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Chitosan based hydrogel: Prospects as a burn wound dressing

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Abstract
Burn trauma is an excruciating form of wound classified under the open wound category, which is of global significance. They are caused by heat, electricity or chemicals. Burn wounds are intractable in nature hence wound dressings are an inevitable part for the proper management of wound healing. Hydrogels are a novel class of functional polymer material that has an exciting prospects in the biomedical industry. The 3-D cross-linked polymer networks in hydrogels can absorb and hold copious Water, while maintaining its structure patent. Moreover, the hydrophilic nature and soft tissue like characteristics make hydrogels emerge as an ideal burn wound dressing agent. In the current study Chitosan- PVA hydrogels are prepared by different methods and their properties are evaluated. The most efficient hydrogel is used for further studies as a prospective dressing material for effective burn wound management. Chitosan-Polyvinyl alcohol (PVA) hydrogel was prepared by cross-linking chitosan, with the synthetic polymer PVA. The cross-linking was done by freeze-thaw technique (physical cross-linking), formaldehyde cross-linking method (chemical cross-linking) and also double cross-linking technique, which is a combination of physical and chemical method. Characterization of the hydrogel formulations was done using FTIR and by analysis of gel fraction, swelling ratio, water absorption percentage and equilibrium water content of the hydrogel. The chemically and dual cross-linked hydrogels were proven to be more effective as compared to the physically cross-linked hydrogel based on physical and chemical characteristics. The study, therefore indicates the suitability of application of chemical and dual cross-linked hydrogels for burn wound management. It also warrants further investigations by in incorporation of potential active ingredients such as anti-inflammatory drugs, various phytochemical constituents (beta- caryophyllene, Eugenol) and others into the hydrogels to synthesize various functional hydrogels that may serve as novel potent alternative for effective burn wound management.

Keywords: Hydrogel, crosslinking, burn wound dressing, phytochemicals

1. Introduction
A burn is an injury to the skin or other organic tissue primarily caused by heat or due to radiation, radioactivity, electricity, friction or contact with chemicals (WHO, 2019). Analysing the statistical data of WHO, it can be seen that during 2015-2019, 550,000 people worldwide died & 37million people were disabled from fire, heat and hot substances. In India around 1000000 people are moderately or severely burnt every year. Thus burn wounds are a global public health concern. The paramount target in burn wound care is to restore the tissue's barrier function as rapidly as feasible while reducing infection, scarring, and contracture.

Burn wound healing occurs by three overlapping stages of inflammation, proliferation and maturation. These processes are influenced by a variety of variables, including the type of burn (from type I to IV), its quality and origin (such as chemical or thermal), the patient's overall health, and any accompanying comorbidities [1]. Despite all the precautionary measures several complications arise during the treatment of burn wound. Slow wound healing, progressive deepening of the burn wound, Secondary infection, pain, hyper trophic scarring pose the major challenges in burn wound therapy [2]. In comparison to other wounds there are a lot of inanimate tissues in burn wound beds due to the high temperature, which hinders normal wound healing. They act as natural medium for potential pathological bacteria causing wound infection [3]. Regeneration of the skin layers in deep or extensive burns poses a great hurdle as the intrinsic capability of re-epithelialization is greatly reduced or absent in such wounds [4].

Skin grafting and early burn wound excision are popular clinical procedures that have greatly improved the results for patients with severe burns by lowering the death rate. To aid in re-epithelialization, prevent wound infection, skin desiccation, and additional skin damage, wound dressings are created [5].

Traditional dry dressing treatments, such those that use absorbent gauze and/or cotton, have limited therapeutic effects and demand frequent dressing changes, which make patients' suffering much worse. Hydrogels, on the other hand, offer a promising substitute to speed up healing by maintaining a moisture balance at the burn site [6]. Hydrogels are cross-linked, three-dimensional (3D) networks of polymers that can absorb and hold a lot of water, while maintaining its structure. It is enabled by the physical or chemical cross linking of different polymer chains. For a substance to be a hydrogel, water must make up at least 10% of the total weight (or volume). Due to their high water content, hydrogels also have a degree of elasticity that is extremely close to that of tissue. The network is hydrophilic because it contains hydrophilic groups like -NH2, -COOH, -OH, -CONH2, -CONH -, and -SO3H[7]. The blending of various polymers is necessary to create hydrogel. Previous tests have shown that a mixture of inert synthetic polymers and natural polymers can be effective. It offers a blend of strong mechanical properties from the synthetic polymer and good bio compatibility and biodegradability of the natural polymer.

