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Characterization of essential ingredients for designing biopolymer-based transdermal patches

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Abstract
The study aimed to characterize the key ingredients used in developing biopolymers-based transdermal patches using Fourier Transmission Infrared (FTIR) spectroscopy, Scanning Electron Microscopy (SEM), Thermogravimetric Analysis (TGA), and rheological analysis. While FTIR spectroscopy and SEM were used to investigate the structural properties and intermolecular interaction within chitosan (CH), methylcellulose (MC), and carboxymethyl cellulose (CMC) as well as wintergreen essential oil (WG oil), the TGA revealed the thermal degradation profiles of CH, MC, and CMC. Rheological analyses revealed that the polymer concentration and the solvent chosen significantly influenced the processability of the polymers. TGA analysis demonstrated that an initial decomposition of CH took place at 275 ^{0}C, while MC and CMC exhibited initial degradation around 260 ^{0}C. Based on the structural, rheological, and thermal properties, the suitability of the characterized biopolymer for fabricating the transdermal patch was demonstrated.

Keywords
Core ingredients, transdermal patch, wintergreen essential oil, biopolymers

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1 Introduction

Transdermal patches (TP) belong to advanced non-invasive drug delivery systems. They offer sustained and controlled release of active pharmaceutical ingredients (APIs) through the skin (dermal region) into the systemic circulation [1]. This process bypasses the conventional oral and injection routes [2, 3]. Current trends and innovations in transdermal patches include smart patches that integrate dose monitoring and adjustable drug release via wearable electronics [4], and combination therapy through which larger molecule drugs like vaccines and peptides can be delivered. Similarly, for environmentally sustainable designs, biopolymer-based patches that incorporate biodegradable polymers such as chitosan, cellulose-based polymers, gelatin, and starch can be prepared [5, 6].

Among these polymers chitosan (CH), methylcellulose (MC), and carboxymethyl cellulose (CMC) have been used in combination with conventional medicines [7] essential and fixed oils [8], and herbal extracts [9] for the preparation of transdermal patches.

CH, MC, and CMC are environmentally friendly and versatile biopolymers with a wide range of applications [10] such as in food industries, water treatment, cosmetics and personal care, agriculture industries, medical, pharmaceutical, and healthcare products [11], textile industries [12], painting industries, construction industries.

CH is a natural biopolymer obtained by the deacetylation of chitin, where the removal of acetyl groups affords amine groups [13]. CH materials (for chemical structure see Figure 1) are environmentally friendly and non-toxic materials that can also be used as an antibacterial and antifungal agent, tissue engineering, skincare, hair care, and drug delivery systems [14–16] and as dietary supplements.

MC is produced by treating cellulose with methyl chloride, which makes MC water soluble to form clear viscous solutions. MC is non-toxic and non-allergic, which makes this polymer suitable for use in food and pharmaceutical industries [16]. MC can be utilized in various fields for its properties and applications as a thickener and stabilizer, gelling agent, emulsifier, wound care, food packaging [17, 18], and drug delivery system [19]. The structure of MC is illustrated in Figure 1.

CMC is a natural polymer derived from cellulose found in plant cell walls. CMC is produced by chemical modification of cellulose, where carboxymethyl groups (-CH_2-COOH) are introduced into the cellulose backbone. CMC (see Figure 1) is water-soluble, which makes it useful in various fields. The applications of CMC in different areas like thickener, binder, thickening agent, excipient, controlled release, wound dressing, and drug delivery system [20, 21]. CMC is an ideal choice for a drug delivery system capable of encapsulating the active drug. CMC exhibits film-forming properties, biocompatibility, and capacity for controlled drug release [22].

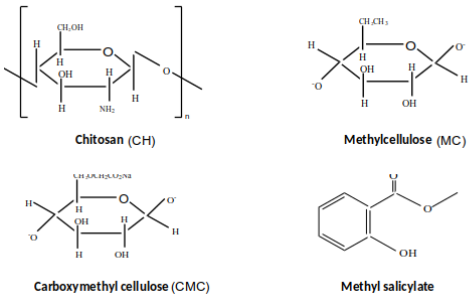

Figure 1: Illustration of chemical structures of chitosan (CH), methylcellulose (MC), carboxymethyl cellulose (CMC), and methyl salicylate, the primary component of wintergreen essential oil (WG oil)

Wintergreen essential oil (WG oil), derived from the leaves of wintergreen plants (*Gaultheria procumbens*), commonly known as Dhasingare in Nepali language, is a natural pain reliever with a long history of medicinal use. The oil is composed of more than 90% methyl salicylate (chemical structure given in Figure 1), a chemical compound well-known for its pain-fighting properties [23]. It has been reported that the WG oil acts as an anti-inflammatory agent, making it effective for soothing muscle pain, and joint pain, and reducing swelling [24], and thus is a common ingredient in topical pain relief products such as balms and ointments employed in the treatment of rheumatism and arthritis [25]. A key development arising from combining WG oil with biopolymers could lead to new, convenient, and affordable transdermal patches for pharmaceutical applications [26–28].

