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CARBOXYMETHYLATED COTTON DRESSINGS

D.V. Parikh, T.A. Calamari, and J.D. Berndsen
Southern Regional Research Center, USDA
New Orleans, LA
Ioan Negulescu
Louisiana State University
Baton Rouge, LA

Abstract

Chronic wounds are not easy to heal. Research in wound physiology has shown that healing is accelerated when the wounds are kept moist. Over the last three decades, occlusive dressings that create a moist wound environment have brought revolutionary changes to the world of wound management. Since 1987, moist wound dressings based on calcium alginates have been commercially available. While alginate dressings produce accelerated healing, they are very expensive. The present work is directed to developing less expensive dressings from chemically modified cotton, which will provide moist healing conditions. This paper reports on the formation of highly absorbent dressings made from the chemical modification of preformed cotton gauze/nonwoven. These dressings would absorb high amounts of body fluid (from exudating wounds) and would be similar to alginate materials. Gauze bandage rolls are modified into highly absorbent carboxymethylated bandage rolls, eliminating the need for any subsequent converting operation. Chemical modification (carboxymethylation, CM-cotton) was carried out by treating cotton gauze rolls or nonwoven rolls with caustic and monochloroacetic acid in 90/10 ethanol/water media. Post treating Na-CM-cotton rolls, on ion exchanging, made it possible to obtain Ca/Na-CM-cotton gauze rolls. Ca/Na-CM-gauze will be competitive with calcium alginate dressings.

Introduction

The principal function of a wound dressing is to provide an optimal healing environment for a wound, since it must be protected from infection and further damage. In general, infection impedes wound healing by damaging the tissue and promoting excessive inflammation.

Traditionally, wounds have been kept dry by covering them with a dry dressing. However, recent research in wound physiology has shown that healing is accelerated when the wound is kept moist. This enhances the formation of granulation tissue (healthy connective tissue) and skin cells. Since 1987, moist wound dressings based on calcium alginates have been made commercially available. While alginate dressings produce accelerated healing, they are very expensive. The present work is directed to developing less expensive dressings from chemically modified cotton, which would promote wound healing under moist conditions. Fresh wounds initially produce a large amount of fluid exudate, which provides a fertile environment for bacterial growth and infection. Thus, an efficient absorption of fluid exudate, while maintaining a sterile environment at the wound site, is preferable. Furthermore, an occlusive dressing (defined as the relative ability of a wound dressing to transmit gases and water vapor from a wound surface to the atmosphere) appears to function by limiting tissue desiccation and secondary damage. By maintaining a moist environment, the epidermal barrier function is rapidly restored. Interestingly, this effect has been noted by the faster rate of epithelialization in moist climates compared with that in an arid one [Brothwell,Winter]. An ideal moist wound dressing should perform the following functions [Giurini]:

1. Maintain a moist environment at the wound site to enhance healing without promoting maceration;
2. Protect the wound site from contamination by providing a barrier against bacteria;
3. Absorb fluid exudates and toxic components;
4. Promote rapid epithelialization;
5. Be non-adherent so that the wound is not traumatized when the dressing is changed; and
6. Permit gaseous exchange.

The moist environment is also conducive to migration of defensive and reparative cells such as macrophages. In an uncomplicated wound such as a donor site, occlusion may decrease the incidence of infection. It is suggested that the scar left by an occlusively dressed wound is more cosmetically acceptable than that left by an exposed wound [Linsky,Wiseman].

In the early 1980s, a moist healing product, generally known as a hydrocolloid wound dressing, was brought to the market by ConvaTec under the brand name Duoderm. This product was made by dispersing hydrophilic polymeric granules, such as sodium methylcellulose, gelatin, and pectin into a poly-isobutyl rubber matrix. When in contact with wound exudates, the polymeric particles absorb water and form a moist surface on the wound surface. While the polymeric particles provide absorbency and gel-forming characteristics, the rubber offers the dressing its adhesiveness [Quin].