Chitosan (CH) is a natural linear polysaccharide with N acetyl-d-glucosamine and -(1-4)-linked d-glucosamine units. It is predominantly found in the form of chitin in the shells of marine organisms. It is one of the materials used most frequently in the creation of hydrogels. It has low toxicity, strong bio compatibility, and immune-stimulating qualities. These characteristics give chitosan a remarkable bio compatibility and help the body heal wounds. Additionally, it can facilitate wound contraction and hasten certain tissues' rate of recovery from injury [8]. Poly vinyl alcohol (PVA) is an inert hydrophilic long-chain polymer obtained by alcoholysis, hydrolysis, or ammonolysis of poly (vinyl acetate) (PVAc). Hydrogels made of a PVA/Chitosan mixture demonstrated improved tensile strength and elongation. The production of hydrogel can be carried out using several cross linking techniques.

The physical crosslinking approach uses secondary forces like hydrogen bonds or hydrophobic forces to create hydrogels from molecular entanglements. Numerous techniques are used, including freeze-thaw, UV exposure, and ultrasonification. Reversible hydrogels are created as a result of physical crosslinking. Chemical crosslinking uses tiny crosslinker molecules like formaldehyde, epoxy compounds, and dialdehyde to generate covalent bonds between polymer strands. Irreversible or permanent hydrogels are created as a result. The physical, chemical, and double crosslinking methodology, which combines the physical and chemical cross linking methods, were used in the current study to make Chitosan-PVA hydrogel. The properties of the generated hydrogels are thoroughly analyzed in order to choose the hydrogel that will perform the best as a wound dressing for research on burn wounds.

2. Materials and Methods

Chitosan (18824), Formaldehyde solution 37% (CISF650825) and Glacial acetic acid, used in the research were of analytical grade procured from) was purchased from M/s Sisco Research Laboratories Pvt. Ltd. PVA(8.43869)was purchased from M/s Merck Life Science Pvt. Ltd. Mumbai.

a. Physical cross linking method

Chitosan (1 g) was added 2% acetic acid solution and magnetically stirred until complete dissolution. 3 g of PVA was dissolved in 300 ml of distilled water at a temperature of 90 °C. The chitosan and PVA solutions were mixed by magnetic stirring for 3hrs. The polymer mix was kept overnight to remove the bubbles. After removing the bubbles, this solution was poured into a petri plates, placed in a deep freezer at -20 °C for 24 h, and then thawed at 25 °C for 4 h, and this cycle was repeated 3 times.

b. Chemical cross linking

Chitosan (1 g) was added 2% acetic acid solution and magnetically stirred until complete dissolution. 3 g of PVA was dissolved in 300 ml of distilled water at a temperature of 90 °C. The chitosan and PVA solutions were mixed by magnetic stirring for 3hrs. 4 mL of formaldehyde as a cross-linker was added to the polymer mix and magnetically stirred for 4hrs. The polymer mix was kept overnight to remove the bubbles. After removing the bubbles, this solution was poured into a petri plates and then dried at 40 °C.

c. Double cross linking

Chitosan (1 g) was added 2% acetic acid solution and magnetically stirred until complete dissolution. 3 g of PVA was dissolved in 300 ml of distilled water at a temperature of 90 °C. The chitosan and PVA solutions were mixed by magnetic stirring for 3hrs. 4 mL of formaldehyde as a cross-linker was added to the polymer mix and magnetically stirred for 4hrs. The polymer mix was kept overnight to remove the bubbles. After removing the bubbles, this solution was poured into a petri plates. After pouring the blended mixture into petri plates, they were kept at -20 °C for 24 h, and then thawed at 25 °C for 4 h, and this cycle was repeated 3 times [9-11].