This combination of natural pain relief and innovative materials holds promise for the future of pain management. The overall characterization of biopolymers is crucial in developing any kind of drug delivery system, including transdermal patches. The present work aims at characterizing CH, MC, CMC, and WG oil to investigate their suitability as building blocks for the fabrication of medicated transdermal patches. The details on the performance of the patches will be the object of other reports (for example [29].

2 Materials and Methods

2.1 Materials

Chitosan (PCode 102433232) and carboxymethyl cellulose (PCode 1002577718) were purchased from

Sigma Aldrich, and low substitution methylcellulose (PCode 29217) was purchased from BDH Chemicals Ltd., Poole England. Acetic acid and glycerol were procured from Thermo-Fischer Scientific. Wintergreen (*Gaultheria procumbens*) essential oil was purchased from Annapurna Pvt. Ltd. in Nepal. Milli-Q water was purified in the laboratory using a Millipore Direct Q8 system with a resistivity of 18.2 M cm (Millipore advantage A10 system, Schwalbach, with Millimark Express 40 filter, Merck, Germany). All the chemicals were used as received.

2.2 Characterization Methods

2.2.1 Scanning Electron Microscopy (SEM) Analysis

CH, MC, and CMC powder samples were mounted on a sample holder using conductive carbon tape. The samples were then sputter-coated with 20 nm of gold film to avoid charging and electron beam damage. A Camscan CS24 Scanning Electron Microscope (Applied Beams, Beaverton, OR, USA), operated at an accelerating voltage of 25 kV, was used.

2.2.2 Fourier Transmission Infra-Red (FTIR) Spectroscopy Analysis

Powder samples of each biopolymer were ground and mixed with potassium bromide (KBr) to form a pellet. The pellet was placed in an FTIR sample holder. Samples were analyzed using a Bruker Tensor 27 FTIR spectrometer (Ettlingen, Germany) using 2 cm^{-1} of the resolution, number of scans 32 in the spectral range of 4000 cm^{-1}- 400 cm^{-1}.

2.2.3 Analysis (TGA)

Approximately 10 mg of the powder sample of each biopolymer was placed in an airtight crucible and placed in the TGA instrument (Q500 V6.7 Build 203, Eschborn, Germany). The samples were analyzed from 50 ^{0}CC to 850 ^{0}CC at a heating rate of 10 ^{o}C/min.

2.2.4 Rheological Measurement and Preparation of Patch

0.5 wt.- % of CH was dissolved in 1 vol.- % of acetic acid, and 1 wt.- % of MC and CMC was dissolved in Milli-Q water. The solution was stirred for 12 h and viscosity was measured using a Bohlin instruments rheometer at 37 ^{o}C, measuring a system of C25 DIN 53019 spindle.

For the preparation of the transdermal patch, after the complete dissolution of CH and MC for 12 h. The MC solution was mixed with the CH solution and mixed for 3 h in a stirring plate. Then the mixture was poured in a 90 mm diameter Petri plate and dried in an oven at 45 ^{o}C for 2 days.

Every experiment was performed 3 times and the average result along with the standard deviation has been presented.

3 Results and Discussion

3.1 Morphology of Biopolymers

SEM analysis was conducted to investigate the particle shape, size, and surface characteristics of the biopolymers. Scanning electron micrographs (SEM) of biopolymer powders, with high-magnification SEM images of each sample displayed to the right, Figure 2.

These micrographs reveal that chitosan (CH) exhibits a flake-like morphology with a smooth, non-porous surface [30] as evident in Figure 2a. Notably, individual CH granules appear larger compared to MC (Figure 2b) and CMC (Figure 2c), potentially attributed to differences in the primary materials while preparing the polymers.

