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Chitosan-Based Hydrogels for Chronic Wound Healing

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Abstract: The process of wound healing is intricate and requires a synchronized reaction from numerous cell types and growth factors to quickly restore the structure and functionality of the skin. Even though there are now several hydrogel-based dressings available, the aging population urgently needs innovative wound care treatment options to handle the increasing incidence of severe acute, and chronic wounds. Chitosan based hydrogels are considered to be the most effective substances for improving wound healing because of their haemostatic, biologically adhesive, biodegradable, biocompatible, non-toxic, and antibacterial properties. In addition, these hydrogels have a variety of biochemical properties that aid in wound healing, such as conductivity, temperature-dependent drug releasability, anti-infection, antioxidation, and good self-healing qualities. The preparation of chitosan-based hydrogels and their properties are summarized.

***Index Terms* – Chitosan, Hydrogel based Dressings, Chronic wounds**

I. INTRODUCTION

One of the most fundamental and important aspects of human civilization has been the healing of wounds. There are reports of wound treatment that ranges from making homemade dressings using herbs to bandaging in order to prevent infection.(Powers *et al.*, 2016). However, previously mentioned conventional wound dressings lack the biochemical capabilities to aid in wound healing, making them often ineffective for chronic wounds with particular conditions such as decubitus, diabetic ulcers, pressure sores, and rheumatologic subtypes.(Koehler, Brandl and Goepferich, 2018). Skin injuries impose a serious risk to human health because proper skin barrier function is essential for body fluid retention, thermal insulation, and defense against external infections.(Ducheyne P *et al.*, 2011)

Each year, thousands of patients had different kinds of skin damage, including burns, ulcers, and other traumatic events, that may be acute or chronic wounds which come with high treatment expenses. As a result, several bandages for wounds have been created to aid in their recovery.(Okabayashi *et al.*, 2009). Even though gauze and cotton wool still account for the majority of the market for wound dressings, the use of more sophisticated dressings like hydro Fibers, alginates, foams, and super absorbent has significantly increased and provides a moist environment for the wound.(Brumberg *et al.*, 2021). In wound dressing, hydrogel may maintain a moist environment, absorb extra tissue exudate, offer superior oxygen permeability, and exhibit regulated release of different bioactive components.(Chen *et al.*, 2018). Hydrogels are networks of hydrophilic polymers that can absorb up to hundreds of times their dry weight in water, with a lower limit of 10–20%. Hydrogels can either deteriorate and finally dissolve or they can be chemically stable. When the networks are held together by secondary forces like ionic, H-bonding, or hydrophobic interactions as well as molecular entanglements, they are referred to be "reversible" or "physical" gels.(Hoffman, 2002)

One of the most popular ingredients for hydrogels is chitosan, which has also been explored for use in wound dressings. It is immune-stimulatory, low toxicity, and very biocompatible actions. Chitosan exhibits favourable effects on wound healing and good biocompatibility as a result of these characteristics. Additionally, it helps fasten the healing of many tissues and aid in the wounds' contraction.(Hamedi *et al.*, 2018). Chitin is a co-polymer of N-acetyl-glucosamine and N-glucosamine units that are dispersed either randomly or in blocks along the biopolymer chain, depending on the technique of processing that yields the biopolymer. The biopolymer is referred to be chitin when the proportion of N-acetylglucosamine units exceeds 50%. On the other hand, chitosan is employed when there are more N-glucosamine units present. Due to its facile solubility in diluted acids, which makes it more accessible for application and chemical reactions, chitosan has been the more well studied form of the biopolymer.(Eugene Khor and Lee Yong Lim, 2003). Consequently, it has been extensively employed in numerous biomedical applications.(Koyano *et al.*, 1998)(Madihally and Matthew, 1999).