Alginate fibers were introduced as the next generation moist wound healing product. On ion exchange of calcium with sodium ions in the wound exudates, the water insoluble calcium alginate fibers slowly convert into a water-soluble sodium alginate, thereby drawing water into the fibers and turning them into a gel. Alginate fibers are thus capable of forming a moist gel *in situ*.

Since 1987, moist wound dressings based on calcium alginates have been available to treat chronic wounds. The leading products include Kaltostat (ConvaTec), Curosorb (Kendall Healthcare), and Sorbsan (Dow B. Sickam). Modern alginate dressings are a blend of calcium alginate and sodium alginate which, on contact with blood or exudate, release calcium ions in exchange for sodium, thereby increasing the local calcium ion concentration and thus stimulating both platelet activation and whole blood coagulation. In the process of ion exchange, the calcium ion is converted to soluble sodium ion (yield sodium alginate), producing a hydrogel that absorbs wound exudate, while providing a moist wound environment [Attwood]. A major disadvantage of the alginate dressings has been their cost.

An exploratory project was undertaken to develop cotton gauze and cotton nonwovens (NW) with high swelling, high water retention, and high total water uptake capabilities, for the development of an inexpensive, moist dressing. The present research approach was to chemically modify cotton gauze through a carboxymethylation [CM] process while still maintaining its gauze/nonwoven structure. Depending on the nature of the substituent and the degree of substitution (DS), cellulose ethers can be produced that are soluble in water. The solubility of cellulose ethers in water also depends to a great extent on the uniformity of substitution. Since both the DS* and the uniform distribution of substituents affect absorbency properties (and thus the end uses) of the cellulose ethers, the proper control of these variables demands considerable attention in the manufacturing process. The final product and its quality also depend on factors, which are inherent to the cellulose structure or to the reagents used in the preparation. These factors include cellulose accessibility, hydroxyl group reactivity and reagent reactivity.

The reaction of carboxymethylation of cellulose is shown in Figure 1. The acidic ether of cellulose is first prepared by the interaction of alkali cellulose and chloroacetic acid. The process is affected with an excess of alkali so that the sodium salt of carboxymethyl cellulose is obtained. By-products of the process include sodium chloride, sodium glycolate, and excess alkali.

*DS reflects the average number of carboxymethyl (-CH_2COONa) groups per anhydroglucose unit of cellulose.

Experimental Procedures

Materials

Bleached cotton gauze rolls (Kerlix large rolls, Kendall Co.), hydroentangled cotton nonwovens, and cotton lap sponges were used.

Caustic soda, monochloroacetic acid, acetic acid, silver nitrate, and ethanol were obtained from Fisher Chemicals. A standard CMC-Na sample, having 0.9 DS, was obtained from Aldrich Chemicals.

Technology

The conventional two-stage carboxymethylation of cotton gauze and nonwovens in aqueous media consisted of sequential treatments first with monchloro acetic acid, air drying, followed by a treatment with caustic soda and a final thorough washing [Reinhardt, Mizutani, Hebeish, Borsa].

A single-stage CM process was developed in 90/10 ethanol/water (9600 mL ethanol along with 840-900 mL of water) that preserves swelling/gelling capabilities until the gauze/nonwoven is moistened/wetted in water or until used as a wound dressing. Bleached absorbent gauze roll or hydroentangled nonwoven (NW) roll was carboxymethylated in a THEN laboratory yarn dyeing machine with a tub capacity to hold nine kerlixed gauze rolls. The machine (12 L capacity), which was built of stainless steel, had gaskets/packings of rubber. Rubber packings were affected by ethyl alcohol. They had to be replaced by Teflon ™ packings. Teflon™ packings are stable up to

500°F and are inert to ethanol. A pump in the machine was capable of circulating solution in the package vessel sothat the solution was in continuous flow through the cotton gauze. This circulation helped in imparting a uniform degree of substitution to the cotton cellulose. Adding chemicals in two steps was found to be beneficial.

