

Hydrogel

Field of the Invention

The disclosure relates to pressure sensitive adhesive (PSA) hydrogel films for dermatological applications, both therapeutic and cosmetic, using monomers, crosslinking agents and plasticizers polymerised with UV light. The new approach provides a simple procedure with precise control over film thickness, minimal usage of solvents and adjustable mechanical, rheological and adhesive properties.

Background to the Invention

Chronic wounds such as venous, diabetic and pressure ulcers cause patients over a prolonged period of time significant pain and emotional distress. Chronic foot ulcers are a major complication of diabetes, accounting for up to 25% of all hospital admissions involving diabetes. Another major resource health cost is created by pressure wounds or ulcers that result, for example, from failure to provide routine nursing or medical care.

The healing of a wound is controlled by complex biological processes that involve a diverse number of cell types. A typical healing process can be divided into 5 distinct, but closely related, stages: clotting stage, acute inflammation stage, matrix deposition stage, capillary formation stage and re-epithelialisation stage. A diverse number of factors control each of these stages. Wounds that exhibit impaired healing, including delayed acute wounds or chronic wounds, generally have failed to progress through the normal stages of healing.

Current treatment methods involve removing pressure from the area, debridement, wound dressing, surgical resection, vascular reconstruction and amputation. Of particular importance are wound dressings as they support the "normal" healing process by providing a barrier preventing bacterial infections, controlling oxygenation and moisture and enabling administration of medication such as antibiotics or materials promoting assimilation of healing factors involved in the healing process.

There has been a significant interest in developing improved wound healing materials and associated products such as transdermal drug delivery patches or scaffolds for tissue engineering. Pressure sensitive adhesives (PSAs) have been used for many years in a variety of medical applications, e.g. transdermal drug delivery patches,⁵⁻⁸ wound healing dressings,⁹⁻¹¹ wound closures,¹² surgical drapes⁴ and scaffolds for tissue engineering.^{4, 13} PSAs are a special class of viscoelastic polymers that adhere to the substrates of various chemical natures under the application of slight external pressures over a short period of

time (1-2 seconds).^{1, 2} The requirements of medical PSAs are challenging as they must be able to exhibit appropriate gel strength and sufficient adhesiveness against varying skin types and at the same time,¹⁴ they should be easily removable from the skin surface without excessive irritation to the skin and leaving no residues on the skin.

5 Hydrogel polymers such as acrylate based hydrogels have been used to produce medical PSAs⁴ as this chemical class has been found to have suitable adhesive properties and a low level of skin irritation. Solvent-free pressure-sensitive adhesives are a relatively new group of PSAs gaining importance due to their reduced solvent consumption and waste emissions. These environmentally friendly adhesives are made from reactive compounds that contain
10 negligible amounts of solvents or other volatile substances. In addition, photo-polymerization enables rapid conversion of monomer or macromer precursor solutions into a gel or solid under physiological conditions potentially useful for medical applications.¹⁷ Photo-polymerization is simply initiated by irradiation with light, such as UV light. Even though there are many advantages in photo-polymerization, some drawbacks are still present, e.g.
15 degradation upon exposure to irradiation.⁹

WO2006/062573 discloses hydrogel dressings based on polyethylene glycol dimethacrylate (DMPEG). DMPEG is combined with potassium chloride, crosslinking agent and PEG and IRGACURE 2959 at a specific pH and cured using a total energy of 550mJ/cm². The resulting hydropatch is 1.5mm thick and was tested for cohesive and adhesive quality.
20 Although, the application claims superior properties of their hydrogels the physical properties are not well defined and therefore difficult to assess.

Moreover, cosmetic products containing anti-oxidants such as L-ascorbic acid, also known as vitamin C, are known to have anti-aging, anti-wrinkle or skin lightening effects. However, due to the instability of many anti-oxidants, in particular, vitamin C as well as the short skin
25 contact time for cream and lotion formulations, consumers may not be able to receive optimal anti-oxidant effects. Transdermal delivery of antioxidants through UV curable pressure sensitive adhesive (PSA) films can prolong the contact time and deliver more anti-oxidant to the skin.

The present disclosure relates to PSA hydrogel films which benefit from both hydrogen and
30 covalent linkage to gain superior adhesive properties and the enhancement of mechanical strength respectively. The photo-polymerization technique allows extremely fast curing and reduces the usage of chemical solvents necessary for traditional polymerisation methods. Moreover, the thickness of the disclosed PSA hydrogel films can be controlled. The optimized film has superior mechanical and rheological properties, [i.e. flexibility, resistance

and bioadhesion] required for a variety of dermatological applications. The disclosure also relates to the combination of the PSA hydrogel with anti-oxidants that have health and cosmetic properties, for example, the combination of the PSA hydrogel with one or more vitamins such as vitamin C and its salts, for example and not by way of limitation magnesium ascorbyl phosphate.

Statements of Invention

According to an aspect of the invention there is provided a biocompatible pressure sensitive adhesive hydrogel comprising: a matrix comprising at least two biocompatible polymers wherein said polymers are photo-crosslinked to at least each other wherein the matrix further includes one or more plasticisers and optionally including one or more therapeutic agents.

In a preferred embodiment of the invention said matrix comprises a first polymer wherein said polymer comprises polyvinylpyrrolidone. Preferably, polyvinylpyrrolidone is provided at about 5-15% w/w of the hydrogel composition, preferably about 10% w/w.

In a preferred embodiment of the invention said matrix comprises a second polymer wherein said polymer comprises polyethylene glycol diacrylate. Preferably, polyethylene glycol diacrylate is provided at about 65-75% w/w of the hydrogel composition, preferably about 70% w/w.

In a preferred embodiment of the invention the molecular weight of polyethylene glycol diacrylate is between 200Da and 4000Da.

Preferably the molecular weight is of 200Da, 400Da, 600Da, 800Da, 1000Da, 1200Da, 1400Da, 1600Da, 1800Da, 2000Da, 2200Da, 2400Da, 2600Da, 2800Da, 3000Da, 3200Da, 3400Da, 3600Da, 3800Da or 4000Da.

In a preferred embodiment of the invention the molecular weight of polyethylene glycol diacrylate is between about 550Da to 600Da; preferably about 575Da.

In a preferred embodiment of the invention the molecular weight of polyvinylpyrrolidone is between about 750,000Da and 1,000,000Da.

In an alternative embodiment of the invention said second polymer is poly(methyl methacrylate).

In a preferred embodiment of the invention said matrix comprises the plasticiser polyethylene glycol. Preferably, polyethylene glycol is provided at about 15-25% w/w of the hydrogel composition, preferably at about 20% w/w.

In an alternative preferred embodiment of the invention said matrix comprises the plasticiser propylene glycol. Preferably, propylene glycol is provided at about 2.5-7.5% w/w of the hydrogel composition, preferably at about 5% w/w.

5 In a preferred embodiment of the invention said matrix comprises combination of polyethylene glycol and propylene glycol. Preferably, polyethylene glycol and propylene glycol are provided at about 19% w/w and about 5% w/w respectively of the hydrogel composition.

In a preferred embodiment of the invention said matrix comprises of polyvinylpyrrolidone, polyethylene glycol diacrylate and polyethylene glycol in a ratio of about 1:7:2.

10 In a preferred embodiment of the invention the elasticity of said hydrogel (elastic modulus, G') is 11.71kPa to about 33.14 kPa. Preferably, about 30.50kPa.

In a preferred embodiment of the invention the viscosity of said hydrogel (viscous modulus, G) is 1.137 kPa to 11.16 kPa.

Preferably, the viscosity of said hydrogel is about G 1.9167 kPa.

15 In a preferred embodiment of the invention the tensile strength [TS] of said hydrogel is 0.06MPa TS to 0.18MPa TS. Preferably the tensile strength is about 0.11MPa TS

In a preferred embodiment of the invention the elongation to break (EB) is between 35 % EB to 85 %. EB Preferably the elongation to break is about 85 % EB.

20 In a preferred embodiment of the invention the adhesion of said hydrogel is from 0.042 N to about 0.79 N (for glass substrate) and from 0.3 N to 0.59 N (for skin substrate). Preferably, the adhesion is about 0.79 N and 0.59 N for glass and skin substrate, respectively.

In a preferred embodiment of the invention said hydrogel is at least 90 μm thick.

Preferably said hydrogel is between about 100-1500 μm thick + / - 10%.

25 In a preferred embodiment of the invention said hydrogel is 100 μm , 200 μm , 300 μm , 400 μm , 500 μm , 600 μm , 700 μm , 800 μm , 900 μm , 1000 μm , 1100 μm , 1200 μm , 1300 μm , 1400 μm or 1500 μm thick.

In a preferred embodiment of the invention said hydrogel is between 600-630 μm thick.

In a preferred embodiment of the invention said pressure sensitive adhesive hydrogel further comprises one or more therapeutic agents.

