



Review article

Smartphone-based wound dressings: A mini-review

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ARTICLE INFO

Keywords:

Wound healing
Chronic wounds
Smart
Mobile
Drug release
Monitoring

ABSTRACT

In spite of remarkable progress in the field of wound curation, treatment of chronic wounds remains a challenge for medical services. The constant rise in the number of patients with chronic wounds and their related financial burden has caused concern for the healthcare system. The complicated and dynamic nature of chronic wounds has increased the curation time and difficulty of wound healing with conventional bandages. Efficient healing of these wounds requires new bandages with the ability of real-time monitoring, data analysis, and drug delivery, which protect the wound against infection and accelerate the treatment process. The recent development of smartphone applications and digital equipment in medicine provides an opportunity for significant improvement in wound care through the incorporation of “smart” technologies into clinical practice. The focus of this review is to provide an overview of the current status of smartphones and digital technology in the management of wounds.

1. Introduction

A wound is a rupture of integrity in the skin, mucosal surface, or organ tissue. Patients undergo pain, stress, and functional disorders caused by wounds [1, 2, 3]. The healing of a wound is a complicated and time-consuming process that is affected by systemic and environmental factors. Age, body type, nutrition, vascular insufficiencies, chronic disease, and immunosuppression are the main systemic factors. The environmental factors also include pressure, edema, necrosis, infection, desiccation, and maceration [4]. Chronic wounds are not able to pass through all natural healing processes in a typical time period and are usually prone to various infections. In more acute cases, a chronic wound may take years to heal because of its delay in the transition from the inflammatory phase to the subsequent wound healing phases [5, 6]. Common chronic wounds, such as bedsores and diabetic foot ulcers (DFUs), are rapidly increasing due to the growth of their related diseases, namely diabetes, paralysis, sickle cell anemia, vasculitis, renal impairment, epidermolysis bullosa (EB), and autoimmune disease. The elderly with underlying diseases such as diabetes are more predisposed to chronic wound trouble, which stems from their already compromised general health and healing ability [2, 7, 8, 9, 10]. Non-healing wounds, as observed in EB patients, create considerable challenges for both patients and healthcare systems [11, 12]. Moreover, they cause various disabilities, frequent hospitalization, and even amputation [13]. The financial burden of wounds imposed on the United Kingdom's healthcare system is estimated to be £5.1 billion [14]. Another report by the American

Alliance of Wound Care Stakeholders reveals that wound care costs in the US reached \$31.7 billion. This study also warns of a concerning increase in chronic wounds because of the increase in the average age of the population and its related number of obesity, diabetes, and lower extremity disease [15].

Accordingly, the healthcare systems are in an attempt to achieve a proactive and preventive adopted approach to wound care. One of the vital parts of this procedure is smart technologies that provide non-invasive quantitative data from the wound healing process and address efficient wound assessment and characterization [16, 17]. Recent smartphone-based wound dressings are able to perform real-time monitoring and present a diagnosis of the chronic wound by continuously collecting physicochemical data from the wound and wirelessly transmitting them to the clinical center to receive remote on-demand treatments [18, 19]. The most brilliant benefit of this smartphone-based dressing is the reduction of the patient's visits to the hospital, which decreases the probability of infection, curation costs, and treatment time, as summarized in Figure 1 [14,20]. There are few reports in the case of smartphone-based dressings for wound healing. Hence, as a primary reference, a mini-review on this point of view could be helpful for future research. In this review, recent advanced progress in smart and controlled drug delivery to the chronic wound based on smartphone applications are presented. Then, smartphone-based monitoring of chronic wounds is explored; and finally, the most important parameters for real-time monitoring of chronic wounds are discussed and recent advances in this field are highlighted.

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Figure 1. Useful features of smartphones for smart wound dressings.

