Señores:

Superintendencia de industria y comercio.

Dirección de nuevas creaciones

E S D

Asunto: Respuesta requerimiento de fondo expediente NC2017/0003295

Yo Edgar Giovanny Acosta Gil, actuando como representante legal de la empresa especialidades Oftalmológicas S.A y en calidad de solicitante del documento NC2017/0003295 doy respuesta al requerimiento de fondo con oficio 841 y señalo lo siguiente**:**

Concerniente a la novedad.

Si bien la novedad no fue afectada, hacemos hincapié en este documento sobre los puntos que nos dan grandes diferencias sobre la materia previa:

De acuerdo a lo expresado en el oficio N° 841 de la superintendencia de industria y comercio, es importante resaltar que la patente US20080021101 no revela una composición igual a la nuestra, por lo anterior relacionaremos a continuación los aspectos diferenciadores de nuestra intención de patente y la patente cuyo fundamento se presentó como evidencia de oposición por parte de Procaps:

COMPARACIÓN PATENTE US2008/002110 A1 **"UN MÉTODO PARA PREPARAR UNA SOLUCIÓN OFTÁLMICA DE LATANOPROST Y SOLUCIÓN RESULTANTE" Y** EL EXPEDIENTE NC2017/0003295 **"VEHÍCULO FARMACÉUTICO PARA ESTABILIZAR LA SUPERFICIE OCULAR EN FORMULACIONES DE COLIRIOS PARA USO CRÓNICO"**

UN MÉTODO PARA PREPARAR UNA SOLUCIÓN OFTÁLMICA DE LATANOPROST Y SOLUCIÓN RESULTANTE US2008/002110 A1	**VEHÍCULO FARMACÉUTICO PARA ESTABILIZAR LA SUPERFICIE OCULAR EN FORMULACIONES DE COLIRIOS PARA USO CRÓNICO**
Se describe un **método para solubilizar** un agente activo **análogo de la prostaglandina F2α**, tal como **latanoprost**, y **un método para preparar una solución oftálmica acuosa** a partir	La presente invención corresponde a un **vehículo**, conformado por excipientes farmacéuticos aceptados, los cuales pueden ser utilizados para el **desarrollo de formulaciones oftálmicas en**

del latanoprost solubilizado para el tratamiento de diversas afecciones oculares. La presente invención concierne además a una solución oftálmica acuosa que resulta del método referido, la cual se caracteriza por su estabilidad química a temperatura ambiente, seguridad, inocuidad y eficacia en el tratamiento del paciente. La nueva solución oftálmica acuosa se distingue porque su valor farmacéutico radica en el manejo de **un vehículo de fácil acceso que no solamente permite la solubilidad del latanoprost sino que también favorece su estabilidad química** y una mayor tolerancia del paciente a su aplicación oftálmica para el tratamiento de su padecimiento.	**forma de solución o suspensión**, especialmente para **medicamentos oftalmológicos crónicos** como los antialérgicos, los antiglaucomatosos y los lubricantes oculares, brindando las características fisicoquímicas adecuadas y adaptables a las necesidades propias del paciente, **conservando la integridad de la superficie ocular.** Estas composiciones tienen como núcleo de su invención el **uso de 2-Hidroxipropilbetaciclodextrina, Ácido Sórbico, Hialuronato de sodio, Carboximetilcelulosa Sódica, Cloruro de Sodio, NaOH o HCL para ajuste de pH y Agua para inyección (WFI).**
El objetivo de la presenta invención es lograr con la incorporación de la Hidroxipropilbetaciclodextrina y el Hialuronato de Sodio en la solución oftálmica un **ambiente beneficioso y protector para la molécula de Latanoprost, reduciendo la descomposición y protegiendo al activo lábil en un ambiente acuoso.** Donde: la **Hidroxipropilbetaciclodextrina aloja el activo en la cavidad lipofílica** y contribuye a la solubilidad en agua y el **Hialuronato de Sodio envuelve al complejo formado**.	La presente invención corresponde a un vehículo farmacéutico para uso en colirios, conformado por excipientes que **restituyen y protegen** las **propiedades fisicoquímicas de la lágrima natural**, este **vehículo** puede ser utilizado **para el desarrollo de cualquier medicamento oftálmico**, para el tratamiento de patologías o alteraciones oculares en forma de solución o suspensión, especialmente para medicamentos oftalmológicos crónicos como los antialérgicos, los antiglaucomatosos, los lubricantes oculares o **cualquier otra patología ocular crónica**. En nuestro caso el **Hialuronato de Sodio se utiliza para proporcionar estabilidad en la interfase de la película lagrimal, mejorando el grado de humectación y la integridad de la superficie ocular**, ya que el Hialuronato de Sodio como tal, es un polímero que se adhiere al epitelio de la córnea, incrementando el tiempo de ruptura de la película lagrimal produciendo un alivio casi instantáneo

	de los síntomas asociados a la sequedad.
En una modalidad preferida de la invención, la solución oftálmica acuosa se caracteriza porque comprende: **latanoprost** en una concentración del **0.005%;**	Nuestra invención corresponde a un **vehículo farmacéutico**, al cual puede incorporarse una **variada cantidad de activos**;
un sistema **amortiguador de pH** que puede ser ácido bórico, ácido cítrico, ácido sórbico, ácido acético, borato de sodio, fosfato monobásico de sodio, fosfato dibásico de sodio, citrato de sodio y acetato de sodio, en un rango de concentraciones que van de 0.001% al 5.0%;	Para regular el valor de pH se utiliza **HCl 10 % o NaOH 10 % c.s.p** para obtener un rango de 5.0 – 7.8 unidades de pH;
uno ó más agentes que incrementen la viscosidad como **hidroxipropilmetilcelulosa, carboximetilcelulosa, metilcelulosa, alcohol polivinílico, hialuronato de sodio, condrointin sulfato, glicerina, glicerol formal, metilidinoglicerol**	Específicamente la invención incluye dentro de sus componentes dos lubricantes dentro del vehículo, los cuales son: **Carboximetilcelulosa Sódica o Hidroxipropilmetilcelulosa** a una concentración entre el 0.2% – 0.3% e **Hialuronato de Sodio** a una concentración entre el 0.15% - 0.20%, los cuales proporcionan estabilidad en la interfase de la película lagrimal, mejorando el grado de humectación y la integridad de la superficie ocular.
y **ciclodextrinas**, en concentraciones que van del **0.05% al 20.0%;**	La concentración de **2-Hidroxipropilbetaciclodextrina** va desde **el 2.0 % - 8.0 %.**
uno ó más agentes **tensoactivos**, humectantes como **polioxil 40 estearato, polisorbato 80, poloxamer y tiloxapol**, en concentraciones que van de **0.01%** al **20.0%**;	Como agente **tensoactivo y osmoregulador** se encuentra el **sorbitol** a concentraciones de **0.2% - 1.0 %.**
uno ó más agentes **reguladores de osmolaridad** como **cloruro de sodio, sorbitol, manitol y dextrosa en una**	Como agentes **reguladores de Osmolaridad** se listan el **Cloruro de Sodio** a concentraciones de **0.4%-**

concentración dentro del rango de 0.6 % a 1.8% expresado como equivalentes químicos de cloruro de sodio;	**1.0%, Sorbitol** a concentraciones de **0.2%-1.0%.**
uno o más **conservadores** como **cloruro de benzalconio, cloruro de benzetonio, tiomersal, nitrato o acetato fenilmercúrico, parabenos, gluconato de clorhexidina, alcohol etílico, cetrimida, perborato de sodio y clorobutanol** en concentraciones adecuadas para proporcionar el efecto antimicrobiano.	Nuestro vehículo cuenta con un perfil de seguridad favorable, pues incluye un **preservante natural como el Ácido Sórbico,** en concentraciones de **0.05% - 0.2%** que no presenta los efectos adversos a nivel corneal como otros preservantes por lo general usados como son el caso del Cloruro de Benzalconio, polyquaternium-1, Thimerosal, Clorobutanol, parabenos, entre otros que generan graves daños al tejido ocular.
Además, puede contener uno o más **agentes antioxidantes** como edetato disódico, metabisulfito de sodio, bisulfito de sodio, acetilcisteina, tiosulfato de sodio y tiourea en concentraciones adecuadas para dar el efecto requerido.	**No contiene agentes antioxidantes** incorporados a la formulación.
cuentan con vehículos que pueden comprender el uso de preservantes tóxicos, tales como: Cloruro de Benzalconio, Timerosal, Metilparabeno, Propilparabeno y Clorobutanol, que genera efectos adversos al contacto con la superficie ocular.	Se hace referencia al daño ocular que producen ciertas sustancias que son utilizadas como excipientes en las formulaciones oftálmicas especialmente en tratamientos crónicos, como por ejemplo las preservadas con derivados del grupo de conservantes de los Amonios cuaternarios, al cual pertenecen entre otros el Poliquaternium-1 y el BAK (Cloruro de Benzalconio), los cuales inducen la toxicidad celular y el daño ocular en una forma dosis dependiente. **En nuestra invención, el único preservante utilizado Acido Sórbico**, a una concentración de 0.05 – 0.20 %, siendo reconocido como una sustancia segura por la FDA, otorgando un beneficio adicional a los pacientes.

Verifican la **estabilidad de la nueva solución oftálmica a patentar**, realizando estudios de estabilidad de tres lotes de producto, hasta un tiempo de 9 meses a dos condiciones de almacenamiento (refrigeración 2°C-8°C y temperatura de 15°C-30°C). Realizando la determinación de los siguientes parámetros: Apariencia, pH, Osmolaridad y Valoración de Latanoprost como indicativo de estabilidad, tomando como referencia la Farmacopea de los Estados Unidos Mexicanos y la United States Pharmacopeia.	**No se realizó estabilidad del vehículo**, ya que los parámetros físicos evaluados no son un atributo indicativo de estabilidad. Se hace énfasis en algunas de las características fisicoquímicas primordiales que deben prevalecer en una formulación en solución o suspensión oftálmica, para emular las condiciones de la lágrima natural y por ende evitar daños durante el tratamiento. Se evalúan la tensión superficial, Osmolaridad, viscosidad, utilizando metodologías descritas en la farmacopea de los estados unidos para el caso de la viscosidad y la osmolaridad, de acuerdo a lo descrito en los capítulos generales 911 y 785 respectivamente. Para la determinación de la tensión superficial se utilizó un método debidamente estandarizado.
Las especificaciones de estas variables fueron: <u>Apariencia</u> Solución viscosa, incolora, transparente y libre de partículas visibles, <u>pH</u> 6.2 – 7.2. <u>Osmolaridad</u> 250-350 mOsm/Kg, <u>latanoprost</u> 90.0 %-110.0% La invención no indica control de la viscosidad.	Las especificaciones de los parámetros evaluados fueron: <u>Tensión superficial:</u> Entre 38 - 45 Dinas/cm. <u>Osmolaridad:</u> 260 – 290 mOsm/L <u>Viscosidad:</u> Mayor de 9 milipoises, Nuestra invención está conformada por un vehículo en el cual se controlan no solo la osmolaridad, sino otros parámetros fisicoquímicos como la viscosidad y Tensión Superficial los cuales no son objeto de dicha patente. No se realiza control de pH pero se especifica que las composiciones pueden contener ácido clorhídrico (HCL) o hidróxido de sodio (NaOH) para regular el pH a valor entre 5.0 y 7.8, de acuerdo a las propiedades del ingrediente activo.

	No se cuantifican activos.
Se realizó un **estudio de estabilidad de** una solución oftálmica de latanoprost para verificar el comportamiento del producto identificado con la marca **XALATAN®** al someterlo a estabilidad y **compararlo** con la **formulación patentada**. Evidenciando que el contenido de latanoprost en la fórmula descrita y reivindicada en la presente solicitud muestra un comportamiento más uniforme que el XALATAN®.	**No se realiza comparación** con ningún otro producto del mercado, ya que nuestro interés radica exclusivamente en el desarrollo de un vehículo cuyas características fisicoquímicas emulen al máximo las características de la película lagrimal, de igual manera no se cuantifica ningún ingrediente activo, ya que no es el objeto de la presente invención.
En las reivindicaciones se hace referencia a: - Método para **solubilizar el latanoprost** para preparar una solución oftálmica acuosa *químicamente estable* para el tratamiento de diversas afecciones oculares, dicho método comprende: a) colocar en un recipiente 5.000 g de latanoprost; b) agregar al recipiente aproximadamente 15 L de una solución que contiene **7.5% de hidroxipropilbetaciclodextrinas, 0.7% de fosfato monobásico de sodio monohidratado, 0.6% de fosfato dibásico de sodio anhidro y 0.2% de hialuronato de sodio**, y agitar de 500 a 550 rpm para disolver el latanoprost; c) esperar a que se disuelva por completo y agregar a la solución de **0.005% a 0.02% de cloruro de benzalconio,** enjuagando siempre con la misma solución con que se disolvió el latanoprost; y d) agitar hasta que se homogeneice la solución. - Método para **preparar una solución oftálmica de Latanoprost**, químicamente estable a temperatura ambiente, para el tratamiento de	- **No se reivindica metodologia** relacionada con la **manufactura** de productos farmacéuticos. - En la reivindicación 1 se indica la composición del vehículo y el rango de porcentaje de cada uno de sus componentes: **2-hidroxipropilbetaciclodextrina: 2.00 – 8.00 %** **Hialuronato de Sodio 0.15 - 0.20 %** **Ácido Sórbico 0.05 - 0.20 %** **Sorbitol 0.20 - 1.00 %** **Principio Activo 0.01- 10 %** **Cloruro de Sodio 0.40 - 1.0%** **Agente Lubricante 0.1% - 0.3%** **Regulador De pH c.s.p.** **Agua c.s.p.** El contenido de Hialuronato de Sodio y de 2-Hidroxipropilbetaciclodextrina, indicado en las reivindicaciones mencionan un rango dentro del cual se encuentran los valores indicados para estos dos compuestos en la patente US2008/002110. Adicional al contenido de Hialuronato de Sodio, **se incluyen como agentes lubricantes la carboximetilcelulosa sódica o hidroxipropilmetilcelulosa o mezcla de los mismos.**

diversas afecciones oculares, dicho método comprende: a) solubilizar un agente análogo de prostaglandina, tal como latanoprost; b) preparar una solución acarreadora; y c) mezclar el latanoprost solubilizado y la solución acarreadora, y completar el volumen a 100 L con agua purificada mientras se agita constantemente por un periodo predeterminado. - **Método para preparar una solución oftálmica acuosa de latanoprost de** acuerdo con la reivindicación 2, en el que **la fase de solubilización del latanoprost comprende las siguientes etapas**: a) colocar 5.000 g de latanoprost en un recipiente de capacidad suficiente y agregar 15 L de una solución que contiene **7.5% de hidroxipropilbetaciclodextrinas, 0.7% de fosfato monobásico de sodio monohidratado, 0.6% de fosfato dibásico de sodio anhidro y 0.2% de hialuronato de sodio**, y agitar de 500 a 550 rpm para disolver el latanoprost; y b) esperar a que se disuelva por completo la solución anterior y agregar **de 0.005 a 0.02% de cloruro de benzalconio,** agitando por aproximadamente 5 minutos para que se homogeneice la solución. - Método para **preparar una solución oftálmica acuosa de latanoprost** de acuerdo con la reivindicación 2, en el que la fase de preparación de la solución acarreadora comprende las siguientes etapas: a) en un tanque de acero inoxidable, se vierten 70 litros de agua purificada a 30°C ± 2°C; b) se inicia agitación de 500 a 550 rpm y se mantiene constante durante todo el proceso de preparación;	- los agentes **reguladores de pH son el ácido clorhídrico (HCL) o hidróxido de sodio (NaOH)** para ajustar el pH a valores entre 5.0 y 7.8, ***no se incluyen soluciones buffer.***

c) **se agregan 7.5 Kg de hidroxipropilbetaciclodextrinas** manteniendo la agitación por aproximadamente 10 minutos para permitir que se disuelva; d) se agregan **700 g de fosfato monobásico de sodio monohidratado** y se espera aproximadamente 5 minutos a que se disuelva por completo; e) se agregan **600 g de fosfato dibásico de sodio anhidro** y se espera aproximadamente 5 minutos a que se disuelva por completo; f) se separan 30 L de esta solución para usarse en la fase de solubilización del latanoprost, y para los enjuagues posteriores, y al resto de la solución se agregan las siguientes materias primas: g) se agregan lentamente **200 g de hialuronato de sodio** manteniendo la agitación por 25 a 35 minutos; y h) se agregan **44 g de cloruro de benzalconio (solución 50%)** previamente disueltos en agua purificada y se espera aproximadamente 5 minutos a que se integre por completo. - Método **para preparar una solución oftálmica acuosa de latanoprost** de acuerdo con la reivindicación 2, en el que después de mezclar la solución de latanoprost y la solución acarreadora se continúa la agitación de 500 a 550 rpm por aproximadamente una hora - Método de las reivindicaciones 1 y 3 En el cual **la ciclodextrina es combinada con el latanoprost para ayudarlo a disolverse y para protegerlo de la hidrolisis**. Una solución oftálmica para el tratamiento de padecimientos oculares, preparados por medio de los métodos divulgados en las presentes reivindicaciones, que comprenden:	

el **medicamento análogo de la prostaglandina es el latanoprost, a una concentración de 0.005%.** **el agente solubilizante derivado de ciclodextrinas, a una concentración aproximada de 7.5 %** **El agente viscosante y lubricante, es el acido hialuronico al 0.2 %** **Sistema de control de pH es ejercido por Fosfato de Sodio y,** **El agente preservante es Cloruro de Benzalconio a una conecntración de 0.02 %**	
La solución oftálmica de la reivindicación 7, es químicamente estable a temperatura ambiente y no requiere refrigeración La solución oftálmica de la reivindicación 7, fue evaluada el contenido de Latanoprost en la solución a dieferentes temperaturas (2°C-8°C, 25°C, 30°C, 40°C), durante un periodo de tres meses, evidenciando que el contenido de Latanoprost se encuentra dentro de especificaciones.	**No se evalúa estabilidad** del producto respecto a diferentes temperaturas.
método para el tratamiento de pacientes con afecciones en el ojo, que comprende administrar una cantidad terapéuticamente adecuada al ojo de un paciente de una solución acuosa que incluye un análogo de la prostaglandina F2α. El método de la reivindicación 10, en el que el medicamento análogo de la prostaglandina F2α es el latanoprost	En nuestro caso los ingredientes activos que pueden acompañar este vehículo, corresponden a todos los que se encuentren debidamente autorizados por la entidad regulatoria para tratamientos oftalmológicos y que puedan ser formulados como soluciones o suspensiones oftálmicas en concentraciones terapéuticas, tales como: atropina, azelastina, azitromicina, azitromicina, bepotastina, brimonidina, brimonidina, brimonidina, brinzolamida, bromfenac, carboximetilcelulosa, carboximetilcelulosa, ciclopentolato,

El ingrediente activo al cual se hace referencia en todo el texto y de acuerdo a lo establecido en las reivindicaciones, es el Latanoprost a una concentración de 0.005%.	ciclosporina, ciprofloxacina, ciprofloxacina, cloranfenicol, cromoglicato, dexametasona, dexametasona, difluprednato, dorzolamida, dorzolamida, epinastina, fenilefrina, fenilefrina, fluoresceína, fluorometolona, fluorometolona, fluorometolona, gatifloxacina, gatifloxacina, gatifloxacina, gentamicina, hialuronato, hidroxipropilmetilcelulosa, ketorolaco, ketotifeno, ketotifeno, latanoprost, loteprednol, meloxicam, moxifloxacina,, nafazolina, ofloxacina, olopatadina, oximetazolina, pilocarpina, prednisolona, prednisolona, proparacaína, proparacaína, rebamipide, tetraciclina, tetrizolina, timolol, tobramicina, tobramicina, tobramicina, travoprost, tropicamida, tropicamida o sus posibles combinaciones. Caracterizado porque el principio activo puede ser una de sus sales farmacéuticamente activas.
La forma farmacéutica a la cual se refiere la patente es una SOLUCIÓN oftálmica	El vehículo es de utilidad tanto en SOLUCIONES como SUSPENSIONES oftálmicas.

Esta información es relevante a la hora de defender el nivel inventivo, el cual es el punto que expondremos a continuación:

Concerniente al nivel inventivo

Para evidenciar el efecto técnico sorprenden de nuestra formulación, se consultó el producto comercial derivado de la solicitud de patente US20080021101, para esto evidenciamos que los inventores forman parte del equipo de trabajo de laboratorio Sophia: el señor Arturo Jiménez Bayardo quien es el Director y el señor Rubén Tornero Montaño, Director de Calidad.