In a preferred embodiment of the invention said therapeutic agent is an anti-bacterial agent. Preferably said anti-bacterial agent is an antibiotic.

In an alternative preferred embodiment of the invention said therapeutic agent is a pro-inflammatory agent.

- 5 In a preferred embodiment of the invention said therapeutic agent is an antibody or active binding fragment of an antibody.

In an alternative preferred embodiment of the invention said therapeutic agent is a pro-inflammatory cytokine or growth factor.

- 10 Preferably said pro-inflammatory cytokine or growth factor is selected from the group consisting of: transforming growth factor (TGF)- β , platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and epidermal growth factor (EGF).

In an alternative preferred embodiment of the invention said therapeutic agent is a chemokine.

- 15 In a further preferred embodiment of the invention said therapeutic agent is an anti-oxidant; preferably, said anti-oxidant is vitamin C, for example L-ascorbic acid.

In a preferred embodiment of the invention said anti-oxidant is magnesium ascorbyl phosphate.

In a preferred embodiment of the invention said anti-oxidant is at least 1% w/w of the hydrogel composition, more preferably at least 2% of the hydrogel composition.

- 20 In a preferred embodiment of the invention said antioxidant is between about 2% w/w to 10% w/w of the hydrogel composition.

In a preferred embodiment of the invention said anti-oxidant is about 5%w/w or about 10% w/w of the hydrogel composition.

In a preferred embodiment of the invention said anti-oxidant is micronized.

- 25 In a preferred embodiment of the invention said hydrogel composition further comprises one or more skin permeation enhancers to enhance anti-oxidant penetration.

In a preferred embodiment of the invention said skin permeation enhancer is selected from the group consisting of: propylene glycol, terpinolene, α -phellandrene, ocimene, myrcene, (1R)-(-)-myrtenal, (S)-(-)-perillaldehyde, carvacrol, thymol, (R)-(-)-carvone, (1R)-(-)-

myrtenol, (-)- α -thujone, (R)-(+)-pulegone, (+)-dihydrocarvone, (-)-carveol, citral, (-)-isopulegol, (+)-dihydrocarveol, (-)-dihydrocarveol, (S)-(-)-citronellal, geraniol, nerol, ($\pm$)-linalool, menthone, β -citronellol, L-(-)-menthol, cyclohexanemethanol, A-humulene, (-)- α -cedrene, (+)- β -cedrene, (+)-aromadendrene, (+)-longifolene, (-)-trans-caryophyllene, (-)-caryophyllene oxide, (-)-epiglobulol, (-)-guaiol, (+)-cedrol, (-)-isolongifolol, (-)- α -santonin, octisalate, (+)-cedryl acetate, retinol, phytol, squalene, ($\pm$)- α -bisabolol, farnesol, ($\pm$)-nerolidol, eucarvone, retinoic acid, β -carotene.

According to an aspect of the invention there is provided a biocompatible pressure sensitive adhesive hydrogel wherein said hydrogel is mounted on a backing substrate to facilitate application to the hydrogel to a subject.

According to an aspect of the invention there is provided a wound dressing comprising a pressure sensitive adhesive hydrogel according to the invention.

According to a further aspect of the invention there is provided a pressure sensitive adhesive hydrogel or wound dressing according to the invention for use in the treatment of wounds in a subject.

In a preferred embodiment of the invention said wound is a chronic wound.

In a preferred embodiment of the invention said chronic wound is a diabetic wound.

In an alternative preferred embodiment of the invention said chronic wound is a venous ulcer.

In an alternative preferred embodiment of the invention said wound is an acute wound.

In a preferred embodiment of the invention said acute wound is a surgical wound.

In an alternative preferred embodiment of the invention said acute wound is a traumatic wound as a result of a contusion or similar.

In a preferred embodiment of the invention said subject is immune suppressed.

In a preferred embodiment of the invention said subject is immune suppressed as a consequence of chemotherapy, steroid therapy or HIV infection.

According to a further aspect of the invention there is provided a pressure sensitive hydrogel according to the invention for use in cosmetic skin repair.

According to a further aspect of the invention there is provided a method to treat a wound in a subject comprising application of a pressure sensitive adhesive hydrogel according the invention to a wound or area surrounding a wound.

Preferably said wound is a chronic or acute wound as herein described.

5 According to a further aspect of the invention there is provided a method to manufacture a pressure sensitive adhesive hydrogel comprising the steps:

- i) forming a first preparation comprising at least two monomers wherein at least one of said monomers is adapted to be photo cross-linked and a photo-initiator;
- 10 ii) forming a second preparation comprising one or more plasticisers;
- iii) combining said first and second preparations to form a mixed preparation;
- iv) casting the mixed preparation in a mold; and
- v) photo-crosslinking the mixed preparation to form a cross-linked hydrogel film.

15 In a preferred method of the invention said first preparation comprises monomers of polyvinylpyrrolidone and polyethylene glycol diacrylate.

In a preferred method of the invention said second preparation comprises polyethylene glycol.

20 In an alternative preferred method of the invention said second preparation comprises propylene glycol.

In a further preferred method of the invention said second preparation comprises both polyethylene glycol and propylene glycol.

In a further preferred method of the invention said mixed preparation comprises an anti-oxidant.

25 In a preferred method of the invention said anti-oxidant is a vitamin.

Preferably said anti-oxidant vitamin is vitamin C, for example L-ascorbic acid.

In a preferred method of the invention said anti-oxidant is magnesium ascorbyl phosphate.

In a preferred method of the invention said anti-oxidant is micronized.

In a preferred method of the invention said first or second preparation further comprises one or more skin permeation enhancers to enhance anti-oxidant penetration.

In a preferred method of the invention said skin permeation enhancer is selected from the group consisting of: propylene glycol, terpinolene, α -phellandrene, ocimene, myrcene, (1R)-
 5 (-)-myrtenal, (S)-(-)-perillaldehyde, carvacrol, thymol, (R)-(-)-carvone, (1R)-(-)-myrtenol, (-)- α -thujone, (R)-(+)-pulegone, (+)-dihydrocarvone, (-)-carveol, citral, (-)-isopulegol, (+)-dihydrocarveol, (-)-dihydrocarveol, (S)-(-)-citronellal, geraniol, nerol, ($\pm$)-linalool, menthone, β -citronellol, L-(-)-menthol, cyclohexanemethanol, A-humulene, (-)- α -cedrene, (+)- β -cedrene, (+)-aromadendrene, (+)-longifolene, (-)-trans-caryophyllene, (-)-caryophyllene
 10 oxide, (-)-epiglobulol, (-)-guaiol, (+)-cedrol, (-)-isolongifolol, (-)- α -santonin, octisalate, (+)-cedryl acetate, retinol, phytol, squalene, ($\pm$)- α -bisabolol, farnesol, ($\pm$)-nerolidol, eucarvone, retinoic acid, β -carotene.

In a preferred method of the invention said photo-initiator is 2-hydroxy-4-(2-hydroxy-ethoxy)-2-methyl-propiophenone 98% (HHEMP).

15 In a preferred method of the invention photo-crosslinking is with UV light between 350-500nm.

In a preferred embodiment of the invention the light intensity of said UV light is about 12.4 W cm².

20 In a preferred embodiment of the invention said photo-crosslinking is between 5-10 seconds at a distance of 5-10cm.

According to a further aspect of the invention there is provided a pressure sensitive adhesive hydrogel obtained or obtainable by the method according to the invention.

25 Throughout the description and claims of this specification, the words "comprise" and "contain" and variations of the words, for example "comprising" and "comprises", means "including but not limited to", and is not intended to (and does not) exclude other moieties, additives, components, integers or steps. "Consisting essentially" means having the essential integers but including integers which do not materially affect the function of the essential integers.

30 Throughout the description and claims of this specification, the singular encompasses the plural unless the context otherwise requires. In particular, where the indefinite article is

used, the specification is to be understood as contemplating plurality as well as singularity, unless the context requires otherwise.

Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein unless incompatible therewith.