2. Smartphone-based wound dressing

Wound healing is a complicated process in nature [21]. The major drawback in wound curation is a lack of sufficient information about the status of the wound bed, such as healing phase, healing rate, and the existence of infection. Therefore, patients with chronic wounds are frequently summoned to the clinical centers to evaluate their healing phase and infection probability. However, this method of monitoring significantly adds to the treatment cost, heightens the stress on the medical centers, and delays the curation, especially for patients who are living in remote areas. The recognition of exact healing phases (hemostasis, inflammation, proliferation, and remodeling) by the clinical operator is the next important challenge since the physiological processes are different in each healing phase, and consequently, each phase requires its own specific biofunctional factors and drugs. For instance, the improper prescription of antibiotics can result in antibiotic-resistant bacteria [6]. The implementation of smartphone-based technologies in medical applications offers a new opportunity for healthcare systems to desire reformations in wound management [22]. The whole compartments of smart wound monitoring is expected to be fast, non-invasive, cost-effective, user-friendly, and finally provide reliable and low-error information to the clinical operators. Smartphone-based wound dressings are used by patients to track wounds at home. Hence, the resulting data from this kind of smart dressing is also important for simple prediction of the wound healing process [23]. In contrast with the traditional wound assessment methods that use direct contact of the measurement instrument such as a ruler or plastic film, smartphone-based techniques can be non-contact in their simplest form and use digital image analysis [22, 24]. The high-quality imaging devices available on recent smartphones can significantly increase the precision and reliability of wound measurements without the need for any special training or extra equipment [25, 26, 27]. In the next two subsections, we describe recent studies on the use of smartphones to monitor wounds, drug delivery, or both of them (Figure 2).

2.1. Smartphone-based wound dressing for drug administration to the wound

Traditional wound dressings such as gauze and cotton wool are used to protect the damaged parts of the body from harsh conditions and contamination [28], but as mentioned above, they can be combined with smart platforms for remote and real-time monitoring. In addition,

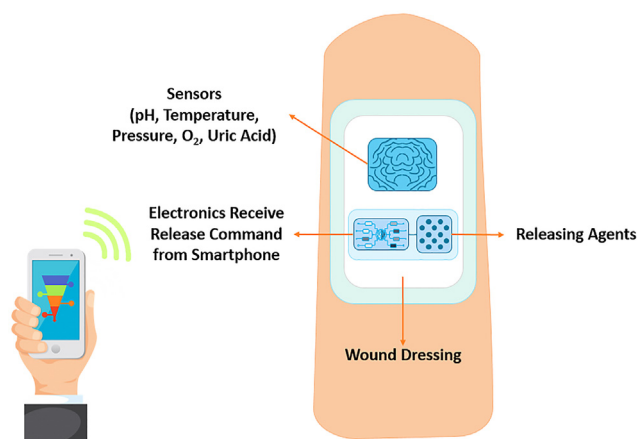


Figure 2. Smartphone-based dressing with the ability of wound monitoring and drug delivery. In this image, the wound dressing has both features, but some wound dressings may have one of these features.

advanced smartphone-based dressings are able to have biological activity either on their own or through the release of drugs and bioactive supplements incorporated within the dressing structure [29]. A wide variety of factors, peptides, or their combination are tested for fueling various physiological processes to lead non-healing wounds toward their natural healing process [30]. In addition to the complexity of chronic wounds and the variety of their related drugs, there are several ways of drug delivery due to the accessibility of cutaneous wounds, such as ointments, dressings, and scaffolds. As a result, efficient treatment of chronic wounds needs advanced personalized dressings, which are proportional to the patient's status and provide controllable delivery of various therapeutics to the wound [31].

A new smartphone-based wound dressing designed for the controlled and programmable release of multiple drugs (Figure 3a) consists of miniaturized pump arrays which are wirelessly controlled by an in-house smartphone-based application. Miniaturized needle arrays (MNAs) are applied in island forms across the dressing structure to enhance the bioavailability of drugs in deeper layers of the wound tissue which was successfully confirmed by *in vitro* study results. Then, the practical potentials of the whole system were examined via delivery of VEGF to the 5-day old full-thickness skin injuries in diabetic mice. The sample animals that received VEGF via MNAs showed efficient and complete healing with no symptoms of scar formation. According to the results, in addition to the real-time monitoring of wound progress and prescription of appropriate therapeutics, the technique of drug delivery and their spatial distribution within the wound bed play a key role in chronic wound treatment [32]. Thermoresponsive drug carriers are another intelligent system for remote drug delivery, a flexible patch made of thermoresponsive drug release and heat stimulator threads for smartphone-aided growth factor delivery to the chronic wound (Figure 3b). The heat stimulator part of the wound dressing is made of conductive core threads as microheaters coated with polyethylene glycol diacrylate-alginate (PEGDA-Alg) hydrogel that is in interaction with the thermoresponsive drug carriers. The practical competence of a smart dressing made of VEGF-loaded fibers was studied on mice with diabetic wounds as an *in vivo* model. In addition, histology and wound closure tests indicate the capabilities of the introduced smart patch in controlling drug delivery to chronic wounds [33].

