Gelatin-based instant gel-forming volatile spray for wound-dressing application

Mohammed Shahidul Islam^{1,3,4} · Jahid M. M. Islam^{1,2} · M Fizar Rahman¹ · Mohammed Mizanur Rahman³ · Mubarak A. Khan¹

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Abstract

This study was a successful endeavor to develop and investigate the suitability of a bioadhesive wound-healing gel based on gelatin for first-aid purposes. Polyethylene glycol (PEG) was used to prepare a denser phase of gelatin chains, and diethyl ether (DEE) was used to introduce high volatility to the solution. The prepared solution was stable in the storage container but rapidly formed (within 3 s) a protective and bioadhesive gel around the wound surface by being sprayed over the wound. Besides, it also suppressed pain and showed moderate antimicrobial activity against *S. aureus*. It was also found highly biocompatible and non-toxic. All the results revealed that the prepared solution could be an effective candidate for treating minor injuries or burn, especially for a first-aid purpose.

Graphic abstract

Keywords Healing gel · Wound-healing spray · Highly volatile gel · Gelatin · PEG

Introduction

Skin is one of the major organs in the human body that maintain and protect in vivo environmental stability (Egert and Simmering 2016). It can be destroyed when the epithelial linings of the skin are disrupted due to accidents, surgical injury, burns, and/or other unprecedented occurrences

Mohammed Shahidul Islam and Jahid M. M. Islam equally contributed.

✉ Mubarak A. Khan
makhan.inst@gmail.com

Extended author information available on the last page of the article

(Hawkins et al. 2018). If a wound is formed, it is clinically important to provide proper treatment to heal the injured skin. Wound healing is a combination of highly integrated molecular and biological events (Wu et al. 2010). Tissue regeneration and growth progress through four distinct phases: (1) the coagulation phase that begins immediately after the injury; (2) the inflammation phase, which initiates shortly after injury (swelling takes place); (3) a proliferation and migratory process begins within days that includes a central healing process where new blood vessels and tissues are formed; (4) the remodeling and maturation phase which may take up to a year and also the time for the formation of scar tissues and new skin development (Hunt et al. 2000; Selvaraj et al. 2015). Immediate and proper care of wounds is essential to prevent trans-epidermal water loss and microbial infection to accelerate the wound-healing time (Tanaka et al. 2005). With the advancement in medical science and technology, there are presently different wound treatment methods available, including wound dressing, therapeutic treatment, and medication. Therefore, the method selection for a particular type of wound is necessary for faster healing. Historically, different dressings have been used for wound treatment. However, it is the twentieth century when modern dressing materials arrived (Daunton et al. 2012). Traditional wound dressing includes gauzes, plasters, lint, natural or synthetic bandages, and cotton wools (Boateng et al. 2008). Though, they were limited in providing a moist environment to the wounded region and consequently replaced by modern dressing with advanced formulations.

Modern dressings are designed not only to protect the wounded region from external infection but also to keep the wound hydrated and promote healing. However, most of the commercialized advanced wound dressings are mainly based on synthetic polymers (Selvaraj et al. 2015). Some notable examples of modern dressings include semi-permeable film dressings, semi-permeable foam dressings, hydrogels dressing, hydrocolloid dressings, and alginate dressings. The other types of wound treating methods are tissue-engineered skin substitutes medicated dressings (Liesenfeld et al. 2009), and composite dressings. These dressings are acquiring increased interest in medical fields because of their biodegradability, biocompatibility, and non-toxicity to the environment. However, there are several limitations associated with the aforementioned modern dressings. For example, composite dressings are expensive and less flexible; semi-permeable film and foam dressings require frequent dressings and are not suitable for wounds with low exudate, and alginate dressing requires another secondary dressing (Selvaraj et al. 2015). For these reasons, biochemists, biologists and tissue engineers are still struggling for the bulk production of tissue-engineered skin substitutes (Catalano et al. 2013).