An embodiment of the invention will now be described by example only and with reference to the following figures

10 Figure 1: The schematic representation of PSA film fabrication process;

Figure 2: (a) Chemical structure of monomers used for preparing PSA films, (b) Proposed crosslinking mechanism for the reaction of UV curable monomers and formation of IPN; PEGDA macromers form a crosslinked network by covalent bonding (responsible for mechanical strength) and PEGDA/PVP are bonded to PEG/or PG (propylene glycol) via hydrogen bonding (responsible for adhesive properties);

Figure 3: Scanning electron micrographs of (a) PVP-PEGDA, (b) PVP-PEGDA-PEG, (c) PG incorporated PVP-PEGDA-PEG copolymer PSA films and (d) Comparison of average number of separated phases per square micrometer in each film;

20 Figure 4: ATR-FTIR spectra of monomers: a) PG, b) PEG, c) PVP, d) PEGDA and fabricated PSA films: e) PEGDA, f) PVP-PEGDA, g) PVP-PEGDA-PEG, h) PVP-PEGDA-PEG-PG (solid arrows, dash arrows and dash circles are attributed to hydroxyl stretching vibration bond, carbonyl stretching bond of PEGDA and carbonyl stretching bond of PVP, respectively);

25 Figure 5 Log-log plot of shear moduli (G' , G'' , G^*) vs. strain for (a) PVP-PEGDA-PEG and (b) PG incorporated PVP-PEGDA-PEG copolymer PSA films with the thickness of 910-1190 μm , fabricated with 7 spacers (frequency = 1 Hz, temperature = 23°C);

Figure 6 Log-log plot of average shear moduli (G' and G'') vs. frequency for (a) PVP-PEGDA-PEG and (b) PG incorporated PVP-PEGDA-PEG copolymer PSA films with the thickness of 910-1190 μm , fabricated with 7 spacers (strain = 0.065%, temperature = 23°C);

30 Figure 7 Stress-strain curve for (a) PVP-PEGDA-PEG and (b) PG incorporated PVP-PEGDA-PEG copolymer PSA films (number of spacers varied from 3 to 7);

Figure 8 (a) PVP-PEGDA-PEG film average peel test run from a rigid substrate, glass, and a flexible one, cadaver pig skin, at a speed of 50.00 mm/min, and nominal peel angel of 180 degree, (b) PG incorporated PVP-PEGDA-PEG film average peel test run from a rigid substrate, glass, and a flexible one, pig skin, at a speed of 50.00 mm/min, and nominal peel angel of 180 degree. (C) Comparison of averaged 180 degree peel force for two different compositions from two different substrates;

Figure 9 (a) Control of thickness in each film (number of spacers varied from 3, 5 and 7), (b) Reproducibility of films with different thickness (S1-S4 refer to four samples of each thickness, each sample's thickness was measured four times. $P < 0.001$, the error bar shows SD);

Figure 10: Quantification of distribution uniformity of Rhod B in PSA films with different thickness using confocal microscopy: (a) Cross-sectional view, (b) 3D view and (c) Fluorescence intensity measurement in different parts of each film with different thickness (number of spacers varied from 3, 5 and 7). $P < 0.001$, the error bar shows SD;

Figure 11: Photographs of pressure sensitive adhesive film. (a) Top photo: the film on the left hand side is an opaque, freshly prepared film. (b) Bottom photo: photo of film taken under microscope;

Figure 12: Photograph of a commercial vitamin C patch;

Figure 13: (A) A chromatogram of released magnesium ascorbyl phosphate [MAP]. The retention time is 4.667 min. (B) A chromatogram of released L ascorbic acid [AA]. The retention time is 3.960 min; and

Figure 14: Comparative release profiles for MAP encapsulated PSA films and commercial vitamin C film in release solution. (A) Cumulative amount of vitamin C, (B) percentage released amount of MAP in 3 hours.

Materials and Methods

Fabrication of Pressure Sensitive Adhesive Films

Before PSA fabrication, the glass coverslips and glass slides were immersed in 95% ethanol solution for 2 hours to clean contaminations from the surface. Then, the coverslips were dried for 30 minutes at 37°C. To fabricate PSAs, fabrication cast was prepared by using two coverslips (Technische Glaswerke Ilmenau GmbH, Germany, 130-170 μm thickness, 22×22 mm) supported on either edges of the same side of a glass slide as "spacers" (Continental

Lab Product Inc., San Diego, CA, USA, 1-1.2 μm thickness, 25.4×76.2 mm) and placing another coverslip on the top to create a cavity in the centre, as shown in Fig. 1.

The UV crosslinkable PEGDA solutions, containing 0.5% w/w of the HHEMP photo-initiator was added to the 25 %w/v solution of PVP in EtOH. To prepare different films with various
 5 adhesion properties, PVP-PEGDA mixture was added to PG and/or PEG. The final PVP-PEGDA-PEG or PVP-PEGDA-PEG-PG precursor solutions were placed on the glass slide using a micropipette and were drawn up by capillary action into the gap between the coverslips and the glass slides. In order to obtain microfabricated pressure sensitive adhesive films with best viscoelasticity and adhesion properties, different ratio of PVP-
 10 PEGDA-PEG and PG incorporated PVP-PEGDA-PEG were tested and finally the optimal ratio for PVP-PEGDA-PEG and PG incorporated PVP-PEGDA-PEG hydrogel films were assigned to be 1:7:2 and 1:7:2:0.5, respectively. The set up was then irradiated with high intensity ultra violet light of 350-500 nm for 7 seconds, with a distance of 6 cm from the light source (the collimating adaptor lens), at an intensity of 12.4 W/cm² using the EXFO
 15 OmniCure S200-XL UV curing station (EXFO, Photonic Solutions Inc., Canada).²⁹ The intensity of the UV light was measured with the OmniCure® R2000 radiometer. A collimating adaptor (EXFO 810-00042) was connected to the UV light guide to obtain evenly-distributed light beams.

After UV irradiation, the precursor solutions exposed to UV light will be crosslinked to form
 20 PSA films, while those precursor solutions that were not exposed to UV will remain as liquid. The fabricated PSA films were developed by removing the remaining un-crosslinked precursor solutions with de-ionized water. Then, the coverslip was carefully removed to ensure that the formed PSA films would remain as one piece for further testing.

Preparation of Pig Skin Samples for Peel Tests

25 Pig skins excised from ear were used in our experiments. The hair of cadaver porcine ear skin were first removed using an electric hair clipper Philishave 241 (Philips, Hong Kong) followed by hair removal cream Veet (Reckitt Benckiser, Poland) to completely remove the hair [30]. The skin samples were gently cleaned with a Kimwipe tissue paper (Kimberly-Clark, Roswell, GA, USA) and subcutaneous fat was removed using a scalpel. The defatted
 30 skin samples were cut into small pieces (with the dimension of 30×50 mm) and conserved frozen at -80°C until they were used. Prior to peel adhesion tests, the frozen skin samples were thawed at room temperature (23°C) for 30 minutes. The thawed pig skin was blotted with Kimwipe tissue paper and affixed under mild tension on a glass slide using paper clips.

The microfabricated pressure sensitive adhesive films were adhered to the skin with the force of a thumb before peel strength measurements were done.

All animal procedures were carried out in compliance with relevant regulations approved by the Institutional Animal Care and Use Committee (IACUC), National University of Singapore (NUS). Approval to collect the porcine skin from local abattoir was granted by Agri-Food and Veterinary Authority (AVA) of Singapore.

10 **Hydrogels Characterization**

Morphologies of PEGDA-Based Hydrogels

Microstructure and surface morphology of microfabricated hydrogel adhesive films were evaluated by a Scanning Electron Microscopy (SEM, JEOL JSM-6700F) analysis operating in the high vacuum/secondary electron imaging mode at an accelerating voltage of 5 kV. The hydrogels specimens were placed in a 50°C oven for 2 hrs so that the samples became completely dry prior to morphological observation. Thereafter, the hydrogel samples were sputter coated with a thin layer of gold alloy to improve the surface conductivity. To compare the microstructure of microfabricated hydrogel films of different compositions (PVP-PEGDA, PVP-PEGDA-PEG and PVP-PEGDA-PEG-PG films), the number of separated phases per square micrometer were counted in at least 35 subdivisions of each SEM image and averaged.

Attenuated Total Reflection (ATR) Fourier Transform Infrared (FTIR) Spectroscopy

Pure PEGDA macromer, and PVP, PEG and PG and hydrogels of PEGDA, PVP-PEGDA, PVP-PEGDA-PEG and PVP-PEGDA-PEG-PG were analyzed by ATR-FTIR to investigate the interactions between the monomers. To examine the chemical structure of microfabricated hydrogel adhesive films, each film was placed on top of the crystal and a pressure arm was positioned over each sample to exert a force of ~ 80 N on the sample. For analysing liquid samples (i.e. PEGDA, PG and PEG), a drop of liquid was placed on top of and covering the diamond crystal. No additional sample preparation was required for ATR-FTIR analysis. Removal of ethanol from prepared hydrogel films was confirmed by ATR-FTIR spectroscopy in the absence of methylene group stretching vibrations at around 2974

and 1378 cm^{-1} . The ATR-FTIR spectra were acquired using a PerkinElmer Spotlight 400 FTIR Imaging System (Perkin Elmer, Shelton, CT USA) with an ATR accessory having a diamond crystal over the range of 4000-600 cm^{-1} at room temperature (23°C).

Measurement of Film Thickness

5 In the fabrication process of the pressure sensitive adhesives films, the number of spacers governs the thickness of films. Each coverslip is approximately 150 μm thick. Increased spacer thickness was achieved by increasing the number of coverslips stacked on either side of the base glass slide as shown in Fig. 1. Depending on the number of spacers used for the fabrication (1, 3, 5 and 7 spacers), the expecting thickness of films would vary from
 10 130-170 μm to 910-1190 μm . The microfabricated hydrogel adhesive films were imaged using a Nikon microscope (Nikon, SMZ 1500, Tokyo, Japan) to quantify the thickness characteristics of each film. For this purpose, the thickness of each film was measured at five different sections (four corners and the middle). To show the thickness reproducibility for each film, four films with the same number of spacers were fabricated and their thickness
 15 was measured for four times.