Ver anexo 2. Relación de personal de laboratorios Sophia con la patente US20080021101.

Es por esta razón que teniendo en cuenta las características del vehículo que refiere nuestra intención de patente, realizamos los análisis fisicoquímicos de los parámetros que emulan las características de la película lagrimal en el producto GAAP ofteno (Latanoprost 0.005 %) de laboratorios Sophia, lote 4016594, fecha de fabricación 18/jul/17, fecha de vencimiento 18/jul/19.

Como puede observarse en el rotulado del producto, presentado a continuación, sus componentes se relacionan con lo establecido en la patente US20080021101, ya que indica como excipientes: *Hialuronato de Sodio, Hidroxipropilbetaciclodextrina, ácido bórico, borato de sodio decahidratado, Edetato disódico dihidratado, Cloruro de Benzalconio como conservador (Sol. al 50 %).* Adicional a lo anterior, *la temperatura de almacenamiento del producto es inferior a 30°C.*

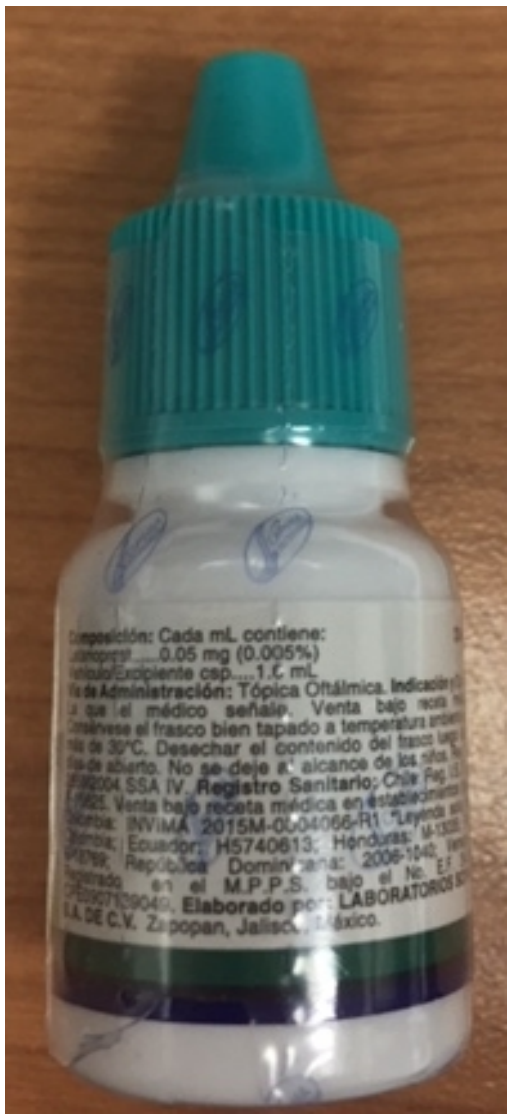
Ver figura 1. Fotografías del rotulado del producto GAAP ofteno.

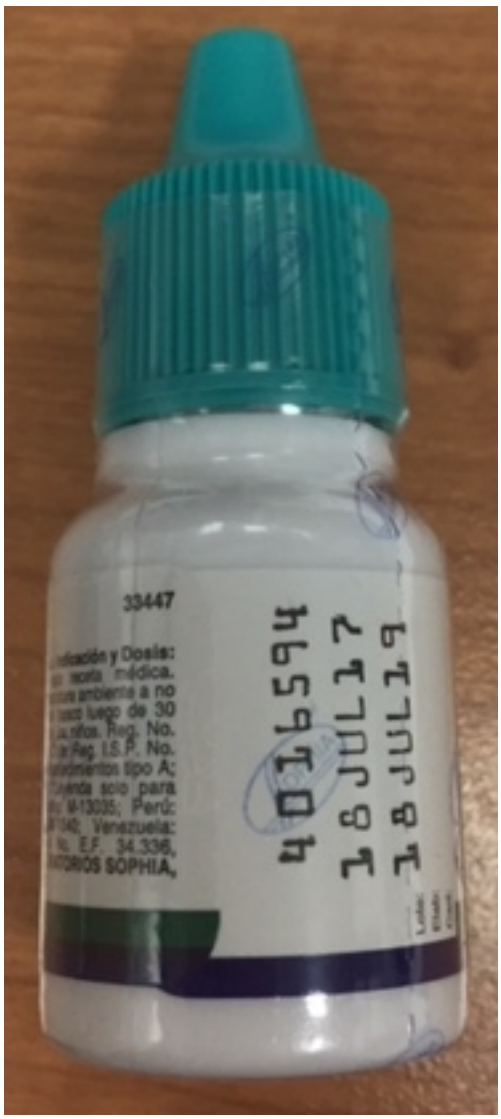
a)


Composición:
Cada mL (20 gotas) contiene:
Latanoprost.....0.05 mg (0.005%)
Vehículo csp.....1.0 mL
Excipientes: Hialuronato de sodio, hidroxipropilbetaciclodextrina, ácido bórico, borato de sodio decahidratado, edetato disódico dihidratado, cloruro de benzalconio como conservador (sol. al 50%), 0.2 mg/mL. Cada gota contiene aproximadamente 0.0025 mg de Latanoprost.
Vía de Administración: Tópica Oftálmica.
Indicación y Dosis: La que el médico señale.
Producto de uso delicado, adminístrese por prescripción y bajo vigilancia médica. Venta bajo receta médica. Consérvese el frasco bien tapado a temperatura ambiente a no más de 30°C. Desechar el contenido del frasco luego de 30 días de abierto. No se deje al alcance de los niños. Este producto no debe ser administrado durante el embarazo o cuando se sospeche su existencia, ni durante la lactancia. Para evitar contaminación, no toque ni ponga en contacto la punta del dispensador con cualquier superficie.
Para mayor información sobre indicaciones, dosis, contraindicaciones y advertencias, leer instructivo anexo.
Reg. No. 285M2004 SSA IV
Elaborado por:
LABORATORIOS SOPHIA, S.A. DE C.V.
Av. Paseo del Norte No. 5255,
Col. Guadalajara Technology Park,
C. P. 45010,
Zapopan, Jalisco, México.
Responsable Sanitario:
Q.F.B. José Rubén Tornero Montaño.
www.sophia.com.mx
GAAP
OFTENO
Latanoprost 0.005%
Solución Oftálmica Estéril
Caja con Frasco Gotero con 3 mL
MEDICAMENTO ESENCIAL*
SOPHIA
SOPHIA
Lote:
Elab:
Cad:
4016594
18/JUL/17
18/JUL/19
C19
1
33446
GAAP
OFTENO
Latanoprost 0.005%
Importado y Distribuido por:
LABORATORIOS OFTÁLMICOS S.R.L.
Solución Oftálmica Estéril
Caja con Frasco Gotero con 3 mL
MEDICAMENTO ESENCIAL*
SOPHIA
SOPHIA
Lote:
Elab:
Cad:
4016594
18/JUL/17
18/JUL/19
C19

b)







Una vez conocido el producto de referencia, realizamos los análisis fisicoquímicos de los **parámetros que emulan las características de la película lagrimal** en el producto GAAP ofteno (Latanoprost 0.005 %) de laboratorios Sophia, lote 4016594, fecha de fabricación 18/jul/17, fecha de vencimiento 18/jul/19.

Se evaluaron los parámetros de osmolaridad, Viscosidad y tensión superficial a productos de uso crónico de nuestros principales competidores (incluyendo el GAAP ofteno®), ya que estas son las características fisicoquímicas objeto de nuestra invención, que deben prevalecer en una formulación en solución o suspensión oftálmica, para emular las condiciones de la lágrima natural y por ende evitar daños en

la superficie ocular durante el tiempo en el cual se administre el medicamento. (ver tabla 1)

Se utilizaron metodologías de análisis descritas en la farmacopea de los estados unidos (USP) para el caso de la viscosidad y la osmolaridad, de acuerdo a lo descrito en los capítulos generales 911 y 785 respectivamente y el parámetro de tensión superficial fue evaluado con un método debidamente estandarizado y validado, ya que este no se incluye en ninguna de las farmacopeas aprobadas en Colombia.

Ver anexo 3. Metodologías de análisis descritas en la USP 40.

Tabla 1. Resultados de análisis viscosidad, Osmolaridad y tensión superficial en productos de uso crónico. (hoja siguiente)

Color rojo: resultado fuera del rango
Color verde: rangos y resultados acorde a parámetros establecidos
Color blanco: libre de preservantes
Color amarillo: no reporta

PRODUCTO	MARCA	LOTE	FECHA DE FABRICACIÓN	FECHA DE VENCIMIENTO	CANTIDAD (UNIDADES)	ACTIVO	CANTIDAD (Separador decimal es el punto)	TITULAR	REGISTRO	VISCOSIDAD mP	OSMOLALIDAD /OSMOLARIDAD mOsm/Kg	TENSIÓN SUPERFICIAL Dinas/cm	IPRESERVANTE
PARÁMETROS FLUIDO LAGRIMAL										**20 - 50**	**260 - 290**	**38 - 45**	
Ejemplo 1 Vehículo a patentar										**20**	**260**	**40**	**Ácido Sórbico**
Ejemplo 2 Vehículo a patentar										**22**	**270**	**41**	**Ácido Sórbico**
Ejemplo 3 Vehículo a patentar										**28**	**280**	**41**	**Ácido Sórbico**
Ejemplo 4 Vehículo a patentar										**25**	**290**	**42**	**Ácido Sórbico**
OLOFTAL 0.2% SOLUCION OFTALMICA	VISION	6P450B	OC 16	OC 18	1	OLOPATADINA CLORHIDRATO EQUIVALENTE A OLOPATADINA BASE	2,0 mg	TECNOQUIMICAS S.A	INVIMA 2011M-0012476	**0,9477**	**283**	**50,83**	**Contiene Cloruro de Benzalconio**
		7J360	AGO 2017	AGO 2019									
BRIMOFTAL® SOLUCION OFTALMICA	VISION	7M396B	SEP 2017	SEP 2019	2	BRIMONIDINA TARTRATO	2,0 mg	TECNOQUIMICAS S.A	INVIMA 2017M-0013147-R1	**1,7478**	**292**	**52,84**	**Contiene Cloruro de Benzalconio**
		6E303B	MY 16	MY 18	3								
KRYTANTEK OFTENO® LIBRE DE CONSERVADORES	SOPHIA	4016194	18/ABR/17	18/ABR/19	1	DORZOLAMINA CLORHIDRATO	20,0 MG	LABORATORIOS SOPHIA S.A. DE C.V.	INVIMA 2017M-0017885	**9,300**	**313**	**78,39**	**Libre de preservantes**
						TIMOLOL MALEATO 6,8 MG	5,0 MG						
						BRIMONIDINA TARTRATO	2,0 MG						
AGGLAD OFTENO ®	SOPHIA	4015466	19/SEP/16	30/SEP/19	2	TARTRATO DE BRIMONIDINA	2,0 MG	LABORATORIOS SOPHIA S.A. DE C.V.	INVIMA 2012M-0000802-R1	**1,3846**	**332**	**48,67**	**Contiene Cloruro de Benzalconio**
BIOFOCUS®	ABBOTT	7A5975	NO TIENE	07. 2019	2	TRAVOPROST	0,04 MG	LABORATORIOS SYNTHESIS S.A.S.	INVIMA 2015M-0016333	**2,9795**	**298**	**51,25**	**Libre de preservantes.**
						TIMOLOL MALEATO EQUIVALENTE A TIMOLOL	5 MG						
GANFORT UD SOLUCION OFTALMICA	ALLERGAN	E79942	NO TIENE	ENE 2019	5	BIMATOPROST	0,12 MG	ALLERGAN INC.	INVIMA 2014M-0015449	**0,7218**	**283**	**64,80**	
						TIMOLOL MALEATO 2,72 MG EQUIVALENTE A TIMOLOL BASE	2 MG						
LUMIGAN® UD	ALLERGAN	E79821	DIC 2016	JUN 2018	30	BIMATOPROST	0,12 MG	ALLERGAN INC	INVIMA 2015M-0016118	**0,7206**	**290**	**63,55**	**Libre de preservantes**
TRUSOPT® SOLUCION OFTALMICA 2%	MSD	M040389	NO TIENE	07 2018	1	DORZOLAMIDA CLORHIDRATO EQUIVALENTE A DORZOLAMIDA BASE 20 MG	22,26 MG	MUNDIPHARMA LABORATORIES GMBH	INVIMA 2007M-006524-R1	**6,583**	**282**	**49,56**	
ALAP 0.2%	PROCAPS	1164658 SL	NO TIENE	10 2019	1	OLOPATADINA CLORHIDRATO 2,2200 MG (EQUIVALENTE A OLOPATADINA BASE)	2 MG	PROCAPS S.A.	INVIMA 2008M-0008401	**0,8391**	**308**	**63,34**	
DORZOPT®	PROCAPS	1076238 SL	NO TIENE	06 2018	1	DORZOLAMIDA CLORHIDRATO 22,26 MG (EQUIVALENTE A DORZOLAMIDA BASE)	20 MG	PROCAPS S.A.	INVIMA 2013M-0002597-R1	**1,3259**	**283**	**44,21**	
		1168398 SL	NO TIENE	10 2019	1	TIMOLOL MALEATO 6,83 MG (EQUIVALENTE A TIMOLOL BASE)	5 MG						
AZARGA® SUSPENSION OFTÁLMICA ESTÉRIL	ALCON	65963	02 17	07 18	2	BRINZOLAMIDA	10 MG	LICHTSTRASSE 35 CH 4056, BASILEA SUIZA	INVIMA 2009M-0010040	**7,5546**	**286**	**47,74**	**Contiene Cloruro de Benzalconio**
						MALEATO DE TIMOLOL 6,8 MG EQUIVALENTE A TIMOLOL BASE	5 MG						
SIMBRINZA® SUSPENSION OFTALMICA	ALCON	17G12DE	NO TIENE	06 2018	2	BRINZOLAMIDA	10 MG	LABORATORIOS ALCON DE COLOMBIA S.A.	INVIMA 2015M-0016682	**6,7883**	**266**	**53,14**	**Contiene Cloruro de Benzalconio**
		17I06MI	NO TIENE	08 2018	1	BRIMONIDINA TARTRATO	2 MG						
LATANOX®	**PROCAPS**	1151126	NO TIENE	06/2019	1	LATANOPROST	50 mcg	PROCAPS S.A.	INVIMA2016M-0004180-R1	**10,28**	**271**	**36,316**	**Contiene Cloruro de Benzalconio**
GAAP OFTENO®	**SOPHIA**	4016594	18/JUL/2017	18/JUL/2019	2	LATANOPROST	50 mcg	LABORATORIOS SOPHIA S.A. DE C.V.	INVIMA2015M-0004066-R1	**1,692**	**349**	**67,644**	**Contiene Cloruro de Benzalconio**

De las anteriores pruebas y resultados se puede analizar lo siguiente:

El preservante empleado en los siguientes productos es Cloruro de Benzalconio:

El Cloruro de benzalconio ha sido uno de los preservantes más utilizados en las formulaciones oftálmicas, razón por la cual es el más estudiado. Como es bien sabido, este tipo de compuestos detergentes exhiben una cabeza hidrófila cargada positivamente y una parte hidrófoba sin carga, lo que permite su fijación en las membranas; así, las interacciones iónicas alteran de forma significativa la bicapa lipídica de las membranas plasmáticas. De este modo, es claro que los preservantes de naturaleza detergente pueden crear aberturas para las sustancias acuosas o iónicas en los espacios intracelulares o intercelulares. Estos efectos bastan para alterar de forma notable las células epiteliales y crear una penetración exagerada de fluido en el estroma, su hidratación y el desarrollo de un edema corneal.

Nuestro vehículo cuenta con un perfil de seguridad favorable, pues incluye un **preservante natural como el Ácido Sórbico,** en concentraciones de **0.05% - 0.2%** que no presenta los efectos adversos a nivel corneal como otros preservantes por lo general usados como son el caso del Cloruro de Benzalconio, polyquaternium-1, Thimerosal, Clorobutanol, parabenos, entre otros que generan graves daños al tejido ocular.

De los productos evaluados contienen Cloruro de Benzalconio:

PRODUCTO	**TITULAR**
OLOFTAL 0.2% SOLUCION OFTALMICA	VISION
BRIMOFTAL® SOLUCION OFTALMICA	VISION
AGGLAD OFTENO ®	SOPHIA
AZARGA® SUSPENSION OFTÁLMICA ESTÉRIL	ALCON
SIMBRINZA® SUSPENSION OFTALMICA	ALCON
LATANOX®	PROCAPS
GAAP OFTENO®	**SOPHIA**

Osmolaridad/Osmolalidad:

La propiedad de la osmolaridad es un factor crítico y determinante en cuanto a la protección de la superficie ocular y la estabilización de la película lagrimal, Es así, como nuestra invención reclama la composición como una solución hipoosmolar, con un valor específico de **260 y 290 mOsm/Kg o mOsm/L** para facilitar el paso del activo al lugar de acción y para proteger la superficie ocular además de estabilizar de la película lagrimal.

Los siguientes productos presentan un valor de Osmolaridad fuera de este rango:

PRODUCTO	**TITULAR**
OLOFTAL 0.2% SOLUCION OFTALMICA	VISION
KRYTANTEK OFTENO® LIBRE DE CONSERVADORES	SOPHIA
AGGLAD OFTENO ®	SOPHIA
BIOFOCUS®	ABBOTT
ALAP 0.2%	PROCAPS
GAAP OFTENO®	**SOPHIA**

<u>Tensión superficial</u>:

Para nosotros la tensión superficial es una propiedad fisicoquímica que constituye otro de los aspectos inventivos de la composición de la presente invención, puesto que coadyuva a distinguirla de otras composiciones convencionales de este tipo. En efecto, la tensión superficial constituye uno de los parámetros críticos y determinantes de la composición de la presente invención, en un valor de 38 a 45 dinas/cm, el cual es similar a la del fluido lagrimal, debido a que aumenta la permanencia del ingrediente activo en la superficie ocular e incrementa el tiempo de ruptura de la película lagrimal, protegiendo la superficie ocular.

De los productos evaluados los siguientes no presentan valores de tensión superficial dentro del rango establecido en nuestra invención:

PRODUCTO	**TITULAR**
OLOFTAL 0.2% SOLUCION OFTALMICA	VISION
BRIMOFTAL® SOLUCION OFTALMICA	VISION
KRYTANTEK OFTENO® LIBRE DE CONSERVADORES	SOPHIA
AGGLAD OFTENO ®	SOPHIA
BIOFOCUS®	ABBOTT
GANFORT UD SOLUCION OFTALMICA	ALLERGAN
LUMIGAN® UD	ALLERGAN
TRUSOPT® SOLUCION OFTALMICA 2%	MSD
ALAP 0.2%	PROCAPS
AZARGA® SUSPENSION OFTÁLMICA ESTÉRIL	ALCON
SIMBRINZA® SUSPENSION OFTALMICA	ALCON
LATANOX®	PROCAPS
GAAP OFTENO®	**SOPHIA**

viscosidad:

Con el vehículo desarrollado, objeto de nuestra invención, se proporcionan rangos de viscosidad que no generan visión borrosa, que oscila en un rango de 20 milipoises a 50 milipoises, es decir un colirio hiperviscoso ligero, que busca favorecer la lubricidad de la superficie ocular y al mismo tiempo ofrecer una mayor resistencia a la dilución de las lágrimas. Aportando un adecuado coeficiente de fricción, que estabiliza la película lagrimal, recuperando la viscosidad pérdida a causa de la patología, retardando su evaporación y permitiendo que se mezcle el medicamento con la unidad funcional lagrimal, sin interferir en la tensión superficial de la película lagrimal.

Ninguno de los productos evaluados se encuentra dentro del rango establecido en nuestra invención.

Ver anexo 4. Resultados de análisis productos de uso crónico evaluados.

CONCLUSIONES:

Lo primero que hay que resaltar es la necesidad biológica y fisicoquímica de las lágrimas naturales. Los componentes de las lágrimas generan que el ojo esté lubricado y sano de manera permanente en condiciones normales. La necesidad de tener una correcta homeostasis de la superficie ocular es primordial.