Soft hydrogels offer excellent properties which overcome most of the challenges associated with the wound dressing,

such as filling irregular wounds and controlled release of bioactive compounds. However, these hydrogels limit gas exchange at the wound site (Li et al. 2021). Besides, there are also concerns about user-friendliness and portability. These problems can be solved by developing a quick gel-forming spray, suitable for applying directly to the wound without contact with cotton swabs or hands, thus reducing the chances of contamination or infection. In most cases, these sprays form thin and bioabsorbing layers, so there is no possibility of having secondary trauma while applying the dressing or re-dressing (Retnowati et al. 2021). Li et al. (2021) developed an EGF-modified curcumin/chitosan nano-spray and applied it on full-thickness wounds created in the rat models. The rats treated with nano-spray formulation showed excellent healing characteristics and had an average wound closure rate of ~ 98% within 12 days (Li et al. 2021). In another study, Chen et al. (2020) designed an antifibrotic drug (pirfenidone)-loaded hyaluronic acid combined lyotropic liquid crystal-based spray dressing that formed self-assembled gel composed of lattice nano-structures. The prepared spray gel showed excellent scar prophylaxis effects and displayed an ideal wound-healing prognosis (Chen et al. 2020). Wayal et al. (2021) prepared a silk-based film-forming spray that could form a gel within 5 min in an open environment (Wayal et al. 2021). All the above-mentioned spray formulations are very promising for wound-healing applications because of their enhanced cell proliferating activity and added comfort. However, improvement is still required, especially on the gel formation time to ensure improved protection against infection and blood loss. The spray solution should have higher viscosity for faster gel formation, and thus can offer better wound care (Khan et al. 2010).

For solving the issues, gelatin-based bioadhesive gels are achieving priority because of their lower production cost, faster healing rate, and effortless application irrespective of the wound location (Jaipan et al. 2017). Collagen and its hydrolyzed derivative, gelatin, are the most appropriate building blocks for preparing wound dressings as they are biomimetic to human skin (Gaspar-Pintilieșcu et al. 2019). Besides, (1) gelatin is more soluble than other ECM proteins; as a result, easier to use for biomedical applications, (2) it has higher availability and is less expensive but possesses a structure chemically similar to collagen, (3) it contains binding moieties to attach with cells, (4) it does not induce toxicity nor antigenicity in the cells, and (5) metabolized gelatin can be used as a precursor for protein biosynthesis and thus can induce the healing process (Bello et al. 2020). Crosslinking is an excellent phenomenon that can increase viscosity by increasing the molecular weight of crosslinked gelatin and leads to an increased mechanical property (Zaman et al. 2011). In recent years, polyethylene glycol (PEG) has achieved significant recognition as a polymeric

excipient that can be used in gelatin solution for added properties like better gelation and increased antimicrobial activity (Adamic et al. 1991; Lee et al. 2020). Nevertheless, a low-cost gelatin-based bioadhesive, as well as spray-like first-aid dressing material, has not been reported. This paper represents developing a gelatin-based PEG bioadhesive gel-forming solution that can easily be applied to minor to moderate wounds irrespective of the injury position. The solution was prepared using readily available, locally produced, and less expensive raw materials. The operating procedure was also very simple, suitable for mass-scale production, and significantly less expensive. Moreover, it was found biocompatible, non-toxic, and environmentally friendly, which offered pain lessening, protection from bacterial infection, and rapid wound-healing properties.

Experimental

Materials

Gelatin (Type B from cattle bones, bloom strength—240 g, and Pharmaceutical grade) granules were supplied by the Global Capsules Limited (G.C.L.), Barisal, Bangladesh. PEG (400 USP/NF) was purchased from BASF. Diethyl ether (DEE) was purchased from Merck, Germany. All other chemicals used were reagent grade.

Methods

Preparation of gelatin/PEG solution

Gelatin solution (30% w/v) was prepared in deionized water at 60 °C. In the case of gelatin/PEG solution, different ratios of PEG (15:1, 15:2, 15:3 and 15:4 w/v, gelatin/PEG) was added into gelatin while dissolving. The mixtures were then allowed to stir at 60 °C until the gelatin dissolved completely.

Preparation of instant gel-forming solution

A 30% gelatin solution coupled with PEG was found to form a solid gel at room temperature which was promising to apply the product on an external wound. Diethyl ether (DEE) was introduced to the system as a highly volatile solvent to keep the solution in liquid state while in the storage container. The amount of DEE was optimized based on its solubility in gelatin/PEG solution and the gelatin/PEG ratio of 15:3 was found as the best combination for DEE incorporation in different proportions. After the incorporation of DEE, the mixtures were shaken vigorously for 15 min with a vortex mixer, VM-2000, at the temperature range of

60–65 °C. The mixtures were settled down for 30 min to monitor the solubility of DEE in gelatin/PEG.