Furthermore, research has demonstrated that a conductive dressing can encourage cellular activity at the wound site, which will accelerate the healing process.(Qu *et al.*, 2019). Consequently, creating a new type of multipurpose dressing that serves several biochemical purposes and encourages wound closure by Biomechanical activity has hardly been documented and remains a challenging and urgent need in the field of wound healing.(Li *et al.*, 2020)

II. MATERIALS AND METHODS

2.1 Materials

Fish scales of *Labeo rohita* (Kannadi Kendai) were obtained from the local markets in ukkadam, Coimbatore. Tencel spun lace, SMMS (spun bond, melt blown, melt blown, spun bond), Bamboo fabric and silicone layer was procured from local markets of Coimbatore. Lemon leaves and rose petals were collected from the local areas. Hydrochloric acid (HCL), sodium hydroxide (NaOH), potassium permanganate (KMnO4), acetic acid (CH3COOH), glutaraldehyde [(CH2)3(CHO)2] and all other reagents were purchased commercially and used without further purification unless otherwise specified.

2.2 Synthesis of chitosan

Fresh rohu fish scales were washed with clean water and rinsed several times in sterile distilled water. Raw fish scales were washed thoroughly using sterile distilled water, dried in oven and soaked in 1% of HCL for about 36 hours followed by demineralization as the fish scales were washed, dried in oven and soaked in 2N NaOH solution for about 36 hours. Then the scales were soaked in potassium permanganate solution (1g of oxalic acid in 100ml of distilled water) for 1 hour for the decolorization. As a result, chitin was extracted and the process of deacetylation was done using 50%w/v NaOH (50 gram of NaOH in 100ml distilled water) that resulted in chitosan as the end product.

2.3 Synthesis of chitosan-based hydrogel

The lemon leaves and rose petals were cleaned with fresh water, dried and then powdered using mechanical grinder and crushed into fine powder using mortar and pestle. 0.1g of powdered sample was weighed and used for synthesis of hydro gel. 1 gram of prepared chitosan was weighed and suspended in 20ml of 2% acetic acid at room temperature for 24 hours with constant stirring (450rpm) to obtain pale yellow gelatinous Chitosan solution. 0.1 g of lemon leaves powder (llp) and rose petals powder (rpp) was dissolved each in 5ml of 2%aqueous acetic acid by continuous stirring for 5 hours (650 rpm) to obtain viscous brown Chitosan/llp/rpp solution.

2.4. Preparation of CS hydrogel solution crosslinked with glutaraldehyde

1ml of aqueous glutaraldehyde (1%) solutions was supplemented to samples of clear brown cs and heat stirred for about 5-10 minutes to form cross-linked Chitosan- based hydro gels. The obtained hydro gels were dried under freeze-drier at -50°c for 24 hours followed by freezing at 90°c for 5 hours for further analysis.

2.4 Fabrication of Wound Dressing

Wound dressing was made of 6 layers including hydrogel and the adhesive layer. The adhesive layer consists of paper followed by SMMS (spun bond, melt blown, melt blown, spun bond) of 33gsm, Bamboo fabric of 300 gsm, Tencel spun lace with 50 gsm layer where the hydrogel is infused between bamboo & Tencel fabric. The last layer was silicone layer that adhere to the dry surfaces without causing trauma and recommended for sensitive wounds.

2.5 Assessment of Antibacterial Activity

A variety of laboratory methods can be used to evaluate or screen the *in vitro* antimicrobial activity of an extract. The most known and basic methods are the disc-diffusion and broth or agar dilution method. Agar plates were inoculated with standardized inoculums of the test microorganism. Then, filter paper discs (about 6 mm in diameter), containing the test compound at a desired concentration are placed on the agar surface. The petri dishes were incubated under suitable conditions. Generally, antimicrobial agent diffuses into the agar and inhibits germination and growth of the test microorganism and then the diameters of inhibition growth zones were measured and noted.

2.6 Physical tests and evaluation

The sample was subjected to physical tests to determine the fabric weight as the fabric was cut through gsm cutter and the weight of the fabric was measured using electronic balance, thickness and air permeability were measured.