Sobre la superficie ocular siempre hay una pequeña cantidad de lágrimas llamada película lagrimal. Una buena salud ocular nos ayuda a tener nuestra película lagrimal en buenas condiciones y de forma recíproca una buena película lagrimal ayuda a tener nuestros ojos sanos. Cuando se utilizan medicamentos de uso crónico, lo ideal es que el vehículo del ingrediente activo no solo estabilice la molécula que ejerce la acción, sino que también ayude a restablecer la película lagrimal. Es por esta razón que nosotros desarrollamos en nuestra invención un vehículo farmacéutico cuya finalidad es emular las características de la película lagrimal, en sus propiedades fundamentales: osmolalidad, viscosidad y tensión superficial. A nivel de formulación lograr que estas tres variables se encuentren en un mismo producto es un logro sin precedentes, porque nunca antes no se había logrado equilibrar estos tres parámetros en un medicamento oftálmico.

Tal esta situación, que realizando una revisión de la ***farmacopea de los Estados Unidos de América USP 40***, encontramos que para el parámetro de Osmolaridad (ver capítulo 771) se encuentra una especificación bastante amplia de tonicidad (con respecto a una solución de Cloruro de Sodio al 0.5 % - 5%, equivalente aproximadamente a 171 – 1711 mOsm/Kg). **Allí se indica que las soluciones hipotónicas se toleran mejor que las soluciones hipertónicas**. Pero el rango de osmolaridad aquí expresado es alto y poco controlado.

Ahora bien, el parámetro de viscosidad se referencia como prueba específica en el capítulo 771 PRODUCTOS OFTÁLMICOS-PRUEBAS DE CALIDAD. En este ítem indican que la inclusión de la evaluación de este parámetro debe basarse en el tipo de forma farmacéutica y en si los cambios en la viscosidad del producto afectarán su desempeño. Esta no es una prueba farmacopéica, aunque forma parte de la especificación del fabricante del medicamento. No referencia especificación alguna, por lo cual es otro de los parámetros que no está controlado.

En el caso de la tensión superficial, la farmacopea NO establece este parámetro en ninguna de las pruebas universales y específicas para productos oftálmicos.

En contraste con lo descrito en la USP, la Tear Film & Ocular Surface Society (TFOS) en el Taller Internacional sobre Síndrome de Ojo Seco II (DEWS II) durante una sesión especial de la Reunión Anual de la Asociación para la Investigación en Visión y Oftalmología (ARVO), estableció la importancia de la osmolaridad y divulgó los valores medios de este parámetro en la película lagrimal, en pacientes que presentan alteraciones en la calidad del fluido lagrimal. En estudios hasta el año 2008 estos valores oscilaron entre 311 y 360 mOsm / L, con un promedio de 326.9 mOsm / L. Los valores promedio obtenidos en los estudios desde 2009 oscilan entre 297 y 337 mOsm / L, con una media general de 315. Se han informado valores más altos de osmolaridad de la película lagrimal dependiendo del grado de severidad del ojo seco. Estos valores demuestran que, si un producto oftálmico posee valores de osmolaridad mayores de 300 mOsm/L, estarían alterando notoriamente la homeostasis de la superficie ocular, por tal razón este parámetro representa un nivel de importancia alto y debe ser tenido en cuenta para el diseño y desarrollo de los medicamentos oftálmicos.

De igual manera, el TFOS indica que a nivel de la película lagrimal el parámetro de tensión superficial es relevante ya que mantiene la alta relación de aspecto de área a volumen de la película lagrimal. La tensión superficial del desgarro en individuos sanos es de 43.6 ± 2.7 mN / m (43.6 ± 2.7 dinas/cm) después de la deslipidación, que es notablemente cercana al límite superior de los valores observados en muestras recolectadas de pacientes con ojo seco, de 49.6 ± 2,2 mN / m (49.6 ± 2,2 dinas/cm). si los valores de este parámetro se encuentran en valores diferentes a los normales, se altera el tiempo de ruptura de la película lagrimal y genera cambios en las características lagrimales.

La Viscosidad también se encuentra referenciada y allí se indica que este parámetro contribuye a aumentar la resistencia de la película lagrimal al adelgazamiento y mejora la estabilidad de la película lagrimal, valores superiores a 50 milipoises generan inconvenientes en el campo visual.

Con lo mencionado demostramos que la osmolaridad, la viscosidad y la tensión superficial son tres parámetros que NO son obligatorios para el control de calidad de un producto terminado para uso oftálmico, pero SI son relevantes en el campo de la salud visual, ya que clínicamente se debe asegurar que la administración de un

medicamento oftálmico no altere la superficie ocular y mas teniendo en cuenta que son pacientes crónicos.

Ver anexo 5. Capítulo general Productos oftálmicos-pruebas de calidad.

Ver anexo 6. TFOS DEWS II, The Ocular Surface. Tear Film Report.

Concluyendo así:

1. Nuestra composición se encuentra correctamente limitada y el documento US20080021101 no afecta la novedad de la invención, ya que ésta no controla los parámetros de viscosidad, tensión superficial y Osmolaridad/Osmolalidad, los cuales son fundamentales para la homeostasis de la superficie ocular.

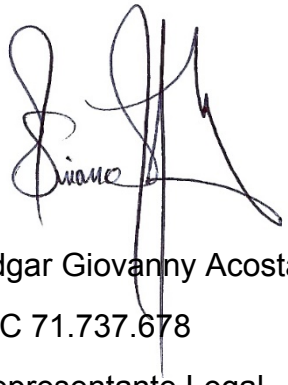
2. Queda demostrado con los resultados de los análisis realizados en el producto GAAP OFTENO® de Laboratorios Sophia, el cual fue desarrollado a partir de la patente de invención US20080021101, que no afecta la novedad ni el nivel inventivo de la presente solicitud, ya que nuestra solicitud de patente obedece a un al hecho de una formulación como “vehículo” y no sobre un activo.

3. Por lo anterior nuevamente se ratifica y se soporta con evidencia técnica comprobada y bibliográfica, que nuestra propuesta de formulación como un vehículo para la aplicación e integración de activos orientados a tratar patologías oftálmicas si cuenta con nivel inventivo, ya que de acuerdo a lo que se ha indicado, una persona medianamente versada en el tema no ve obvia la propuesta que tenemos, puesto que en los productos evaluados y en las referencias que el INVIMA establece, estos parámetros no se encuentran controlados, y para el caso de nuestra solicitud que se basa tanto en su aplicación como un “vehículo”, como en los controles que se tienen de este (osmolaridad, viscosidad y tensión superficial), los cuales permiten garantizar una integración adecuada y estable del activo, garantizando así seguridad al paciente, ya que además cuenta con conservantes naturales y está libre de sustancias con impacto negativo a largo plazo en la salud ocular.

Concerniente a las reivindicaciones:

De acuerdo a los requerimientos del examen de fondo se realiza la modificación de las reivindicaciones, las cuales son presentadas en el anexo 1.

Cordialmente,



Edgar Giovanny Acosta Gil

C.C 71.737.678

Representante Legal

Especialidades Oftalmológicas S.A

Anexos

Anexo 1. Reivindicaciones Modificadas

REIVINDICACIONES MODIFICADAS

1- Vehículo farmacéutico para estabilizar la superficie ocular en formulaciones de colirios para uso crónico caracterizado porque está conformado por los siguientes compuestos:

2-HIDROXIPROPILBETACICLODEXTRINA	2.00 - 8.00 %
HIALURONATO DE SODIO	0.15 - 0.20 %
ÁCIDO SÓRBICO	0.05 - 0.20 %
SORBITOL	0.20 - 1.00 %
PRINCIPIO ACTIVO	0.01- 10 %
CLORURO DE SODIO	0.40 - 1.0%
CARBOXIMETILCELULOSA SÓDICA	
Y/O HIDROXIPROPILMETILCELULOSA	0.1% - 0.3%
REGULAR DE PH	c.s.p.
AGUA	c.s.p.

2- Vehículo farmacéutico para estabilizar la superficie ocular en formulaciones de colirios para uso crónico según reivindicación 1 caracterizado porque el principio activo se selecciona entre atropine, azelastina, azitromicina, azitromicina, bepotastina, brimonidina, brimonidina, brimonidina, brinzolamida, bromfenac, carboximetilcelulosa, carboximetilcelulosa, ciclopentolato, ciclosporina, ciprofloxacina, ciprofloxacina, cloranfenicol, cromoglicato, dexametasona,

dexametasona, difluprednato, dorzolamida, dorzolamida, epinastina, fenilefrina, fenilefrina, fluoresceína, fluorometolona, fluorometolona, fluorometolona, gatifloxacina, gatifloxacina, gatifloxacina, gentamicina, hialuronato, hidroxipropilmetilcelulosa, ketorolaco, ketotifeno, ketotifeno, latanoprost, loteprednol, meloxicam, moxifloxacina,, nafazolina, ofloxacina, olopatadina, oximetazolina, pilocarpina, prednisolona, prednisolona, proparacaína, proparacaína, rebamipide, tetraciclina, tetrizolina, timolol, tobramicina, tobramicina, tobramicina, travoprost, tropicamida, tropicamida o sus posibles combinaciones.

3- Vehículo farmacéutico para estabilizar la superficie ocular en formulaciones de colirios para uso crónico según reivindicación 2 caracterizado porque el principio activo puede ser una de sus sales farmacéuticamente activas.

4- Vehículo farmacéutico para estabilizar la superficie ocular en formulaciones de colirios para uso crónico según reivindicación 1 caracterizado porque las composiciones pueden contener ácido clorhídrico (HCL) o hidróxido de sodio (NaOH) para regular el pH a valor entre 5.0 y 7.8

Anexo 2. Relación de personal de laboratorios Sophia con la patente US20080021101.

US 20080021101A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2008/0021101 A1**

Jimenez-Bayardo et al. (43) **Pub. Date: Jan. 24, 2008**

(54) **METHOD OF PREPARING A LATANOPROST OPTHALMIC SOLUTION AND THE RESULTING SOLUTION**

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(86) PCT No.: **PCT/MX04/00034**

§ 371(c)(1),
(2), (4) Date: **Sep. 21, 2007**

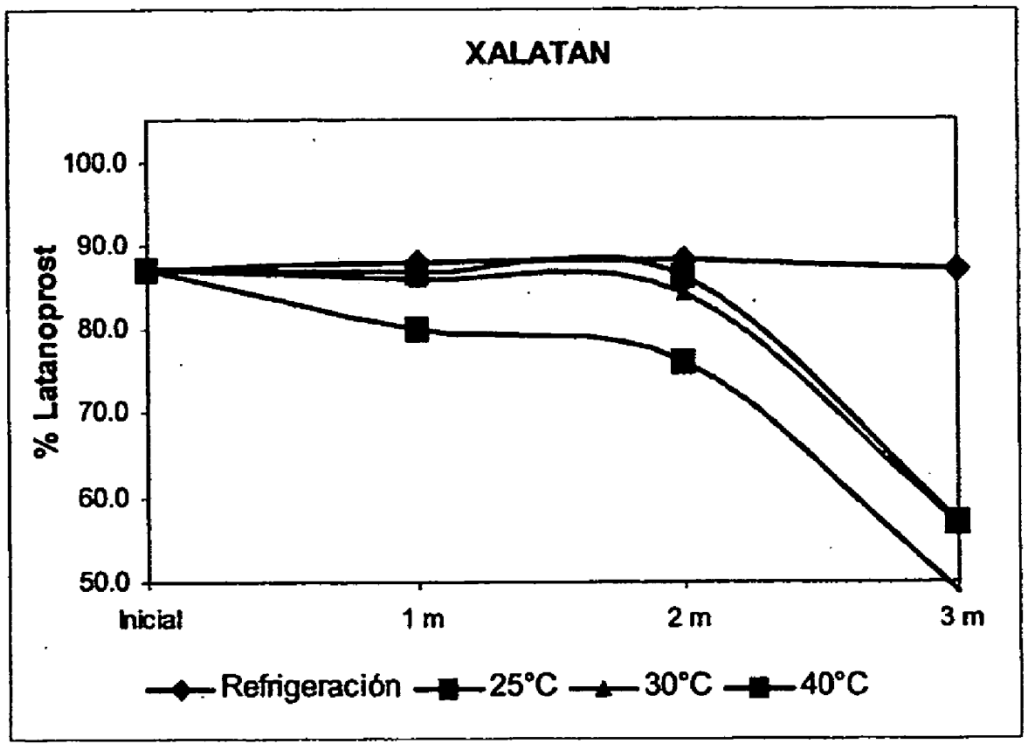
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A61P 27/02 (2006.01)

(52) **U.S. Cl.** **514/530**

(57) **ABSTRACT**

A method of solubilizing an analog active agent of the prostaglandin F2α, such as latanoprost, is described and a method of preparing an ophthalmic solution of the solubilized latanoprost for the treatment of distinct ocular ailments. This invention also refers to an ophthalmic aqueous solution resulting from the aforementioned method, which is characterized by its chemical stability at room temperature, its safety, and innocuousness and efficiency in the treatment of the patient. The new ophthalmic aqueous solution is distinguished because its pharmaceutical value is found in the handling of a vehicle of easy access that not only permits the solubility of latanoprost, but also promotes its chemical stability and a greater tolerance of the patient with its ophthalmic application for the treatment of the patient's ailment.





Historia de Laboratorios Sophia

Distante puede parecer el año 1946, cuando Don Pablo Jiménez Camarena fundó en una de las céntricas calles de la ciudad de Guadalajara, un pequeño laboratorio con el nombre en honor a su madre, Laboratorios Sophia.

Así pasó el tiempo al igual que varias generaciones, pero la visión de nuestro fundador se ha mantenido vigente, y ahora a más de 68 años, nos hemos convertido en un laboratorio líder en investigación e innovación de medicamentos oftálmicos, con presencia en 16 países en el continente americano y una organización integrada por más de 500 personas al servicio de la industria.

Podría dedicar varias páginas relacionadas con la historia de Laboratorios Sophia, desde los emocionantes días de Don Pablo Jiménez Camarena, pasando por el estratégico camino hacia la modernidad bajo la dirección de Don Arturo Jiménez Bayardo, hasta los dinámicos días de globalización que hoy vivimos.

Resulta simplemente fascinante recordar nuestro pasado, sin embargo; apenas y nos podemos detener a reflexionar en ello, porque para nosotros hay algo todavía más importante: el futuro.



El futuro representa una preparación y compromiso que estamos listos para afrontar. Sobresaliente en el siglo pasado, renovada y vestida para este siglo XXI, Laboratorios Sophia sabe que de todos sus recursos el más importante es su gente, por ello contamos con un equipo de profesionales sumamente preparados, motivados y comprometidos; además de una dinámica organización y una sobresaliente administración de nuestros recursos para realizar nuestra misión día a día.

A fin de mantenernos al filo de la competitividad, hemos realizado grandes inversiones en infraestructura, investigación y desarrollo y programas de capacitación y aprendizaje que integran nuestras inversiones en capital, producto y elemento humano, dando como resultado un laboratorio líder nacional e importante competidor en Latinoamérica, con un alto reconocimiento de la comunidad médica oftalmológica.

Un indudable ejemplo hacia la constante excelencia es la construcción de nuestra nueva planta, un laboratorio corporativo, con un alto estándar a nivel mundial y lo último en tecnología. Preparado para estar presente en todos los mercados del orbe, que sumado a un equipo internacional de trabajo y productos innovadores definen la pauta para las próximas décadas.

Estamos preparados para abordar este prometedor futuro, el cual deseamos construir en conjunto con todos nuestros colaboradores, clientes y accionistas con un solo fin: Contribuir con la salud visual del mundo.

Cordialmente,
Lic. Jorge E. González G.
Vicepresidente Corporativo.

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Laboratorios Sophia presente en la X Expo Farmacia y XVI Cosmética Empresarial

Con la finalidad de fortalecer la vinculación Universidad- Industria Farmacéutica y promover la superación técnica y científica de los alumnos mediante la creación y desarrollo de productos farmacéuticos, cosméticos, naturales y de síntesis, el Departamento de Farmacobiología, a través de las Academia de Farmacia Básica y Aplicada, realizó la X Expo Farmacia y XVI Cosmética Empresarial, el pasado 3 de diciembre en la explanada del módulo E.

La Expo Farmacia y Cosmética Empresarial, nace a partir de la necesidad de fomentar en el alumno el concepto de calidad y superación a través de la actualización de sus conocimientos, habilidades, aptitudes y actitudes.

Este evento representa una ventana de proyección para que los alumnos tengan la oportunidad de interactuar con los colegas y empresarios que laboran o dirigen la industria farmacéutica y, por otra parte, propicia que las autoridades establezcan acuerdos y/o convenios para lograr beneficios que impacten positivamente en el aspecto financiero y académico, para elevar la calidad de la formación de los futuros egresados que se desarrollarán en la industria farmacéutica.

El Mtro. Héctor Manuel González Martínez, Presidente de la Academia de Farmacia Básica, explicó que los alumnos presentan sus trabajos de investigación o prácticas realizadas en el laboratorio de tecnología farmacéutica, cosmetología y síntesis de fármacos, asesorados por sus profesores.

Las modalidades que se llevan a cabo son trípticos, videos, carteles a manera de investigación y juegos como memoramas, tiro al globo, entre otros, con pruebas farmacopeicas, temas de legislación como son normas y reglamentos que controlan la fabricación de los medicamentos; lo anterior con el propósito de que el alumno se familiarice de una manera divertida con ellos.

En esta ocasión el evento contó con la presencia de Rubén Tornero Montaño, Director de Calidad de los Laboratorios Sophia, "estamos presentes para establecer una vinculación con la academia y al mismo tiempo mostrar lo que estamos haciendo, mucho de lo que hacemos tiene un campo de acción para todos los estudiantes que se encuentran en esta Casa de Estudios", aseguró. El Laboratorio Sophia ofreció una conferencia en la que dio a conocer los productos oftálmicos que fabrican, desarrollan y venden y los campos de acción que ofrecen.

El impacto que tiene este tipo de eventos es la obtención de apoyos para proyectos de investigación, donaciones, espacios para desarrollo de tesis, prácticas profesionales, bolsa de trabajo, entre otros.

El evento que se realiza cada semestre, es coordinado por los presidentes de la Academia de Farmacia Básica y Aplicada, apoyados por los profesores de las diversas asignaturas y con la participación de aproximadamente 400 alumnos de la Licenciatura en Químico Farmacobiólogo.

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Anexo 3. Metodologías de análisis descritas en la USP 40.

LÍMITE DE CUANTIFICACIÓN

Para la determinación de la configuración absoluta, no hay límite de cuantificación (QL, por sus siglas en inglés). El límite de cuantificación para el exceso enantiomérico puede determinarse llevando a cabo una determinación de la cuantificación del exceso enantiomérico porcentual para el estándar de validación de dicroísmo circular vibracional de α-pineno puro para una serie de valores de exceso enantiomérico, llevando a cabo un análisis quimiométrico de valores de exceso enantiomérico de dicroísmo circular vibracional predicho y realizando una determinación del error cuadrático medio, según se ilustra, por ejemplo, en el capítulo ⟨1782⟩.

Criterios de validación: El procedimiento analítico debe ser capaz de determinar el analito con precisión y exactitud a un nivel equivalente a aproximadamente el 1% de exceso enantiomérico para α-pineno puro.

LINEALIDAD

Se debe demostrar una relación lineal entre la concentración y la respuesta del analito, preparando no menos de 5 soluciones estándar con concentraciones que abarquen la concentración anticipada de la solución de prueba. Posteriormente, se debe evaluar la curva estándar usando métodos estadísticos apropiados, tales como regresión de mínimos cuadrados, para el área o la altura del pico de una banda de dicroísmo circular vibracional seleccionada o para todo el espectro, usando análisis quimiométrico tal como la regresión de mínimos cuadrados parciales. Para experimentos que no generan una relación lineal entre la concentración y la respuesta del analito, se deben aplicar métodos estadísticos apropiados para describir la respuesta analítica.

Criterios de validación: Los *Criterios de validación* aceptan el coeficiente de correlación por encima de 0,95 para una gráfica lineal de exceso enantiomérico real en función del exceso enantiomérico predicho por dicroísmo circular vibracional.

ROBUSTEZ

La confiabilidad de un método analítico debe demostrarse mediante cambios deliberados en parámetros experimentales, tales como cambios en la resolución espectral, concentración o longitud de paso para la medición de dicroísmo circular vibracional.