Drug Distribution

To check the distribution uniformity of drugs within the PSA hydrogel films, the model drug Rhod B (0.09 wt%), was incorporated into the PEGDA-based PSA films by dissolving it in the polymer precursor solution before UV irradiation. To assess the quality of drug distribution in
 20 films, Nikon microscope (Nikon, SMZ 1500, Tokyo, Japan) and Confocal Laser Scanning Microscope (CLSM, A1R-Nikon, Tokyo, Japan) were used to capture the fluorescence cross-sectional and three-dimensional image of each film respectively. The intensity of fluorescence in each film was optically scanned at different depth intervals (2 μm) in three different parts (two corners and one center) using CLSM to reconfirm the uniformity of drug
 25 distribution within PSA films.

Measurements of Rheological Properties

The rheological properties of the PSA hydrogels were determined using a Bohlin Gemini rotational rheometer (Bohlin Gemini HR nano, Bohlin Co., UK) equipped with 20 mm diameter parallel plates. The hydrogel film sample was placed between an upper plate
 30 fixture of 20 mm parallel plate and a stationary surface before being subjected to sinusoidal oscillations. The gap between the two surfaces was set according to the thickness of each film.

Dynamic Strain Sweep Tests

In a dynamic strain sweep test conducted at 1 Hz and 23°C, elastic or storage modulus G' (a measure of elasticity), loss modulus G'' (a measure of viscosity) versus strain profiles were generated as strain increased from 0.0001 to 100 percent. The linear response region or Linear Viscoelastic Region (LVER) for the dynamic frequency experiments was determined with a strain sweep, whereby a range of incremental shear stresses (1-106 Pa) were applied on the samples. Critical strain, the onset of hydrogel film rupture, was considered as the strain level where G' began to drop^{9, 32, 33}

Dynamic Frequency Sweep Tests:

The dynamic viscoelastic behaviour of hydrogels of PVP-PEGDA-PEG and PVP-PEGDA-PEG-PG were also investigated using the same rheometer. A parallel plate geometry (20 mm) was used for the measurements under small strain amplitude (0.065 percent) to maintain intact gel structure (within the LVER). Dynamic frequency sweep tests were carried out at 23°C to observe the G' and G'' as a function of a wide range of oscillation frequencies (0.01-100 Hz). In each case, measurements were reproduced using three samples of the same composition and G' and G'' were plotted vs. frequency.¹

Tensile Tests

Tensile tests were carried out with an Instron 5848 Microtester (Massachusetts, USA), using a 5 N load cell at room temperature (23°C). The hydrogel samples were cut into a rectangular shape, with a gauge length of 25 mm, width of 11 mm and different thicknesses (varied from 390-510 μm to 910-1190 μm). Samples were placed between the clamps and subjected to tension until the hydrogels lost their integrity. The tensile strain was measured as the change in the length of the film divided by the initial length of the film. The tensile stress was obtained by dividing the force by the original cross-sectional area of the film. Using these data, the stress-strain curve was plotted for each measurement to represent the mechanical properties of hydrogel.³

Peel Adhesion Tests

An Instron 5848 Microtester (Massachusetts, USA) was used to measure peel strengths of PSA films (11 mm width, 45 mm length, with two different thickness of 650 μm and 900 μm) against either a rigid (glass slide) or a flexible (cadaver porcine skin) surface at room temperature (23°C) with a 5 N load cell. Rigid substrates (i.e. glass slide) were tested for comparison with skin. The peeling adhesion testing was carried out at a rate of 50 mm/min

and a peel angle of 180°. Peel strengths were measured in triplicates, as continuous peel tests over 1 minute.³⁴ The glass slide was cleaned with acetone prior to testing to remove impurities on its surfaces. The skin sample was carefully wiped with tissue paper between each peel experiment.³⁵ The outer surface of the skin was in contact with adhesive film for the testing.

PSA films comprising magnesium ascorbyl phosphate (MAP)

L-ascorbic acid (AA), magnesium ascorbyl phosphate (MAP), poly(ethylene glycol) diacrylate, 2-hydroxy-4-(2-hydroxy-ethoxy)-2-methyl-propiophenone 98% (HHEMP), and polyvinylpyrrolidone (PVP, Mn 360 000) were purchased from Sigma-Aldrich, USA. Propylene glycol (PG) and tetrabutylammonium hydroxide was purchased from Alfa Aesar, UK. Potassium dihydrogen phosphate was supplied by AnalaR Normapur. Milli-Q water (Millipore, Bedford, MA, USA) was used in this study. All chemicals were used as supplied.

Fabrication of MAP encapsulated films

The PSA films were fabricated using a photopolymerization method that was developed previously (59). Before fabrication of PSA films, glass coverslips and glass slides were immersed in 95% ethanol solution for 2 hours to remove any surface contamination and then dried for 30 minutes at 37°C.

To prepare the pre-polymer solution, 15% w/v solution of PVP in ethanol, UV crosslinkable PEGDA solution containing 0.5% w/w of HHEMP photo-initiator, PEG and PG were mixed together in the ratio of 1:7:2:0.5 respectively. MAP was ground to fine powder and added to the final pre-polymer solution. The resulting suspension was vortexed vigorously to ensure a homogenous suspension was obtained.

A fabrication cast was prepared using coverslips and glass slides. Three coverslips were stacked on each of the two edges of a glass slide as spacers. Another coverslip was placed on top of the spacers to create a cavity. The suspension was placed on the glass slide using a micropipette and drawn into the cavity between the coverslips and the glass slides by capillary action. The pre-polymer suspension was irradiated for 7 seconds in the EXFO OmniCure S200-XL UV curing station (EXFO, Photonic Solutions Inc., Canada). The light source used was an UV light of 350-500nm at a high intensity of 12.4 W cm⁻² with a distance of 6 cm from the glass slides. After irradiation, excess precursor solution was removed by deionized water.

HPLC method development

Two HPLC methods were employed to determine the amount of AA and MAP in the commercial patch and PSA films respectively. In both methods, the column used was Hypersil ODS C18 reverse column (ODS hypersil, Thermo Scientific; 4.6 × 250 mm, 5 µm). The setup was controlled by Hitachi L2000 LaChrom Elite HPLC system and HPLC separation was conducted at ambient temperature.

To determine the amount of MAP, a reversed-phase ion-pair liquid chromatography method was used (60). The mobile phase contained 0.020 M tetrabutylammonium hydroxide and 0.025M potassium dihydrogen phosphate, adjusted to pH 6.8 by phosphoric acid and mixed with acetonitrile in a ratio of 77:23 v/v. The flow rate was set at 1.00 ml min⁻¹. The wavelength was set to 260 nm

To determine the amount of AA, the mobile phase used was 0.025M potassium dihydrogen phosphate solution adjusted to pH 3.0 by phosphoric acid. The flow rate was set at 1.00ml min⁻¹. The UV detector was operated at 270 nm.

***In vitro* release study**

PSA films with MAP concentrations of 10%, 5% and 2% w/w were fabricated. Commercial films and PSA films were then cut in 20mmx10mm dimension and each of the cut films was placed in 15mL of release phase, containing water and glycerol (1:1 v/v). At predetermined sampling points (up to 3 hours), 1 mL of release solution was collected. The rest of release solution was removed and replaced with 15 mL of fresh release. The triplicates of each concentration were placed in thermostatic incubator at 32°C with magnetic stirrers. The samples collected were analyzed by ion-pair HPLC method.

Example 1

Microfabricated PSA hydrogels

Most photo-polymerization methods involve long exposure times to UV, which can potentially compromise the stability of the incorporated drugs, such as proteins, peptides, etc.^{36, 37} In our approach, microfabricated PSA hydrogels were obtained at low polymerization time of 5-10 seconds which is not expected to compromise the stability of incorporated drugs (Fig. 1). This amount of time is significantly lower than that of other polymers, such as PVP, where UV-exposure up to 30 minutes has been used for fabrication of microstructures.³⁸ On the other hand, PEG based acrylates have been shown to be crosslinked by using a wide range of exposure times³⁹⁻⁴¹ and factors such as polymer concentration, molecular weight, energy

used, presence of solvents, photo-initiator concentration and presence of oxygen will influence curing properties.⁴²

Moreover, as photo-polymeric reactions can also be influenced by the intensity of the light source used, we aimed to find the right combination of polymerization time and the UV intensity for fabricating PSA hydrogels.⁴³ It was found that a combination of polymerization time of 7 seconds and intensity of 12.4 W/cm² was suitable for our method.

