



Published in final edited form as:

*Ocul Surf.* 2019 April ; 17(2): 360–364. doi:10.1016/j.jtos.2019.02.005.

## The Optimum Temperature for the Heat Therapy for Meibomian Gland Dysfunction

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### Abstract

**Purpose**—Numerous devices have been developed to warm the eyelid as a therapy for Meibomian gland dysfunction. The optimum temperature for such therapy was determined.

**Methods**—Meibum lipid disorder versus temperature was calculated from previously published phase transition parameters measured using infrared spectroscopy. Phase transition parameters were calculated from meibum obtained from donors with Meibomian gland dysfunction ( $M_{MGD}$ ), donors who were susceptible to dry eye after hematopoietic stem cell transplantations ( $M_{HSCT}$ ) and meibum from donors without dry eye ( $M_n$ ).

**Results**—Heating  $M_n$  to 40 °C increases the lipid disorder by 20.4% to 90 %. Heating the meibum another 4 degrees increases the disorder to 95%.  $M_{MGD}$  is 73.2 % disordered with no heating. Heating  $M_{MGD}$  to 41.5 °C increases the disorder by 26.8 % to 90 % disordered. Heating  $M_{MGD}$  another 5.1 °C increases the disorder to 95%. As meibum from donors who had hematopoietic stem cell transplantations,  $M_{HSCT}$ , is much more ordered, 56.9 % disordered compared with  $M_n$  and  $M_{MGD}$ , a higher temperature above safety limits, 52 and 59 °C is need to disorder  $M_{HSCT}$  to 90 and 95% disorder.

**Conclusions**—Heating the eye lid above the phase transition temperature of meibum increases the disorder of meibum lipid which could ameliorate dry eye symptoms. The optimum temperature for disordering  $M_n$  and  $M_{MGD}$  to 90% maximum disorder is 40 and 41.5 °C, respectively. Safety issues and discomfort should be considered in obtaining an optimal level of disorder, especially for severe cases of dry eye.

### Keywords

Dry Eye; Heat Therapy; Infrared Spectroscopy; Meibum; Phase Transition

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## Introduction

Dry eye affects 5 to 30% of people internationally and meibomian gland dysfunction is the leading cause.<sup>1</sup> Meibomian gland dysfunction (MGD) occurs when the meibomian glands become blocked and are incapable of delivering lipid to the tear film surface. Upon blockage, inflammation ensues exasperating dry eye symptoms such as foreign body sensation, itching and burning. Dry eye can lead to visual impairment and reduced quality of life.<sup>2,3</sup>

Conventional therapy of MGD includes lid expression and massage, thermal treatments and medicinal therapy.<sup>4</sup> Elevated eyelid temperature delivers more meibomian oil to the eyelid.<sup>5</sup> Numerous devices have been developed to warm the eyelid<sup>6–21</sup> and the warming relieves dry eye symptoms,<sup>13,15–18,21</sup> improves meibum score,<sup>11,15,16</sup> increases tear breakup time,<sup>11,15–17</sup> and tear lipid layer thickness<sup>14</sup> and ameliorates dry eye related morphological changes in the meibomian gland.<sup>11,16–18</sup> One study found that heating did not improve their breakup time or lipid layer thickness.<sup>14</sup> Too high of a temperature should be avoided as heat could cause injury to the eyelid skin,<sup>22</sup> increase vulnerability to the corneal molding,<sup>23,24</sup> and contribute to presbyopia and cataract.<sup>25</sup>

Insights regarding the effect of temperature on the structure and ‘melting’ of meibum can be gleaned from the most comprehensive study of the phase transition characteristics of meibum that used Fourier transform infrared spectroscopy (FTIR) to follow the order to disorder transition of meibum with temperature.<sup>26</sup> FTIR could be used to measure lipid conformation with as little as 0.1 mg of meibum. Conformation is defined as the arrangement of atoms in a molecule that differ by rotation about a single double bond. Hydrocarbon chain conformation is important to the order (fluidity), strength of lipid-lipid interactions, and lipid structure in general. The frequency of the symmetric CH<sub>2</sub> stretching band near 2850 cm<sup>-1</sup> ( $\tilde{\nu}_{\text{sym}}$ ) was used to estimate the *trans* to *gauche* rotamer content of the hydrocarbon chains (Fig. 1a and b),<sup>27</sup> and it increased with an increase in temperature (Fig. 1c) concurrent with a decrease in intensity.<sup>27,28</sup>