3. Characterization of the synthesized hydrogel

3.1 Physical Characterization of Hydrogel

a. Gel Fraction Percentage

The pieces of hydrogel samples (2 x 2 cm) were dried for 6 h at 50 °C (Wo). The dried hydrogel samples were immersed in 10 mL distilled water in petri dishes for 24 h up to a constant weight. After 24 hrs the hydrogel samples were taken out from petri dishes to remove the soluble parts. The gels were dried again at 50 °C (We). The gel fraction percentage was calculated as:

Gel fraction % = (We/Wo) x 100

Where Wo and We are the weights of hydrogel samples dried for 6h at 50 ºC before and after soaking, respectively[13].

b. Swelling Measurement

The pieces of hydrogel samples (2 x 2 cm) were dried at 60°C for 12 h (Wa). Then soaked in pH 7.4 phosphate buffer solution (PBS) at 37 °C (Ws). The formula for calculation of swelling ratio (SR) is given below:

SR % = (Ws/Wd) x 100

Where Wd and Ws are the weights of hydrogel samples dried for 12 h at 60 °C and soaked in PBS at 37 °C respectively [14].

c. Water absorption percentage

The hydrogel samples were immersed in distilled water at regular intervals of time at a constant temperature of 37 °C. After the excessive surface water was removed with filter paper, the weight of swollen gel was measured until there was no further increase in weight. Water absorption was measured by the equation:

Water absorption % = [(Ws-Wd)/ Wd] × 100

Where Ws is the weight of swollen sample and Wd is the weight of dried sample[15]

d. Equilibrium water content

The quantitative representation of water absorbed by hydrogels is represented as the equilibrium water content (EWC). The same protocol mentioned for water absorption percent above was used for the determination of this parameter also. Equilibrium water content was measured by the equation:

Equilibrium water content (%) = [(Ws-Wd)/Ws] × 100

Here, Ws is the mass of the swollen gel at time t (equilibrium time) and Wd is the mass of the dry gel at time 0 [16].

3.2 Chemical characterization of hydrogel

Attenuated Total Reflectance-Fourier Transform Infrared (ATR-FTIR) Analysis

Cross-linking of the polymeric hydrogel was determined using ATR-FTIR spectrum analysis. A Perkin-Elmer Spectrum Two FTIR spectrometer with Attenuated Total Reflectance was used for the analysis. The ATR accessory is seen above the sampling station. After each sampling, he ATR diamond crystal was carefully cleaned with pure isopropanol. A 2mm of film sample was carefully placed on the diamond crystal surface to cover the ATR diamond window or to focus the laser beam. Each spectrum's absorbance under 60 N value was recorded. The spectra were scanned between 4000 and 400 cm" at a resolution of 4 cm [17].

3.3 Morphological characterization of the hydrogel

By employing a field emission scanning electron microscope, the surface topography of the hydrogel sample that has been selected following physical and chemical evaluation was investigated (TESCAN VEGA-3LMU). A 1 cm^2 piece of hydrogel was placed on a double-sided tape on a single pin aluminium SEM stab and then subjected for sputter coating with gold on a rotation stage for 5s at 40 mA in a sputter coater. Using an In-lens detector (20 kV), high resolution secondary electron pictures were obtained at the proper magnifications for on-screen presentation. The imaging parameters were as follows: resolution of 20.0 kx, working distance of 9.02 mm, and aperture size of 10.4 µm (standard aperture).

4. Results and Discussion

Fig 1: (a) Physically crosslinked; (b) Chemically crosslinked; (c) Double crosslinked hydrogels

4.1 Physical characterization

Table 1: Physical characterization of the three hydrogel samples

Characteristics	Physically cross linked Hydrogel	Chemically cross linked Hydrogel	Double cross linked Hydrogel
Gel Fraction %	46	66	72
Swelling Index	203.1	534.5	581.6
Equilibrium Water Content	63.5	83.1	87.3
Water Absorption %	173.9	494.4	524.6

The hydrogel film's dimension stability is gauged by its gel fraction percent. The hydrogel's non-gel component will dissolve in water, leaving behind a residue that is the true gel component. Physically cross-linked Chitosan-PVA hydrogel in this study had a gel fraction percentage of 46%, compared to 66 and 72 percent for chemically and double cross-linked hydrogels. This shows that chemically and double crosslinked hydrogels have more than 50 percent gel portion and physically crosslinked hydrogel have less than 50 percent gel fraction. As a result, a higher dimensional stability has been attributed to the chemically and double crosslinked hydrogels. Increased crosslinking density revealed increased dimensional stability of the hydrogel, and the gel fraction % increases with increasing crosslinking density [11].