Measurement of viscosity and pH

The intrinsic viscosity of the solutions was determined using HAAKE Rheometer with the controlled temperature at 29.5 °C (room temperature) and 37 °C (body temperature). The E2000 standard liquid (viscosity was 1900 mPas at 20 °C), obtained from the Thermo Scientific was used to calibrate the instrument. The pH values of the prepared solutions were measured with a digital pH meter (Philips, PW-9409, UK) with an efficiency level of ± 0.3 at both of the control temperatures of 29.5 °C and 37 °C.

Estimation of membrane formation time

Gelatin/PEG/DEE solutions of different compositions were sprayed on simulated human skin at 37 °C, and the time required to form the gel was measured using a digital stopwatch (Casio, Sf19).

Fourier transformed infrared spectroscopy (FTIR) analysis

The FTIR spectroscopy of gelatin, gelatin/PEG, and gelatin/PEG/DEE solutions was performed by IRPrestige-21 (200VCE) Fourier transform infrared spectrophotometer, SHIMADZU, Japan. Wavenumber range was 400–4000/cm with a resolution of 1/cm. The FTIR spectrum was taken in a transmittance mode.

Antimicrobial property

Staphylococcus aureus (*S. aureus*) was used to measure the antimicrobial property of the prepared wound-healing gel as *S. aureus* is the leading cause of wound infection (Lin et al. 2019). At first, nutrient agar plates (plate count agar, Oxoid, UK) were prepared on sterile Petri dishes and spread with *Staphylococcus aureus* (*S. aureus*) bacteria. 10 μ L of optimized pure gelatin, gelatin/PEG, and gelatin/PEG/DEE solutions were then added to the agar plates. The plates were incubated for 24 h at 37 °C. The zone of inhibition was measured after the incubation period.

In vitro cytotoxicity study

In vitro cytotoxicity test was performed using brine shrimp lethality bioassay, as suggested by Rahman et al. (2013). Brine shrimp lethality bioassay is a primary toxicity screening procedure used as an initial screening of bioactive compounds. To study the cytotoxic effect of the prepared gelatin/PEG/DEE spray, at first the healing gel was prepared from the spray solution and dried overnight at room temperature

and kept in a vacuum desiccator. Then, brine shrimps (*Artemia salina*) eggs were hatched in sterile artificial seawater (pH 8.5) under constant aeration for 48 h. Twenty newly hatched active nauplii were collected and transferred to a Petri dish containing 50 mL artificial seawater mixed with different concentrations of healing gel. Live nauplii were counted after overnight incubation at room temperature. Percentages of nauplii mortality were calculated, which represented the cytotoxic effect of the prepared gel-forming solution. Gel free artificial seawater was served as negative control, and an anticancer drug, vincristine sulfate was used for positive control.

In vitro biocompatibility

The biocompatibility of the prepared solutions was evaluated using heparinized human blood, following the procedure suggested by Khan et al. (2016). Blood samples were diluted with different ratios of gel-forming solutions and incubated for 2 h at 37 °C. Distilled water was used as a control treatment where RBC was lysed due to hypotonic shock. After the incubation, blood samples were placed on glass slides and observed under a light microscope.

Results and discussion

Viscosity and pH of the gel-forming solution

Because of its simplicity and accuracy, viscosity is regarded as a valuable characteristic of polymer solution since the beginning of polymer science. The viscosity of polymer solutions is dependent on many interacting variables, such as molar mass, structure and conformation of polymer molecules, polymer concentration, polymer–solvent interaction, solvent viscosity, and shear rate. The prepared gel-forming solution showed increased viscosity up to a certain level of PEG addition and then decreased (Table 1). The viscosity increased as PEG caused repulsion of the gelatin molecules,

which eventually enriched into a denser phase, thus increasing the shear stress (Lee et al. 2020). A dipole–dipole interaction occurred between the electron-donating amino group of the gelatin polypeptide chains and the electron-accepting hydrogen of PEG, which enhanced the molecular interaction (Zaman et al. 2011). This was an important finding as the solution with higher viscosity was expected to form gel more rapidly. However, after the 15:3 ratio, viscosity decreased at room temperature, which might have happened because of some unreacted PEG. On the other hand, in the case of body temperature (37 °C), viscosity was found to increase gradually up to 15:4 gelatin:PEG ratio, but the solution showed very poor miscibility with DEE. Therefore, 15:3 gelatin:PEG ratio was optimized for DEE mixing.