Meibum conformation has been measured in human meibum<sup>29,30</sup> with age,<sup>26,27,31,32</sup> and MGD,<sup>26,33,34</sup> dry eye associated with hematopoietic stem cell transplantation<sup>26</sup> and to measure the influence of makeup,<sup>35</sup> sebum,<sup>36</sup> squalene<sup>37</sup> and treatment efficacies for dry eye.<sup>38,39</sup> Lipid saturation was the major factor that contributed to lipid order and thermodynamics.<sup>22,40</sup>

The phase transition temperature (T<sub>t</sub>) is the temperature where half of the lipids that that undergo a phase transition are melted. The T<sub>t</sub> measured by FTIR spectroscopy of meibum from donors without dry eye (Mn) is 30.3 °C, similar to that measured by microscopy,<sup>41</sup> 32.1 ± 0.1 °C, birefringence,<sup>42</sup> 32 ± 2 °C, DSC,<sup>43</sup> 30.2 ± 0.1 °C, reflectance,<sup>44</sup> 32 ± 1 °C, 34 ± 1.3<sup>45</sup> and observation 35–40,<sup>49</sup> 35 – 40 °C,<sup>50</sup> 32 – 36 °C,<sup>51</sup> 32–39 °C, and 35–40 °C,<sup>46</sup> and 34 ± 1.3<sup>45</sup> for meibum from patients with MGD (M<sub>MGD</sub>). The T<sub>t</sub> for meibum was slightly lower than that of the surface temperature of the eye, 33.4 °C, and eye lid, 36 °C.<sup>47</sup> The T<sub>t</sub> increases with MGD<sup>26,33,34,46</sup> and decreases with age.<sup>26,27,32,32</sup> Elevated % *trans* rotamers as a result of an increase in T<sub>t</sub> and a decrease in cooperativity are likely to cause

gross changes in the structure and properties of meibomian films at the air/tear surface in *vivo*. Ordered lipids may form discontinuous patchy tear film lipid layers which in turn will result in deteriorated spreading,<sup>53</sup> decreased surface elasticity and attenuated capability to restore its structure between blinks. This topic has been reviewed.<sup>54</sup>

In this study, the optimal temperature for melting 90 to 95 % of the meibum lipid was calculated retrospectively from phase transition parameters measured previously.<sup>26,34</sup>

## Methods

Lipid order at a selected temperature was calculated from the average phase transition parameters given in Table 1 using the following equation from citation 26:

$$Order = (2855.36 - (min + ((max - min)/(1 + (T/Tt)^{hill}))))/7.36 * 100 \quad \text{Equation 1:}$$

Where order is % *trans* rotamers, min is the minimum  $\tilde{\nu}_{sym}$ , max is the maximum  $\tilde{\nu}_{sym}$ , T is the temperature in °C, hill is the relative cooperativity, Tt is the transition temperature in °C. Lipid disorder, % *gauche* rotamers, at 36 °C, the temperature of the eye lid was calculated from lipid order using the following equation:

$$disorder = 100 - order \quad \text{Equation 2:}$$

The % maximum change was calculated by adjusting the disorder scale so that the minimum disorder at about 20 % is 0 % and the maximum disorder at about 80 % is 100 %. Maximum change was calculated from the following equation and plotted versus temperature in Figures 2 B and C:

$$\% \text{ maximum change} = (disorder - disorder \text{ min})/(disorder \text{ max} - disorder \text{ min}) * 100$$

Equation 3:

Where disorder is the disorder at a select temperature calculated from equation 2, disorder min is the minimum disorder at the minimum  $\tilde{\nu}_{sym}$ , disorder max is the maximum disorder at maximum  $\tilde{\nu}_{sym}$ .

The temperature at 90 and 95 % maximum disorder was calculated by extrapolation from the curves in Figures 2 B and C.

## Collection of Meibum

Meibomian glands were expressed by lightly compressing the eyelids with strict attention to avoid touching the eyelid margin during expression. All four eyelids were expressed, and approximately 0.5 mg of meibum was collected per individual. The expressate was collected

with a platinum spatula and dissolved in a vial of chloroform. None of the samples were pooled. Participants were recruited from the Kentucky Lions Eye Center and the James Graham Brown Cancer Center in Louisville, Kentucky. Written informed consent was obtained from all donors and protocols and procedures were approved by the University of Louisville Institutional Review Board Institutional Review Board # 11.0319, August, 2016. All procedures were in accordance with the Declaration of Helsinki.

