holes ($\sim 0.4 \text{ mm}$ diameter) and then sealed with transparent, water-proof tape (3M Corporation).

[0066] Methods: Expandable Polymer Composite Characterization

[0067] Thermally expandable polymers have been previously used by several research groups to manipulate the fluids inside microfluidics systems^{14-16,20,25}. The thermally expandable polymer consists of small microspheres which encapsulates a gas, where its internal pressure increases upon heating and its size increases around 7 times more (FIGS. 2a-2c). This causes the expandable composite to increase in size towards the reservoir area and pushes the loaded fluid towards the microfluidic channels. Spin coating speed of the composite determines the thickness of the film (FIG. 2d). We investigated the thickness change effect on the drug infusion ratio (FIGS. 2e-2f) and the size of expansion for different electrode sizes (FIG. 2g). Extension time was also investigated for different power inputs (FIG. 2h).

[0068] Methods: Operation of the Device

[0069] We used thermally expandable composite as an actuator layer of the personalized medicinal platform which was triggered by heating the electrodes beneath. Each reservoir was enabled using a bench setup (Keithley 2400C Sourcemeter) or battery based system (CR2032 Lithium Coin Cell Battery). We have different volumes of reservoirs for different drugs. Predetermined portions of the drugs can be mixed by manipulating the reservoirs using a thermally expandable layer. Fluids come from different reservoirs **323** and mix through the microfluidic channels. When the composite expands over the heater, it pushes the fluids outside the reservoir towards the microfluidic channels. Expansion is assumed to be complete when most of the fluids inside the reservoirs are ejected. Water solutions with different colors and different pH values were used to test the system's capabilities (FIGS. 3a-3b). Microfluidic mixing capability

of the device was validated both experimentally (FIG. 3c) and through simulation (FIGS. 3d-3e).

[0070] As an effort to demonstrate the application of this personalized medicinal platform, an integrated system for wireless and programmable actuation of the heating elements was developed. A driver circuitry was constructed to provide sufficient current for all heating elements to reach a certain temperature (above 85°C .). The schematic of the current driver circuit and details of the operation are provided in FIG. S4 (Supplementary Information) with the testing setup and heating profile results in FIG. S3. Smartphone based operation of the system was also demonstrated using a specific designed app.

[0071] We have shown a microfluidics-based wearable medicinal preparation platform to pursue the goal of the adaptive on-demand instantaneous in-situ personalization of medicinal preparation which can have a unique impact on global healthcare. Instead of the "one size fits all" treatment approaches for healthcare issues, the reported portable system can prepare drugs, vitamins, and minerals depending on the needs of the individual. The system successfully demonstrated the drug preparation on demand using an expandable polymer composite to mechanically pump drugs from reservoirs upon triggering a heater electrode underneath. We have also shown the high performance CMOS integrated operation of the personalized medicinal preparation platform with wearable sensors and smartphones to instantaneously respond to one's physiological condition. In the future, the number of reservoirs can be increased to include more drugs and different dosages.

[0072] Moreover, drug delivery systems and therapeutic actuators can be integrated to deliver produced drugs, and perform therapeutic actions, respectively.

Extended Experimental Procedures

Thermal Simulations

[0073] Table 1 shows the relevant properties of different materials for the thermal simulation and experimental results of the heaters, related to FIG. 1h. ρ , c_p , σ , k represent the density, heat capacity at constant pressure, electrical conductivity and thermal conductivity, respectively.

TABLE 1

Material	ρ (kg/m ³)	C_p (J/kg/K)	σ (S/m)	k (W/m/K)
Gold	19300	129	7.1e^6	317
Polyimide	1300	1100	6.6e^{-16}	0.15
Quartz glass	2210	730	1e^{-14}	1.4

[0074] Laser patterned heater (180 nm thick gold on $125 \mu\text{m}$ thick polyimide substrate) was adhered to a 1 cm thick quartz glass substrate. The bottom surface of the glass substrate was provided with a constant room temperature (25°C .). The surfaces of the device in contact with the surrounding air undergo natural convection. The relevant properties of the materials used in the heater setup are reported in Table 1. For an input power delivered to the heaters, the three dimensional (3D) finite element analysis (FEA) of the setup was carried out to report the stationary study of the heater temperature distributions, as shown in FIG. 1h. It can be observed that the thermal simulations of the heaters are in good agreement with the experimental results (FIG. 1f). Moreover, from the heat map it can be

observed that for any activated heater, the temperature increases to above 80° C. only in the regions around the heater surface. Since, the activation temperature for expandable polymer is 80° C., it is contemplated that only the regions of expandable polymer immediately around the activated heater surface expand, which is experimentally verified by FIG. 2g.