The viscosity showed that the temperature had a significant effect on the gel formation property of gelatin/PEG solution, which could drastically affect the shelf-life of the gel-forming solution. Therefore, it was necessary to customize the solution so that it can stay at the liquid phase throughout the storage period, especially at room temperature. In this regard, DEE was introduced to the gelatin/PEG solution, which increased the liquidity of the solution. In addition, because of the highly volatile nature, the DEE kept the solution in the liquid phase at room temperature but did not affect the gel-forming property. Moreover, DEE is well known as an anesthetic agent (Pavlovič et al. 2020). Therefore, the introduction of DEE also provided added comfort to the gel-forming solution.

Table 2 represents the effect of DEE addition on the viscosity of the gelatin/PEG solution at both room temperature and human body temperature. It was found that the viscosity decreased with increasing DEE content at room temperature but interestingly decreased for the same at human body temperature (37 °C). This phenomenon can be explained by correlating with the boiling point of DEE. As DEE is characterized by a low boiling point (34.6 °C) and high volatility (Joshi and Thipse 2019), it underwent rapid evaporation at 37 °C. This evaporation induced some water molecule

Table 1 Viscosity and pH of PEG added gelatin solution at 37 °C and room temperature (29.5 °C)

Sample no.	Gelatin/PEG ratio (w/v)	Viscosity (mPa s)		pH	
		29.5 °C	37 °C	29.5 °C	37 °C
1	15:0	35.2	5.2	6	6.2
2	15:1	40.8	5.4	6.1	6.2
3	15:2	54.6	5.4	6.1	6.3
4	15:3	58.1	5.6	6.2	6.3
5	15:4	31.3	6.5	6.2	6.4

The final concentration of gelatin in solution was 30% w/v in PEG mixed distilled water

Table 2 Viscosity and pH of DEE mixed gelatin/PEG (15:3 w/v) solution at 37 °C and room temperature (29.5 °C)

Sample no.	Gelatin/PEG (15:3): DEE (v/v)	Viscosity (mPa s)		pH	
		29.5 °C	37 °C	29.5 °C	37 °C
1	1:0.25	49.5	6	6.2	6.3
2	1:0.5	41.2	6.5	6	6
3	1:0.75	28.4	9	5.9	5.8
4	1:1	20.5	7.5	5.9	5.9

The final concentration of gelatin in the gelatin/PEG solution was 30% w/v in PEG mixed distilled water. The solution was then mixed with DEE in different v/v ratios

evaporation as well, which ultimately led to increased gelatin concentration in the solution, thus increasing the viscosity.

On the other hand, no significant change in the pH was found with respect to PEG or DEE addition. All the formulations had slightly acidic pH, which were very suitable for being a wound-dressing material.

Gel-forming property

For being a successful first-aid spray dressing material, it is essential to form a gel or membrane-like structure, which can protect the wounds from infection and maintain the proper moist environment for healing. The faster it forms the gel/membrane, the better will be the performance. Besides, the quick gel-forming property ensures the comfortability of the first-aid spray. Figure 1 represents the required gel formation time for various first-aid spray formulations. It was found that although the DEE incorporation led to decreased viscosity of the solution, it had a positive effect on the gel formation property. The gel formation time gradually decreased with increased DEE content. This occurred because of the highly volatile nature of DEE. DEE helped keep the solution in liquid form when trapped inside the spray bottle, but it quickly vaporized after the spraying. This vaporization also increased water evaporation from the solution, which was responsible for the quick gel formation. In the case of 1:1 DEE gelatin/PEG (100 mL gelatin/PEG and 100 mL DEE), the spray solution formed gel within 3 s, whereas it was 8 s for DEE-free gelatin/PEG solution. However, DEE content higher than the 1:1 ratio did not show any better results. This may be attributed to the optimum saturation of DEE with water. DEE content higher than the 1:1 ratio might not

induce further water evaporation and thus did not affect the gel formation.