2.2. Smartphone-based wound dressing for monitoring of wound parameters

New progress in electronic and designation of the mobile application has raised hopes to achieve the advanced smart tools that provide sufficient diagnostic information and treat chronic wounds by interfering in

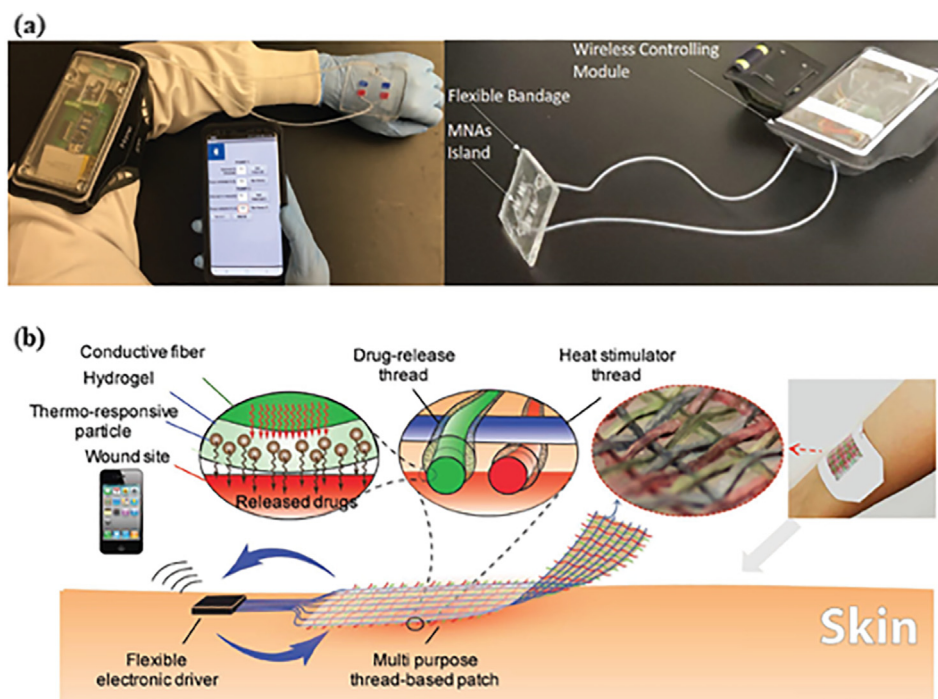


Figure 3. (a) A wirelessly controlled smart bandage with 3D-printed miniaturized needle arrays. Reprinted with the permission of Ref [32]. (b) A textile dressing for temporal and dosage-controlled drug delivery. Reprinted with the permission of Ref [33].

healing processes and preventing infection. Such smart technologies are able to precisely sense, report the collected information, and respond to an on-demand prescription. Sensors are the first necessary step in this way. By providing a clear map from the key parameters of wound condition, sensors can decrease the wound-care decision-making time without the need for frequent clinical visits and changing of the wound dressing. Finally, such advances offer a reduction of healthcare costs and time of hospitalization [34, 35]. pH, temperature, pressure, wound oxygenation level, and the amount of uric acid are the key parameters in wound monitoring, which are described below in detail.

2.2.1. pH

The pH is related to the activity of hydrogen ions in a solution and varies from the number 0 to 14 [36]. The main physiological pathways of the human body take place at pH = 7. Hence, the inner environmental pH of the human body is maintained at a neutral range, while the pH of skin naturally varies from 4 to 6 [37]. Skin damage and rupture can change its natural pH. Each healing phase of the wound has a different pH value [38], but in general, wound repair mechanisms take place in an acidic environment (similar to the natural skin in its healthy time) [7, 38, 39]. Chronic wounds, however, tend to have neutral and basic pH in the range of 7.15–8.90 [40] and even reach pH of 10 in the case of bacterial infection [41, 42, 43, 44]. Therefore, tracking skin pH during wound healing provides reliable information about the healing process and early symptoms of non-healing or infection trajectory [39, 40, 45, 46, 47].