The produced hydrogel was evaluated in terms of its ability to swell in aqueous medium. Dry hydrogel's capacity to absorb water suggests that chitosan-PVA-based hydrogel's ability to hold water was reversible. The hydrogel's maximal swelling index, for double crosslinked hydrogel, was 581.6 percent of its dry weight. Hydrogel that has been chemically crosslinked demonstrated a 534.5%. Hydrogel that has been physically crosslinked displayed a decreased swelling index of 203.1 percent. The findings demonstrated that hydrogels with double crosslinking and chemical crosslinking have a great capacity to absorb water. With longer immersion times, the

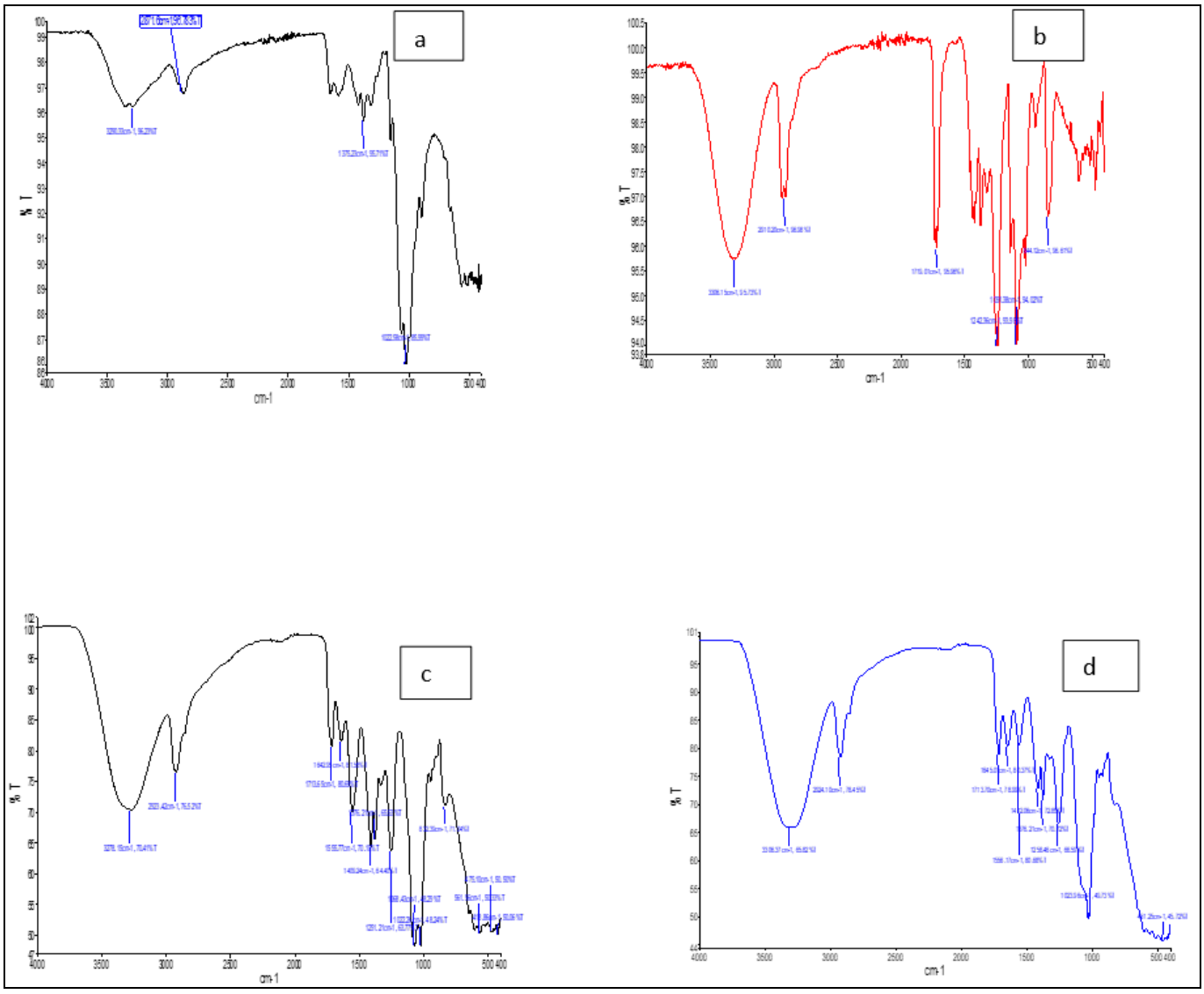
hydrogel samples showed an increasing water absorption until it nearly reached an equilibrium level. For physically, chemically, and double crosslinked hydrogels, the values were 173.9% of dry weight, 494.4% of dry weight, and 524.6% of dry weight, respectively. The equilibrium water content for the physically, chemically, and double crosslinked hydrogels was 63.5 percent, 83.1 percent, and 87.3 percent, respectively. A higher percentage indicates that it has the potential to effectively prevent the buildup of exudate in wound beds and to create a moist environment locally at the wound site.