Fluidic Simulations

[0075] A 3D FEA was carried out to observe the simultaneous flow of liquids through the micromixer structure of 100 µm from the channels of reservoirs A and B, respectively. The liquids flowing from reservoirs A and B were water mixed with a yellow colored dye of concentration 30 mol/m³ and water mixed with a blue colored dye of concentration 20 mol/m³, respectively. The density and dynamic viscosity of water were 1000 kg/m³ and 1e⁻³ (Pa·s), respectively. The flow rate at the inlet of the channels of reservoirs, the diffusion coefficient and the pressure at the outlet of the structure were 5e⁻¹¹ m³/s, 4e⁻¹⁰ m²/s and 0 Pa, respectively. This resulted in the laminar flow of the liquids through the microfluidic structure. The simulation result for the stationary study of the concentration plot is shown in FIG. 3d. It can be observed that the two liquids are completely mixed around 5th column of the mixer. Moreover, we have varied the flow rate at the input of the channels and observed the complete mixing of fluids at different column numbers, as shown in FIG. 3e. It

can be observed that as the flow rate is increased, the complete mixing of fluids occurs at higher column numbers.

[0076] Electronics for Wireless and Programmable Actuation of Medicinal Platform

[0077] As an effort to demonstrate the application of micro-fluidic medicinal platform, an integrated system for wireless and programmable actuation of the heating elements is developed. A current driver circuitry is constructed to provide sufficient current for all heating elements to reach a certain temperature. A micro-controller provides a mean to programmatically actuate each heater by turning on specific driver transistor. Each driver circuit consists of an NPN BJT with a base resistor; the base resistor acts to limit the bias current flowing to the gate that will ultimately control the current through the collector. A current limiting resistor is also connected in series with each heating element allowing a better control of the maximum current thus temperature generated. The schematic of the current driver circuit is provided in FIG. 5 with the testing setup and heating profile results in FIGS. 6a and 6b. The current flowing across the heater can be found by,

$$I_c = (V_{cc} - V_{ce}) / (R_c + R_{heater})$$

[0078] After specifying a definite current flowing through the heating element, the base resistor can then be found by substituting the value to,