### Diagnosis of Normal and Dry Eye Status

Clinical diagnosis parameters of dry eye can be found in citation 34 as copied briefly below. Normal status was assigned when the patient's meibomian gland orifices showed no evidence of keratinization or plugging with turbid or normal status was assigned when the patient's meibomian gland orifices showed no evidence of keratinization or plugging with turbid or thickened secretions, and no dilated blood vessels were observed on the eyelid margin. Normal donors did not recall having dry eye symptoms. Plugging of the meibomian glands in at least 5 of 10 orifices in the central portion of the upper eyelid was a requirement for diagnosis. The character of meibomian gland-expressed secretion had to be turbid, turbid with clumps, or paste like. Inflammation of the eyelid margin, as evidenced by swelling of the eyelid margin and 2+ vascular injection of the posterior lid margin, was necessary for diagnosis. Symptoms were measured on a four-point categorical scale of none, mild, moderate, or severe, according to the subject's response to questions regarding itching, burning, foreign body sensation, eyelid redness, and eyelid swelling. Signs evaluated were slit lamp-observed conjunctival injection, fluorescein tear breakup time, ocular surface staining with fluorescein, appearance of the eyelid margin, and character of meibomian gland orifices. Donors of  $M_{HSCT}$  were diagnosed with MGD and aqueous deficient dry eye based on Schirmer's strip test.

### Results

Lipid disorder begins to increase around 20 °C, where about 20 % of the lipid is disordered. Maximum disorder is reached between 40 and 50 °C, where about 80 % of the lipid is disordered (Fig. 1 A). Table 2 lists the average % of maximum disorder of meibum. Table 2 results are discussed: At 36 °C, the temperature of the meibomian gland, the % maximum lipid disorder of  $M_n$  is 79.6. Heating  $M_n$  to 40 °C increases the % of maximum lipid disorder by 20.4% to 90 %. Heating the meibum another 4 degrees increases the % of maximum disorder to 95%.  $M_{MGD}$  is at 73.2 % of maximum disorder with no heating. Heating  $M_{MGD}$  to 41.5 °C increases the % of maximum disorder by 26.8 % to 90 % disordered. Heating  $M_{MGD}$  another 5.1 °C increases the % of maximum disorder to 95%. As  $M_{HSCT}$  is much less disordered, 56.9 %, compared with  $M_n$  and  $M_{MGD}$ , higher temperatures, 51.5 and 59 °C are needed to disorder  $M_{HSCT}$  to 90 and 95% of maximum disorder, respectively.

As  $M_n$  is 66.3 % disordered at 36 °C, the temperature necessary for  $M_{MGD}$  and  $M_{HSCT}$  to reach the disorder level of  $M_n$  is 38.5 °C and 42.0 °C.

## Discussion

As discussed in the Introduction, heating the eye lid is a therapy for dry eye. The effects of eye lid warming devices on tear film parameters have been reviewed in this journal.<sup>55</sup> It is reasonable to speculate that the heating ‘melts’ the meibum lipid, unblocking the meibomian glands and ameliorating the inflammation caused by the blockage. Melting should not be used to describe meibum fluidity changes since melting is associated with a phase change from solid to liquid. However, meibum is not a solid at low temperatures, but in a gel phase that is 20 % disordered. Furthermore, meibum is not a liquid at higher temperatures, but in a liquid crystalline phase that is about 80 % disordered. That is why the physical biochemists use the term ‘gel to liquid crystalline phase transition’ instead of ‘melting’.

The current study suggests the optimum temperatures for disordering Mn and M<sub>MGD</sub> to 90% maximum disorder is 40 and 41.5 °C, respectively (Table 2). As can be seen in Figure 2, at temperatures near the plateau of disorder there is a minimal increase in disorder with changes in temperature. Heating the meibum another 4 °C above the temperatures listed above only results in 5% more disorder. Given that there is a 5 °C difference in temperature between heat applied on the external eyelid surfaces and that which reaches the inner surface of the lids where the meibum is located,<sup>48</sup> to obtain 90 % disorder, the optimal applied heat must be 45 to 46.5 °C at the surface of the eye lid for Mn and M<sub>MGD</sub>, respectively. At temperatures above 45 °C, discomfort and safety are a factor to consider.<sup>22–25</sup> However sub optimal temperatures are still effective since the T<sub>t</sub> of meibum is 30 to 32 °C and heating the eye lid to temperatures above the T<sub>t</sub> results in significant disordering of the lipid. It should be noted that heating M<sub>MGD</sub> just 2.5 °C to 38.5 °C disorders M<sub>MGD</sub> to 66 %, the level of disorder of Mn.