FTIR analysis

FTIR spectroscopy is an outstanding tool for identifying functional groups because those functional groups show similar absorption frequencies in different molecules. The change in the chemical environment of the gelatin-like polymers or other molecules might affect the original frequencies. This environmental change leads to the change in width and intensity of the spectrum bands as well as the molecular conformation. The FTIR spectra of gelatin solution, gelatin/PEG solution, and developed gelatin/PEG/DEE gel are shown in Fig. 2. The most relevant peaks in the FTIR spectrum came from the peptide bonds of proteins, such as C=O stretching at 1651/cm, N–H bending at 1550/cm, and C–N stretching at 1250/cm for amide I, amide II, and amide III, respectively. The strong, broad peak observed in the region of 3200–3600/cm was because of the free and bound –NH– and –OH groups that were able to form hydrogen bonds with C=O groups of the peptide linkage present in the gelatin structure. The difference in the intensities of the C=O, N–H and C–N bonds among gelatin, gelatin/PEG, and modified gel (gelatin/PEG/DEE) is the most significant observation indicating the change in gelatin structure due to the PEG addition. Another significant observation was found at about 1100/cm C–C–O and C–C–H bonds. A strong, sharp peak for modified gel, but a weak, sharp peak was found for gelatin. In addition, the peak shifted to a little higher frequency than the pure gelatin for the modified gel.

Fig. 1 Variation of gel-forming time of gelatin/PEG solution with respect to DEE addition to 100 mL of gelatin PEG solution

Comment;

240- sample (Gelatin+PEG+DEE)

240 Gelatin (Pure Gelatin)

240 Gelatin+PEG

Fig. 2 Comparison among the spectra of different first-aid spray formulations. **A** Pure gelatin, **B** gelatin/PEG solution and **C** gelatin/PEG/DEE gel

Fig. 3 Comparison of the bacterial growth on agar plates treated by prepared solutions. **A** Pure gelatin solution (P.G) and gelatin/PEG solution (G + PEG) did not show any bacterial growth inhibition; **B** gelatin/PEG/DEE showed moderate growth inhibition for *S. aureus*

Antimicrobial property

Figure 3 shows the antimicrobial property of the prepared wound-healing solution against *S. aureus*, which is one of the most dominating wound-infecting bacteria (Neopane et al. 2018). Agar plates containing pure gelatin and gelatin/PEG did not show any inhibition zone, suggesting that pure gelatin and gelatin/PEG solution had no antimicrobial activity against the bacteria. On the other hand, agar plate containing gelatin/PEG/DEE solution showed a moderate zone of inhibition which indicated the bactericidal activity. Therefore, it is assumed that this antimicrobial activity was mainly derived from the action of DEE.

Cytotoxicity

Table 3 represents the cytotoxic activity of the prepared gel-forming solution, which was attributed to the mortality rate of nauplii. Experimental results suggested that the prepared healing gel had no cytotoxic effect up to 1.5 mg/mL concentration, whereas 0.5 mg/mL vincristine sulfate showed 100% nauplii mortality. However, a slight nauplii mortality was observed at 4.0 mg/mL and the above healing gel concentration. Therefore, it can be said that although the mortality rate increased up to 20% at 15.5 mg/mL healing gel solution, the nauplii death not necessarily happened due to the toxic effect of the prepared healing gel. There might be two reasons for some nauplii death: (a) a viscous layer of gelatin might be formed on the nauplii gills and thus decreased oxygen permeability and (b) low dissolved oxygen level in the healing gel-treated artificial seawater. However, the most possible reason for nauplii death might be the viscous layer formation on nauplii gills, as increased gel concentration led to increased gelatin in the solution, which could form a barrier membrane. This gelatin membrane inhibited oxygen permeability into the gills and caused nauplii death.