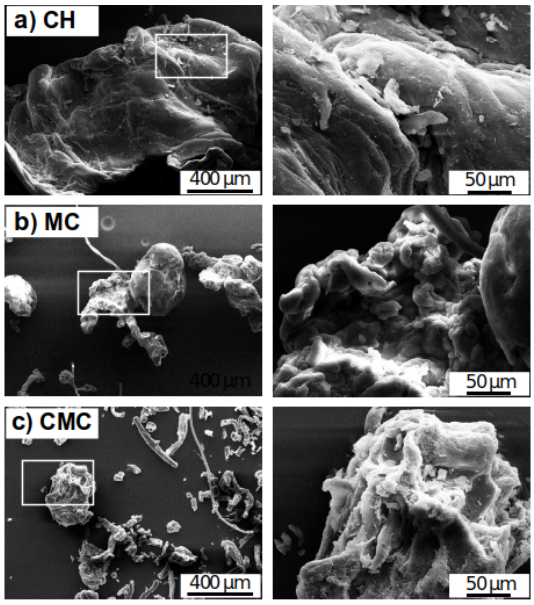

Figure 2: Scanning electron micrographs of biopolymers: a) CH, b) MC, and c) CMC; a part of each micrograph on the left (indicated by a white rectangle) has been magnified on the right.

The most common initial material for CH is chitin [30], but MC and CMC are cellulose-based materials synthesized from plant cell walls [31, 32]. The cellulose-based polymers (MC and CMC) display a fibrous structure and smaller particle sizes than CH granules [33]. In the case of CH, the degree of acetylation influences its particle morphology [34].

In contrast to CH and MC, CMC has been found to exhibit smaller particle sizes and a granular, ir-

regular structure, likely due to the substitution during its synthesis. Other factors that may contribute to the observed structural variations among CH, MC, and CMC include processing techniques and the chemicals used during preparation.

3.2 Spectroscopic Characterization of Biopolymers and WG Oil

Figure 3a presents the FTIR spectra of CH, MC, CMC, and WG oil, revealing subtle differences across certain spectral regions. Figure 3b depicts the extended spectral region (2000 cm $^{-1}$ to 600 cm $^{-1}$) of the FTIR spectra of the samples. The region provides a clearer understanding of the spectral similarities between MC and CMC, as well as the prominent spectral signature of methyl salicylate, a key component of wintergreen essential oil.

A broad band observed around 3400 cm^{-1} in all samples (CH, MC, CMC, and WG oil) is characteristic of O-H stretching vibrations. In CH, this broadband further confirms the presence of both hydroxyl and amine groups [5]. Consistent with previous findings by Santosh Kumar et al., a common band near 2925 cm^{-1} is observed in all attributed to C-H stretching vibration of aliphatic chains of chitosan backbone in CH [35], and methylene/methyl groups within the cellulose structures of MC, CMC and WG oil.

In addition, for CH, a band at 1460 cm^{-1}, characteristic of amine II vibrations (N-H bending), indicates the presence of free amino groups [36]. The CH_2 bending vibration of the methylene group was observed at 1322 cm^{-1}. Additionally, strong bands at 1167 cm^{-1} and 1089 cm^{-1} were assigned to C-O-C bending vibrations of glycosidic linkages (Figure 1) and C-O vibration of carbohydrates was observed respectively. In the case of MC, a band characteristic of C-O-C ether linkages was observed at 1460 cm^{-1} [37]. C-H bending vibrations and typical -glycosidic linkage in cellulose were observed at 943 cm^{-1}.

In the CMC spectrum, a characteristic peak of the carboxymethyl group was observed at 1606 cm^{-1}, corresponding to asymmetric and symmetric stretching vibrations of COO- group [38]. C-H bending vibrations of methylene and methyl groups are observed at 1331 cm^{-1}. Finally, a band at 1064 cm^{-1} can be attributed to C-O stretching vibrations of polysaccharides.

In the case of WG, in agreement with Samira Mendes et. al., a band at 1584 cm^{-1} was attributed to aromatic C=C stretching vibrations, indicative of a benzene ring in methyl salicylate. C-O stretching vibrations of ester linkages were observed at 1257.5 cm^{-1}. Additionally, bands at 1095 cm^{-1} and 763 cm^{-1} were assigned to C-O stretching vibrations of alcohols/ phenols and aromatic C-H bending vibrations, respectively [39].