The optical monitoring of both pH and glucose levels in diabetic chronic wounds is made possible by multifunctional hydrogel wound dressings (Figure 4). Real-time tracking of wound pH is easily attainable by incorporating nontoxic phenol red (exhibits obvious color from yellow in pH 6 to red in pH 8) within the zwitterionic poly-carboxybetaine (PCB) hydrogel structure. The wound glucose variations can be indicated by embedding glucose oxidase (GOx) and horseradish peroxidase (HRP) enzymes into the PCB hydrogel. The color changes of the diabetic wound tissue are detected by a smartphone-based application. In order to achieve an *in vivo* validation, visible red, blue, and green (RGB) colors of taken images of diabetic mice wounds were analyzed by a smartphone application, and their related fitting equations were obtained to monitor

the glucose and pH variation. Additionally, reported smartphone-based wound dressing indicates excellent pro-healing ability compared with commercial DuoDerm dressing for the treatment of diabetic chronic wounds [48]. According to the results, the introduced smart dressing has advantages over existing commercial technologies, including (1) providing the pH map of the diabetic wound by an array of printed sensors; (2) maintaining the desired moisture needed for wound healing by using hydrogel structure; and (3) providing conformal coverage to the wounded tissues [49]. More economical smartphone-based wound dressing alternatives can be designed by immobilization of pH indicator molecules on the cellulose particles. Instead of image capturing by the patient, the reading of color changes by indicator molecules is up to an electronic chip that is attached to the wound dressing and is able to perform a real-time report of the collected data to the patient's smartphone via a novel radio-frequency identification (RFID)-based contact-less platform. The electronic reader is also able to wirelessly transfer quantitative pH data to a clinical computer and is continuously

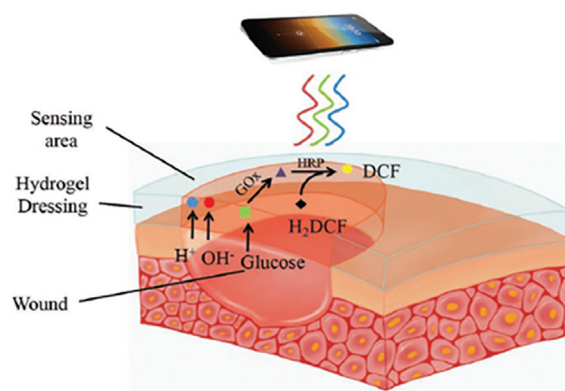


Figure 4. A multifunctional pro-healing zwitterionic hydrogel for simultaneous optical monitoring of pH and glucose in diabetic wound treatment. GOx: glucose oxidase, HRP: horseradish peroxidase, DCF: dichlorofluorescein. Reprinted with the permission of Ref [48].

aware of the wound status. This new reported smart wound dressing is low-cost, fast, and more reliable since the sensing data is detected without patient interference. Moreover, immobilized pH indicators and electronic data readers can be added to commercial dressings and improve their smart abilities [50]. A low-cost, flexible, reusable, and non-invasive smartphone-based dressing is designed for wireless pH monitoring and early detection of infection. In contrast with previous reports, this system benefits from an electrochemical sensor, including reference and working electrodes. The changes in electrical potential between electrodes are translated into the changes in H^+ ion concentration in the solution. Both flexible electrodes have a similar structural base consisting of polyethylene terephthalate film (PET) coated with indium tin oxide (ITO), while the reference electrode is modified with silver and the working electrode with polyaniline (PANI) coating. A flexible battery-less electronic data transmitting platform receives sensing information from the electrochemical sensor and sends it to the patient's smartphone via wireless communication [51]. If instead of the one electrochemical pH sensor in the previous report, all bandage structures were filled with lots of sensing points, it would be possible to create a pH map of the entire wound surface. Actually, each pH sensor reports its local pH to the patient's smartphone, and integration of all bandage points by the mobile application provides a colorful pH map of the wound. In such sensing, bandages are made from PANI functionalized pH sensing threads and an electronic data transformer, which collects sensing data from each point. The use of advanced technology in clinical evaluations to perform pH mapping aided by smartphone applications significantly improves the ability of smart bandages to sense deep and non-uniform wounds [52].

2.2.2. Temperature

Due to the fragile nature of biomolecules and the special conditions of biochemical reactions, temperature plays an important role in the activity of all living organisms, and the healing process of wounds is no exception [20, 46, 53, 54, 55, 56, 57]. In the case of wound healing, a limited increase in temperature is related to inflammation of wound tissue, but a prolonged temperature increase of $>1.11\text{ }^\circ\text{C}$ in chronic wounds usually indicates bacterial infection [58]. The most common method of determining this temperature is the palpation of the surrounded wound by clinical operators or own patients. In acute cases, wound infection can obviously be detected by simultaneous inflammatory symptoms such as redness, swelling, pain, and heat [4]. However, the early detection of temperature changes by wound infection needs a more sensitive and precise method of monitoring. Fortunately, there are reasonably priced electronic sensors for temperature that are commercially available and can be easily integrated with common wound dressings.