The PVP, PEGDA, PEG and PG biocompatible monomers, Fig. 2(a), were selected for this fabrication approach based on their biocompatibility and the UV curability (PVP and PEGDA). The fabrication process involved free radical polymerization using HHEMP as the photo-initiator. Hydrophilic PEGDA macromers which possess $\text{C}=\text{C}$ bonds at their chain ends, were easily photo-crosslinked by themselves, forming a solid network through radical polymerization. The chemical crosslinkings between them lead to the formation of covalent bondings. UV irradiation of the PVP-PEGDA-PEG and PVP-PEGDA-PEG-PG polymer precursor solutions resulted in copolymerization of the monomers and the formation of white, translucent, adhesive and flexible films, presumably in which PEGDAs covalently were bonded together (reason of proper mechanical strength of the film), while PG and/or PEG were physically crosslinked to PVP monomers and/or PEGDA via hydrogen bonding (reason of proper adhesive properties), as both PG and PEG are hydrogen donors. According to the proposed mechanism for the photo-polymerization, the HHEMP photo-initiator molecules dissociated into radicals by means of UV light absorbance at the outset of the reaction, demonstrated in Fig. 2(b). Subsequently, the formed initiator radicals react with the PEGDA macromer generating active center, which could propagate through PEGDA carbon-carbon double bonds to form kinetically growing, reactive chains. It is also possible that the radical formation propagates through a pendant vinyl group of PEGDA by which a 3D polymeric network of hydrogels will form.⁴⁴

As for PVP monomers, following the UV irradiation they just get entrapped in the PEGDA 3D hydrogel network. Besides, PEGDA and entrapped PVP could be physically crosslinked with PG/or PEG through noncovalent crosslinking which would lead to the formation of hydrogen bonding networks.²⁸ Therefore an interpenetrating polymer network (IPN) will form, composed of 3D crosslinked PEGDA network (covalent bonding), linear PVP polymer (entrapped in the 3D network), PG and/or PEG (hydrogen bonding with PEGDA/or PVP).

Using different numbers of spacers (varied from 1 to 7), we were able to make hydrogels in different dimensions (maximum 20x22 mm, with the thickness varying from 130 μm to 1190

μm). The transparency of the films was variable depending on the gel thickness. The thicker the microfabricated pressure sensitive adhesive hydrogels, the more opaque the films.

Before performing the tensile tests on the microfabricated PSA hydrogels, they were subjected to the “thumb tack test”,⁴⁵ (a qualitative test) for the preliminary determination of their adhesion properties. The thumb was simply pressed against the microfabricated PSA films and the relative adhesive property was evaluated. Based on the qualitative observations from the thumb tack test, it was found that the PG incorporated PVP-PEGDA-PEG microfabricated hydrogels had better adhesion properties comparing to the PVP-PEGDA-PEG, as they had more affinity to the glass slide and the resistance toward peeling off was higher. To confirm this, further tests were conducted to characterize the morphological, mechanical and rheological properties of the microfabricated films.

Example 2

Morphological Characterization by SEM

Fig. 3(a), (b) and (c) represent the microstructure morphologies of PVP-PEGDA non-adhesive hydrogel, PVP-PEGDA-PEG and PG incorporated PVP-PEGDA-PEG microfabricated pressure sensitive hydrogels, respectively. It can be seen from these images that in comparison with the PVP-PEGDA and PVP-PEGDA-PEG hydrogels, the surfaces of the PVP-PEGDA-PEG-PG hydrogels possess a denser porous-network structure. Fig. 3(d) shows the comparison between the microstructure of microfabricated hydrogel films with different compositions (PVP-PEGDA, PVP-PEGDA-PEG and PVP-PEGDA-PEG-PG films) in regard to the existent number of separate phases per square micrometer for at least 35 subdivisions of the each SEM image. It was observed that the average density of the separate phases of PVP-PEGDA films was increased by incorporating PEG and PG. From the analysis of all SEM micrographs of the fabricated hydrogels, it is shown that the morphology of films became increasingly more packed and dense by the incorporation of PEG and PEG/PG into the fabricated PVP-PEGDA hydrogels. The difference in morphology between the PVP-PEGDA-PEG and PVP-PEGDA-PEG-PG hydrogels, shown in Fig. 3(b) and (c), could be explained as the influence of PG. Here, PG is performing the role of partial crosslinking agent via hydrogen bonding, which causes the denser crosslinking network structure in PVP-PEGDA-PEG-PG films. These observations are also in agreement with the hypothesis that hydrogels with a maximum number of electrostatic interactions (hydrogen bonding in this case) have a tighter structure and improved network stability.⁴⁶

Example 3

Spectral Characterization of Dried PSA Hydrogels

One of the reliable ways to detect hydrogen bonding between polymers is IR spectroscopy, in the analysis of which, a shift to lower frequencies and drastic increase in absorbance in the frequency range of 2500-4000 cm^{-1} is taken as evidence for the occurrence of hydrogen bonds involving O-H functional groups as donors and C=O as acceptors. This effect is often accompanied by the broadening of O-H and C=O stretching peaks.^{47, 48} By comparing the ATR-FTIR spectra of pure PG, PEG, PVP, PEGDA, PVP-PEGDA-PEG and PG incorporated PVP-PEGDA-PEG copolymer hydrogels, shown in Fig. 4, an effect similar to the extensive hydrogen bond formation can be observed.

Physical crosslinking (hydrogen bonding) degree was measured from the ATR-FTIR spectra of copolymers (i.e. PVP-PEGDA-PEG and PVP-PEGDA-PEG-PG) in carbonyl and hydroxyl stretching vibration regions. The degree of hydrogen bonding interactions can be deduced from changes in the peak position of the C=O stretching band (shown by dash arrows for PEGDA and dash circles for PVP) and O-H stretching vibration band (shown by solid arrows), where as demonstrated in Fig. 4, hydrogen bonding is evidenced by a shift to lower wavenumbers and broadening.^{48, 49} In Fig. 4(c) and (d), the sharp band in 1690 and 1760 cm^{-1} region represent the C=O stretching band of PVP and PEGDA respectively. These bands can be attributed to carbonyl groups that are free, but bound by PVP-PVP or PEGDA-PEGDA dipole interactions. In PVP-PEGDA-PEG Fig. (g) and PVP-PEGDA-PEG-PG Fig. (h), although no shift to lower wavenumbers was observed, slight broadening of C=O stretching bands was noticed, which is attributed to the C=O stretching band of either PVP or PEGDA (or both) hydrogen-bonded to PEG/or PG.⁵⁰

On the other hand, the mechanical strength provided by the crosslinked PEGDA molecules is critical for PSA, especially while handling the films. The covalent bonding between PEGDA molecules can be attributed of the C=C stretching band of the acrylate group visible at the 1635 cm^{-1} in un-crosslinked macromer but is lost when PEGDA molecules are photo-crosslinked (due to conversion of carbon-carbon double bond to carbon-carbon single bond), as seen in the Fig. 4 (d) and (e).^{51, 52} This phenomenon however gets masked due to the C=O stretching of PVP in Fig. 4 (f), (g) and (h).

As it has been established by ATR-FTIR spectroscopy of the copolymers spectra, Fig. 4(g) and (h), the physical crosslinking is due to hydrogen bondings between the proton donating hydrogen atoms of PEG/or PG terminal hydroxyl groups and the electronegative oxygen atoms of carbonyl groups in PVP/or PEGDA.⁵³ The PG and PEG monomer spectra, Fig. 4(a) and (b), have a broad, singlet O-H peak at around 3580-3400 cm^{-1} due to one reactive OH

group at each end of PG and PEG molecules. Therefore, each PG or PEG molecule is capable of forming two hydrogen bonds with the carbonyl groups in PVP/or PEGDA repeat units, acting as a physical crosslinker of PVP/or PEGDA chains. Due to hydrogen bonding, the hydroxyl stretching vibration band of PG and PEG, Fig. 4(a) and (b), broaden and shift to a lower wavenumbers, $\sim 3700\text{-}3200\text{ cm}^{-1}$, as observed in PVP-PEGDA-PEG (g) and PVP-PEGDA-PEG (h) spectra.⁴⁹

Example 5

Control of thickness and Drug Distribution

The robustness of our approach to microfabrication and controlling the thickness of the polymeric films under study was evidenced by the linear relationship between the number of utilized spacers for the fabrication of the films (1, 3, 5 and 7 spacers) and their measured thickness as depicted in Supplementary Information, SI 1(a). SI 1(b) shows the thickness reproducibility for each of the four microfabricated PVP-PEGDA PEG pressure sensitive hydrogel films with the same number of spacers (1, 3, 5 and 7 spacers).

Incorporation of Rhod B as a model drug into the PSA films during the fabrication yielded uniformly distributed microfabricated PVP-PEGDA-PEG-Rhod B films. This was testified by cross-sectional and three-dimensional imaging analysis of various films with different thicknesses (390-510 to 910-1190 μm) as shown in SI 2(a) and (b). Estimation of Rhod B content by fluorescent intensity measurement at different spots of each film, indicated that the model drug was distributed uniformly, throughout the films, as shown in SI 2(c).