III. Results and Discussion

3.1 Antibacterial Activity Chitosan Solution

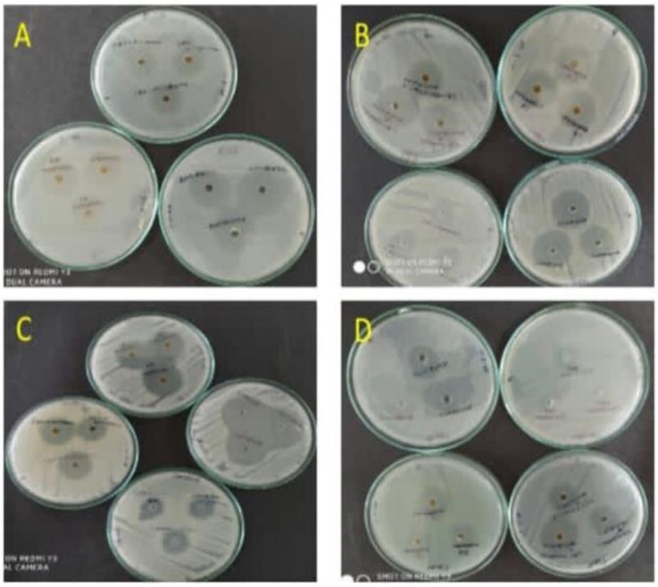

Figure 1: (Antibacterial activity against: A- *Escherichia coli*, B- *Klebsiella pneumoniae*,

C *Bacillus subtilis*, D- *Pseudomonas Aeruginosa*)

Table 1: Anti-bacterial activity of four different combination- based hydrogel with antibiotic

Microbial strains	ZOI of Chitosan solution (cm)	ZOI of Antibiotic(cm)	ZOI of Chitosan based hydrogel (cm)	ZOI of Chitosan based hydrogel + antibiotic(cm)
Escherichia coli	0.7	1.1	1.1	1
Klebsiella pneumoniae	0.8	1.3	0.9	1.3
Bacillus subtilis	1	1.2	1.5	1
Pseudomonas Aeruginosa	0.2	1.6	0.5	0.5

From **Figure 1** and **Table 1**, it is evident that the chitosan solution showed 0.7, 0.8,1 and 0.2 (in cm) zone of inhibition against *E. coli, Klebsiella pneumoniae, Bacillus subtilis* and *Pseudomonas Aeruginosa* respectively. Antibiotic showed 1.1, 1.3, 1.2, and 1.6 (in cm) zone of inhibition against *E. coli, Klebsiella pneumoniae, Bacillus subtilis* and *Pseudomonas Aeruginosa* respectively. Chitosan based hydrogel showed 1.1, 0.9, 1.5 and 0.5 (in cm) zone of inhibition against *E. coli, Klebsiella pneumoniae, Bacillus subtilis* and *Pseudomonas Aeruginosa* respectively. And Chitosan-based hydrogel + antibiotic exhibited 1, 1.3, 1 and 0.5 (in cm) zone of inhibition against *E. coli, Klebsiella pneumoniae, Bacillus subtilis* and *Pseudomonas Aeruginosa* respectively.

3.2 Antibacterial Qualitative Test (Aatcc147)

The hydrogel-based chitosan wound dressing sample was subjected to qualitative Assessment (AATCC147) against the test organism *E. coli* and *Bacillus subtilis* that is shown in the **Table 2** and **Figure 2** were given below. The result obtained states that the Chitosan hydrogel based wound dressing showed 13mm zone of inhibition against *E. coli* and 12mm zone of inhibition against *Bacillus subtilis.*

Figure 2: A) Anti-bacterial activity against *E. coli*; B) Anti-bacterial activity against *Bacillus subtilis*

Table 2: Antibacterial Activity of wound dressing

S. No	Test Organisms	ZOI (in mm)
1	*E. coli*	13mm
2	*Bacillus subtilis*	12mm

3.3 Evaluation of Fabric weight

Table 3: GSM of the Fabric

FABRIC	WEIGHT (in gsm)
SMMS Fabric	33
Bamboo Fabric	50
Tencel Fabric	300

The fabric weight of the chitosan-based hydrogel wound dressing sample were tested and the results were given in the **Table 3** which showed 33 gsm for SMMS fabric, 50 gsm for Bamboo fabric, 300 gsm for Tencel fabric.