The water-absorbing ability of the dry hydrogel suggested that the chitosan-PVA hydrogel's water-holding potential was reversible. Suflet *et al.*, (2021) found that larger swelling ratios are produced by the synthesised hydrogels' increased porous architectures. By absorbing wound exudate and lowering the risk of infection, the hydrogels' capacity to absorb water helps to hasten the healing of wounds. Furthermore, swelling is a crucial factor in regulating the release of drugs (Hassan *et al.*, 2018).

4.2 Chemical Characterization

4.2.1 FTIR: FTIR is used to evaluate the degree of cross linking among the three hydrogels. Figure 2 illustrates the spectra of the individual components as well as that of the cross linked hydrogels. It is possible to observe the way the peak shifts as a result of interactions between various polymer chains and the creation of new bonds or complexes.

Peaks are seen in the chitosan spectra at 3290.33 cm-1, which correspond to O-H groups, and at 2871.6 cm-1, which is linked to N-H stretching. Similarly, PVA absorbance was detected in the spectra for -OH and -CH stretching, respectively, at 3306.15 cm-1 and 2910.2 cm-1[9].When compared to the O-H and N-H groups in PVA and chitosan, the O-H and N-H groups in hydrogel have long, tapered, and broad spectrum forms. This demonstrates the cross linking between the two polymer chains that caused the O-H and N-H group accumulation. With respect to the physically cross linked hydrogel, the chemically cross linked and double-crosslinked hydrogels displayed greater intensity at the O-H and N-H peaks, indicating better cross linking. Simal results were observed by Barleany *et al.* (2023) [28], where an interpenetrating network (IPN) is formed when PVA and chitosan are crosslinked. This results in the accumulation of -OH and -NH groups as well as a longer, more intense spectral shape.