Example 6

Rheological Properties

In the rheological study on our PSA hydrogel films we employed both dynamic strain sweep and dynamic frequency sweep tests. In the dynamic strain sweep test, the viscoelasticity of films were measured over a wide range of shear rates (0.0001-100% strain). Oscillatory deformation is applied to the PSA films and the material response is monitored at a constant frequency (1 Hz) and temperature (23°C). The strain dependence of G' , as a rheological property of gels, is a measure of the brittleness and rigidity of the junctions within the structure.⁵⁴ Our PSA hydrogels as a viscoelastic material, exhibit both elasticity of solids and viscosity of liquids. Fig. 5 shows the change of the moduli (elastic (G'), viscous (G'') and complex (G^*) modulus) of the PVP-PEGDA-PEG (a) and PVP-PEGDA-PEG-PG (b) PSA hydrogel films, with the thickness of 910-1190 μm (fabricated with 7 spacers), as functions of

various oscillating strain amplitudes, γ . The strain corresponds to the deformation of the networks caused by the applied shear stress. The elastic modulus remains stable under small strains and decreases abruptly, i.e. onset of nonlinearity, when γ surpasses a certain value γ_0 (so called critical strain) which indicates bond breakage within the networks of hydrogels.^{54, 55}

The PVP-PEGDA-PEG and PVP-PEGDA-PEG-PG microfabricated PSA hydrogels can withstand up to 0.5% and 0.8% of the strain, respectively. Below the critical strain, the mesh-like microstructure of the films is intact and above this, it crumbled. This shows that the three-dimensional microstructure of PSA films, with or without PG in the composition, can withstand a strain up to the critical strain value, i.e. 0.8% and 0.5% respectively, without showing any change in elasticity. However, the three-dimensional network cannot stand any further increase in the applied strain and ultimately it collapses. This collapse is reflected in the decrease of the elastic modulus of the hydrogel. The length and position of the LVER of the elastic modules can be used as a measure of the stability of a PSA structure over a range of strain and as an indication of the ability to resist flow, since structural properties are best related to elasticity.³²

As observed in the Fig. 5(b), the PG incorporated films have longer LVER and higher critical strain values comparing to films without PG incorporation, Fig. 5(a). Therefore, PG incorporated PSA films have a higher rheological stability and elasticity (flexibility).

Using the dynamic frequency sweep test, the effect of frequency on the viscoelastic properties of hydrogels as a function of time was studied. The values of G' and the G'' can be used to confer the behaviour of PSA films under a certain strain. If $G' > G''$, then the material is more solid-like than liquid-like.³²

The frequency sweep rheological test was done in LVER areas (shown in Fig. 5) with constant deformation ($\gamma = 0.065\%$) and changing frequency from 0.1 Hz to 100 Hz. This test describes the structure type of the PSA films according to their moduli (G' and G''). Fig. 6(a) shows viscoelastic properties of the PVP-PEGDA- PEG hydrogels, whereas Fig. 6(b) displays the viscoelastic properties of the PG incorporated PVP-PEGDA-PEG hydrogels. As presented in the figure, for all the microfabricated PSA hydrogels, G' was greater than G'' over the entire frequency range, which is consistent with the solid-like, elastic nature of the hydrogels, in other words hydrogel behaved as a viscoelastic solid. As perceived in the figure, the G' and G'' of the PSA hydrogels are fairly independents of frequency over a wide range of frequencies. The nearly independent and weak dependence of G' and G'' with

frequency, accordingly, is due to both the covalent network (chemical crosslinking) and physical nature of the network (hydrogen bonding, physical crosslinking).

Both hydrogel films, as shown in Fig. 6, retained their predominating elastic nature (up to 10 Hz of frequency) as G' are about ten times higher than G'' . But, with a higher frequency of more than 10 Hz, G'' gradually approach nearer to the G' , shifting slightly more toward viscous nature. The upturn in G'' for both hydrogel compositions, at the higher frequencies suggests the onset of a structural change in the hydrogel network, which is most likely viscous flow.^{1, 9}

The presence of PEG and PEG-PG in the composition of the PSA films, play significant roles in maintaining the viscoelasticity of the hydrogels besides the adhesion properties. Frequency sweeps over at least three decades of frequency were used to provide an indication of the type of gel formed in our PSA films as a correlation to the proposed mechanism earlier in the study. As it was shown in Fig. 2, we have both covalent bondings and hydrogen bondings in the structure of the microfabricated PSA hydrogels. According to the moduli trends of our microfabricated PSAs, shown in Fig. 6(a) and (b), they could be classified as a well-structured (gelled) system, due to earlier noted results (i.e. $G' > G''$ and almost independency of frequency). Therefore, the PVP-PEGDA-PEG and PG incorporated PVP-PEGDA-PEG microfabricated PSA hydrogels can be considered as much of chemical (crosslinked) gels as physical (noncovalent linkages) gels. To some extent, Fig. 6, represents the effect of PG incorporation on the storage modulus (G'), which denotes elastic property and the loss modulus (G'') which represents viscous property of hydrogels with respect to frequency. From comparison of (a) and (b), it is clear that after PG incorporation G' and G'' are increased. This indicates that the PG incorporated PVP-PEGDA-PEG hydrogel films are more elastic because PG is responsible to develop more physical cross-linking (hydrogen bonding) in the hydrogels.

Example 7

Tensile Testing

For the characterization of PSA films, the tensile strength (TS) and the elongation to break (EB%) are two important mechanical properties in terms of their resistance to abrasion and flexibility, respectively. Films tailored for dermatological applications must be flexible enough to follow the movements of the skin and sustain a comfortable feel, and at the same time withstand the mechanical abrasion caused by bodily movement (especially on curved areas, such as knees and elbows) or external objects for example clothes.^{46, 56} Hence, PSA films

with higher EB% (strain percentage) and TS (stress, MPa or N/mm²) are preferred for the TDD applications.

The tensile test was done on microfabricated PSA hydrogel films. Tensile stress vs. strain curves for the microfabricated PVP-PEGDA-PEG and PG incorporated PVP-PEGDA-PEG hydrogels (fabricated with 3, 5 and 7 number of spacers) are shown in Fig. 7(a) and (b), respectively. The PSA hydrogel films of both compositions fabricated with one spacer had a thickness range of 130-170 μm , which were too delicate to be suitable for tensile measurements, due to difficulty in handling. Representative stress-strain curves for microfabricated PSA hydrogels with two different compositions and with 3 different thicknesses showed distinctly different profiles, although all exhibited a toe and linear elastic region and scaffolds experienced necking before deformation.

The PG incorporated PVP-PEGDA-PEG hydrogels, with 3, 5, or 7 spacers, exhibited ultimate tensile strength of 0.06-0.12 MPa and a reasonable elongation to break of 65-85%, Fig. 7(b). The high elongation is attributed to ability of the physical cross-links to dissipate energy. In comparison, the PVP-PEGDA-PEG, fabricated with 3, 5, or 7 spacers, demonstrated a tensile strength between 0.09 and 0.18 MPa and a percent elongation at failure between 35-55%. These results can be explained as a consequence of the less impacted structure and absence of PG in the structure, which made the sample more brittle and less elastic and flexible.

Hydrogel composition was shown to have an observable impact on the tensile properties of the PSAs. There is a correlation between the morphology of hydrogels and the stress-strain curves. For PG incorporated PVP-PEGDA-PEG films the morphology was more impacted with denser distribution of the separated phases, Fig. 3(c), compared to the hydrogels without PG, Fig. 3(b). The stress-strain curve of PG incorporated PVP-PEGDA-PEG hydrogels with more compacted structure showed approximately 1.5-fold higher tensile strain (i.e., elongation) than the corresponding hydrogels without PG, as shown in Fig. 7(a) and (b) respectively.

Also by looking at each plot individually, it can be concluded that for each composition by increasing the thickness of microfabricated films from 390-510 μm to 910-1190 μm , the elasticity decreases and the deformation point appears earlier.

Overall, the incorporation of PG reduced the ultimate tensile stress comparing to the hydrogels without PG as shown in Fig. 7(b). As expected, the ultimate tensile strain (EB%) of

the PG incorporated hydrogels exhibited opposite trends compared with the ultimate stress (TS).

Based on these evaluations, it is found that although incorporation of PG in the PSA films adversely affects the TS when compared with the films without PG, the advantage of its presence in the films by increasing EB% is more obvious which had a significant effect on the elasticity of the PSA films. A small change in the tensile stress magnitude leads to a larger change in the tensile strain percentage of PG incorporated hydrogel films, showing they possess a larger elastic region, and the deformation occurs later (up to 85% before deformation), which makes these films better-ductile films as compared to those without PG.