The combination of a temperature sensor and ultraviolet (UV)-responsive hydrogel provides both infection monitoring and on-demand antibiotic therapy of infected wounds. In this system, an electronic sensor continuously monitors the wound temperature; an electronic transformer sends information from the sensor to the smartphone via Bluetooth. It would be a certain diagnosis of wound infection if the wound temperature remained higher than $40\text{ }^\circ\text{C}$ for a defined period of time. In that case, the UV-LEDs integrated with the wound dressing will be activated, and finally the UV-responsive hydrogel will be forced to release its encapsulated antibiotics into the wound tissue (Figure 5a) [59]. Mechanical rigidity and low biocompatibility are the main obstacles to the use of electronic temperature sensors for medical applications. In a recent study, electronic parts of a smart dress, including a temperature sensor, a power source, and a data analyzer, are placed within a stretchable polyamide substrate. All electronic parts are connected with serpentine metal. The resulting system is coated with polydimethylsiloxane (PDMS). Finally, the fabricated electronic part is integrated with a layer of the collagen-chitosan porous scaffold. The fabricated smartphone-based wound dressing is able to continuously monitor the wound temperature and send real-time information to the patient's mobile. Moreover,

the incorporation of the electronics into the porous collagen-chitosan layer enhances the biocompatibility and pro-regeneration effect of the wound dressing (Figure 5b) [60]. The temperature sensor, pH sensor, and drug release hydrogel can be incorporated into a flexible polyethylene terephthalate (PET) substrate to fabricate a networked closed-loop automated patch for monitoring and treatment of chronic wounds. In such flexible and biocompatible automatic smart dressing, all sensing data is collected from the sensors and, after processing, sent to the patient's smartphone. Then, related commands for drug-releasing are decided by the mobile application and sent back to the thermoresponsive fibers embedded in the wound dressing structure [61].

2.2.3. Pressure

By imposing compression over the wound, venous flow improves, and wound healing speeds up consequently [62, 63]. This type of curement is usually applied to venous leg ulcers (VLUs) and requires specific kinds of compression bandages to be applied by trained clinicians. The desire is to impose pressure of approximately 40 mmHg at the ankle, which decreases as it moves up the leg [64]. The measuring of sub-bandage pressure is necessary to know if adequate or excessive pressure is being applied or if pressure is changing over time. Inappropriate compression may worsen venous insufficiency and lead to tissue necrosis if continued [65]. Hence, real-time and smart monitoring of wound compression can provide more needed information for efficient curement of chronic wounds.

In a recent report, the smart dressing with the ability to monitor the bleeding, wound pH, and external pressure on the wound site was successfully designed and fabricated. Quantitative measurements of the wound status are continuously transformed into a mobile application for real-time monitoring of the wound healing process. A capacitance to digital converter (CDC) measures the initial value of the sensor capacitance after wearing the bandage. Any changes in the sensor's capacitance are compared with its initial amount by a smartphone application and translated into the wound pressure changes. Then, the appropriate command for balancing wound pressure is presented to the patient by their smartphone. In this way, an efficient connection between the patient and their smart dress is formed to enhance the healing process [66]. In another study, a battery-less pressure sensor powered by a smartphone via an electromagnetic field was applied to perform real-time monitoring of chronic wounds. The real-time sensing information data was collected and, after being wirelessly transmitted to the smartphone, analyzed by a user-friendly phone application (SenseAble app). The introduced pressure sensor and its related electronic circuits can be installed on the various commercial wound dressing to award wound compression changes during the healing phases [67].

2.2.4. Wound oxygenation

Like most biological reactions, wound healing strongly depends on oxygen consumption because of its fundamental role in the wound healing process, including collagen deposition, epithelialization, fibroplasia, angiogenesis, and infection resistance [68]. At low oxygen levels, wounded tissue undergoes hypoxia, which leads to disruption of the healing process and consequently prolonged hospitalization [69, 70, 71]. The partial pressure of oxygen in the non-healing wound and healthy tissues is obviously different as it is between 5 mmHg and 20 mmHg, whereas in healthy tissue, it varies between 30 and 50 mmHg [70].