Typical water-soluble sodium-CM-gauze (#104) was made as follows:

> Cotton gauze (nine kerlixed gauze rolls, 320 g) was first treated with caustic soda, 600 g (dissolved in 600 g of water and alcoholated with ethanol, 8000 g) for 15 minutes at 100°F to swell the cotton and increase the accessibility of hydroxyl groups before treating the gauze in the same bath with alcoholated monochloroacetic acid, 720 g (in ethanol, 1600 g) and caustic soda, 240 g (dissolved in water, 240 g) for 4

to 5 hours at 155±3°F. Temperature and pH of the solution were continuously monitored. Initial and final pHs were in the range of 9.3 to 9.4. At the end of the desired reaction time, the bath was drained. The gauze was neutralized with alcoholated acetic acid, 350 mL, for 15 minutes at 110°F and the CM-gauze was thoroughly washed in 90/10 ethanol/water to free it from unreacted chemicals, sodium chloride and acetate by-products. Purity of the CM-cellulose was ensured by giving an additional wash in 90/10 ethanol/water. Na-CM-gauze was centrifuged (hydroextracted) and dried.

The reaction parameters were varied to produce CM-cellulose with a different DS.

Ca/Na-CM-gauze was prepared by a two-step process of post treating Na-CM-cotton. In the first step, CM-gauze rolls (100 g) were acidulated with a liter solution of 2.0 g/L of glacial acetic acid in 85/15 ethanol/water for 40 minutes, then washed in 85/15 ethanol/water and dried at 122 ± 3° F. In the second step, the acidulated rolls were treated with 4% calcium chloride in 85/15 ethanol/water for 4 hours at 70°-80° F and the treatment of the fortified solution by adding 2% calcium chloride in 85/15 ethanol/water for an additional 2 hours.

The Aldrich sodium salt of CMC sample (control), and the CM-cotton developments were examined for decomposition points, and percent char under the differential scanning calorimetery (DSC). The samples were heated at the rate of 10°C per minute between 25°C to 600°C and plots of thermal behavior were recorded.

The CM-fabric samples were conditioned at 65% R.H. at 72° F for two days before being taken for standard test procedures to measure the absorbency characteristics: ASTM D 2495 for percent moisture regain, and ASTM D 2402-90 for Water Retention Value (WRV). WRV technique measures the amount of chemically bound water retained by unit weight of the fibrous material after it has been soaked and subsequently centrifuged under conditions that effectively remove the loosely held water between fibers.

In the Dunk-and-Drain test for wettability and capacity, a strip of CM-gauze or nonwoven of 1 to 2 g was rolled loosely and dropped into water contained in a 1L beaker. The sample was allowed to stay submerged in water for 30 seconds and drained for 30 seconds. The absorbent capacity was determined by weighing the sample immediately after it was drained for 30 seconds. Commercially available alginate dressings were evaluated by the Dunk-and-Drain test for comparison with CM-development. Wet samples from a Dunk-and-Drain test were determined for water uptake after specified periods of drying at 100° F. Wicking rate was determined on strips (18cm long x 2.6cm wide) by immersing 3mm strips in water, at 70 ± 1° F, contained in a 250 mL beaker. Sightner dye was dissolved in water so that the rising water line could be read easier. The rise in height of the colored water on the samples after 10 seconds and 60 seconds was measured and gain in weight was recorded. The breaking strength was determined using ASTM.

Results and Discussion

Since the carboxymethylated cellulose from the conventional two-stage process contained a water-soluble product, it did not preserve the swelling and gelling characteristics of CM-cotton. Apparently, the process is only suitable for low DS gauze. Medium to high DS products get partially or fully dissolved during the final washing in water.