The optimal temperature for disordering M<sub>HST</sub> to 90% maximum disorder is 52 °C (Table 2), so a surface temperature of 57 °C is need. The higher temperature is due to due to a high T<sub>t</sub> (34 °C) and broad phase transition due to low cooperativity (Hill coefficient). Discomfort and safety prohibits heating the eye lid surface to the optimal temperature of 57 °C. Perhaps the high temperature needed for severe cases of dry eye, as with M<sub>HST</sub>, could limit the success of heat therapy in this cohort and others. It should be noted that heating M<sub>HST</sub> 6 °C to 42 °C disorders M<sub>MGD</sub> to 66 %, the level of disorder of Mn.

In conclusion, the current study indicates that heating the eye lid above the T<sub>t</sub> of meibum which is 30 to 34 °C, increases the disorder of meibum lipid which could ameliorate dry eye symptoms. Safety issues and discomfort should be considered in obtaining an optimal level of disorder, especially for severe cases of dry eye.

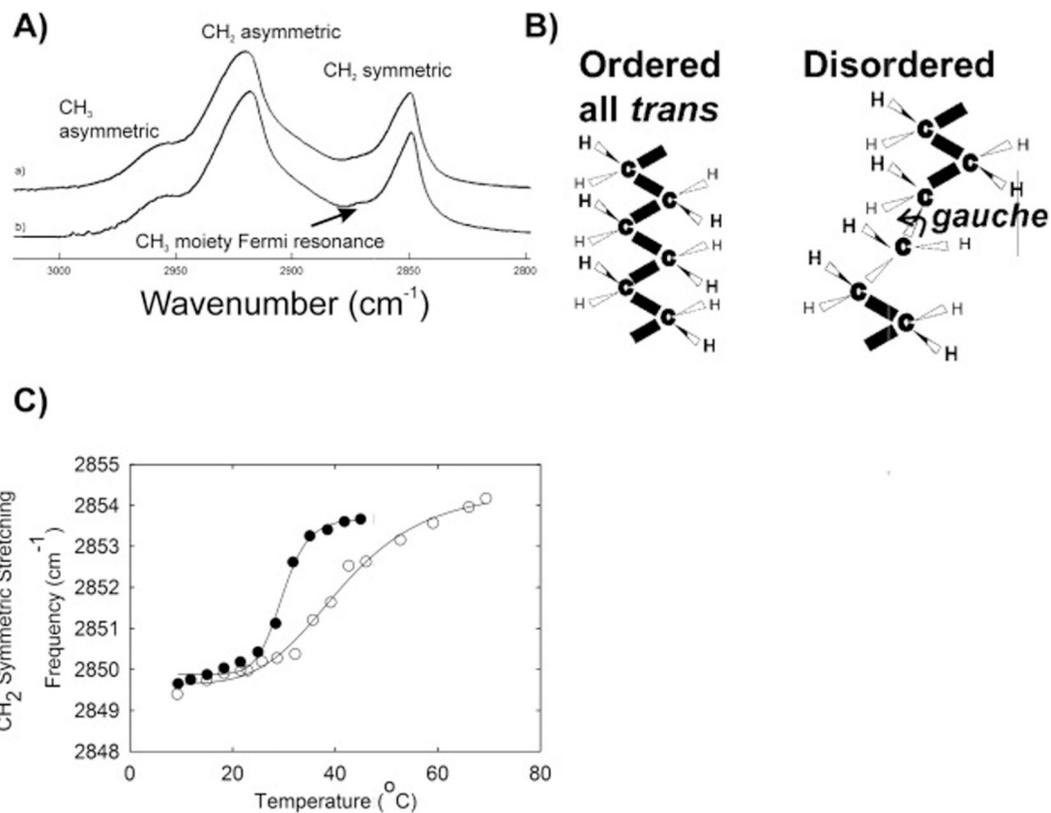
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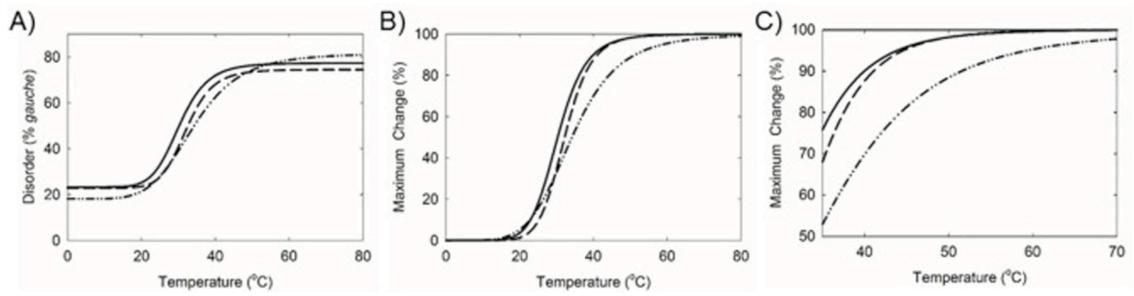
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**Figure 1.**