Integration of a miniaturized oxygen monitoring system with the bioactive wound dressing will enable the clinical staff to quickly and easily provide a treatment regimen specified by the individual patient status and the possibility of personalized therapy. Regarding oxygen monitoring, the most critical point of care is the permeability of the bandage structure in order to allow oxygen molecules to pass across and reach the sensor. For this purpose, a study suggests a three-dimensional (3D) printed bandage from the TangoPlus (TangoPlus FLX930) and oxygen permeable hydrogel. An electrochemical galvanic cell implemented on parylene-C was selected as an oxygen sensor made from

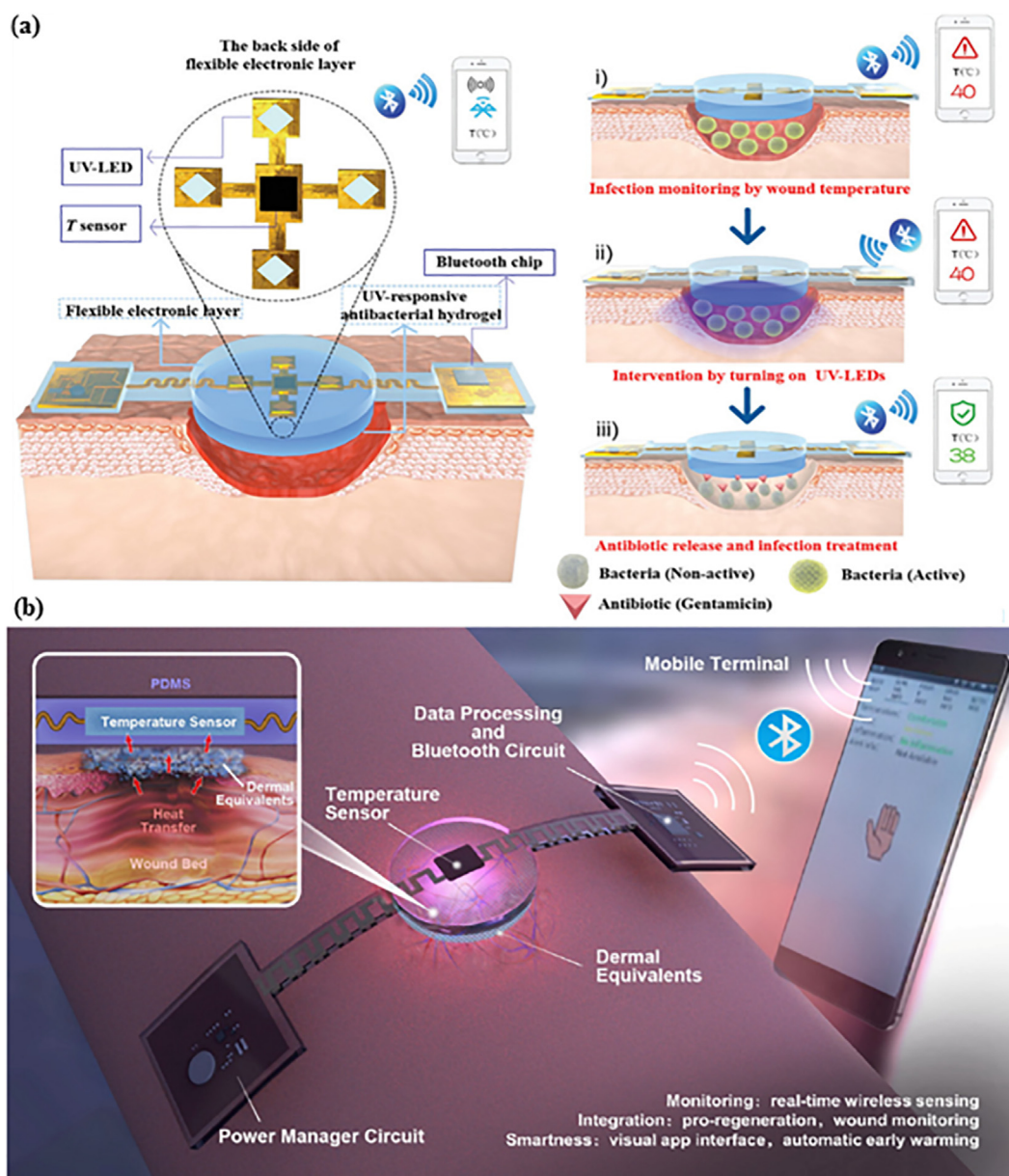


Figure 5. (a) Smart, flexible electronics-integrated wound dressing for real-time monitoring and on-demand treatment of infected wounds. Reprinted with the permission of Ref [59]. (b) Flexible wound healing system for pro-regeneration, temperature monitoring, and infection early warning. Reprinted with the permission of Ref [60].