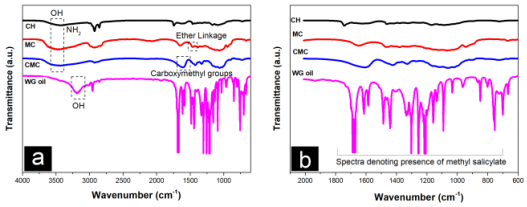

Figure 3: FTIR spectroscopy analysis of a) CH, MC, CMC, and WG oil, and b) magnified view of the spectral region from 2000 cm $^{-1}$ to 600 cm $^{-1}$

3.3 Thermogravimetric Analyses of the Biopolymers

The plot in Figure 4a represents the weight loss profile of CH, MC, and CMC. All the polymers exhibit a significant weight loss and increase in temperature, which shows the thermal decomposition of CH, MC, and CMC. Among the three polymers, CH appears to have the lowest thermal stability among the three biopolymers. This might indicate that CH decomposes more easily compared to MC and CMC. It seems that CMC has the highest thermal stability because the weight loss starts at higher temperatures and indicates more resistance to thermal degradation [10, 40]. The chemical structure and composition of these biopolymers play a crucial role in determining thermal stability.

Figure 4b illustrates that for CH powder, the primary decomposition occurred at 274 ^{o}C, attributed to the breakdown of the polymeric structure and the cleavage of glycosidic bonds (see Figure 1 for chemical structures). A final decomposition step was observed around 481 °C, which might be of different chemical bonds and functional groups within the CH structure.

In the case of MC, the initial decomposition started around 260 ^{0}C, associated with the degradation of the methylcellulose and the release of volatile degradation products and small organic molecules due to the breakdown of methyl ether groups. Figure 3b indicates that MC undergoes approximately 10 % decomposition at 457 ^{o}C, which might be attributed to the breakdown of complex materials that remain still during the synthesis process.

In contrast to the findings of Thomas et al. (2016), CMC exhibited an initial decomposition of around 38 % at 260 ^{o}CC, likely due to the degradation of both carboxymethyl groups and the polymeric backbone. A second phase of decomposition occurred at about 700 ^{o}CC, with an approximate weight loss of 21 %, suggesting further breakdown into similar molecules. A residual mass was observed at ca. 800 ^{o}C, likely consisting of a carbonaceous substance [41].

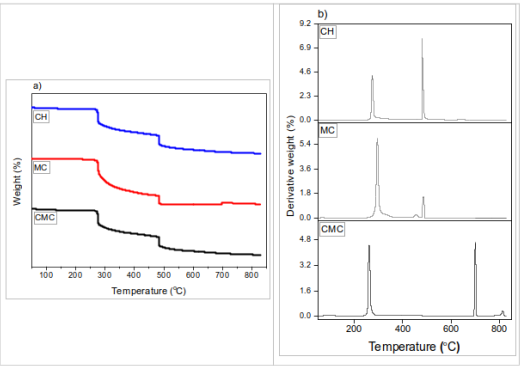

Figure 4: Thermogravimetric analysis (TGA) curves of CH, MC, and CMC a) Weight loss as a function of temperature, b) Derivative weight loss curves. Measurements were conducted under a nitrogen flow rate of 50 mL/min within a temperature ranging from 50 ^{0}C to 850 ^{0}C.

Generally, higher onset temperatures indicate greater thermal stability. This notion is in agreement with earlier research works related to the stable nature of the CMC, in which the latter was used for environmental applications [42], [43]. The results demonstrate better weight degradation stability of the CMC compared to CH and MC. The TGA profile shows that the initial weight loss is due to moisture release, which is almost absent in the case of CH, MC, and CMC because the samples selected for analysis were stored in closed containers and freeze-dried before analysis.

3.4 Rheological Analysis of Biopolymers

The rheological study aimed to assess the stability and overall performance of these polymers during processing and transdermal patch preparation. Figure 5 illustrates the viscosity of CH, MC, and CMC as a function of concentration whereby water is used as a control solution. To simplify the preparation process, a lower concentration of CH was used to compare with the MC and CMC. Despite the lower concentration (0.5 wt.- %), CH exhibited a viscosity of 0.23 Pa.s whereas, the viscosity of MC and CMC was much lower.

In the case of MC and CMC 1 wt.- % of solution was used where the viscosity was found to be 0.04 Pa.s and 0.014 Pa.s respectively. In MC, the observed decrease in viscosity at specific temperatures is attributed to its thermoreversible property, specifically the hydrophobic interactions of methoxy groups [44]. In the case of CMC, viscosity is significantly influenced by the degree of substitution and the ionization state of the carboxyl group [45]. The difference in viscosity is likely due to the degree of deacetylation of chitosan [46] and the alignment of electrostatic forces, especially the positively charged amino group and glycosidic linkage [47].