4.3 Verificación

La reglamentaciones sobre Buenas Prácticas de Fabricación Vigentes de los EE.UU. [Título 21 del CFR 211.194(a)(2)] indican que los usuarios de los procedimientos analíticos, según se describe en la *USP–NF*, no están obligados a validar dichos procedimientos cuando se proveen en una monografía. En vez de esto, los usuarios simplemente deben verificar la aptitud en condiciones reales de uso.

El objetivo de una verificación de procedimiento es demostrar que el procedimiento, según se prescribe en una monografía específica, puede ser llevado a cabo por los analistas con exactitud, especificidad y precisión adecuadas usando los instrumentos y las soluciones muestra de moléculas quirales disponibles. Si la verificación del procedimiento farmacopeico siguiendo la monografía no es exitosa, el procedimiento podría no ser adecuado para el uso con el artículo en análisis (para información adicional, ver *Verificación de Procedimientos Farmacopeicos* ⟨1226⟩). Podría ser necesario desarrollar y validar un procedimiento alternativo según lo permitido por las *Advertencias Generales, 6.30 Métodos y Procedimientos Alternativos y Armonizados*.

La verificación de los métodos farmacopeicos debe incluir, como mínimo, la realización de los parámetros de validación para especificidad, exactitud, precisión y límite de cuantificación, cuando resulte apropiado, según se indica en *4.1 Validación*.

⟨785⟩ OSMOLALIDAD Y OSMOLARIDAD

INTRODUCCIÓN

La presión osmótica tiene una importancia fundamental en todos los procesos biológicos donde hay difusión de solutos o transferencia de líquidos a través de membranas. La ósmosis sucede cuando un disolvente, pero no las moléculas de soluto, pasa a través de una membrana semipermeable desde regiones de menor a mayor concentración para llegar al equilibrio. Es muy importante para los profesionales conocer las presiones osmóticas para poder determinar si una solución parenteral es hipoosmótica, isoosmótica o hiperosmótica. Una medición cuantitativa de la presión osmótica facilita la dilución requerida para producir una solución isoosmótica con respecto a la sangre entera.

PRESIÓN OSMÓTICA

La presión osmótica de una solución depende del número de partículas en la solución y, por lo tanto, se la considera como una propiedad coligativa. Una partícula puede ser una molécula o un ión o una especie agregada (por ejemplo, un dímero) que puede existir en forma diferenciada en solución. Una solución presenta un comportamiento ideal cuando no hay interacción entre los solutos y el disolvente, excepto cuando las moléculas del disolvente están unidas a los solutos mediante enlaces de hidrógeno o enlaces covalentes coordinados. En el caso de tales soluciones que contienen un soluto no disociado, la presión osmótica (π) es directamente proporcional a su molalidad (el número de moles de soluto por kilogramo de disolvente):

$$\pi = (\rho RT/1000)m$$

en donde ρ es la densidad del disolvente a la temperatura T (en la escala absoluta); R es la constante universal del gases; y m es la molalidad de la solución. Para el caso de una solución real que contiene más de un soluto, la presión osmótica se calcula por la fórmula:

$$\pi = (\rho RT/1000)\Sigma\nu_i m_i \Phi_{m,i}$$

en donde ν_i es el número de partículas formadas por la disociación de una molécula del $i$ésimo soluto (el número ordinal del soluto); $\nu_i = 1$ para solutos no iónicos (que no se disocian); m_i es la molalidad del $i$ésimo soluto (el número ordinal del soluto); y $\Phi_{m,i}$ es el coeficiente osmótico molal del $i$ésimo soluto. El coeficiente osmótico molal tiene en cuenta la desviación de una solución con respecto al comportamiento ideal. Su valor depende de la concentración del soluto o los solutos en la solución, de sus propiedades químicas y de sus características iónicas. El valor del coeficiente osmótico molal de un soluto se puede determinar experimentalmente midiendo el descenso del punto de congelación a diferentes concentraciones molales. A concentraciones de interés farmacéutico, el valor del coeficiente osmótico molal es menos de uno. El coeficiente osmótico molal disminuye al aumentar la concentración del soluto *(Tabla 1)*.

OSMOLALIDAD

La osmolalidad de una solución ξ_m se representa mediante la fórmula

$$\xi_m = \Sigma\nu_i m_i \Phi_{m,i}$$

La osmolalidad de una solución real se corresponde con la molalidad de la solución ideal que contiene solutos que no se disocian y se expresa en osmoles o miliosmoles por kilogramo de disolvente (Osmol por kg o mOsmol por kg, respectivamente), una unidad que es similar a la molalidad de una solución. Así, la osmolalidad es la medida de la presión osmótica ejercida por una solución real a cada lado de una membrana semipermeable. Al igual que la presión osmótica, otras propiedades coligativas de la solución, tales como la disminución de la presión de vapor, la elevación del punto de ebullición y el descenso del punto de congelación, también están directamente relacionadas con la osmolalidad de la solución. Así, la osmolalidad de una solución se determina típicamente con la mayor exactitud y conveniencia midiendo el descenso del punto de congelación (ΔT_f):

$$\Delta T_f = k_f \xi_m$$

en donde k_f es la constante crioscópica molal, que es una propiedad del disolvente. Para el agua, el valor de k_f es 1,860° por Osmol. Es decir, 1 Osmol de un soluto agregado a 1 kg de agua hace descender el punto de congelación en 1,860°.

OSMOLARIDAD

La osmolaridad de una solución es una cantidad teórica expresada en osmoles por L (Osmol por L) de una solución y se usa ampliamente en la práctica clínica porque expresa los osmoles en función del volumen. La osmolaridad no se puede medir pero se calcula teóricamente a partir del valor de osmolalidad medido experimentalmente.

A veces, la osmolaridad (ξ_c) se calcula teóricamente a partir de las concentraciones molares:

$$\xi_c = \Sigma\nu_i c_i$$

en donde ν_i es la que se define anteriormente y c_i es la concentración molar del $i$ésimo soluto (el número ordinal del soluto) en solución. Por ejemplo, la osmolaridad de una solución que se prepara disolviendo 1 g de vancomicina en 100 mL de solución de cloruro de sodio al 0,9% se puede calcular de la siguiente manera:

$[3 \times 10\ g/L/1449{,}25(\text{peso mol. de vancomicina}) + 2 \times 9\ g/L/58{,}44(\text{peso mol. de cloruro de sodio})] \times 1000 = 329\ mOsmol/L$

El resultado sugiere que la solución es ligeramente hiperosmótica dado que la osmolalidad de la sangre está entre 285 y 310 mOsmol por kg. Sin embargo, la solución ha resultado ser hipoosmótica y tiene una osmolalidad determinada experimentalmente de 255 mOsmol por kg.[1] El ejemplo ilustra que los valores de osmolaridad calculados teóricamente a partir de la con-

[1] Kastango, E.S. y Hadsway, L. *International Journal of Pharmaceutical Compounding 5*. (2001) 465–469.

que la presión osmótica está relacionada con la osmolalidad y no con la osmolaridad. Más significativamente, la discrepancia entre los resultados experimentales y los cálculos teóricos se debe a que la presión osmótica de una solución real es menor que la de una solución ideal debido a las interacciones entre las moléculas del soluto o entre las moléculas del soluto y del disolvente en una solución. Estas interacciones reducen la presión que ejercen las moléculas del soluto sobre la membrana semipermeable, lo que reduce los valores experimentales de la osmolalidad en comparación con los valores teóricos. Esta diferencia está relacionada con el coeficiente osmótico molal (Φ_m). El ejemplo también ilustra la importancia de determinar experimentalmente la osmolalidad de una solución, en vez de calcular el valor teóricamente.

MEDICIÓN DE LA OSMOLALIDAD

Normalmente, el valor de osmolalidad de una solución se determina midiendo el descenso del punto de congelación de una solución.

Aparato

El aparato, un osmómetro para medir el descenso del punto de congelación, consiste en lo siguiente: un medio para enfriar el recipiente utilizado para la medición; un resistor sensible a la temperatura (termistor), con un dispositivo adecuado para medir la diferencia de potencial o de corriente y que puede graduarse en función de cambios de temperatura o en osmolalidad; y un mecanismo para mezclar la muestra.

Los osmómetros que miden la presión de vapor de las soluciones se emplean con menor frecuencia. Requieren un volumen de muestra más pequeño (generalmente aproximadamente 5 µL), aunque la exactitud y precisión de los resultados de las determinaciones de osmolalidad son comparables a las obtenidas mediante el uso de osmómetros que dependen de la observación del punto de congelación de las soluciones.

Soluciones Estándar

Preparar las *Soluciones Estándar* como se indica en la *Tabla 1*, según sea necesario.[2]

Tabla 1. Soluciones Estándar para Calibración del Osmómetro[a]

Soluciones Estándar (Peso en g de cloruro de sodio por kg de agua)	Osmolalidad (mOsmol/kg) (Σ_m)	Coeficiente Osmótico Molal ($\Phi_{m,NaCl}$)	Descenso del Punto de Congelación (°) ΔT_f
3,087	100	0,9463	0,186
6,260	200	0,9337	0,372
9,463	300	0,9264	0,558
12,684	400	0,9215	0,744
15,916	500	0,9180	0,930
19,147	600	0,9157	1,116
22,380	700	0,9140	1,302

[a] Adaptado de la *Farmacopea Europea*, 4a Edición, 2002, pg. 50.

Solución de Prueba

En el caso de un sólido para inyección, reconstituir con el diluyente apropiado según se indica en las instrucciones del etiquetado. En el caso de soluciones, usar la muestra tal como se encuentra. [NOTA—Se puede diluir una solución para que quede dentro del intervalo de medición del osmómetro, si fuera necesario, pero el resultado se deberá expresar como el resultado de la solución diluida y NO se debe multiplicar por un factor de dilución para calcular la osmolalidad de la solución original, a menos que se especifique algo diferente en la monografía. El coeficiente osmótico molal es una función de la concentración. Por lo tanto, cambia con la dilución.]

[2] Se pueden usar soluciones comercialmente disponibles para calibración de osmómetros, con osmolalidades iguales o diferentes a las que se listan en la *Tabla 1* y estandarizadas con métodos rastreables al NIST.

Procedimiento

Primero, calibrar el instrumento según las instrucciones del fabricante. Confirmar la calibración del instrumento con, por lo menos, una solución de la *Tabla 1* de manera que la osmolalidad de la *Solución Estándar* se encuentre dentro de 50 mOsmol/kg del valor esperado de la *Solución de Prueba* o en el centro del intervalo esperado de osmolalidad de la *Solución de Prueba*. La lectura del instrumento debe estar dentro de ±4 mOsmol por kg de la *Solución Estándar*. Introducir un volumen adecuado de cada *Solución Estándar* en la celda de medición conforme a las instrucciones del fabricante y poner en marcha el sistema de enfriamiento. En general, el dispositivo de mezcla se programa para que opere a una temperatura inferior a la temperatura más baja esperada de descenso del punto de congelación. El aparato indica cuando se ha logrado el equilibrio. Si fuera necesario, calibrar el osmómetro utilizando un dispositivo de ajuste adecuado de modo que la lectura corresponda a la osmolalidad o al valor de descenso del punto de congelación de la *Solución Estándar* que aparece en la *Tabla 1*. [NOTA—Si la lectura del instrumento indica el descenso del punto de congelación, la osmolalidad se puede derivar usando la fórmula apropiada en *Osmolalidad*.] Repetir el procedimiento con cada *Solución de Prueba*. Leer la osmolalidad de la *Solución de Prueba* directamente o calcularla a partir del valor obtenido para el descenso del punto de congelación.

Suponiendo que el valor del coeficiente osmótico es esencialmente el mismo ya sea que la concentración se exprese en molalidad o molaridad, la osmolalidad de una solución determinada experimentalmente se puede convertir en osmolaridad de la misma manera que la concentración de una solución se convierte de molalidad a molaridad. A menos que una solución esté muy concentrada, la osmolaridad de una solución (ξ_c) se puede calcular a partir de su osmolalidad determinada experimentalmente (ξ_m):

$$\xi_c = 1000\xi_m / (1000 / \rho + \Sigma w_i v_i)$$

donde w_i es el peso en g; y v_i es el volumen específico parcial, en mL por g, del *i*ésimo soluto (el número ordinal del soluto). El volumen específico parcial de un soluto es el cambio en volumen de una solución cuando se disuelve 1 g adicional de soluto en la solución. Este volumen se puede determinar midiendo las densidades de la solución antes y después de agregar el soluto. Los volúmenes específicos parciales de las sales son generalmente muy pequeños, alrededor de 0,1 mL por g. Sin embargo, los otros solutos son generalmente mayores. Por ejemplo, los volúmenes específicos parciales de los aminoácidos están entre 0,6 mL y 0,9 mL por g. Se puede demostrar por la ecuación anterior que correlaciona la osmolaridad con la osmolalidad que,

$$\xi_c = \xi_m (\rho - c)$$

donde ρ es la densidad de la solución y c es la concentración de soluto total, ambas expresadas en g por mL. Por lo tanto, alternativamente, la osmolaridad puede calcularse también a partir de la osmolalidad determinada experimentalmente a partir de la medición de la densidad de la solución mediante un método adecuado y el peso total del soluto, después de la corrección por contenido de agua, disuelto por mL de la solución.

⟨786⟩ ESTIMACIÓN DE LA DISTRIBUCIÓN DEL TAMAÑO DE PARTÍCULA POR TAMIZADO ANALÍTICO

El tamizado es uno de los métodos más antiguos para clasificar los polvos y los gránulos según la distribución del tamaño de partícula. El tamizado utilizando un lienzo tejido como tamiz, consiste básicamente en clasificar las partículas según su tamaño intermedio (es decir, según su ancho o amplitud). Se recomienda el tamizado mecánico si la mayoría de las partículas superan los 75 µm aproximadamente. Si se trata de partículas más pequeñas, durante el tamizado se observa que su escaso peso no ejerce la fuerza suficiente para contrarrestar las fuerzas de adhesión y cohesión superficial, que hacen que las partículas se aglutinen unas con otras y al tamiz. Por este motivo, las partículas que se esperaría que pasaran por el tamiz, en realidad no lo hacen. Para este tipo de materiales se recomienda emplear otros métodos de agitación, como por ejemplo el tamizado con un chorro de aire o el tamizado sónico. No obstante, el tamizado se puede emplear en algunos casos para algunos polvos o gránulos cuya mediana de tamaño de partícula sea inferior a 75 µm, siempre que el método se pueda validar. En términos farmacéuticos, el tamizado es el método de preferencia para clasificar polvos o gránulos sin mezclas más gruesos. El método es especialmente atractivo ya que tanto los polvos como los gránulos se clasifican solamente en función del tamaño de partícula y en la mayoría de los casos el análisis se puede efectuar con el material seco.

Entre los factores limitantes que presenta el método se encuentran la necesidad de contar con una cantidad de muestra apreciable (según sea la densidad del polvo o de los gránulos y el diámetro de los orificios del tamiz, generalmente como mínimo 25 g) y la dificultad que presentan polvos o gránulos oleosos o cohesivos que obstruyen los orificios del tamiz. En esencia, el método estima el tamaño en dos dimensiones ya que el pasaje a través del orificio del tamiz a menudo presenta mayor dependencia del ancho y del espesor máximos que del largo.

Este método está destinado a estimar la distribución del tamaño de partícula total de un material sin mezclar. No está dise-

tubo capilar abiertos a la presión atmosférica, registrar el tiempo, en segundos, requerido para que el líquido fluya desde la marca superior hasta la marca inferior en el tubo capilar. [NOTA—El tiempo de flujo mínimo debe ser 200 segundos.]

Calibración y Cálculo de las viscosidades cinemática y newtoniana del fluido muestra: Proceder según se indica en el *Método I*. Para ciertos viscosímetros capilares simples de tubo en forma de U, determinar la constante del viscosímetro a la misma temperatura que el líquido de muestra en análisis.

⟨912⟩ VISCOSIDAD—MÉTODOS ROTATORIOS

El principio del método se basa en medir la fuerza (torque) que actúa sobre un rotor cuando éste rota a una velocidad angular constante o velocidad de rotación en un líquido. Los reómetros o viscosímetros rotatorios se usan para medir la viscosidad de fluidos newtonianos y no newtonianos. Los siguientes procedimientos se usan para determinar la viscosidad de fluidos newtonianos o la viscosidad aparente de fluidos no newtonianos. La viscosidad calculada de los fluidos newtonianos debe ser la misma (dentro del error experimental), independientemente de la velocidad de corte (o velocidad de rotación). Dada la dependencia de la viscosidad con respecto a la temperatura, la temperatura de la sustancia que se está midiendo se debe controlar dentro de ±0,1°, a menos que se especifique algo distinto en la monografía individual. [NOTA—Para más información, ver el capítulo *Reometría* ⟨1911⟩.]

• **MÉTODO I. VISCOSÍMETROS DE ROTOR**

Aparato: En el viscosímetro de rotor, la viscosidad aparente se determina haciendo girar un rotor con forma de cilindro o disco, según se muestra en la *Figura 1* y la *Figura 2*, respectivamente, sumergido en un gran volumen de líquido.

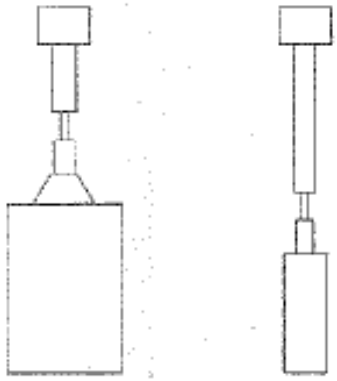


Figura 1. Rotores con forma de cilindro.

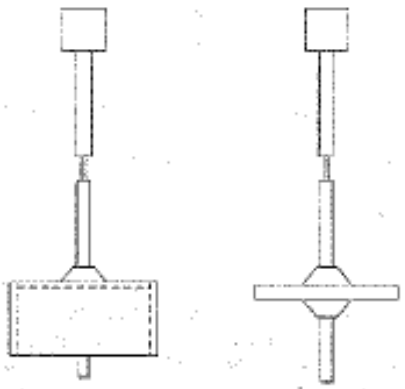


Figura 2. Rotores con forma de disco.

No se puede calcular una viscosidad absoluta debido a la gran distancia existente entre el rotor y la pared del recipiente, o a la geometría del rotor. El torque empleado para mantener una velocidad angular dada proporciona una medida de la resistencia del líquido a fluir, pero a menudo esto se describe como una viscosidad aparente.

Se pueden usar otros tipos de viscosímetros de rotor, siempre que la exactitud y la precisión no sean menores que las obtenidas con los viscosímetros descritos en este capítulo.

Procedimiento: Cuando la medición de la viscosidad se realiza en un vaso de precipitados o vaso, y debido a que la velocidad de corte es desconocida, para poder conseguir reproducibilidad entre laboratorios que miden la viscosidad usando instrumentos diferentes, deben informarse los siguientes parámetros junto con la medida de la viscosidad:

1. Tamaño y especificaciones geométricas del rotor
2. Velocidad angular o velocidad de rotación del rotor
3. Temperatura de la sustancia de prueba

El rotor debe sumergirse a la profundidad recomendada, manteniendo al menos 1 cm de distancia con el fondo y con las paredes del recipiente.

La preparación de la muestra de prueba, incluyendo la equilibración de temperatura, se especifica en cada monografía individual. Seguir las recomendaciones del fabricante del instrumento con respecto a la carga de la muestra, la selección del rotor y la operación del viscosímetro.

Comprobación de la calibración: Comprobar la calibración de la configuración de un viscosímetro particular a la temperatura de prueba, usando uno o más fluidos de viscosidad conocida (estándares de viscosidad newtoniana). Los valores de viscosidad de los estándares de calibración deben contener el valor de viscosidad esperado del líquido de muestra. [NOTA—Para ayudar a verificar la linealidad del aparato, se sugiere realizar mediciones de un estándar de viscosidad newtoniana a distintas velocidades de rotación a la temperatura de prueba.]

Se considera que un viscosímetro está calibrado cuando las viscosidades aparentes medidas están dentro de ±5% de los valores indicados.

En general, la calibración, operación y limpieza del viscosímetro se deben llevar a cabo de acuerdo con las recomendaciones del fabricante del instrumento.