a) Infrared spectra of the CH stretching region at  $22^{\circ}\text{C}$  of a typical 36 year-old Caucasian adolescent female without dry eye (top), and a typical 31 year-old Caucasian adolescent female with dry eye and Hematological Stem Cell Transplantations (bottom). b) Schematic showing *trans* and *gauche* conformations in lipid hydrocarbon chains. The greater the number of *trans* rotamers, the tighter the lipids pack, the stronger the van der Waals forces, the greater the lipid order and higher the lipid phase transition temperature.

Copied from citation 26.



**Figure 2.**

Human meibum average phase transitions calculated from the parameters in Table 1. (—) meibum from donors without dry eye. (---) meibum from donors with meibomian gland dysfunction. (- · -) meibum from donors who had hematological stem cell transplantations.

**Table 1.**

Phase transition parameters from citation 26.

Parameter	Source of Meibum		
	Without dry eye	Hematopoietic Stem Cell Transplantations	Meibomian Gland Dysfunction
Transition Temperature ( °C)	30.3 ± 0.4	34.2 ± 0.9	32.2 ± 0.6
Cooperativity (Hill coefficient)	7.9 ± 0.4	5.4 ± 0.3	9.0 ± 0.4
Order 36.0 °C (% <i>trans</i> )	35 ± 1	48 ± 2	40 ± 2
Order 33.4 °C (% <i>trans</i> )	40 ± 1	54 ± 2	44 ± 1
enthalpy (kcal/mol)	142 ± 6	121 ± 7	153 ± 7
entropy (kcal.mol/degree)	0.48 ± 0.02	0.39 ± 0.02	0.49 ± 0.02
Magnitude (cm <sup>-1</sup> )	4.0 ± 0.1	4.7 ± 0.5	3.8 ± 0.6
Minimum Frequency (cm <sup>-1</sup> )	2849.71 ± 0.06	2849.33 0.06	2849.68 ± 0.06
Maximum Frequency (cm <sup>-1</sup> )	2853.69 ± 0.09	2854.00 ± 0.09	2853.48 ± 0.08
Order 33.4 °C – 36.0 °C (% <i>trans</i> )	4.8 ± 0.2	5.4 ± 0.2	5.9 ± 0.3
n	35	23	48

± standard error of the mean

**Table 2.**

## Meibum Hydrocarbon Disorder Parameters

<b>Cohort:</b>	<b>No Dry Eye</b>	<b>Meibomian Gland Dysfunction</b>	<b>Hematopoietic Stem Cell Transplantations</b>
Disorder at 36 °C (% <i>gauche</i> )	66 ± 2	61 ± 2	54 ± 3
% of Maximum Disorder at 36 °C	80 ± 2	73 ± 2	57 ± 3
Temperature at 90% Maximum Disorder (°C)	40 ± 2	41 ± 2	52 ± 3
Temperature at 95% Maximum Disorder (°C)	44 ± 2	45 ± 2	59 ± 3
Temperature at 66 % Disorder (°C)	36 ± 2	42 ± 2	39 ± 3
n	35	48	23

± 90% confidence limit from the Student's t distribution curve