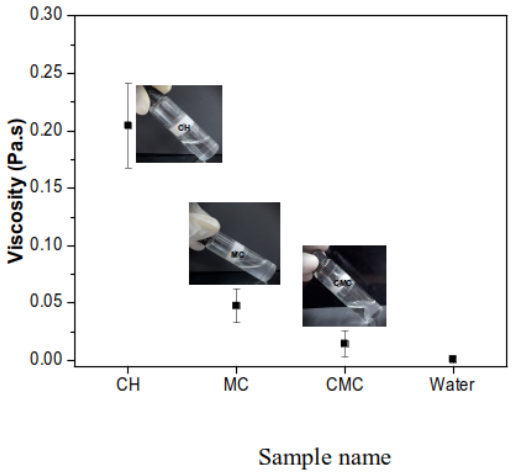

Figure 5: The viscosity of CH, MC, and CMC solutions was determined using a rheometer concerning water. Accompanying photographs represent the visual appearance of the CH, MC, and CMC solutions.

From the rheology study, it can be revealed that the molecular weight of the polymer, concentration, and solvent are crucial factors that affect the viscosity of the polymeric solution. As TGA analyses the decomposition and stability, rheology gives information about the flowability due to structural breakdown.

3.5 Structural Characterization of the Transdermal Patch

As already mentioned earlier, details on the structure-performance correlation of the patch prepared *via* various processing routes have been reported elsewhere [29]. Here, we report briefly the structural characterization of the patch observed by optical imaging and scanning electron microscopy (SEM). The photograph of the transdermal patch prepared using CH and MC is shown in Figure 6a. The SEM analysis shows the surface morphology of the blank transdermal patch prepared using CH and MC (Figure 6b). Highly porous and uneven alignment was observed which might be due to excess exposure to temperature during the drying process and water loss via evaporation while drying (Figure 6). This kind of structural arrangement might be useful for the entrapment of active pharmaceutical active ingredients (APIs) especially essential oils that are well-known for pain management or pain relief.

While preparing the transdermal patches, the polymeric contents, a combination of plasticizers, and viscosity aid in fabricating uniform and consis-

tent structural configuration across the patch. This assessment not only ensures the adherence ability of the patch but also maintains the shelf life of the patch and the release of the drug at a controlled rate.

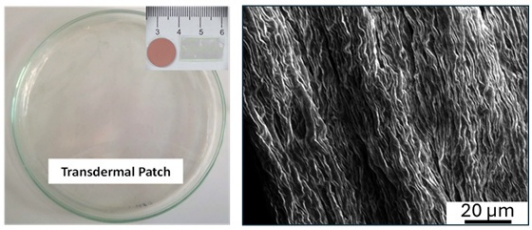

Figure 6: Photograph (left) and SEM micrograph (right) showing the morphology of the transdermal patch prepared using CH and MC.

4 Conclusion

This study has characterized the properties of the basic ingredients of a transdermal patch comprising chitosan (CH), methylcellulose (MC), and carboxymethyl cellulose (CMC) to be enriched with wintergreen oil by different techniques such as SEM, IR, TGA, and rheological analyses.

The SEM imaging of the biopolymers reveals distinct differences in their particle morphology. CH displays a smooth, non-porous, flake-like surface with larger granules compared to MC and CMC, which have fibrous structures and smaller particle sizes. CH's larger granules are likely due to its chitin base, while MC and CMC are derived from cellulose.

All samples exhibit a broad FTIR band around 3400 cm^{-1}, indicating the O-H stretching vibrations. CH and WG oil also show amine (NH_2) and hydroxyl groups, while MC and CMC display cellulose-related features, as expected. WG oil reveals aromatic and ester vibrations associated with the methyl salicylate.

CH exhibits the lowest thermal stability, starting decomposition at lower temperatures, while CMC shows the highest stability, starting decomposition at higher temperatures and with less weight loss. MC has thermal stability similar to CH. All the biopolymers have thermal stability suitable for their use as transdermal patch fabrication.

Future research will focus on optimizing biopolymer ratios and properties and essential oil selection to further advance the development of effective patches for pharmaceutical applications.

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Authors Contribution

PP: Performing experiments, analysis of results, drafting the first manuscript; **EM**: Analysis of results, and interpretation; **HS**: Funding acquisition, conceptualization, supervision, and editing of the manuscript; **RA**: Co-drafting of manuscript, funding acquisition, conceptualization,and supervision; **AA**: Supervision, and editing of the manuscript; **RM**: Supervision, data analysis and interpretation

Conflict of Interest Statement

The authors declare that they have no conflicts of interest. All the authors have read and approved the manuscript.

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