silver (cathode) and electroplated zinc (anode) electrodes. Moreover, potassium hydroxide gel saturated on filter paper is applied as the electrolyte, and a layer of PDMS is used as the oxygen-selective membrane. Incorporation of a sensor/wireless readout system on the permeable smart bandage creates a comfortably wearable platform for real-time monitoring of the wound healing process and the existence of infection [72].

2.2.5. Uric acid

Elevated uric acid can be a symptom of wound severity and oxidative stress in chronic wounds [73]. As an inflammation enhancer, uric acid can drive chronic wounds to an acute state by increasing the concentration of reactive superoxide radicals in the wound bed, which can disrupt the normal activity of biomacromolecules such as proteins, lipids, and nucleic acids [73, 74]. Real-time tracking of this biomarker concentration in the wound can provide reliable information about the wound healing process [75].

The great potential of enzymes as excellent sensitivity, selectivity, and biocompatibility are applied in the fabrication of amperometric uric acid biosensors. In a wearable biosensor, working electrodes are fabricated by immobilization of urate oxidase enzyme on the screen-printing Prussian blue (PB) modified carbon electrodes and a reference electrode made from silver. The two electrodes are incorporated into chitosan polymers as a biocompatible bandage. The product of the enzymatic oxidation of uric acid is hydrogen peroxide. Then, the PB-carbon electrode catalytically reduces the hydrogen peroxide, which is realized by the sensor as uric acid concentration. After processing, the sensing data is sent to the smartphone [76]. Alternatively, a battery-free and multifunctional smartphone-based dressing is fabricated from a flexible double-layer consisting of a disposable sensing layer and a reusable, flexible electronic layer with the ability to detect temperature, pH, and uric acid. In addition, it is able to control the release of antibiotics against wound infection (Figure 6). The top layer is composed of flexible circuit boards for wireless power harvesting, sensing signal

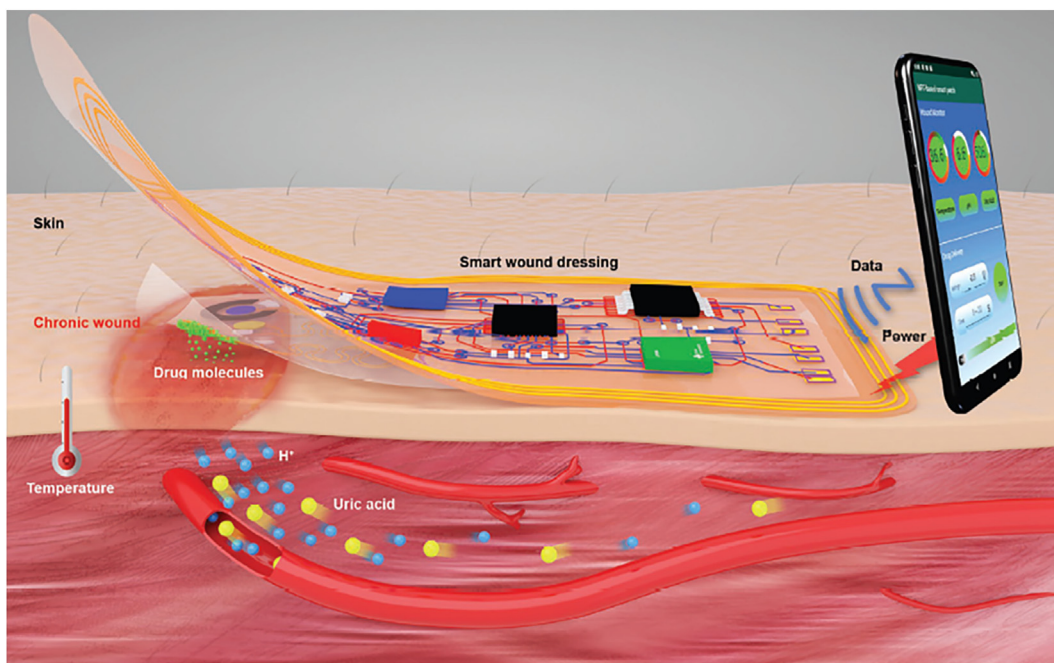


Figure 6. Battery-free and wireless smart wound dressing for wound infection monitoring and electrically controlled on-demand drug delivery. Reprinted with the permission of Ref [77].