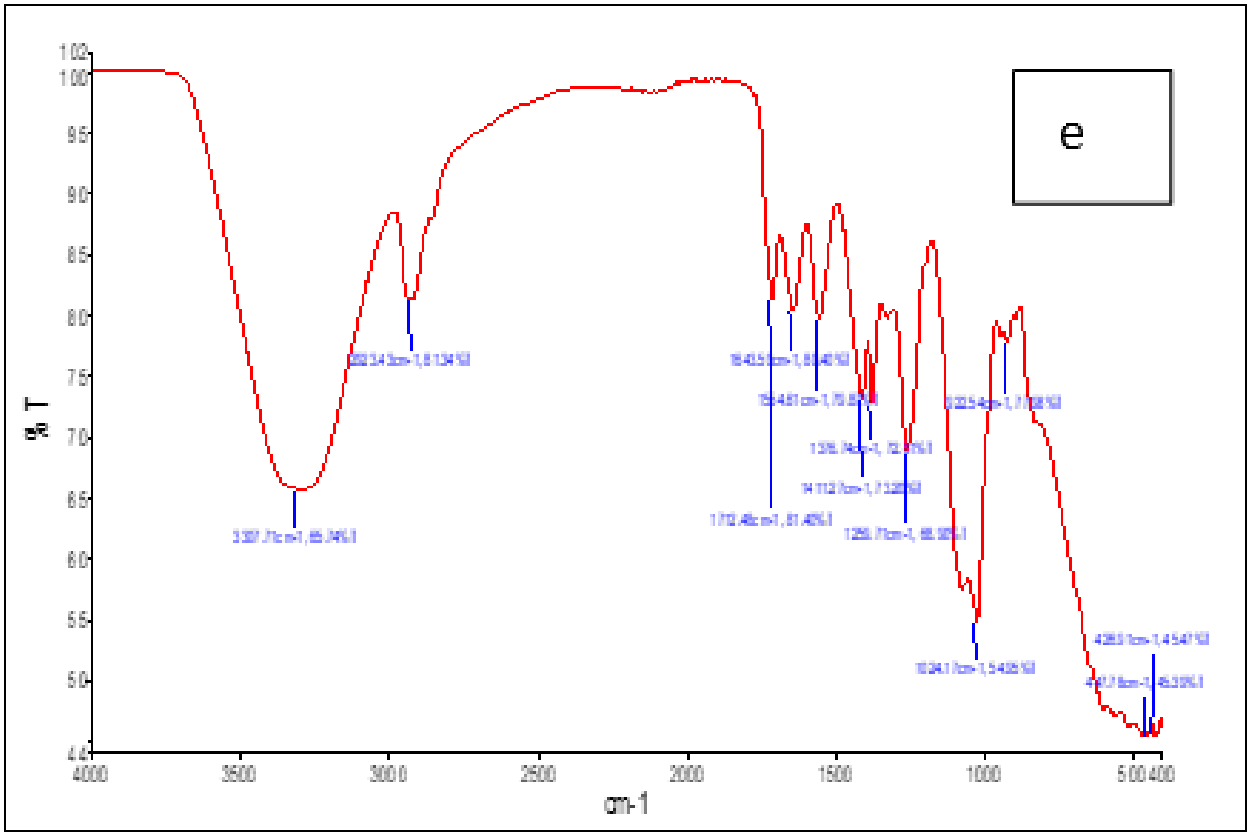


Fig 2: FTIR spectrum (a) Chitosan; (b) PVA; (c) Physically crosslinked; (d) Chemically crosslinked; (e) Double crosslinked hydrogel

4.3. Morphological Characterization

4.3.1 SEM

Scanning electron microscopy (SEM) was utilised for examining the selected hydrogel's surface morphology in order to determine the smoothness and homogeneity of the film. A SEM picture of the double cross-linked chitosan-PVA hydrogel showed that the hydrogel film's structure was smooth and porous. The crosslinking of PVA and chitosan triggered the development of a porous hydrogel. The area between the polymer fibres, which may accommodate fluids in between the fibrillary structure, was evident in the cross-sectional image.

The chitosan PVA hydrogel was synthesised in a work by Wang *et al.*, (2021) [10], and it was observed to contain many surface pores with pore frameworks of high integrity and interconnectivity, showing good overall stability of the hydrogel. Drug storage and gradual release are facilitated by this porous structure of the hydrogel. The cross-sectional image showed that the polymer fibres had voids between them, enabling the fibrillary structure to hold fluids.

In comparison to the present study, similar results were obtained by Iqbal *et al*, (2020) [12] showing tiny pore size with smooth or even surface in the scanning electron microscopy images of a crosslinked GG/CS/PVA blends.

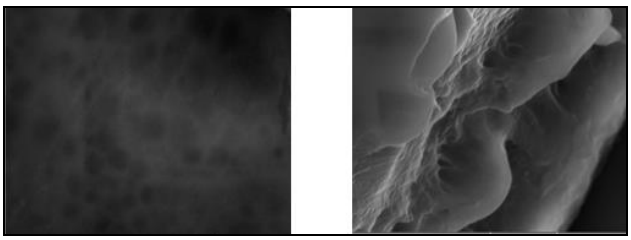


Fig 3: Scanning electron microscopic images of beta-caryophyllene incorporated hydrogel (A) Surface topography (mag-20kx) (B) Cross sectional view (mag-10kx)

5. Conclusion

Three different procedures were used in the current work to create chitosan and PVA hydrogels. The freeze-thaw technique, formaldehyde-based chemical cross linking, and a combination of the first two techniques. The synthesized hydrogels were evaluated for their physical and chemical characteristics. The double cross linked hydrogel displayed more substantial crosslinking in FTIR examination. The physical characterization also revealed that it had a higher than 50% gel fraction, a good swelling ratio, good water absorption, and an equilibrium water content. Hydrogel that has been chemically cross linked showed results that were comparable to those of double crosslinked hydrogel. As a result of the current investigation, double crosslinked hydrogel has come across as a suitable candidate and can be further investigated as a potential dressing material for burn wound treatment.

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