- **MÉTODO II. REÓMETROS DE CILINDROS CONCÉNTRICOS**

Aparato: En los reómetros de cilindros concéntricos, la viscosidad aparente se determina colocando el líquido en el espacio entre el cilindro interno y el cilindro externo. Los reómetros rotatorios de tensión controlada y de velocidad controlada están disponibles comercialmente en configuraciones con especificaciones geométricas absolutas (p.ej., espacios anulares muy pequeños entre los cilindros concéntricos) que permiten calcular las viscosidades aparentes de fluidos no newtonianos. Los reómetros de tensión de corte controlada miden las velocidades de corte resultantes al aplicar una fuerza o torque dado (la tensión). Los reómetros de velocidad de corte controlada miden la tensión de corte (del torque sobre el eje del rotor) resultante de la aplicación de una velocidad de corte dada (o velocidad de rotación). Los reómetros rotatorios de cilindros concéntricos en ocasiones reciben el nombre de reómetros de vaso y cilindro ("cup-and-bob"). El uso de estos reómetros implica consideraciones adicionales de diseño, dependiendo de si lo que gira es el cilindro externo (el vaso) o el cilindro interno (el cilindro). Los reómetros de vaso rotatorio reciben el nombre de sistemas Couette, mientras que los reómetros de cilindro interno rotatorio se denominan sistemas Searle, según se muestra en la *Figura 3* y la *Figura 4*, respectivamente.

Las variables en la *Figura 3* y la *Figura 4* se definen como:

M = torque que actúa sobre la superficie del cilindro (N · m)
R_0 = radio del cilindro externo (m)
R_1 = radio del cilindro interno (m)
h = altura de inmersión del cilindro interno en el medio líquido (m)
ω = velocidad angular (radianes/s)
η = viscosidad (Pa · s)
v = velocidad (m/s)

Procedimiento: Colocar una cantidad suficiente de fluido de prueba en el reómetro y dejar que la muestra alcance el equilibrio térmico, según se indica en la monografía individual. Poner en funcionamiento el reómetro siguiendo el procedimiento recomendado por el fabricante del instrumento. Para sistemas no newtonianos, la monografía indica el tipo de reómetro que se debe usar y las velocidades de corte a las que se deben realizar las mediciones. Determinar las viscosidades aparentes, cambiando la velocidad de corte (o la tensión de corte, si se usa un reómetro de tensión de corte controlada) en un intervalo apropiado para el uso del material en análisis. A partir de una serie de este tipo de mediciones de viscosidad, se puede obtener la relación entre la velocidad de corte y la tensión de corte de un líquido no newtoniano.

- **MÉTODO III. REÓMETROS DE CONO Y PLACA**

Aparato: En los reómetros de cono y placa, el líquido se introduce en el espacio fijo entre un disco o placa planos y un cono los cuales forman un ángulo definido. El ángulo del cono garantiza una velocidad de corte constante debido al aumento del espacio y de la velocidad lineal conforme aumenta la distancia desde el origen. La medición de viscosidad se puede realizar haciendo girar el cono o la placa, según se muestra en la *Figura 5* y la *Figura 6*, respectivamente. [NOTA—Puesto que el volumen de muestra es pequeño, incluso una pequeña pérdida absoluta de disolventes puede ocasionar un gran cambio porcentual en la viscosidad. Dicha pérdida tiene una importancia particularmente relevante para disolventes volátiles pero puede ser significativa incluso para disolventes no volátiles como el agua.]

Las variables en la *Figura 5* y la *Figura 6* se definen como:

ω = velocidad angular (radianes/s)
M = torque que actúa sobre la superficie de la placa plana o del cono (N · m)
α = ángulo entre la placa plana y el cono (radianes)
R = radio del cono (m)

Procedimiento: Proceder según se indica en el *Método II. Reómetros de Cilindros Concéntricos.*

- **MÉTODO IV. REÓMETROS DE PLACAS PARALELAS (O DE DISCOS PARALELOS)**

Aparato: Los reómetros de placas paralelas son similares a los reómetros de cono y placa, salvo que la muestra que se va medir se introduce en el espacio entre las dos placas o discos planos paralelos. Las mediciones se realizan normalmente manteniendo la placa o disco inferior estacionario mientras que la placa o disco superior rota a una velocidad angular constante, ω (*Figura 7*).

Las variables en la *Figura 7* se definen como:

ω = velocidad angular (radianes/s)
R = radio de la placa (m)
h = distancia entre las dos placas paralelas (m)

A diferencia de lo que ocurre con el reómetro de cono y placa, la velocidad de corte entre las placas paralelas aumenta con la distancia desde el origen del eje de rotación debido a que las velocidades lineales aumentan para una velocidad angular dada con un espacio constante. De esta manera, se obtiene una velocidad de corte promedio. A pesar de esto, algunas de las ventajas del reómetro de placas paralelas incluye la facilidad de carga de la muestra (especialmente para líquidos muy viscosos o semisólidos blandos) y su aptitud para suspensiones de partículas. Para suspensiones, el espacio debe fijarse a una altura suficiente para evitar que las partículas se muelan entre las placas. El usuario puede definir el espacio entre las placas paralelas (dentro de límites prácticos) y por lo tanto, ante la ausencia de partículas grandes, se pueden usar espacios más estrechos. Al igual que con los reómetros de cono y placa, la pérdida de disolvente por evaporación puede afectar en gran medida la viscosidad de la muestra, por lo que deben tomarse precauciones para minimizar la pérdida de disolvente.

Procedimiento: Proceder según se indica en *Método II. Reómetros de Cilindros Concéntricos.*

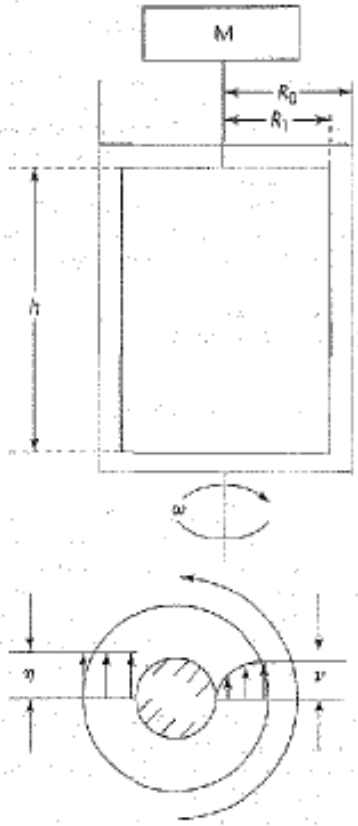


Figura 3. Sistema de cilindros concéntricos Couette para reometría rotacional.

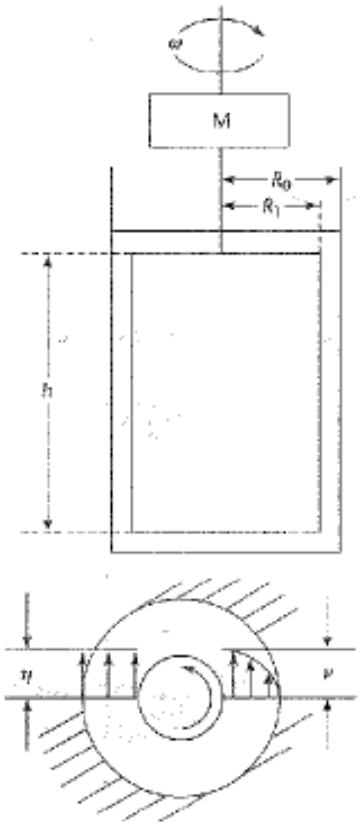


Figura 4. Sistema de cilindros concéntricos Searle para reometría rotacional.

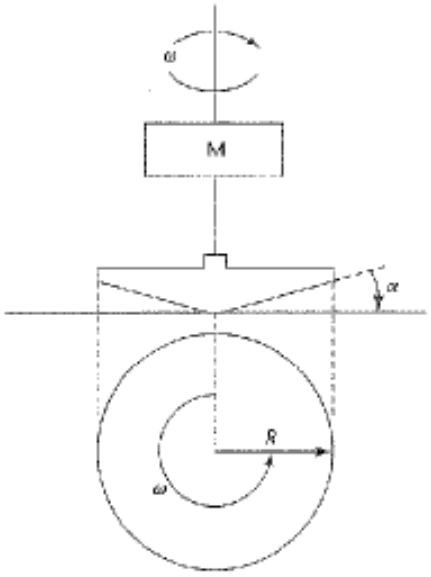


Figura 5. Reómetro rotatorio de cono y placa con cono giratorio.

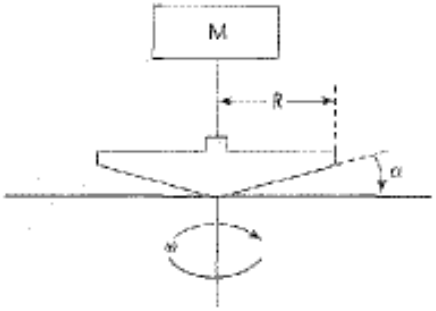


Figura 6. Reómetro rotatorio de cono y placa con placa giratoria.

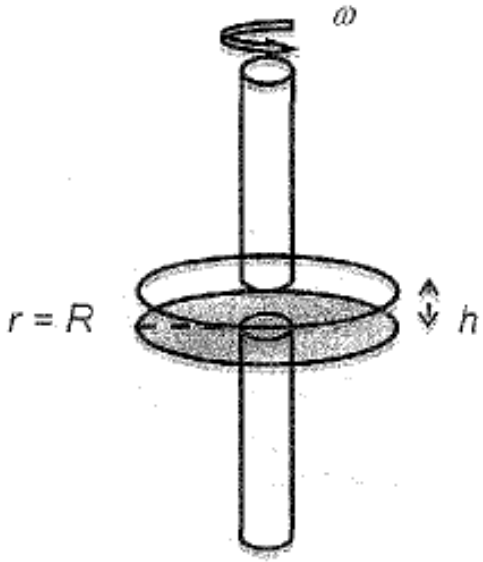


Figura 7. Reómetro rotatorio de placas paralelas.

Anexo 4. Resultados de análisis productos de uso crónico evaluados.

Resultados ejemplos relacionados en nuestra solicitud de patente, expediente NC2017/0003295

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REPORTE DE ANÁLISIS/ANALYSIS REPORT

Muestra/Sample #: 242714

Empresa / Company: ESPECIALIDADES OFTALMOLOGICAS S.A. **Telf. / Phone:** 448 19 18

Sede / Headquarters: Sede principal Carrera 37 A No. 2 Sur 104, Loma Alejandria, Poblado, Medelli

Producto / Product: VEHÍCULO FARMACÉUTICO PARA ESTABILIZAR SUPERFICIE OCULAR ENFORMULACIONES DE COLIRIO PARA USO CRÓNICO

Muestra / Sample: Ejemplo 1

Fecha de Recepción / Reception date: 31/08/2017 **Temp. de Recepción / Temp. Reception:** 27,3°C

Cantidad / Amount: 1 Unidad/ 1 unit

Contenedor / Container: Frasco gotero con tapa/Dropper bottle with lid

Enviada por /Send by: Tatiana María Gómez Gaviria

Aspecto / Aspect: Liquido translucido, libre de particulas extrañas/ Translucent liquid, free of foreign particles
Olor / Smell: Inobjetable/ Unobjectionable
Color / Color: Incoloro/ Colorless

Análisis Fisicoquímico/ Physicochemical Analysis	Fecha/ Date	Unidad/ Unit	Resultado/ Result	Especificaciones(**)/ Specifications(**)	Método/ Method
Osmolalidad/Osmolality	01/09/2017	mOsm/Kg	260	NA	USP 40 <785>

(**) Según Norma / Acoordinng to Standard:

(*) Métodos acreditados/Methods Accredited: ONAC, Certificado/Certificate: 10-LAB-053 Fecha/Date: 2014-09-05 ISO/IEC 17025:2005

NOTA: Este resultado corresponde, exclusivamente a la muestra recibida y analizada en el laboratorio/This result correspond only to the sample received and analyzed by the laboratory

Luz E. Osorio Castaño
T.P. 01345801606001664
Química Farmacéutica U de A
Coordinadora
Fecha / Date: 01/09/2017

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Muestra/Sample #: 242717

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Sede / Headquarters: Sede principal Carrera 37 A No. 2 Sur 104, Loma Alejandria, Poblado, Medellí

Producto / Product: VEHÍCULO FARMACÉUTICO PARA ESTABILIZAR SUPERFICIE OCULAR ENFORMULACIONES DE COLIRIO PARA USO CRÓNICO

Muestra / Sample: Ejemplo 2

Fecha de Recepción / Reception date: 31/08/2017 **Temp. de Recepción / Temp. Reception:** 27,3°C

Cantidad / Amount: 1 Unidad/ 1 unit

Contenedor / Container: Frasco gotero con tapa/Dropper bottle with lid

Enviada por /Send by: Tatiana Maria Gómez Gaviria

Aspecto / Aspect: Liquido translucido libre de particulas extrañas/Translucent liquid, free of foreign particles
Olor / Smell: Inobjetable / Unobjectionable
Color / Color: Incoloro/ Colorless

Análisis Fisicoquímico/ Physicochemical Analysis	Fecha/ Date	Unidad/ Unit	Resultado/ Result	Especificaciones(**)/ Specifications(**)	Método/ Method
Osmolalidad/Osmolality	01/09/2017	mOsm/Kg	270	NA	USP 40 <785>

(**) Según Norma / Acoordinng to Standard:

(*) Métodos acreditados/Methods Accredited: ONAC, Certificado/Certificate: 10-LAB-053 Fecha/Date: 2014-09-05 ISO/IEC 17025:2005

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Sede / Headquarters: Sede principal Carrera 37 A No. 2 Sur 104, Loma Alejandria, Poblado, Medellí

Producto / Product: VEHÍCULO FARMACÉUTICO PARA ESTABILIZAR SUPERFICIE OCULAR ENFORMULACIONES DE COLIRIO PARA USO CRÓNICO

Muestra / Sample: Ejemplo 3

Fecha de Recepción / Reception date: 31/08/2017 **Temp. de Recepción / Temp. Reception:** 27,3°C

Cantidad / Amount: 1 Unidad/ 1 unit

Contenedor / Container: Frasco gotero con tapa/Dropper bottle with lid

Enviada por /Send by: Tatiana Maria Gómez Gaviria

Aspecto / Aspect: Liquido translucido libre de particulas extrañas/ Translucent liquid, free of foreign particles
Olor / Smell: Inobjetable/ Unobjectionable
Color / Color: Incoloro/ Colorless

Análisis Fisicoquímico/ Physicochemical Analysis	Fecha/ Date	Unidad/ Unit	Resultado/ Result	Especificaciones(**)/ Specifications(**)	Método/ Method
Osmolalidad/Osmolality	01/09/2017	mOsm/Kg	280	NA	USP 40 <785>

(**) Según Norma / Acoordinng to Standard:

(*) Métodos acreditados/Methods Accredited: ONAC, Certificado/Certificate: 10-LAB-053 Fecha/Date: 2014-09-05 ISO/IEC 17025:2005

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Producto / Product: VEHÍCULO FARMACÉUTICO PARA ESTABILIZAR SUPERFICIE OCULAR ENFORMULACIONES DE COLIRIO PARA USO CRÓNICO

Muestra / Sample: Ejemplo 4

Fecha de Recepción / Reception date: 31/08/2017 **Temp. de Recepción / Temp. Reception:** 27,3ºC

Cantidad / Amount: 1 Unidad/1 unit

Contenedor / Container: Frasco gotero con tapa/Dropper bottle with lid

Enviada por /Send by: Tatiana María Gómez Gaviria

Aspecto / Aspect: liquido translucido libre de particulas extrañas/ Translucent liquid, free of foreign particles
Olor / Smell: Inobjetable/ Unobjectionable
Color / Color: Incoloro/ Colorless

Análisis Fisicoquímico/ Physicochemical Analysis	Fecha/ Date	Unidad/ Unit	Resultado/ Result	Especificaciones(**)/ Specifications(**)	Método/ Method
Osmolalidad/Osmolality	01/09/2017	mOsm/Kg	290	NA	USP 40 <785>

(**) Según Norma / Acoordinng to Standard:

(*) Métodos acreditados/Methods Accredited: ONAC, Certificado/Certificate: 10-LAB-053 Fecha/Date: 2014-09-05 ISO/IEC 17025:2005

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Producto / Product: VEHÍCULO FARMACÉUTICO PARA ESTABILIZAR SUPERFICIE OCULAR ENFORMULACIONES DE COLIRIO PARA USO CRÓNICO

Muestra / Sample: Ejemplo 5

Fecha de Recepción / Reception date: 31/08/2017 **Temp. de Recepción / Temp. Reception:** 27,3ºC

Cantidad / Amount: 1 Unidad/ 1 unit

Contenedor / Container: Frasco gotero con tapa/Dropper bottle with lid

Enviada por /Send by: Tatiana María Gómez Gaviria

Aspecto / Aspect: Liquido translucido libre de particulas extrañas/Translucent liquid, free of foreign particles
Olor / Smell: Inobjetable/ Unobjectionable
Color / Color: Incoloro/ Colorless

Análisis Fisicoquímico/ Physicochemical Analysis	Fecha/ Date	Unidad/ Unit	Resultado/ Result	Especificaciones(**)/ Specifications(**)	Método/ Method
Osmolalidad/Osmolality	01/09/2017	mOsm/Kg	265	NA	USP 40 <785>

(**) Según Norma / Acoordinng to Standard:

(*) Métodos acreditados/Methods Accredited: ONAC, Certificado/Certificate: 10-LAB-053 Fecha/Date: 2014-09-05 ISO/IEC 17025:2005

NOTA: Este resultado corresponde, exclusivamente a la muestra recibida y analizada en el laboratorio/This result correspond only to the sample received and analyzed by the laboratory

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EL ALIADO PRECISO

Informe de resultado tensión superficial

Equipo

Dataphysics OCA15





Características del equipo:

Medida	Rango
Ángulo de contacto [°]	0 – 180 ° ± 0.1°
Tensión superficial e interfacial [Dinas/cm]	0.01 2000 Dinas/cm ± 0.01 Dinas/cm

Condiciones de medición:

Técnica usada: Gota - péndulo
Jeringa utilizada: Halmilton de 1 mL
Temperatura: 25 ° C Laboratorio, el equipo no cuenta con control de temperatura sobre la muestra.
Dosificación: 1 uL/ seg

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Edificio Copérnico
Tel: (+57) 1 467 3792
(+57) 1 467 3776

cecoltec
EL ALIADO PRECISO

Muestras

Código Cecoltec	Nombre de la muestra	Lote
C948-TS1	Vehículo farmacéutico para estabilizar la superficie ocular	EJ 1
C948-TS2	Vehículo farmacéutico para estabilizar la superficie ocular	EJ 2
C948-TS3	Vehículo farmacéutico para estabilizar la superficie ocular	EJ 3
C948-TS4	Vehículo farmacéutico para estabilizar la superficie ocular	EJ 4
C948-TS5	Vehículo farmacéutico para estabilizar la superficie ocular	EJ 5

Resultados

Muestra	Medición 1 (Dinas/cm)	Medición 1 (Dinas/cm)	Medición 1 (Dinas/cm)	Medición 1 (Dinas/cm)	Medición 1 (Dinas/cm)	Promedio (dinas/cm)	Des. STD (Dinas/cm)
EJ 1	39,82	40,02	40,08	40,36	40,11	40,08	0,17
EJ 2	41,23	40,58	40,89	41,05	41,24	41,00	0,25
EJ 3	41,05	41,08	40,91	41,2	41,03	41,05	0,09
EJ 4	41,85	42,15	41,9	42,2	41,95	42,01	0,14
EJ 5	43,2	43,05	42,89	43,01	42,95	43,02	0,11

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Resultado viscosidad

Equipo

Kinexus Pro (www.malvern.com)



Muestra

Código CECOLTEC	Nombre de la muestra
C948-CF1	Vehículo farmacéutico para estabilizar la superficie ocular EJ1

Condiciones de la medida

Sistema de medida: Plato – Plato 40
Tratamiento:

Tasa de cizalladura: 5,000 s-1 a 20,000 s-1
Muestreo: 15 puntos.
Gap: 0.1 mm
Temperatura: 25 °C ± 0.01 °C