Biocompatibility

The morphology of the gel-forming solution-treated red blood cells (RBCs) is shown in Fig. 4. Light microscopic analysis of the prepared slides at 10×100 magnification revealed that the RBCs were intact when incubated at 1:3 (w/v) gel-forming solution/blood ratio. Normal saline and pure gelatin also showed similar results, but distilled water caused cell lysis at the same ratio (Fig. 4). These results confirmed the biocompatibility of the prepared wound-healing spray (Khan et al. 2016).

Wound-healing characteristics of the gel-forming solution

The above discussion suggested that the prepared wound-dressing spray rapidly forms a biocompatible, non-toxic and antimicrobial gelatin/PEG bioadhesive membrane around the wounded area with added anesthetic effect due to DEE. These properties enabled the spray to provide immediate protection and retain a moist environment to the wound site, thus offering pain reduction and comfort. It was reported that the wound dressed with gelatin membrane had promoted cell movement in early granulation tissue. It was also found to bind and act as a repository for a large family of cytokines and thus acted as an artificial ECM, which ultimately promotes the wound-healing process (Bhowmik et al. 2017). Our previous research suggested that gelatin/PEG membrane offered impermeability to microorganisms while maintaining proper water–vapor permeability. The overall effect accelerated the healing process significantly and reduced scar formation (Zaman et al. 2011). In these regards, as the current gel-forming formulation was proven to form a gelatin/PEG membrane around the wounded area, it is expected that the developed gel-forming solution can be used clinically for the treatment of minor burns, pressure areas, donor sites and a variety of minor injuries including abrasions and lacerations.

Table 3 Mortality of brine shrimp (*Artemia salina*) nauplii at different concentrations of instant gel-forming solution in saline water

Sample no.	Sample name	Dose (mg/mL)	No. of nauplii present before incubation	No. of nauplii present after overnight incubation	Mortality (%)
1	Instant gel	0	20	20	0
2	Instant gel	0.5	20	20	0
3	Instant gel	1.5	20	20	0
4	Instant gel	4	20	19	5
5	Instant gel	7	20	17	15
6	Instant gel	14.5	20	17	15
7	Instant gel	15.5	20	16	20
8	Vincristine sulfate	0.5	20	0	100

Fig. 4 Microscopic view of human red blood cells. **A** RBC was lysed due to 2 h distilled water incubation; **B** intact RBC after 2 h of gelatin/PEG/DEE solution incubation suggested the biocompatibility of the prepared wound-dressing material

Conclusion

An instant gel-forming highly volatile solution was prepared, characterized, and evaluated for bioadhesive wound-healing application. A 30% gelatin solution with PEG (15:3, gelatin/PEG, w/v) was optimized for the primary solution preparation and then stabilized by mixing with diethyl ether at 1:1 v/v ratio. The antimicrobial study revealed that the pure gelatin and gelatin/PEG membrane had no antimicrobial effect, but gelatin/PEG/DEE solution exhibited a significant inhibition effect on *S. aureus*. Furthermore, FTIR spectra of the gelatin/PEG solution revealed molecular interaction between gelatin and PEG in solution, leading to increased gelation property. The developed gel also showed no cytotoxic effect and was found highly biocompatible. Therefore, it can be assumed that the developed gelatin/DEE/PEG solution can provide a highly hydrated, peri-cellular, and growth-conductive environment. These optimum conditions simulated the cell migration and assembly of ECM and other matrix components, which ultimately led to accelerated wound healing. Thus, this research revealed a successful development of a new bioadhesive wound-healing material that can be more effective and convenient than the conventional wound-dressing materials, especially as an alternative to traditional first-aid dressing.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical approval This research does not require any ethical approval as there was no test was conducted on human or animal.

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Authors and Affiliations

Mohammed Shahidul Islam^{1,3,4} · Jahid M. M. Islam^{1,2} · M Fizur Rahman¹ · Mohammed Mizanur Rahman³ · Mubarak A. Khan¹

¹ Institute of Radiation and Polymer Technology, Bangladesh Atomic Energy Commission, Savar, Dhaka 1349, Bangladesh

² School of Science, Monash University Malaysia, 47500 Subang Jaya, Selangor, Malaysia

³ Department of Applied Chemistry and Chemical Engineering, University of Dhaka, Dhaka 2000, Bangladesh

⁴ Department of Chemistry and Biochemistry, Texas Tech University, 1204 Boston Avenue, Lubbock, TX 79409, USA