The single-stage CM process using 90/10 ethanol/water preserved the swelling/gelling characteristics. Heize et. al. obtained carboxymethylated cellulose via heterogeneous reactions in isopropanol and water [11]. The major merits of the single-stage development were in:

1. Preserving the fibrous form of gauze/nonwoven while retaining its strength.
2. Producing low-to-high DS cotton by custom etherification, and
3. Imparting desired properties of improved moisture regain, high bound water, high total water uptake, and swellability.

Table I shows the superiority of the single-stage development over the two-stage CM process. By varying reaction parameters, CM-products of different DS were obtained. Low DS created hygroscopic gauze that did not have surface gelling characteristics. Medium DS created surface gelling characteristics, and high DS created swelling, gelling, and subsequently solubilizing characteristics, Table II. By suitably controlling the reaction parameters, it was possible to produce products with precise gelling and solubilizing, or non-gelling characteristics to custom match the end-use wound healing requirements. The strength characteristics of these dressings have remained intact, Table III. Desired characteristics can be further enhanced or newer desired characteristics can be imparted by post treatment of CM-gauze.

Since the CM-cotton developments were designed for healthcare applications, the CM-products were sterilized with ethylene oxide (EO). The products passed the cell culture, primary skin irritation and intracutaneous irritation tests. No adverse toxicological or environmental factors are reported for cellulose ethers in general. In fact, some purified carboxymethylcelluloses, methylcelluloses, and hydroxypropylcelluloses are approved as a direct food additive [Cellulose]. A significant use of

CM-cellulose is also found in pharmaceuticals for skin care products such as ointments, lotions, and creams [Aqualon]. Potential applications of the CM developments are listed in Table IV.

The DSC profiles (percent weight loss vs. temperature) on highly swelling and gelling CM-cotton #103 and on surface gelling CM-cotton #109 were identical to the control Aldrich sample (Fig. 7-9). Both of the samples show similar water loss, nearly 15% by weight, as compared to the control. After the initial weight loss, the weight of the samples was stable until onset decomposition of cellulose occurred at about 250°C. Char yield was about 35% indicating good carboxymethylation in these samples.

Moisture Retentive Properties

Percent moisture regain, absorbency factor (water/gauze, g/g), and water retention (g/g) by a centrifuge test of various CM samples are shown in Table V. Sample #104 has very high moisture regain (21.2%) and high water retention (Bound water, 11.0 g/g). Data of bound water indicate that CM-gels are capable of holding water tenaciously even under pressure. A swellable CM-cotton may also be an absorbent for physiological liquids such as urine, blood, and perspiration. This product can find an application in the absorbent core of a baby diaper.

Figure 2 shows the water retained in samples [Dunk-and-Drain test] at zero minutes and after oven drying at 100° F at different intervals of time up to 150 minutes. At zero time of drying, sample #104 retained 60.0 g of water, whereas the control gauze retained only 9.1 g. After 150 minutes of drying, sample #104 retained 43.09 g of water as compared to 0.15 g in the control gauze (data on control gauze at 150 min. not shown in the chart). Since the healthy human body temperature is around 98.6° F, it was planned to use a drying temperature of 100° F. These data have shown that the CM-dressings maintain a moist environment at 100° F.

Since a burn dressing has to be multifunctional, i.e., antimicrobial, highly absorbent, moist, and non-adherent, and since Silvadene™ and silver nitrate are used on burn patients for their antimicrobial property, it was decided to study silver nitrate retention on these dressings by repeating Dunk-and-Drain in 0.5% silver nitrate solution and drying the samples at 100 ° F. Figure 3 shows silver nitrate retained for drying at 100 ° F up to 5 hours on these samples. Samples #104, #109, and #106 showed respectively the retentions of 22.32 g, 11.11 g, and 6.31 g subsequent to drying for 5 hours, as compared to the retention of only 0.14 g in the control gauze. Again, the data indicate possible suitability of CM samples for moist healing as well as for treating a burn patient whose immune system might have been compromised. (No burn patients have actually been treated with this dressing).