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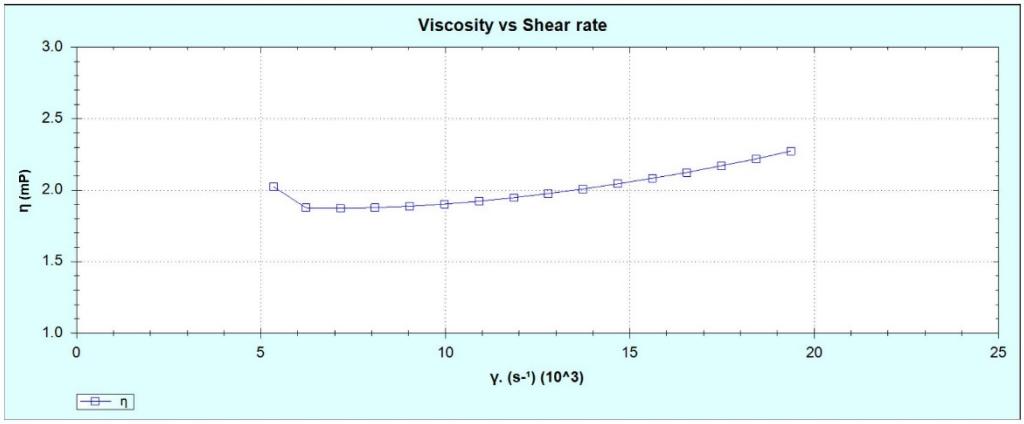
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EL ALIADO PRECISO

Tabla de datos

t[s]	T [C°]	Esfuerzo [Pa]	Tasa de cizalladura [s^{-1}]	Viscosidad [mP]
7.5	25	10.81	5342	20.24
15	25	11.67	6217	18.77
22.5	25	13.4	7155	18.73
30	25	15.19	8092	18.77
37.5	25	17.05	9033	18.88
45	25	18.98	9976	19.03
52.5	25	20.98	10910	19.23
60	25	23.08	11850	19.47
67.5	25	25.28	12790	19.76
75	25	27.57	13730	20.08
82.5	25	29.99	14670	20.44
90	25	32.52	15610	20.84
97.5	25	35.14	16550	21.24
105	25	37.97	17490	21.71
112.5	25	40.89	18430	22.19
120	25	44.02	19360	22.73

Grafico reporte



Viscosidad final

Valor	Unidad
20.12	mP

Resultado viscosidad

Equipo

Kinexus Pro (www.malvern.com)



Muestra

Código CECOLTEC	Nombre de la muestra
C948-CF2	Vehículo farmacéutico para estabilizar la superficie ocular EJ 2

Condiciones de la medida

Sistema de medida: Plato – Plato 40
Tratamiento:

Tasa de cizalladura: 5,000 s-1 a 20,000 s-1
Muestreo: 15 puntos.
Gap: 0.1 mm
Temperatura: 25 °C ± 0.01 °C

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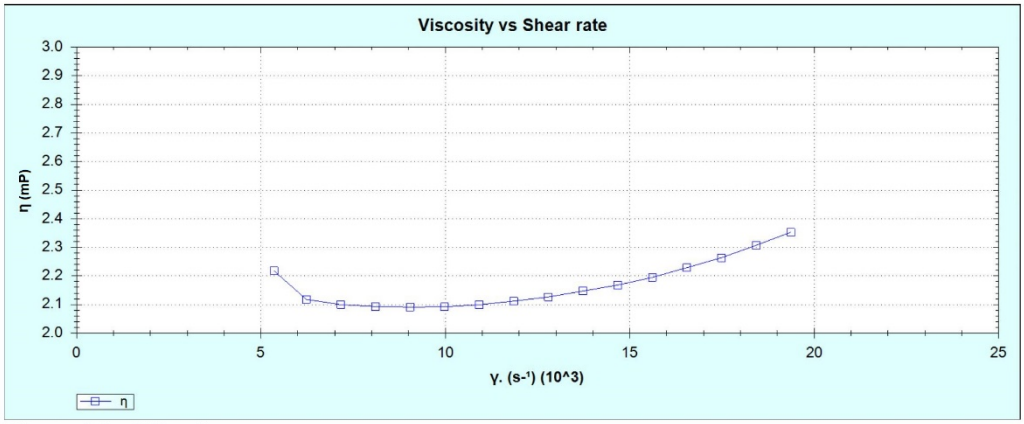
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EL ALIADO PRECISO

Tabla de datos

t[s]	T [C°]	Esfuerzo [Pa]	Tasa de cizalladura [s^{-1}]	Viscosidad [mP]
7.5	25.01	11.87	5351	22.18
15	25.01	13.19	6228	21.18
22.5	25.01	15.04	7165	20.99
30	25.01	16.96	8103	20.93
37.5	25.01	18.9	9041	20.91
45	25.01	20.87	9978	20.92
52.5	25.01	22.91	10920	21.01
60	25.01	25.03	11850	21.12
67.5	25.01	27.2	12790	21.26
75	25.01	29.48	13730	21.47
82.5	25.01	31.81	14670	21.68
90	25.01	34.26	15610	21.95
97.5	25.01	36.88	16550	22.29
105	25.01	39.58	17480	22.64
112.5	25.01	42.51	18430	23.07
120	25.01	45.56	19360	23.53

Grafico reporte



Viscosidad final

Valor	Unidad
21.7	mP

Resultado viscosidad

Equipo

Kinexus Pro (www.malvern.com)



Muestra

Código CECOLTEC	Nombre de la muestra
C948-CF3	Vehiculo farmaceutico para estabilizar la superficie ocular EJ 3

Condiciones de la medida

Sistema de medida: Plato – Plato 40
Tratamiento:

Tasa de cizalladura: 5,000 s-1 a 20,000 s-1
Muestreo: 15 puntos.
Gap: 0.1 mm
Temperatura: 37 °C ± 0.01 °C

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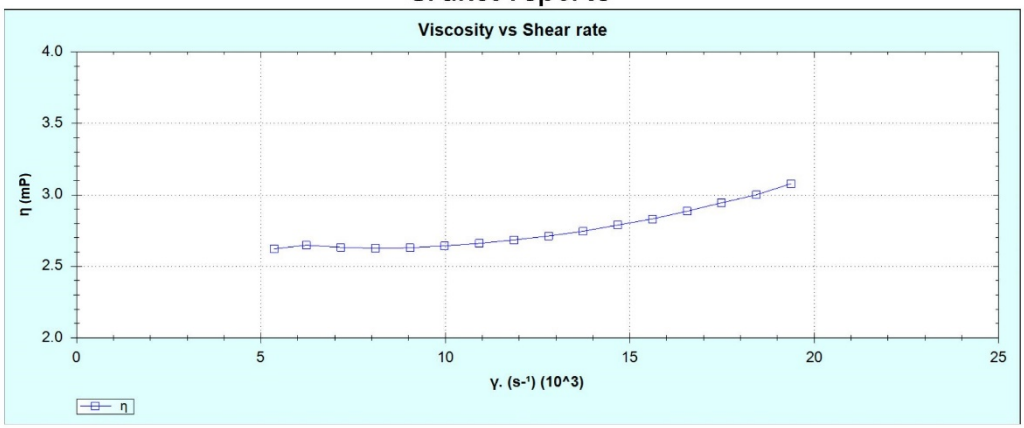
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EL ALIADO PRECISO

Tabla de datos

t[s]	T [C°]	Esfuerzo [Pa]	Tasa de cizalladura [s^{-1}]	Viscosidad [mP]
7.5	25	14.03	5352	26.33
15	25	16.49	6228	26.48
22.5	25	18.87	7165	26.39
30	25	21.29	8103	26.6
37.5	25	23.78	9041	26.3
45	25	26.38	9978	26.44
52.5	25	29.04	10920	26.6
60	25	31.84	11860	26.85
67.5	25	34.71	12800	27.12
75	25	37.71	13730	27.46
82.5	25	40.92	14670	27.89
90	25	44.22	15610	28.32
97.5	25	47.77	16550	28.86
105	25	51.5	17490	29.45
112.5	25	55.3	18430	30.01
120	25	59.62	19370	30.78

Grafico reporte



Viscosidad final

Valor	Unidad
27.70	mP

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Resultado viscosidad

Equipo

Kinexus Pro (www.malvern.com)



Muestra

Código CECOLTEC	Nombre de la muestra
C948-CF4	Vehículo farmacéutico para estabilizar la superficie ocular EJ 4

Condiciones de la medida

Sistema de medida: Plato – Plato 40
Tratamiento:

Tasa de cizalladura: 5,000 s-1 a 20,000 s-1
Muestreo: 15 puntos.
Gap: 0.1 mm
Temperatura: 25 °C ± 0.01 °C

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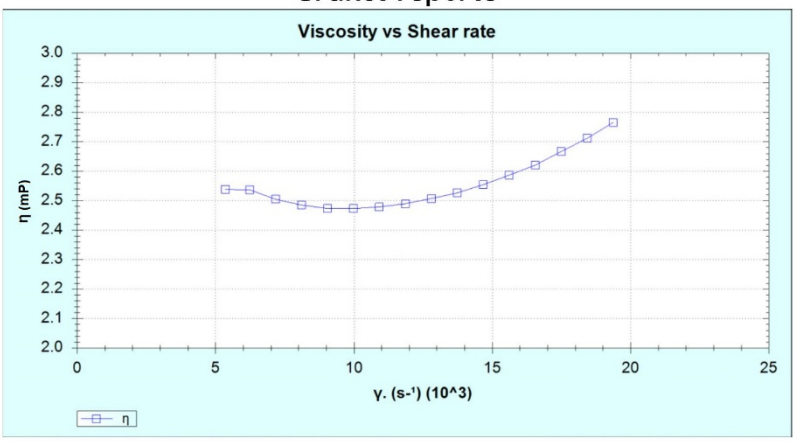
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EL ALIADO PRECISO

Tabla de datos

t[s]	T [C°]	Esfuerzo [Pa]	Tasa de cizalladura [s^{-1}]	Viscosidad [mP]
7.5	25.06	13.25	5351	24.76
15	25.07	15.27	6228	24.52
22.5	25.07	17.33	7165	24.19
30	25.07	19.45	8103	24.05
37.5	25.07	21.63	9041	23.93
45	25.06	23.89	9978	23.95
52.5	25.05	26.21	10920	24.01
60	25.05	28.63	11850	24.15
67.5	25.04	31.14	12800	24.34
75	25.04	33.75	13730	24.57
82.5	25.03	36.48	14670	24.86
90	25.03	39.26	15610	25.15
97.5	25.02	42.3	16550	25.56
105	25.02	45.43	17490	25.98
112.5	25.02	48.7	18430	26.43
120	25.02	52.36	19370	27.04

Grafico reporte



Viscosidad final

Valor	Unidad
24.8	mP

Resultado viscosidad

Equipo

Kinexus Pro (www.malvern.com)



Muestra

Código CECOLTEC	Nombre de la muestra
C948-CF5	Vehículo farmacéutico para estabilizar la superficie ocular EJ 5

Condiciones de la medida

Sistema de medida: Plato – Plato 40
Tratamiento:

Tasa de cizalladura: 5,000 s-1 a 20,000 s-1
Muestreo: 15 puntos.
Gap: 0.1 mm
Temperatura: 25 °C ± 0.01 °C

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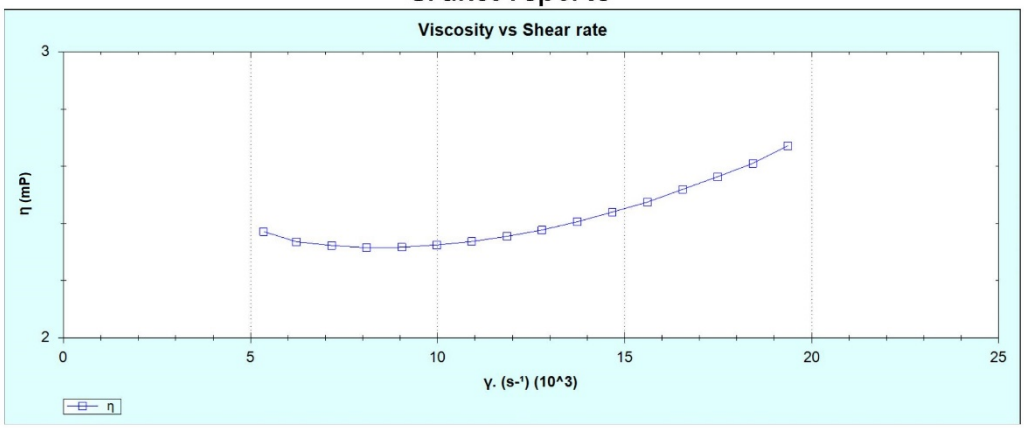
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EL ALIADO PRECISO

Tabla de datos

t[s]	T [C°]	Esfuerzo [Pa]	Tasa de cizalladura [s^{-1}]	Viscosidad [mP]
7.5	25	12.69	5351	23.72
15	25	14.55	6228	23.36
22.5	25	16.64	7165	23.23
30	25	18.76	8103	23.15
37.5	25	20.95	9040	23.17
45	25	23.2	9978	23.25
52.5	25	25.51	10920	23.37
60	25	27.91	11850	23.55
67.5	25	30.41	12790	23.77
75	25	33.04	13730	24.06
82.5	25	35.8	14670	24.4
90	25	38.63	15610	24.75
97.5	25	41.69	16550	25.19
105	25	44.84	17490	25.64
112.5	25	48.1	18430	26.1
120	25	51.73	19370	26.71

Grafico reporte



Viscosidad final

Valor	Unidad
24.2	mP

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Resultados productos de uso crónico comercializados en Colombia

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REPORTE DE ANÁLISIS/ANALYSIS REPORT

Muestra/Sample #: 244595

Empresa / Company: ESPECIALIDADES OFTALMOLOGICAS S.A. **Telf. / Phone:** 448 19 18

Sede / Headquarters: Sede principal Carrera 37 A No. 2 Sur 104, Loma Alejandria, Poblado, Medellí

Producto / Product: LATANOX

Muestra / Sample: Lote: 1151126; Fecha de Vencimiento: 06/2019; Fabricante: Procaps

Fecha de Recepción / Reception date: 2017/09/20 **Temp. de Recepción / Temp. Reception:** 16,4ºC

Cantidad / Amount: 1 Unidad /1 unit

Contenedor / Container: Frasco gotero con tapa/ Dropper bottle with lid

Enviada por /Send by: Tatiana María Gómez Gaviria

Aspecto / Aspect: Liquido translucido / Translucent liquid
Olor / Smell: Inobjetable/ Unobjectionable
Color / Color: Incoloro/ Colorless

Análisis Fisicoquímico/ Physicochemical Analysis	Fecha/ Date	Unidad/ Unit	Resultado/ Result	Especificaciones(**)/ Specifications(**)	Método/ Method
Osmolalidad/Osmolality	2017/09/20	mOsm/Kg	271	NA	USP 40 <785>

(**) Según Norma / Acoordinng to Standard:

(*) Métodos acreditados/Methods Accredited: ONAC, Certificado/Certificate: 10-LAB-053 Fecha/Date: 2014-09-05 ISO/IEC 17025:2005

NOTA: Este resultado corresponde, exclusivamente a la muestra recibida y analizada en el laboratorio/This result correspond only to the sample received and analyzed by the laboratory

Luz Elena Osorio C

Luz E. Osorio Castaño
T.P. 01345801606001664
Química Farmacéutica U de A
Coordinadora
Fecha / Date: 2017/09/20

Fecha de Impresión/printing date: 2017/09/20

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FIN DE INFORME/ END OF REPORT

Veracidad a toda ¡Prueba!

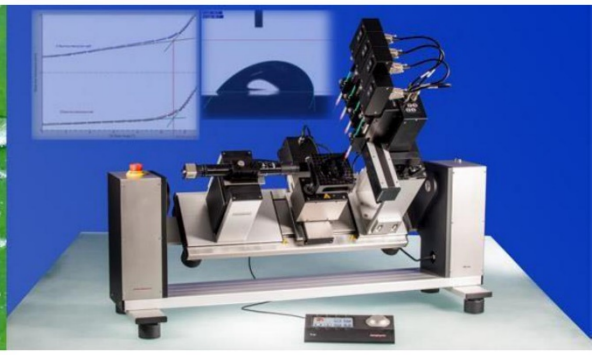
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EL ALIADO PRECISO

Informe de resultado tensión superficial

Equipo

Dataphysics OCA15





Características del equipo:

Medida	Rango
Ángulo de contacto [°]	0 – 180 ° ± 0.1°
Tensión superficial e interfacial [Dinas/cm]	0.01 2000 Dinas/cm ± 0.01 Dinas/cm

Condiciones de medición:

Técnica usada: Gota - péndulo
Jeringa utilizada: Halmilton de 1 mL
Temperatura: 25°C temperatura de muestra. El laboratorio y el equipo no cuentan con control de temperatura sobre la muestra.
Dosificación: 1 uL/ seg

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EL ALIADO PRECISO

Muestras

Código Cecoltec	Nombre de la muestra	Lote
C988-TS2	Latanox	Lote 1151126

Resultados

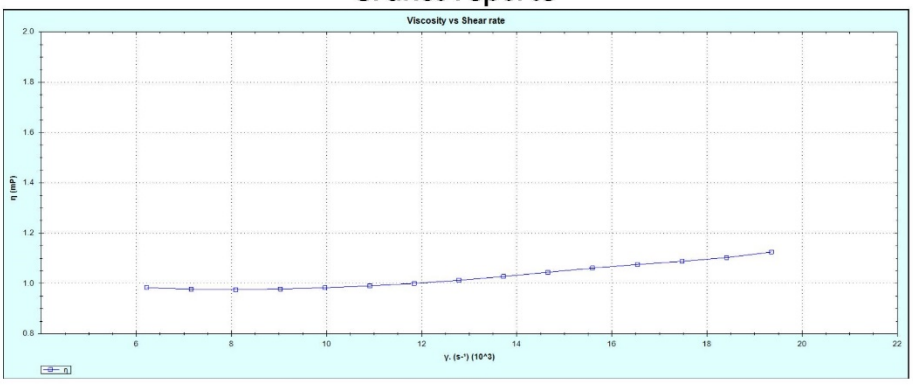
Muestra	Medición 1 (Dinas/cm)	Medición 2 (Dinas/cm)	Medición 3 (Dinas/cm)	Medición 4 (Dinas/cm)	Medición 5 (Dinas/cm)	Promedio (Dinas/cm)	Desviación estándar (Dinas/cm)
Latanox Lote 1151126	36,13	35,97	36,15	36,28	36,09	36,124	0,11

cecoltec
EL ALIADO PRECISO

Tabla de datos

t[s]	T [C°]	Esfuerzo [Pa]	Tasa de cizalladura [s^{-1}]	Viscosidad [mP]
15	25.01	6.11	6217	9.835
23	25.01	7	7155	9.777
30	25.01	7.89	8092	9.754
38	25	8.83	9030	9.782
45	25	9.8	9967	9.833
53	25	10.8	10900	9.907
60	25	11.85	11840	10.01
68	25	12.94	12780	10.13
75	25	14.1	13720	10.28
83	25	15.31	14660	10.45
90	25	16.55	15590	10.61
98	25	17.79	16540	10.76
105	25	19.02	17480	10.88
113	25	20.32	18410	11.03
120	25	21.78	19350	11.25

Grafico reporte



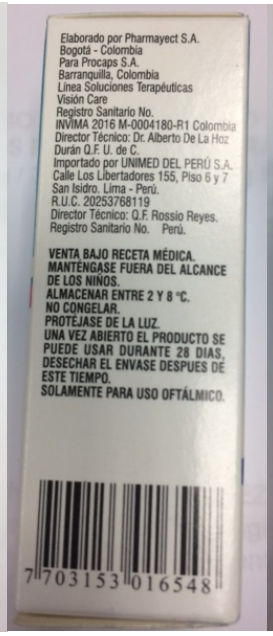
Viscosidad final

Valor	Unidad
10.28	mP

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5 mL
SOLUCIÓN OFTÁLMICA
PROCAPS
Latanox®
LATANOPROST 50 mcg/mL


Elaborado por Pharmayect S.A.
Bogotá - Colombia
Para Procaps S.A.
Barranquilla, Colombia
Línea Soluciones Terapéuticas
Visión Care
Registro Sanitario No.
INVIMA 2016 M-0004180-R1 Colombia
Director Técnico: Dr. Alberto De La Hoz Durán Q.F. U. de C.
Importado por UNIMED DEL PERÚ S.A.
Calle Los Libertadores 155, Piso 6 y 7
San Isidro. Lima - Perú.
R.U.C. 20253768119
Director Técnico: Q.F. Rossio Reyes.
Registro Sanitario No. Perú.
VENTA BAJO RECETA MÉDICA.
MANTÉNGASE FUERA DEL ALCANCE DE LOS NIÑOS.
ALMACENAR ENTRE 2 Y 8 °C.
NO CONGELAR.
PROTÉJASE DE LA LUZ.
UNA VEZ ABIERTO EL PRODUCTO SE PUEDE USAR DURANTE 28 DIAS, DESECHAR EL ENVASE DESPUES DE ESTE TIEMPO.
SOLAMENTE PARA USO OFTÁLMICO.
7 703153 016548


COMPOSICIÓN: cada mL de solución oftálmica contiene:
Latanoprost ..... 50 mcg
Excipientes c.s.p. 1 mL.
VÍA DE ADMINISTRACIÓN:
Colombia: conjuntival. Perú y otros países: oftálmica.
DOSIFICACIÓN: según criterio médico. 1 mL = 36 gotas.
CONTRAINDICACIONES, PRECAUCIONES Y ADVERTENCIAS:
Hipersensibilidad conocida a alguno de los componentes del producto. El latanoprost debe usarse con precaución en pacientes con antecedentes de inflamación intraocular y deberá ser evitado en pacientes con inflamación intraocular activa. Pacientes con afaquia o pseudofaquia. Pacientes con factores de riesgo de padecer edema macular. Puede cambiar gradualmente el color del ojo incrementando la cantidad de pigmento café. Antes de comenzar el tratamiento debe advertirse la posibilidad de un cambio de color de los ojos. Un tratamiento unilateral puede resultar en una heterocromía permanente. Para las personas que utilizan lentes de contacto se recomienda quitárselos antes de la aplicación y después de 10 a 15 minutos colocarlos nuevamente. Para evitar contaminación no toque ni ponga en contacto la punta del dispensador con cualquier superficie.
El preservante Cloruro de Benzalconio puede depositarse en los lentes de contacto blandos, estos deben colocarse 15 minutos despues de la aplicación del fármaco.
PROCAPS

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REPORTE DE ANÁLISIS/ANALYSIS REPORT

Muestra/Sample #: 257561

Empresa / Company: ESPECIALIDADES OFTALMOLOGICAS S.A. **Telf. / Phone:** 448 19 18

Sede / Headquarters: Sede principal Carrera 37 A No. 2 Sur 104, Loma Alejandria, Poblado, Medelli

Producto / Product: BRIMOFTAL

Muestra / Sample: Lote: 6E303B; Laboratorio: Tecnoquímicas S.A.