$$I_b = I_c / h_{FE}$$

$$R_b = (V_i - V_{be}) / (3 * I_b)$$

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- 1-31. (canceled)
32. An apparatus for personal health maintenance, comprising:
- a carrier member;
 - at least one sensor attached at least indirectly to the carrier member and configured for measurement of at least one physiological parameter of a user;
 - an attachment device connected to the carrier member for maintaining the sensor in operative proximity with the user;
 - at least one reservoir provided on the carrier member and containing a preselected composition;
 - a dispensing mechanism provided on the carrier member in operative contact with the reservoir; and
 - an electronic processor mounted to or carried by the carrier member and operatively connected to the sensor for receiving a signal encoding a measurement of the physiological parameter from the sensor,
- wherein the processor is configured to determine a divergence of the physiological parameter from a predetermined magnitude, the processor is operatively connected to the dispensing mechanism for ejecting, from the reservoir, an amount of the preselected composition to be administered to the user to reduce divergence of the physiological parameter from the predetermined magnitude.
33. The apparatus of claim 32, wherein the dispensing mechanism includes an expandable polymer composite layer, which includes gas-filled micro-bubbles or microspheres.
34. The apparatus of claim 33, wherein the dispensing mechanism further includes:
- an electric circuit with at least one heating element proximate the expandable polymer composite layer.
35. The apparatus of claim 32, wherein the reservoir is part of a microfluidic circuit disposed on a substrate included in the carrier member.
36. The apparatus of claim 35, wherein the dispensing mechanism includes a micro-electrical circuit disposed on the substrate in juxtaposition to the reservoir.
37. The apparatus of claim 36, wherein the dispensing mechanism further includes gas-filled microspheres adjacent the reservoir, the micro-electrical circuit including a heating element juxtaposed to the microspheres.
38. The apparatus of claim 32, wherein the physiological parameter is body temperature, blood pressure, pulse rate, skin hydration, perspiration state, respiration rate, glucose level, or oxygen content.
39. The apparatus of claim 32, wherein the sensor is a temperature sensor, an electrical conductivity or electrical resistance detector, or a pressure sensor.
40. The apparatus of claim 32, wherein the dispensing mechanism includes a nozzle to dispense the amount of the preselected composition into or onto an ingestible substance.
41. The apparatus of claim 32, further comprising:
- an alert signal generator operatively connected to the processor for prompting the user to take action to ingest the amount of the preselected composition.
42. A microfluidic dispensing assembly comprising:
- a substrate;
 - at least one reservoir provided on the substrate and containing a preselected composition;
 - a dispensing mechanism provided in juxtaposition to the at least one reservoir, the dispensing mechanism including an expandable polymer composite layer; and
 - an electronic processor operatively connected to the dispensing mechanism for operating the dispensing mechanism to eject, from the reservoir, an amount of the preselected composition.
43. The microfluidic dispensing assembly of claim 42, wherein the expandable polymer composite layer includes gas-filled micro-bubbles or microspheres.
44. The microfluidic dispensing assembly of claim 43, wherein the dispensing mechanism further includes an electric circuit with at least one heating element proximate the expandable polymer composite layer, the processor being operatively connected to the electric circuit.
45. The microfluidic dispensing assembly of claim 42, wherein the reservoir is part of a microfluidic circuit disposed on the substrate.
46. The microfluidic dispensing assembly of claim 42, further comprising:
- a sensor operatively connected to the processor; and
 - an attachment mechanism for maintaining the sensor in operative engagement with a user,
- wherein the processor is configured to receive a signal encoding a measurement of a physiological parameter from the sensor, the processor is configured to determine a divergence of the physiological parameter from a predetermined magnitude, the processor is operatively connected to the dispensing mechanism for ejecting, from the reservoir, an amount of the preselected composition to be administered to the user to reduce divergence of the physiological parameter from the predetermined magnitude.
47. An apparatus for personal health maintenance, comprising:
- a carrier member;
 - at least one sensor attached at least indirectly to the carrier member and configured for measurement of at least one physiological parameter of a user;
 - at least one reservoir provided on the carrier member and containing a preselected composition;
 - a dispensing mechanism provided on the carrier member in operative contact with the reservoir; and
 - an electronic control operatively connected to the dispensing mechanism for operating the dispensing mechanism to eject, from the reservoir, an amount of the preselected composition to be administered to the user to reduce divergence of the physiological parameter from a predetermined magnitude.

48. The apparatus of claim **47**, wherein the dispensing mechanism includes:

an expandable polymer composite layer, which includes gas-filled micro-bubbles or microspheres; and
an electric circuit with at least one heating element proximate the expandable polymer composite layer.

49. The apparatus of claim **47**, wherein the reservoir is part of a microfluidic circuit disposed on a substrate included in the carrier member.

50. The apparatus of claim **49**, wherein the dispensing mechanism includes a micro-electrical circuit disposed on the substrate in juxtaposition to the reservoir.

51. The apparatus of claim **47**, wherein the sensor is a temperature sensor, an electrical conductivity or electrical resistance detector, or a pressure sensor.

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摘要(译)

用于个人健康维护的设备具有传感器，该传感器至少间接地附接至承载构件，该传感器又可附接至用户或受试者，并且被配置用于测量用户的至少一个生理参数。储液罐包含预选的成分。电子处理器可操作地连接到传感器，以从传感器接收编码生理参数的测量值的信号，该处理器被配置用于确定生理参数与预定量的偏差，该处理器可操作地连接到分配机构，用于喷射从储器中，向使用者施用一定量的组合物以减少生理参数与预定量值的差异。分配机构包括可膨胀的聚合物复合材料层，其具有通过加热元件的操作而可膨胀的充气微泡或微球。