Wicking and absorbency properties of the CM samples are shown in Figures 4 and 5. The wicking height of the hygroscopic sample #106 was higher than that of surface gelling #109, which in turn was higher than highly swelling #104. Hydration of the outer surface of CM-cotton results in the formation of a viscous gel layer that inhibits further wetting or wicking. In other words, the phenomenon of "gel-blocking" occurs in sample #104. Although the gel blocking occurs in #104, its uptake of water was significantly higher than the other samples (Figure 5).

Calcium/Sodium-CM-Cotton

CM-cotton presently produced has been 100% sodium salt of CM-cotton. In the two-step post treatment of CM-cotton, Ca/Na-CM-cotton was obtained by partially converting Na-CM-cotton into Ca-CM-cotton. (It was not possible to obtain Ca-CM-cotton from Na-CM-cotton in a one step process.) In the first step of acidulation, sodium ions in the fibers are partially replaced by the hydrogen ions (producing H-CM-cotton), which are then replaced by calcium ions in the second step. Since Ca-CM-cotton is less water-soluble than Na-CM-cotton, the resulting product of Ca/Na-CM-cotton will be less soluble (or less absorbent) than the 100% Na-CM-cotton. As shown in figure 6, the Na-CM-product will be more absorbent than the Ca-CM-product, which is more absorbent than the H-CM-product. Absorbency of these products depends on the degree of substitution. The higher the DS, the higher the absorbency. It is possible to produce dressings with varying ratios of calcium and sodium compositions. To obtain the dressings with higher calcium content, repeat treatments with calcium salts are required. Water absorption capacity of Ca-CM-cotton development and alginate dressings were evaluated in Table VI. The data indicate that the #112-CA-10-1HR dressing has calcium content higher than those in the commercially available alginate dressings. If these dressings (calcium/sodium-CM-cotton) are applied on dry non-exudating wounds, no absorption takes place, and no gel is formed. There is no benefit of the dressing. These dressings are useful on exudating wounds. Additional research and extensive clinical evaluation will be required to fully exploit this development. It is easy to envisage that successful development of such products (calcium/sodium-CM-products), will cost less than and be competitive with alginate dressings.

Summary

A highly swellable, water retentive cotton fiber gauze or nonwoven may be obtained by partial carboxymethylation with a degree of substitution in which the fiber does not lose strength but absorbs fluid when wet. The carboxymethylated gauze roll offers dressings of good conformity and high absorbency, thus making it an ideal wound dressing material. Such carboxymethylation is obtained by treating cotton gauze or nonwoven roll in alcoholic caustic and monochloroacetic acid using 90/10

ethanol/water. The CM fabric may be sterilized by ethylene oxide. Sterilization should be possible by gamma or alternative methods although these were not tried. The CM-cotton appears to be a potential candidate for use as a moist bandage and dressing especially on burn patients. Post treating CM-gauze with calcium salt solution in ethanol/water will produce Ca/Na-CM-gauze. This product will cost less than and will be competitive with the conventional calcium/sodium alginate dressings.

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Table 1. Two-stage versus single-stage carboxymethylation.

Two-stage Features	Single-stage Features
CM development in water	CM development in alcohol
Good for low DS	Good for low-medium- and high-DS
Economical	Expensive
Not suitable for medium to high DS cotton	Preserves swelling

Table 2. CM-Cotton Products.

Sample Code	DS	Description
#101	Medium (0.150-0.180)	Surface gelling of hydroentangled cotton nonwoven; strength unaltered.
#103	Medium-High (0.280-0.300)	Highly gelling and with glue like properties.
#104	Medium-High (0.287-0.310)	Water soluble cotton/gauze rolls; initial gelling, then subsequently dispersing in water.
#106	Low (0.002-0.003)	No surface gelling; Hygroscopic with out surface gelling characteristics.
#109	Medium (0.099-0.130)	Surface gelling cotton gauze rolls; yarn/gauze strength unaltered.