Enhancement of EB% by PG incorporation, as a plasticizer, may be attributed to its placement in between PVP-PEGDA polymer chains through hydrogen bonding which spaces the polymer chains apart. This separation/spacing leads to weakening of the polymer intermolecular binding, allowing the polymer molecules to move more freely and result in the increasing flexibility of hydrogel films and a decreasing tensile strength.^{57, 58}

This indicates that the incorporation of PG into our PSA films always increases the flexibility of the films and that utilizing more number of spacers in fabrication (increasing of the thickness) produces the highest increase in the EB%. It should also be noted that PVP-PEGDA-PEG films exhibit a lower flexibility when compared with PG incorporated PVP-PEGDA-PEG films with the same thickness. According to the presented results of TS and EB% attained from stress-strain curves, PG incorporated PVP-PEGDA-PEG film with the thickness of 390-510 μm (fabricated with 3 spacers) is the film presenting the best functional properties for the potential dermatological applications because it presents a better overall tensile strength and elasticity as it can be stretched to almost 85% of its original length.⁴⁶

Example 8

Peel Testing

The peel adhesion testing was accomplished at a peel angle of 180° and a fixed rate of 50 mm/min. Three different microfabricated PSA hydrogel samples of each condition (i.e. change of composition and thickness) were tested. The peel strengths and the displacement of the films against both rigid (i.e. glass slide) and flexible (i.e. cadaver porcine skin) substrates were recorded. The maximum detachment force is noted and considered as a measure of adhesive force. The peel force of each film is plotted as a function of its displacement.^{6, 34, 45}

According to the data collected, PG incorporation has a noticeable influence on the peel strengths of the microfabricated PSA films. The results of the peel testing for PVP-PEGDA-PEG and PG incorporated PVP-PEGDA-PEG films against either glass slide or skin are shown in Fig. 8(a) and (b) respectively. As it can be observed from the figures, incorporation of PG into the films considerably increased the peel strengths of the PSA films compared to those without PG. The maximum peel force against glass slide was 0.79 N, 0.42 N and 0.59 N, 0.3 N against skin samples, respectively, for PSA films with PG and without PG.

The low peel strength of the PVP-PEGDA-PEG films with no PG incorporated is consistent with the morphology observed in SEM experiments. The increased number of voids present in the PVP-PEGDA-PEG films, Fig. 3(b), in other words the less packed structure of these films, lowered both the localized adhesive thickness and the contact area which leads to a reduction in the peel strength. While the PVP-PEGDA-PEG adhesive films had a similar thickness to that of the other samples (i.e. PG incorporated PVP-PEGDA-PEG PSA films), due to the less dense structure, the amount of adhesive on the surface of substrate was reduced. The reduced contact area also decreased the amount of mechanical interlocking. The combination of these properties would lower the peel strength on any PSA as it does for the PVP-PEGDA-PEG PSA films. It is also apparent that the peel strength of either of the compositions encounters a reduction when the substrates changed from glass to skin. As for the PG incorporated films, the maximum peel force reduced from 0.79 N to 0.59 N and for the films without PG incorporation, the maximum peel force reduced from 0.42 N to 0.3 N by switching the substrate from glass to skin.

The peel strengths average of all the three measurements for each film type (PVP-PEGDA-PEG with or without PG incorporation), against both surfaces were recorded in Newton and shown in Fig. 8(c) for comparison. As noted, the PG incorporated films possess the highest peel strength against the rigid surfaces and the PSA films without PG possess the smallest peel strength against the flexible surface.

Removal of the PSA films from different substrates involves the work done in the extension of the adhesive, distortion of the backing during the stripping action and the separation of the adhesive/surface interface.^{34, 58} As for our studies no backing layer was involved and just the adhesive films, PVP-PEGDA-PEG and PG incorporated PVP-PEGDA-PEG PSA, were used in the peeling test. The debonding of our adhesive films was via "Adhesive failure Case I" mode which means when the PSA films were peeled away from either of substrates, i.e. glass and pig skin cadaver, they were stripped cleanly, leaving no visible adhesive residue on the substrates.³⁴

Generally, a PSA should be able to flow into the cavities of the substrate (so called viscosity), in order to interact tightly with the surface of the substrate.⁵⁷ When it makes a close contact with the surface of substrate because of its viscoelastic properties then it will be able to make molecular interactions such as Van der Waals forces with the skin or substrate. The PSA-skin bonds can be built by stronger interactions (i.e. hydrogen bonding), following the initial adhesion.^{34, 58} So, enhancements of adhesion by incorporation of PG may be attributed to the improvement of viscoelastic properties of films and hence a better wetting effect. Also these changes may be due to enhancement of the number of hydrogen bondings in the network, as PG has two hydroxyl groups.

Besides peel strength measurements for two different compositions of films (without and with PG incorporation) against both soft and hard surfaces, the effect of varying the thickness of adhesive while keeping other factors constant was also studied. The effect of adhesive thickness, either 650 μm or 900 μm thick, on peel strength was almost negligible.

Thus, according to these results, it was noted that the peel force would increase with the incorporation of PG, and/or utilizing a hard substrate instead of a flexible one, but not when the film thickness changes from 650 μm to 900 μm .

Example 9

Pressure sensitive adhesive film fabrication

The films were measured by microscope to have an average thickness of about 600-630 μm . Freshly prepared films were opaque and the films turned transparent over time possibly due to evaporation of ethanol (Figure 11). The films stick well to glass surface after being pressed by the thumb.

Example 10

Commercial vitamin C patch

Commercial vitamin C patch has the thickness of about 210 μm . The product includes kidney shaped patches individually stored in aluminium wrapping to minimize product exposure to light and oxygen (Figure 12). A bottle of oil solvent is included to assist the removal of the patches and the residues of the adhesives on the skin.

Example 11

HPLC method development

For HPLC method used to determine concentration of MAP in the samples, the concentration range of standard solution was from 1.0 $\mu\text{g/mL}$ to 20.0 $\mu\text{g/mL}$. As the HPLC method used to determine concentration of AA in commercial film is less sensitive, a concentration range of 10 $\mu\text{g/mL}$ to 400 $\mu\text{g/mL}$ was prepared. 20 μL of standards were injected. The chosen standard curves had r^2 values of more than 0.99. The chromatograms of the two methods are shown in Figure 13.

Example 12

In vitro release study

Since MAP is encapsulated in the films as suspensions, the initial slower rate of release could be accounted for by dissolution of MAP within the first 30 minutes. After that, the rate of MAP release increases rapidly and then decreases gradually after some time. On the other hand, the commercial film has the fastest rate of release in 30 minutes. After 30 minutes, the rate decreases with time.

UV curable pressure adhesive films can be used to encapsulate magnesium ascorbyl phosphate for cosmetic use. It is a gentler adhesive compared to the commercial product. Future work could consider improve the release profile by using micronized magnesium ascorbyl phosphate to improve the initial release rate while still being able to encapsulate a high concentration of MAP. Further study can be done to test the level of skin permeation and permeation enhancers can be incorporate into the film to increase penetration of magnesium ascorbyl phosphate.

Table 1 Average weight of MAP, released amount and percentage of release amount of PSA films with three different concentrations.

PSA films	Weight of MAP (mg)	Released amount (mg)	Percentage of released amount (%)
2.0%	1.98 $\pm$ 0.66	1.42 $\pm$ 0.58	53.58% $\pm$ 1.88%
5.0%	6.14 $\pm$ 0.13	1.64 $\pm$ 0.23	26.58% $\pm$ 3.35%
10.0%	12.18 $\pm$ 0.11	3.81 $\pm$ 0.61	31.25% $\pm$ 4.87%

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Claims

1. A biocompatible pressure sensitive adhesive hydrogel comprising: a matrix comprising at least two biocompatible polymers wherein said polymers are photo-crosslinked to at least each other wherein the matrix further includes one or more plasticisers and one or more therapeutic agents.
2. The hydrogel according to claim 1 wherein said matrix comprises a first polymer wherein said polymer comprises polyvinylpyrrolidone.
3. The hydrogel according to claim 2 wherein polyvinylpyrrolidone is provided at about 5-15% w/w of the hydrogel composition.
4. The hydrogel according to any one of claims 1 to 3 wherein said matrix comprises a second polymer wherein said polymer comprises polyethylene glycol diacrylate.
5. The hydrogel according to claim 4 wherein polyethylene glycol diacrylate is provided at about 65-75% w/w of the hydrogel composition.
6. The hydrogel according to any one of claims 1 to 5 wherein the molecular weight of polyethylene glycol diacrylate is between 200Da and 4000Da.
7. The hydrogel according to any one of claims 1 to 3 wherein said second polymer is poly (methyl methacrylate).
8. The hydrogel according to any one of claims 1 to 7 wherein said matrix comprises the plasticiser polyethylene glycol.
9. The hydrogel according to claim 8 wherein polyethylene glycol is provided at about 15-25% w/w of the hydrogel composition.
10. The hydrogel according to any one of claims 1 to 7 wherein said matrix comprises the plasticiser propylene glycol.
11. The hydrogel according to claim 10 wherein propylene glycol is provided at about 2.5% -7.5 w/w of the hydrogel composition.
12. The hydrogel according to any one of claims 8 to 11 wherein said matrix comprises combination of polyethylene glycol and propylene glycol.
13. The hydrogel according to claim 12 wherein polyethylene glycol and propylene glycol are provided at about 19% w/w and about 5% w/w respectively of the hydrogel composition.