Fecha de Recepción / Reception date: 2018-02-06 **Temp. de Recepción / Temp. Reception:** 26,1°C

Cantidad / Amount: 1 Unidad/ 1 unit

Contenedor / Container: Frasco gotero con tapa/ Dropper bottle with lid

Enviada por /Send by: Tatiana María Gómez Gaviria

Aspecto / Aspect: Líquido translúcido, homogéneo, libre de particulas extrañas/ Translucent, homogeneous liquid free of foreign particles.

Olor / Smell: Inobjetable/Unobjectionable

Color / Color: Leve Amarillo/ Light yellow

Análisis Fisicoquímico/ Physicochemical Analysis	Fecha/ Date	Unidad/ Unit	Resultado/ Result	Especificaciones(**)/ Specifications(**)	Método/ Method
Osmolalidad/Osmolality	2018-02-06	mOsm/Kg	292	NA	USP 40 <785>

(**) Según Norma / Acoordinng to Standard:

(*) Métodos acreditados/Methods Accredited: ONAC, Certificado/Certificate: 10-LAB-053 Fecha/Date: 2014-09-05 ISO/IEC 17025:2005

NOTA: Este resultado corresponde, exclusivamente a la muestra recibida y analizada en el laboratorio/This result correspond only to the sample received and analyzed by the laboratory

Luz Elena Osorio C

Luz E. Osorio Castaño
T.P. 01345801606001664
Química Farmacéutica U de A
Coordinadora
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FIN DE INFORME/ END OF REPORT

Veracidad a toda ¡Prueba!

Resultado viscosidad

Equipo

Kinexus Pro (www.malvern.com)



Muestra

Código CECOLTEC	Nombre de la muestra	Lote
C1178 - CF1	Biofocus (abbol)	7A5975
C1178 - CF2	Azarga (Alcon a Novrtis company)	65963
C1178 - CF3	Simbrinza (Alcon a Novrtis company)	17G12DE
C1178 - CF4	Oloftal (tecnoquimicas)	7J360
C1178 - CF5	Brimoftal (tecnoquimicas)	7M396B
C1178 - CF6	Agglad ofteno (sophia)	4015466
C1178 - CF7	Lumigan (al ergan)	E79821
C1178 - CF8	Ganfort (alle gan)	E79942
C1180 - CF1	Dorzopt	1076238 SL C
C1184 - CF1	Alap 0,2% (procaps)	1164658 SL C
C1184 - CF2	Krytan tek ofteno (sophia)	4016194
C1184 - CF3	Trusopt (MSD)	M040389

Condiciones de la medida

Sistema de medida: Plato - Plato 40
Tratamiento:

Tasa de cizalladura: 5,000 s-1 a 20,000 s-1
Muestreo: 15 puntos.
Gap: 0.1 mm
Temperatura: 25 °C ± 0.01 °C

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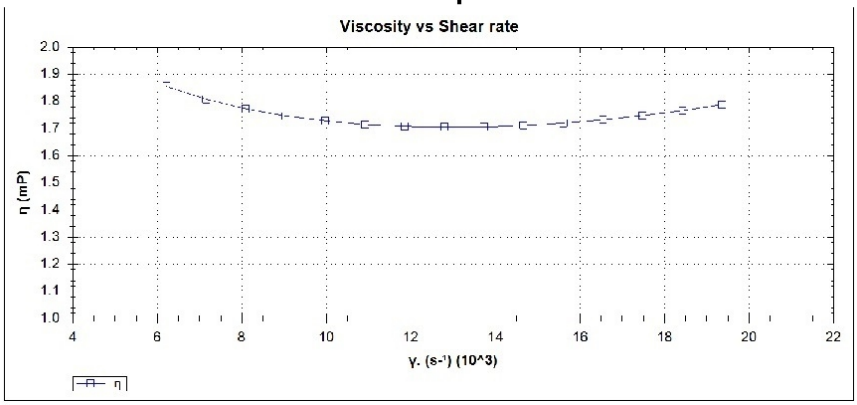
cecoltec
EL ALIADO PRECISO

Brimoftal (tecnoquimicas) 7M396B

Tabla de datos

t[s]	T [C°]	Esfuerzo [Pa]	Tasa de cizalladura [s^{-1}]	Viscosidad [mP]
15	25	11.54	6217.00	1.856
22.5	25	12.94	7155.00	1.809
30	25	14.35	8092.00	1.773
37.5	25	15.78	9030.00	1.747
45	25	17.24	9971.00	1.729
52.5	25	18.71	10910.00	1.715
60	25	20.24	11850.00	1.708
67.5	25	21.82	12790.00	1.706
75	25	23.41	13730.00	1.706
82.5	25	25.09	14660.00	1.711
90	25	26.84	15600.00	1.721
97.5	25	28.67	16550.00	1.733
105	25	30.57	17480.00	1.749
112.5	25	32.54	18420.00	1.766
120	25	34.63	19360.00	1.789

Grafico reporte



Viscosidad final

Valor	Unidad
1.7478	mP

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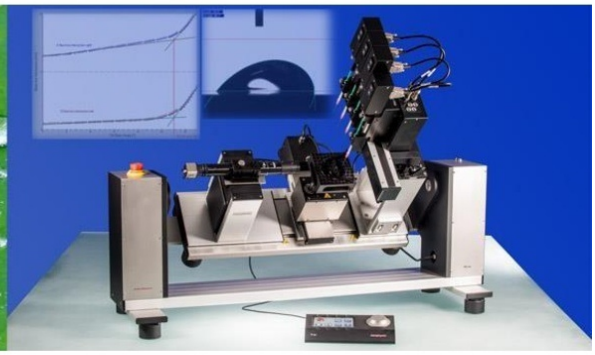
cecoltec
EL ALIADO PRECISO

Informe de resultado tensión superficial

Equipo

Dataphysics OCA15





Características del equipo:

Medida	Rango
Ángulo de contacto [°]	0 – 180 ° ± 0.1°
Tensión superficial e interfacial [Dinas/cm]	0.01 2000 [Dinas/cm] ± 0.01 [Dinas/cm]

Condiciones de medición:

Técnica usada: Gota - péndulo
Jeringa utilizada:Halmilton de 1 mL
Temperatura: 25 ° C
Dosificación: 1 uL/ seg

cecoltec
EL ALIADO PRECISO

Muestras

Código Cecoltec	Nombre de la muestra	Lote
C1178 - TS1	Biofocus (abbot)	7A5975
C1178 - TS2	Azarga (Alcon a Novrtis comoany)	65963
C1178 - TS3	Simbrinza (Alcon a Novrtis company)	17G12DE
C1178 - TS4	Oloftal (tecnoquimicas)	7J360
C1178 - TS5	Brimoftal (tecnoquimicas)	7M396B
C1178 - TS6	Agglad ofteno (soohia)	4015466
C1178 - TS7	Lumigan (allergan)	E79821
C1178 - TS8	Ganfort (allergan)	E79942
C1180- TS1	Dorzopt	1076238 SL C
C1184 - TS1	Alap 0,2% (procaps)	1164658 SL C
C1184 - TS2	Krytan tek ofteno (sophia)	4016194
C1184 - TS3	Trusopt (MSD)	M040389

Resultados

Muestra	Medida 1 (Dinas/cm)	Medida 2 (Dinas/cm)	Medida 3 (Dinas/cm)	Medida 4 (Dinas/cm)	Medida 5 (Dinas/cm)	Promedio (Dinas/cm)	Desviación
C1178 - TS1	51.13	51.09	51.37	51.18	51.5	51.25	0.16
C1178 - TS2	47.76	47.45	47.42	48.22	47.85	47.74	0.29
C1178 - TS3	52.94	53.8	52.86	52.96	53.15	53.14	0.34
C1178 - TS4	50.22	50.17	50.58	51.86	51.32	50.83	0.66
C1178 - TS5	53.81	52.21	53.49	52.28	52.4	52.84	0.67
C1178 - TS6	48.31	48.7	48.75	48.79	48.78	48.67	0.18
C1178 - TS7	63.46	63.25	63.31	63.89	63.83	63.55	0.26
C1178 - TS8	64.88	64.33	64.9	64.89	65	64.80	0.24
C1180- TS1	44.32	43.71	44.08	44.3	44.65	44.21	0.31
C1184 - TS1	63.28	63.32	63.62	63.19	63.27	63.34	0.15
C1184 - TS2	78.94	78.26	77.42	78.58	78.77	78.39	0.54
C1184 - TS3	49.87	49.26	49.77	49.28	49.6	49.56	0.25

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Brimoftal®
Brimonidina Tartrato 0,2%
MUESTRA MÉDICA
Prohibida su venta
Vision
Solución oftálmica estéril
5 mL
MEDICAMENTO ESENCIAL
Brimoftal®
Brimonidina Tartrato 0,2%
Composición: Cada mL de Solución Oftálmica Estéril de Brimoftal® contiene Brimonidina Tartrato 2,0 mg, excipientes c.s. (Cada mL contiene 29 gotas). Posología: Según prescripción médica. Vía de administración: Tópica oftálmica. Contraindicaciones y advertencias: Contraindicado en pacientes con hipersensibilidad al Tartrato de Brimonidina o a cualquiera de los componentes de esta medicación. Contraindicado en pacientes que se encuentran recibiendo una terapia inhibitoria de la monoamino oxidasa (MAO). Advertencias: Usar con precaución en pacientes con depresión, insuficiencia coronaria o cerebral, fenómeno de Raynaud, hipotensión ortostática o tromboangeitis obliterante. Pacientes con problemas renales o hepáticos, con enfermedades cardiovasculares severas, embarazo y lactancia.
El cloruro de benzalconio como preservante, puede depositarse en los lentes de contacto blandos, estos deben retirarse y colocarse como mínimo 15 minutos después.
Evite contaminar el contenido y la punta del gotero. Evítese el congelamiento y manténgase en posición vertical.
EL PRODUCTO DEBE SER UTILIZADO HASTA 28 DÍAS DESPUÉS DE ABIERTO. ALMACENAR A TEMPERATURA INFERIOR A 30 °C. MANTÉNGASE FUERA DEL ALCANCE DE LOS NIÑOS. VENTA BAJO FÓRMULA MÉDICA.
Fabricado por Tecnofar TQ S.A.S., Villa Rica - Colombia
Comercializado por Tecnoquímicas S.A., Cali - Colombia
Colombia: Reg. San. No. INVIMA 2012 M-0013147
Cualquier inquietud comuníquese con la línea 01 8000 523339.
0815-2T
L.6E303B
F. MY 16
V. MY 18
8185262


Brimoftal®
Brimonidina Tartrato 0,2%
MUESTRA MÉDICA
Prohibida su venta
Vision
Solución oftálmica estéril
5 mL
MEDICAMENTO ESENCIAL
L-7M396B
F-SEP 2017
V-SEP 2019
8185262

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Medellín - Colombia

REPORTE DE ANÁLISIS/ANALYSIS REPORT

Muestra/Sample #: 257559

Empresa / Company: ESPECIALIDADES OFTALMOLOGICAS S.A. **Telf. / Phone:** 448 19 18

Sede / Headquarters: Sede principal Carrera 37 A No. 2 Sur 104, Loma Alejandria, Poblado, Medellí

Producto / Product: SIMBRINZA

Muestra / Sample: Lote: 17I06MI; Laboratorio: Alcon a Novrtis company

Fecha de Recepción / Reception date: 2018-02-06 **Temp. de Recepción / Temp. Reception:** 26,1°C

Cantidad / Amount: 1 Unidad/ 1 unit

Contenedor / Container: Frasco gotero con tapa/ Dropper bottle with lid

Enviada por /Send by: Tatiana María Gómez Gaviria

Aspecto / Aspect: Producto opalescente, homogéneo, libre de particulas extrañas/ Opalescent, homogeneous product, free of foreign particles.

Olor / Smell: Inobjetable/Unobjectionable

Color / Color: Blanco/White

Análisis Fisicoquímico/ Physicochemical Analysis	Fecha/ Date	Unidad/ Unit	Resultado/ Result	Especificaciones(**)/ Specifications(**)	Método/ Method
Osmolalidad/Osmolality	2018-02-06	mOsm/Kg	266	NA	USP 40 <785>

(**) Según Norma / Acoordinng to Standard:

(*) Métodos acreditados/Methods Accredited: ONAC, Certificado/Certificate: 10-LAB-053 Fecha/Date: 2014-09-05 ISO/IEC 17025:2005

NOTA: Este resultado corresponde, exclusivamente a la muestra recibida y analizada en el laboratorio/This result correspond only to the sample received and analyzed by the laboratory

Luz Elena Osorio C

Luz E. Osorio Castaño
T.P. 01345801606001664
Química Farmacéutica U de A
Coordinadora
Fecha / Date: 2018-02-07

Fecha de Impresión/printing date: 2018-02-07

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Resultado viscosidad

Equipo

Kinexus Pro (www.malvern.com)



Muestra

Código CECOLTEC	Nombre de la muestra	Lote
C1178 - CF1	Biofocus (abbol)	7A5975
C1178 - CF2	Azarga (Alcon a Novrtis company)	65963
C1178 - CF3	Simbrinza (Alcon a Novrtis company)	17G12DE
C1178 - CF4	Oloftal (tecnoquimicas)	7J360
C1178 - CF5	Brimoftal (tecnoquimicas)	7M396B
C1178 - CF6	Agglad ofteno (sophia)	4015466
C1178 - CF7	Lumigan (al ergan)	E79821
C1178 - CF8	Ganfort (alle gan)	E79942
C1180 - CF1	Dorzopt	1076238 SL C
C1184 - CF1	Alap 0,2% (procaps)	1164658 SL C
C1184 - CF2	Krytan tek ofteno (sophia)	4016194
C1184 - CF3	Trusopt (MSD)	M040389

Condiciones de la medida

Sistema de medida: Plato - Plato 40
Tratamiento:

Tasa de cizalladura: 5,000 s-1 a 20,000 s-1
Muestreo: 15 puntos.
Gap: 0.1 mm
Temperatura: 25 °C ± 0.01 °C

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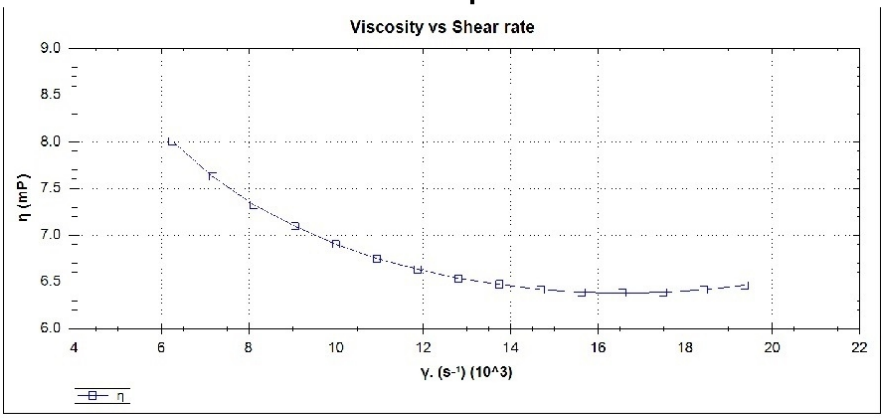
cecoltec
EL ALIADO PRECISO

Simbrinza (Alcon a Novrtis company) 17G12DE

Tabla de datos

t[s]	T [C°]	Esfuerzo [Pa]	Tasa de cizalladura [s^{-1}]	Viscosidad [mP]
15	25	49.98	6240.00	8.009
22.5	25	54.74	7177.00	7.626
30	25	59.46	8118.00	7.325
37.5	25	64.29	9056.00	7.098
45	25	69	9994.00	6.904
52.5	25	73.79	10930.00	6.751
60	25	78.78	11870.00	6.637
67.5	25	83.72	12810.00	6.538
75	25	88.98	13740.00	6.474
82.5	25	94.25	14680.00	6.419
90	25	99.77	15620.00	6.388
97.5	25	105.7	16560.00	6.386
105	25	111.7	17490.00	6.388
112.5	25	118.3	18430.00	6.417
120	25	125.2	19370.00	6.465

Grafico reporte



Viscosidad final

Valor	Unidad
6.7883	mP

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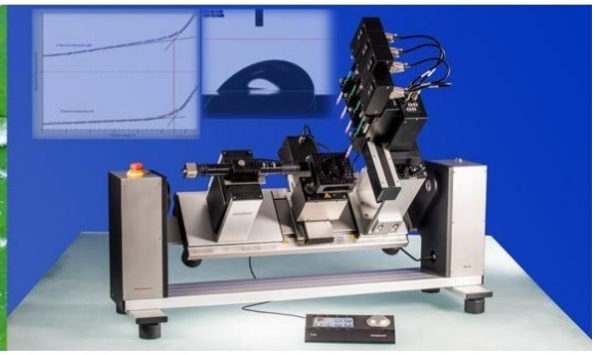
cecoltec
EL ALIADO PRECISO

Informe de resultado tensión superficial

Equipo

Dataphysics OCA15





Características del equipo:

Medida	Rango
Ángulo de contacto [°]	0 – 180 ° ± 0.1°
Tensión superficial e interfacial [Dinas/cm]	0.01 2000 [Dinas/cm] ± 0.01 [Dinas/cm]

Condiciones de medición:

Técnica usada: Gota - péndulo
Jeringa utilizada:Halmilton de 1 mL
Temperatura: 25 ° C
Dosificación: 1 uL/ seg

cecoltec
EL ALIADO PRECISO

Muestras

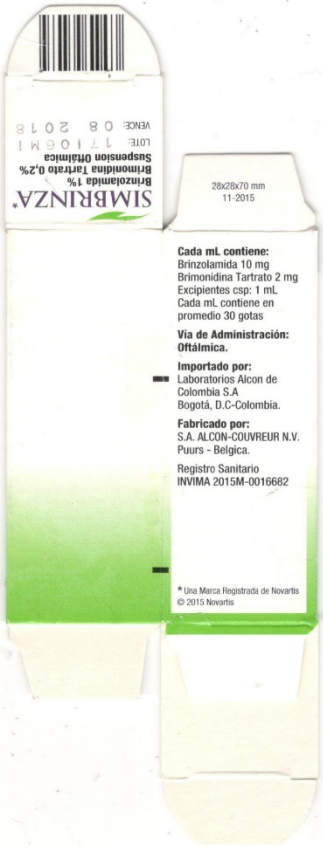
Código Cecoltec	Nombre de la muestra	Lote
C1178 - TS1	Biofocus (abbot)	7A5975
C1178 - TS2	Azarga (Alcon a Novrtis comoany)	65963
C1178 - TS3	Simbrinza (Alcon a Novrtis company)	17G12DE
C1178 - TS4	Oloftal (tecnoquimicas)	7J360
C1178 - TS5	Brimoftal (tecnoquimicas)	7M396B
C1178 - TS6	Agglad ofteno (soohia)	4015466
C1178 - TS7	Lumigan (allergan)	E79821
C1178 - TS8	Ganfort (allergan)	E79942
C1180- TS1	Dorzopt	1076238 SL C
C1184 - TS1	Alap 0,2% (procaps)	1164658 SL C
C1184 - TS2	Krytan tek ofteno (sophia)	4016194
C1184 - TS3	Trusopt (MSD)	M040389