Table 3. Dry Strip Tensile.

Kerlix Gauze Roll	Strength	% Elongation
Untreated Control	24.9*	12.8*
Hygroscopic #106	34.3*	13.4*
Untreated Control	32.1	49.5
Water Soluble #104	28.3	63.6
Surface Gelling #109	43.8	22.6
Hygroscopic #106	34.5	66.4

*Crimping was stretched out and then breaking strength was determined

Table 4. Applications.

In moist healing.
Non-adhering dressings (like in oil emulsion dressings).
Wound packing.
Burn bandages/dressings with silver nitrate.
Antimicrobial gauze/nonwovens

Table 5. Moisture Regain, Absorbency Factor, and Water Retained after Centrifugation.

Gauze Roll	% Moisture Regain	DS	Dunk-N-Drain Absorbency Factor, g/g	Centrifuge Absorbency Factor, g/g
Water soluble #104	21.2	0.287	19.0-24.0	10.99*
Surface Gelling #109	9.4	0.099	9.5	2.17
Hygroscopic #106	7.9	0.002	10.2	1.52
Untreated (control) gauze	6.6	---	7.5-9.0	1.10

*Part of the sample may be lost because it might have been solubilized.

Table 6. Test Results: Modified Dunk-And-Drain.

Sample	Water Absorbed (g/g)	Remarks
#112-CA-10-1HR	11.1	Gels, has one-time-use, wet integrity
#113-0-Control	20.65	Water soluble, disintegrates in excess water
Algosteril	19	No gelling, very good wet integrity
Kaltostat	20	More gelling, wet integrity

Time of testing: 130 sec

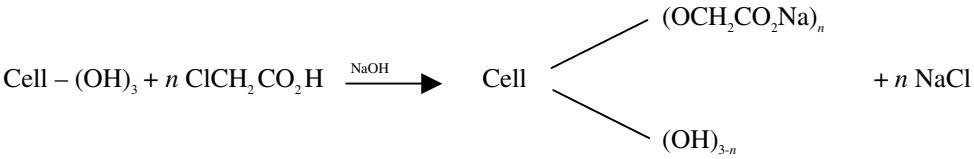

Figure 1. CM Reaction.

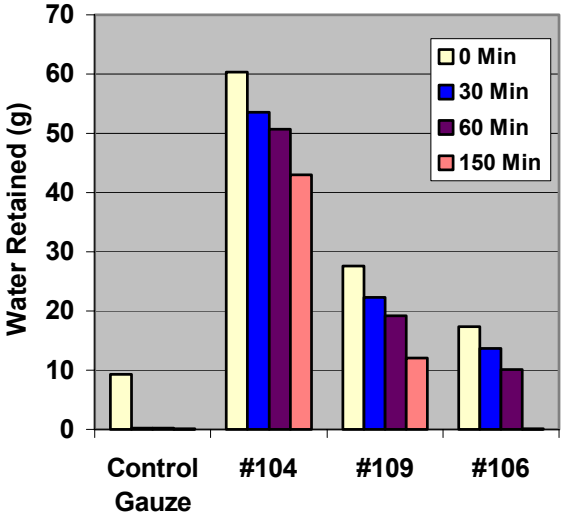

Figure 2. Wet Dunk-And-Drain Samples in water, dried at 100° F for specified times.