14. The hydrogel according to any one of claims 1 to 13 wherein said matrix comprises of polyvinylpyrrolidone, polyethylene glycol diacrylate and polyethylene glycol in a ratio of about 1:7:2.

15. The hydrogel according to any one of claims 1 to 14 wherein the elasticity of said hydrogel (elastic modulus G') is 11.71kPa to about 33.14 kPa.

16. The hydrogel according to any one of claims 1 to 15 wherein the viscosity of said hydrogel (viscous modulus, G'') is 1.137 kPa to 11.16 kPa.

17. The hydrogel according to any one of claims 1 to 16 wherein the tensile strength [TS] of said hydrogel is 0.06MPa TS to 0.18MPa TS.

18. The hydrogel according to any one of claims 1 to 17 wherein the elongation to break is 35 EB % to 85 EB %.

19. The hydrogel according to any one of claims 1 to 18 wherein the adhesion of said hydrogel is 0.042 N to about 0.79 N (for glass substrate) and 0.3 N to 0.59 N (for skin substrate)

20. The hydrogel according to any one of claims 1 to 19 wherein said hydrogel is at least 90 μm thick.

21. The hydrogel according to claim 20 wherein said hydrogel is between about 100-1500 μm thick + / - 10%.

22. The hydrogel according to claim 20 or 21 wherein said hydrogel is between 600-630 μm thick.

23. The hydrogel according to any one of claims 1 to 22 wherein said therapeutic agent is an anti-bacterial agent.

24. The hydrogel according to any one of claims 1 to 22 wherein said therapeutic agent is a pro-inflammatory agent.

25. The hydrogel according to any one of claims 1 to 22 wherein said therapeutic agent is an antibody or active binding fragment of an antibody.

26. The hydrogel according to any one of claims 1 to 22 wherein said therapeutic agent is a pro-inflammatory cytokine or growth factor.

27. The hydrogel according to any one of claims 1 to 22 wherein said therapeutic agent is a chemokine.

28. The hydrogel according to any one of claims 1 to 22 wherein said therapeutic agent is an anti-oxidant.

5 29. The hydrogel according to claim 28 wherein said anti-oxidant is vitamin C.

30. The hydrogel according to claim 29 wherein vitamin C is L-ascorbic acid.

31. The hydrogel according to claim 30 wherein said anti-oxidant is magnesium ascorbyl phosphate.

32 The hydrogel according to any one of claims 28 to 31 wherein said anti-oxidant is at
10 least 1% w/w of the hydrogel composition.

33. The hydrogel according to claim 32 wherein said antioxidant is between 2% w/w to 10% w/w of the hydrogel composition.

34. The hydrogel according to claim 33 wherein said anti-oxidant is about 5%w/w or about 10% w/w of the hydrogel composition.

15 35. The hydrogel according to any one of claims 28 to 34 wherein said anti-oxidant is micronized.

36. The hydrogel according to any one of claims 28 to 35 wherein said hydrogel composition further comprises one or more skin permeation enhancers to enhance anti-oxidant penetration.

20 37. The hydrogel according to claim 36 wherein said skin permeation enhancer is selected from the group consisting of: propylene glycol, terpinolene, α -phellandrene, ocimene, myrcene, (1R)-(-)-myrtenal, (S)-(-)-perillaldehyde, carvacrol, thymol, (R)-(-)-carvone, (1R)-(-)-myrtenol, (-)- α -thujone, (R)-(+)-pulegone, (+)-dihydrocarvone, (-)-carveol, citral, (-)-isopulegol, (+)-dihydrocarveol, (-)-dihydrocarveol, (S)-(-)-citronellal, geraniol,
25 nerol, ($\pm$)-linalool, menthone, β -citronellol, L-(-)-menthol, cyclohexanemethanol, A-humulene, (-)- α -cedrene, (+)- β -cedrene, (+)-aromadendrene, (+)-longifolene, (-)-trans-caryophyllene, (-)-caryophyllene oxide, (-)-epiglobulol, (-)-guaiol, (+)-cedrol, (-)-isolongifolol, (-)- α -santonin, octisalate, (+)-cedryl acetate, retinol, phytol, squalene, ($\pm$)- α -bisabolol, farnesol, ($\pm$)-nerolidol, eucarvone, retinoic acid, β -carotene.

38. The biocompatible pressure sensitive adhesive hydrogel according to any one of claims 1 to 37 wherein said hydrogel is mounted on a backing substrate to facilitate application to the hydrogel to a subject.

39. A wound dressing comprising a pressure sensitive adhesive hydrogel according any one of claims 1 to 38.

40. A pressure sensitive adhesive hydrogel or wound dressing according to any one of claims 1 to 39 for use in the treatment of wounds in a subject.

41. The hydrogel according to claim 40 wherein said wound is a chronic wound.

42. The hydrogel according to claim 41 wherein said chronic wound is a diabetic wound.

43. The hydrogel according to claim 41 wherein said chronic wound is a venous ulcer.

44. The hydrogel according to claim 40 wherein said wound is an acute wound.

45. The hydrogel according to claim 44 wherein said acute wound is a surgical wound.

46. The hydrogel according to claim 44 wherein said acute wound is a traumatic wound as a result of a contusion or similar.

47. The hydrogel according to any one of claims 40 to 46 wherein said subject is immune suppressed.

48. A pressure sensitive hydrogel according to any one of claims 1 to 38 for use in cosmetic skin repair.

49. A method to manufacture a pressure sensitive adhesive hydrogel comprising the steps:

- i) forming a first preparation comprising at least two monomers wherein at least one of said monomers is adapted to be photo cross-linked and a photo-initiator;
- ii) forming a second preparation comprising one or more plasticisers;
- iii) combining said first and second preparations to form a mixed preparation;
- iv) casting the mixed preparation in a mold; and
- v) photo-crosslinking the mixed preparation to form a cross-linked hydrogel film.

50. The method according to claim 49 wherein said first preparation comprises monomers of polyvinylpyrrolidone and polyethylene glycol diacrylate.

51. The method according to claim 49 or 50 wherein said second preparation comprises polyethylene glycol.

5 52. The method according to claim 49 or 50 wherein said second preparation comprises propylene glycol.

53. The method according to claim 49 or 50 wherein second preparation comprises both polyethylene glycol and propylene glycol.

54. The method according to any one of claims 49 to 53 wherein said mixed preparation
10 includes one or more therapeutic agents.

55. The method according to any one of claims 49 to 54 wherein said mixed preparation comprises an anti-oxidant.

56. The method according to claim 55 wherein said anti-oxidant is a vitamin.

57. The method according to claim 56 wherein said anti-oxidant L-ascorbic acid.

15 58. The method according to claim 57 wherein said anti-oxidant is magnesium ascorbyl phosphate.

59. The method according to any one of claims 49 to 58 wherein said anti-oxidant is micronized.

60. The method according to any one of claims 55 to 59 wherein said first or second
20 preparation further comprises one or more skin permeation enhancers to enhance anti-oxidant penetration.

61. The method according to claim 60 wherein said skin permeation enhancer is selected from the group consisting of: propylene glycol, terpinolene, α -phellandrene, ocimene, myrcene, (1R)-(-)-myrtenal, (S)-(-)-perillaldehyde, carvacrol, thymol, (R)-(-)-carvone, (1R)-
25 (-)-myrtenol, (-)- α -thujone, (R)-(+)-pulegone, (+)-dihydrocarvone, (-)-carveol, citral, (-)-isopulegol, (+)-dihydrocarveol, (-)-dihydrocarveol, (S)-(-)-citronellal, geraniol, nerol, ($\pm$)-linalool, menthone, β -citronellol, L-(-)-menthol, cyclohexanemethanol, A-humulene, (-)- α -cedrene, (+)- β -cedrene, (+)-aromadendrene, (+)-longifolene, (-)-trans-caryophyllene, (-)-caryophyllene oxide, (-)-epiglobulol, (-)-guaiol, (+)-cedrol, (-)-isolongifolol, (-)- α -santonin,

octisalate, (+)-cedryl acetate, retinol, phytol, squalene, ($\pm$)- α -bisabolol, farnesol, ($\pm$)-nerolidol, eucarvone, retinoic acid, β -carotene.

62. The method according to any one of claims 49 to 61 wherein said photo-initiator is 2-
5 hydroxy-4-(2-hydroxy-ethoxy)-2-methyl-propiophenone 98% (HHEMP)

63. The method according to any one of claims 49 to 62 wherein photo-crosslinking is with UV light between 350-500nm.