3.4 Evaluation of Fabric Thickness

Table 4: Thickness of Fabric in mm

Fabric	Thickness in (mm)
SMMS Fabric	0.25
Bamboo Fabric	0.50
Tencel Fabric	0.50

From the **Table 4**, the thickness of the subjected sample was evaluated to be 0.25mm, 0.50mm, 0.50mm for SMMS fabric, Bamboo fabric, Tencel Fabric respectively.

3.5 Evaluation of Air Permeability

Table 5: Air Permeability of the fabric

Fabric	R1+R2+R3=X	Average=x/5.07	Air Flow(cm^3/sec)
SMMS Fabric	0,200,6 =206	206/5.07	40.7
Bamboo Fabric	0,100,10 =110	110/5.07	21.6
Tencel Fabric	80,300,18 =118	118/5.07	20.5

From **Table 5**, the air permeability of the samples was evaluated to be 40.7, 21.6, 20.5 (cm^3/sec) for SMMS fabric, Bamboo fabric and Tencel fabric respectively.

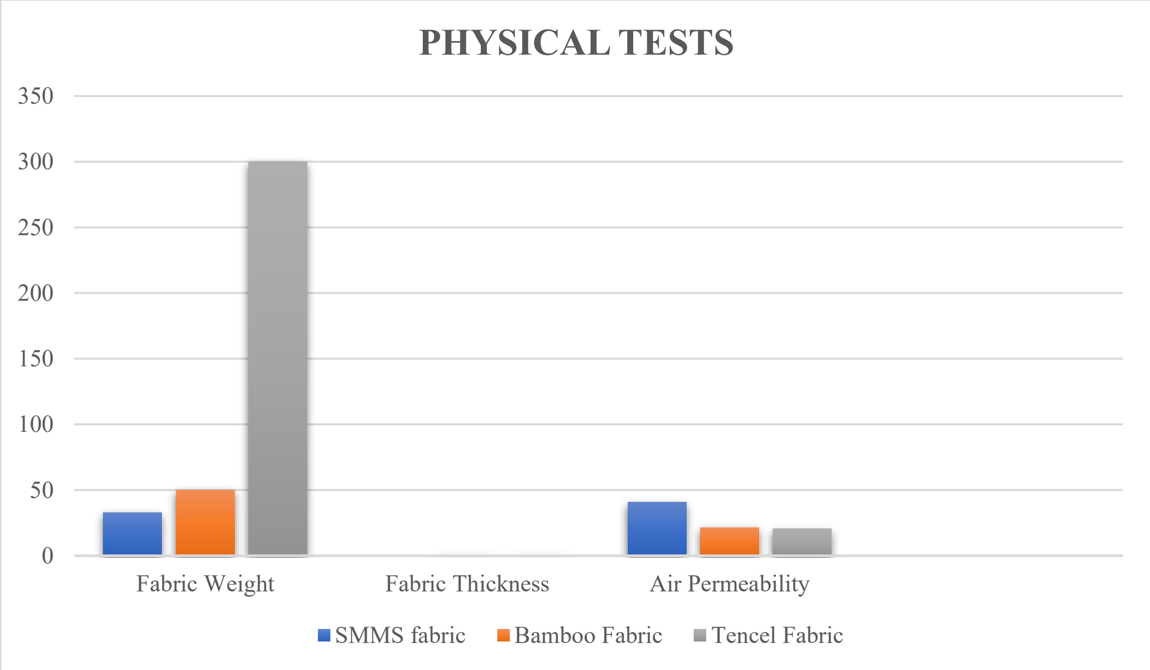

Figure 3: Physical test result comparison

IV. CONCLUSION

Chitosan based hydrogels films were successfully prepared for potential wound dressings. Chitosan based hydrogels were synthesized by cross linking agent glutaraldehyde and found to be effective as hydrogel dressings are biodegradable, biocompatible, have strong mechanical properties, and absorb water well and due to its abundance, biocompatibility, biodegradability, non-toxicity, and antibacterial qualities, chitosan (CS), a partly deacetylated derivative of chitin, is a special substance when creating biomaterials for biomedical purposes.

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