Table 1. An overview of smartphone-based wound dressings with self-designed and commercial smart bandages.

Sensor	Drug delivery	Communication to smartphone	App	In vitro test	In/Ex vivo test	Ref.
pH	—	Image processor used after capturing by phone (MATLAB)	—	NIH 3T3 cells	Mouse	[48]
Glucose	—	Image processor used after capturing by phone (MATLAB)	—	NIH 3T3 cells	Pig	[59]
Temperature	Gentamicin	Bluetooth	—	NIH 3T3 cells	Pig	[60]
Temperature	—	Bluetooth	—	NIH 3T3 cells	Rat	[77]
Uric acid pH	Cefazoline	NFC	—	—	Mouse	[43]
Uric acid pH	—	RF transceiver IC	—	—	Pig skin	[49]
pH	Gentamicin	Image processor used after capturing by smartphone (ImageJ)	iDerm	Human keratinocytes and fibroblasts	Pig skin	[78]
pH	—	Image processor used after capturing by phone (MATLAB)	—	Human keratinocytes	—	[51]
pH	—	NFC	—	—	—	[52]
pH	—	Bluetooth	—	—	—	[79]
pH	Ciprofloxacin	Bluetooth	—	—	Human	[66]
Bleeding Pressure pH	—	IEEE 802.15.4	—	—	—	[67]
Temperature Strain	—	NFC	SenseAble	CPR Manikin	—	[72]
Oxygen	—	Xbee	—	—	—	[76]
Uric acid	—	NFC	—	—	—	[32]
—	VEGF	Bluetooth	—	HUVECs	Mouse	[33]
—	VEGF	Bluetooth	LightBlue Bean	HUVECs	—	[80]
—	Rhodamine isocyanate as a model	Bluetooth	LightBlue Bean	—	—	[50]
pH	—	NFC	—	—	—	[61]
pH	Cefazoline	Bluetooth	LightBlue Bean	Human Keratinocytes	—	[81]
Temperature	—	Image process after capturing by smartphone (RGB detection)	—	NIH3T3 cells	Mouse	[82]
pH	—	Image process after capturing by smartphone (RGB detection)	—	NHDF cells	Mouse	[83]
pH	—	Image process after capturing by smartphone (RGB detection)	—	NIH3T3 cells	Mouse	

analyzer, drug release controller, and wireless data transmitter. The bottom layer includes a uric acid sensor, pH sensor, and drug delivery electrodes, which are incorporated into the polyimide (PI) substrate. Coating with PDMS made the lower layer stretchable and biocompatible. The bottom layer senses the amount of wound uric acid and wirelessly sends processed data to the smartphone. Then the commands for antibiotic release are sent to the wound dressing if needed [77]. Paper-based smart bandages (OPSBs) are practical, advanced wound dressings based on smartphone applications and potentiostat electrochemical sensors. This fabricated smart dress is a real example of efficient integration between electronic technologies and medical science. The other advantages of these fabricated systems are presented as follows: (i) low cost, flexible, breathable, lightweight, and reusable structure; (ii) compatible with mass-scale production techniques, such as spray deposition or roll-to-roll printing [43].

In addition, the smartphone-based wound dressings reported in the literature are summarized in Table 1.

3. Conclusions and future outlook

Chronic wounds are a major concern for the healthcare system due to their complicated, prolonged, and expensive treatment process. The process of chronic wound curation depends on several systemic and environmental factors that vary among patients. Therefore, any efficient curation method must be personalized for each patient. Smartphone-based wound dressings are a new advanced procedure to improve chronic wound curation by real-time monitoring of wound status via smart sensing, data processing, data transferring, and automated drug delivery to the chronic wound. There are many reviews and reports in the field of smart wound dressings [16, 17, 20, 84, 85, 86, 87, 88, 89], but as far as we know, there are no reviews about mobile-based smart wound dressings. This review shows that there are a few studies in the field of smartphone-based wound dressings. Even these few fabricated platforms have not yet been tested on humans and are not commercially available. As a result, the field of smartphone-based wound dressings is taking its first steps toward resolving chronic wound healing obstacles, and there is a strong necessity for more studies in this interdisciplinary field of science and technology.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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