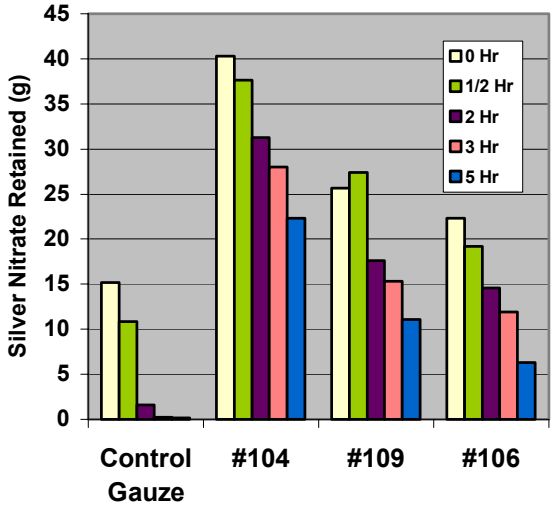

Figure 3. Wet Dunk-And-Drain Sample in silver nitrate, dried at 100° F for specified times.

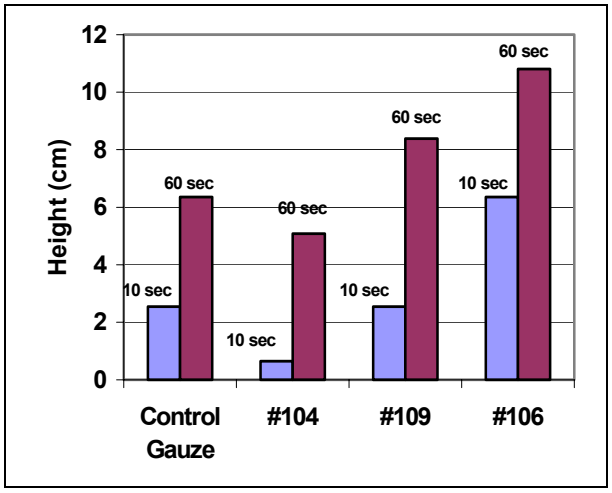

Figure 4. Wicking height (cm) for sample strips (18cm x 2.6cm).

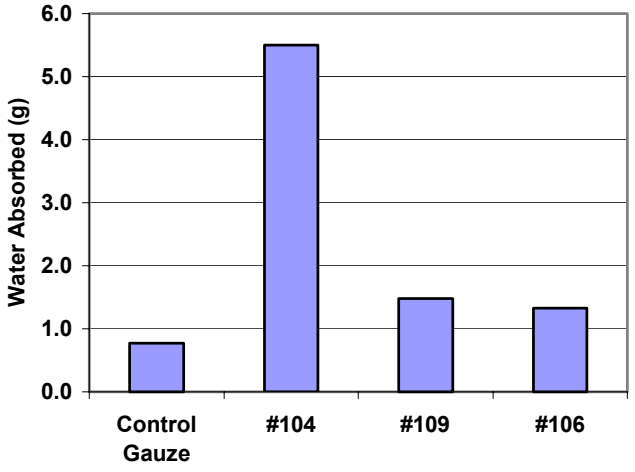

Figure 5. Water absorbed (g) during wicking.

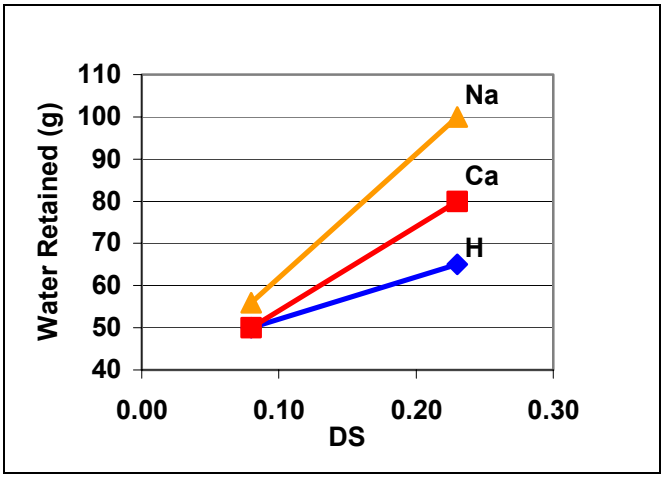

Figure 6. DS Dependence: Water retained and salt type (Na, Ca, H) of CM-cotton.