Resultados

Muestra	Medida 1 (Dinas/cm)	Medida 2 (Dinas/cm)	Medida 3 (Dinas/cm)	Medida 4 (Dinas/cm)	Medida 5 (Dinas/cm)	Promedio (Dinas/cm)	Desviación
C1178 - TS1	51.13	51.09	51.37	51.18	51.5	51.25	0.16
C1178 - TS2	47.76	47.45	47.42	48.22	47.85	47.74	0.29
C1178 - TS3	52.94	53.8	52.86	52.96	53.15	53.14	0.34
C1178 - TS4	50.22	50.17	50.58	51.86	51.32	50.83	0.66
C1178 - TS5	53.81	52.21	53.49	52.28	52.4	52.84	0.67
C1178 - TS6	48.31	48.7	48.75	48.79	48.78	48.67	0.18
C1178 - TS7	63.46	63.25	63.31	63.89	63.83	63.55	0.26
C1178 - TS8	64.88	64.33	64.9	64.89	65	64.80	0.24
C1180- TS1	44.32	43.71	44.08	44.3	44.65	44.21	0.31
C1184 - TS1	63.28	63.32	63.62	63.19	63.27	63.34	0.15
C1184 - TS2	78.94	78.26	77.42	78.58	78.77	78.39	0.54
C1184 - TS3	49.87	49.26	49.77	49.28	49.6	49.56	0.25

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SIMBRINZA*
Brinzolamida 1%
Brimonidina Tartrato 0,2%
Suspensión Oftálmica
LOTE: 17108M1
VENCE: 08 2018
28x28x70 mm
11-2015
Cada mL contiene:
Brinzolamida 10 mg
Brimonidina Tartrato 2 mg
Excipientes csp: 1 mL
Cada mL contiene en promedio 30 gotas
Vía de Administración: Oftálmica.
Importado por:
Laboratorios Alcon de Colombia S.A
Bogotá, D.C-Colombia.
Fabricado por:
S.A. ALCON-COUVREUR N.V.
Puurs - Belgica.
Registro Sanitario
INVIMA 2015M-0016682
* Una Marca Registrada de Novartis
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590/43816-0
590/43816-0
590/43816-0
MUESTRA MÉDICA
PROHIBIDA SU VENTA
SIMBRINZA*
Brinzolamida 1%
Brimonidina
Tartrato 0,2%
Suspension
Oftálmica
Estéril
Alcon
a Novartis company
2,5 mL
Contraindicaciones, Advertencias y Precauciones:
Ver inserto.
El preservante Cloruro de Benzalconio puede depositarse en los lentes de contacto blandos, estos deben colocarse 15 minutos después de la aplicación del fármaco.
Posologia: Según Criterio Médico
Venta con Formula Médica
MANTENER FUERA DEL ALCANCE DE LOS NIÑOS.
Almacenar a temperatura inferior a 30 °C.
Desechar 32 dias después de abierto.
10.


SIMBRINZA*
Brinzolamida 1%
Brimonidina Tartrato 0,2%
Suspensión Oftálmica
LOTE: 17G12DE
VENCE: 06 2018
28x28x70 mm
11-2015
Cada mL contiene:
Brinzolamida 10 mg
Brimonidina Tartrato 2 mg
Excipientes csp: 1 mL
Cada mL contiene en promedio 30 gotas
Vía de Administración: Oftálmica.
Importado por:
Laboratorios Alcon de Colombia S.A
Bogotá, D.C-Colombia.
Fabricado por:
S.A. ALCON-COUVREUR N.V.
Puurs - Belgica.
Registro Sanitario
INVIMA 2015M-0016682
* Una Marca Registrada de Novartis
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Laboratorio de Análisis S.A.S.

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www.tecnimicro.net
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Medellín - Colombia

REPORTE DE ANÁLISIS/ANALYSIS REPORT

Muestra/Sample #: 257558

Empresa / Company: ESPECIALIDADES OFTALMOLOGICAS S.A. **Telf. / Phone:** 448 19 18

Sede / Headquarters: Sede principal Carrera 37 A No. 2 Sur 104, Loma Alejandria, Poblado, Medellí

Producto / Product: AZARGA

Muestra / Sample: Lote: 65963; Laboratorio: Alcon a Novrtis company

Fecha de Recepción / Reception date: 2018-02-06 **Temp. de Recepción / Temp. Reception:** 26,1°C

Cantidad / Amount: 1 Unidad/ 1 unit

Contenedor / Container: Frasco gotero con tapa/ Dropper bottle with lid

Enviada por /Send by: Tatiana María Gómez Gaviria

Aspecto / Aspect: Producto opalescente, homogéneo, libre de partículas extrañas/ Opalescent, homogeneous product, free of foreign particles.

Olor / Smell: Inobjetable/Unobjectionable

Color / Color: Blanco/White

Análisis Fisicoquímico/ Physicochemical Analysis	Fecha/ Date	Unidad/ Unit	Resultado/ Result	Especificaciones(**)/ Specifications(**)	Método/ Method
Osmolalidad/Osmolality	2018-02-06	mOsm/Kg	286	NA	USP 40 <785>

(**) Según Norma / Acoordinng to Standard:

(*) Métodos acreditados/Methods Accredited: ONAC, Certificado/Certificate: 10-LAB-053 Fecha/Date: 2014-09-05 ISO/IEC 17025:2005

NOTA: Este resultado corresponde, exclusivamente a la muestra recibida y analizada en el laboratorio/This result correspond only to the sample received and analyzed by the laboratory

Luz Elena Osorio C

Luz E. Osorio Castaño
T.P. 01345801606001664
Química Farmacéutica U de A
Coordinadora
Fecha / Date: 2018-02-07

Fecha de Impresión/printing date: 2018-02-07

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FIN DE INFORME/ END OF REPORT

Resultado viscosidad

Equipo

Kinexus Pro (www.malvern.com)



Muestra

Código CECOLTEC	Nombre de la muestra	Lote
C1178 - CF1	Biofocus (abbol)	7A5975
C1178 - CF2	Azarga (Alcon a Novrtis company)	65963
C1178 - CF3	Simbrinza (Alcon a Novrtis company)	17G12DE
C1178 - CF4	Oloftal (tecnoquimicas)	7J360
C1178 - CF5	Brimoftal (tecnoquimicas)	7M396B
C1178 - CF6	Agglad ofteno (sophia)	4015466
C1178 - CF7	Lumigan (al ergan)	E79821
C1178 - CF8	Ganfort (alle gan)	E79942
C1180 - CF1	Dorzopt	1076238 SL C
C1184 - CF1	Alap 0,2% (procaps)	1164658 SL C
C1184 - CF2	Krytan tek ofteno (sophia)	4016194
C1184 - CF3	Trusopt (MSD)	M040389

Condiciones de la medida

Sistema de medida: Plato - Plato 40
Tratamiento:

Tasa de cizalladura: 5,000 s-1 a 20,000 s-1
Muestreo: 15 puntos.
Gap: 0.1 mm
Temperatura: 25 °C ± 0.01 °C

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(+57) 4 313 8144

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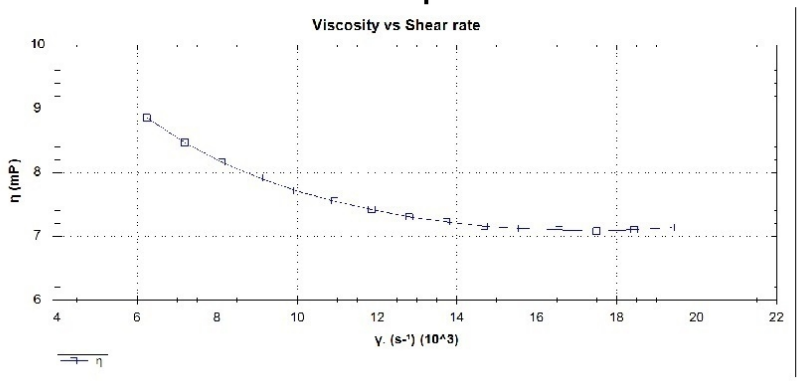
cecoltec
EL ALIADO PRECISO

Azarga (Alcon a Novrtis company) 65963

Tabla de datos

t[s]	T [C°]	Esfuerzo [Pa]	Tasa de cizalladura [s^{-1}]	Viscosidad [mP]
15	25	55.29	6240.00	8.86
22.5	25	60.85	7181.00	8.473
30	25	66.24	8118.00	8.16
37.5	25	71.68	9056.00	7.915
45	25	77.06	9994.00	7.71
52.5	25	82.55	10930.00	7.551
60	25	88.05	11870.00	7.419
67.5	25	93.54	12810.00	7.304
75	25	99.29	13740.00	7.224
82.5	25	105.1	14680.00	7.158
90	25	111.2	15620.00	7.121
97.5	25	117.6	16560.00	7.101
105	25	123.9	17490.00	7.084
112.5	25	130.9	18430.00	7.104
120	25	138.2	19370.00	7.136

Grafico reporte



Viscosidad final

Valor	Unidad
7.5546	mP

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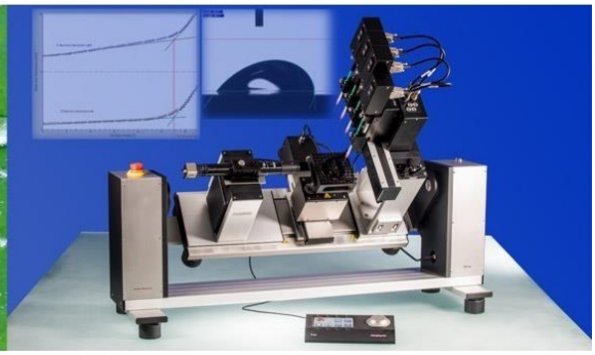
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EL ALIADO PRECISO

Informe de resultado tensión superficial

Equipo

Dataphysics OCA15





Características del equipo:

Medida	Rango
Ángulo de contacto [°]	0 – 180 ° ± 0.1°
Tensión superficial e interfacial [Dinas/cm]	0.01 2000 [Dinas/cm] ± 0.01 [Dinas/cm]

Condiciones de medición:

Técnica usada: Gota - péndulo
Jeringa utilizada:Halmilton de 1 mL
Temperatura: 25 ° C
Dosificación: 1 uL/ seg

cecoltec
EL ALIADO PRECISO

Muestras

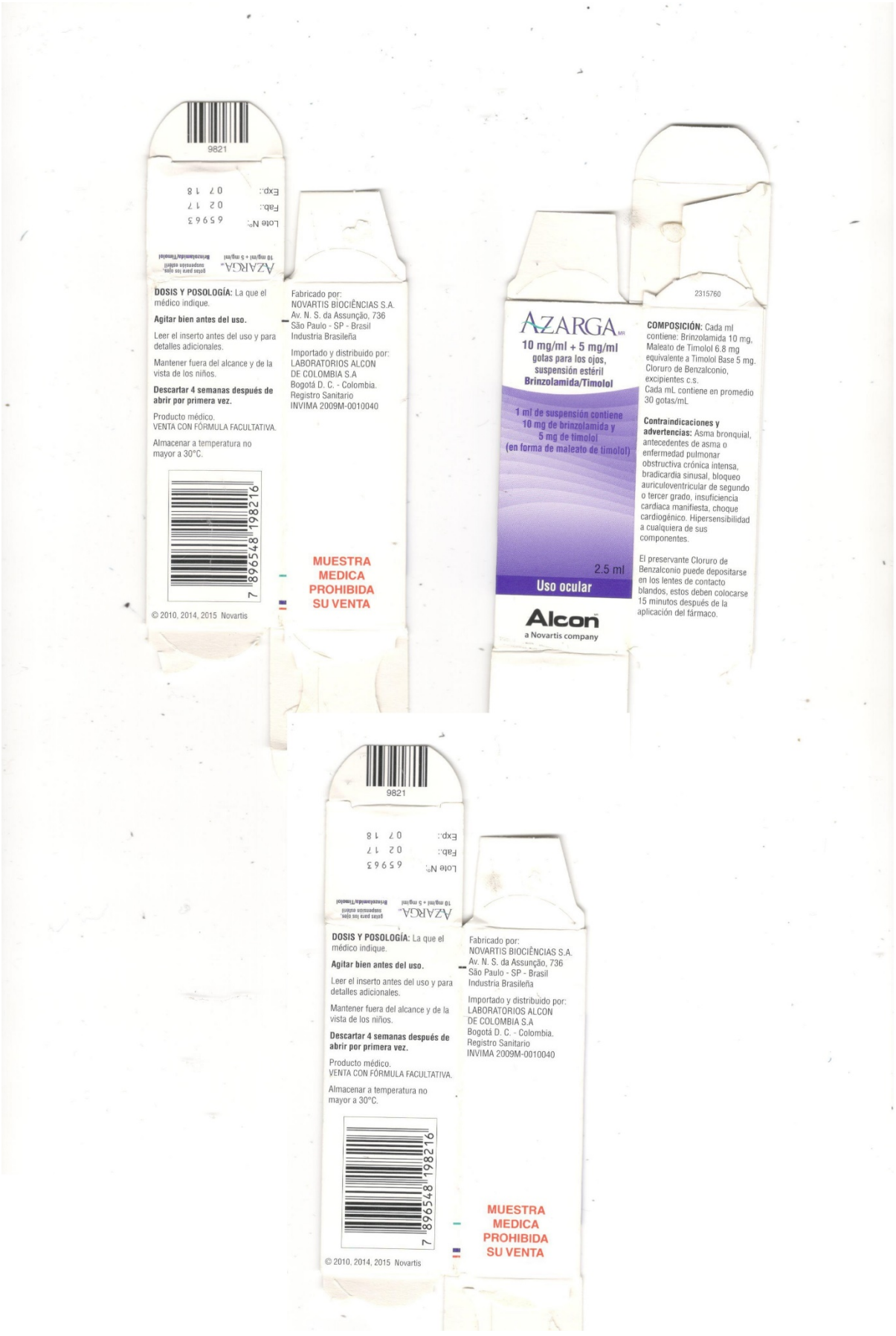
Código Cecoltec	Nombre de la muestra	Lote
C1178 - TS1	Biofocus (abbot)	7A5975
C1178 - TS2	Azarga (Alcon a Novrtis comoany)	65963
C1178 - TS3	Simbrinza (Alcon a Novrtis company)	17G12DE
C1178 - TS4	Oloftal (tecnoquimicas)	7J360
C1178 - TS5	Brimoftal (tecnoquimicas)	7M396B
C1178 - TS6	Agglad ofteno (soohia)	4015466
C1178 - TS7	Lumigan (allergan)	E79821
C1178 - TS8	Ganfort (allergan)	E79942
C1180- TS1	Dorzopt	1076238 SL C
C1184 - TS1	Alap 0,2% (procaps)	1164658 SL C
C1184 - TS2	Krytan tek ofteno (sophia)	4016194
C1184 - TS3	Trusopt (MSD)	M040389

Resultados

Muestra	Medida 1 (Dinas/cm)	Medida 2 (Dinas/cm)	Medida 3 (Dinas/cm)	Medida 4 (Dinas/cm)	Medida 5 (Dinas/cm)	Promedio (Dinas/cm)	Desviación
C1178 - TS1	51.13	51.09	51.37	51.18	51.5	51.25	0.16
C1178 - TS2	47.76	47.45	47.42	48.22	47.85	47.74	0.29
C1178 - TS3	52.94	53.8	52.86	52.96	53.15	53.14	0.34
C1178 - TS4	50.22	50.17	50.58	51.86	51.32	50.83	0.66
C1178 - TS5	53.81	52.21	53.49	52.28	52.4	52.84	0.67
C1178 - TS6	48.31	48.7	48.75	48.79	48.78	48.67	0.18
C1178 - TS7	63.46	63.25	63.31	63.89	63.83	63.55	0.26
C1178 - TS8	64.88	64.33	64.9	64.89	65	64.80	0.24
C1180- TS1	44.32	43.71	44.08	44.3	44.65	44.21	0.31
C1184 - TS1	63.28	63.32	63.62	63.19	63.27	63.34	0.15
C1184 - TS2	78.94	78.26	77.42	78.58	78.77	78.39	0.54
C1184 - TS3	49.87	49.26	49.77	49.28	49.6	49.56	0.25

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9821
Exp.: 07 18
Fab.: 02 17
Lote N°: 65963
AZARGA
10 mg/ml + 5 mg/ml
gotas para los ojos, suspensión estéril
Brinzolamida/Timolol
DOSIS Y POSOLOGÍA: La que el médico indique.
Agitar bien antes del uso.
Leer el inserto antes del uso y para detalles adicionales.
Mantener fuera del alcance y de la vista de los niños.
Descartar 4 semanas después de abrir por primera vez.
Producto médico.
VENTA CON FÓRMULA FACULTATIVA.
Almacenar a temperatura no mayor a 30°C.
7 896548 198216
© 2010, 2014, 2015 Novartis
Fabricado por:
NOVARTIS BIOCIÊNCIAS S.A.
Av. N. S. da Assunção, 736
São Paulo - SP - Brasil
Industria Brasileña
Importado y distribuido por:
LABORATORIOS ALCON
DE COLOMBIA S.A
Bogotá D. C. - Colombia.
Registro Sanitario
INVIMA 2009M-0010040
MUESTRA MEDICA PROHIBIDA SU VENTA
2315760
AZARGA MR
10 mg/ml + 5 mg/ml
gotas para los ojos, suspensión estéril
Brinzolamida/Timolol
1 ml de suspensión contiene 10 mg de brinzolamida y 5 mg de timolol (en forma de maleato de timolol)
2.5 ml
Uso ocular
Alcon
a Novartis company
COMPOSICIÓN: Cada ml contiene: Brinzolamida 10 mg, Maleato de Timolol 6.8 mg equivalente a Timolol Base 5 mg, Cloruro de Benzalconio, excipientes c.s.
Cada mL contiene en promedio 30 gotas/mL
Contraindicaciones y advertencias: Asma bronquial, antecedentes de asma o enfermedad pulmonar obstructiva crónica intensa, bradicardia sinusal, bloqueo auriculoventricular de segundo o tercer grado, insuficiencia cardiaca manifiesta, choque cardiogénico. Hipersensibilidad a cualquiera de sus componentes.
El preservante Cloruro de Benzalconio puede depositarse en los lentes de contacto blandos, estos deben colocarse 15 minutos después de la aplicación del fármaco.

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info@tecnimicro.net
www.tecnimicro.net
Carrera 42 # 10-37
Medellín - Colombia

REPORTE DE ANÁLISIS/ANALYSIS REPORT

Muestra/Sample #: 257566

Empresa / Company: ESPECIALIDADES OFTALMOLOGICAS S.A. **Telf. / Phone:** 448 19 18

Sede / Headquarters: Sede principal Carrera 37 A No. 2 Sur 104, Loma Alejandria, Poblado, Medellí

Producto / Product: TRUSOPT

Muestra / Sample: Lote: 040314-1; 510538V; Laboratorio: MSD

Fecha de Recepción / Reception date: 2018-02-06 **Temp. de Recepción / Temp. Reception:** 26,1ºC

Cantidad / Amount: 1 Unidad/ 1 unit

Contenedor / Container: Frasco gotero con tapa/ Dropper bottle with lid

Enviada por /Send by: Tatiana María Gómez Gaviria

Aspecto / Aspect: Producto translúcido, homogéneo, libre de particulas extrañas/ Translucent, homogeneous product, free of foreign particles.

Olor / Smell: Inobjetable/Unobjectionable

Color / Color: Incoloro/Colorless

Análisis Fisicoquímico/ Physicochemical Analysis	Fecha/ Date	Unidad/ Unit	Resultado/ Result	Especificaciones(**)/ Specifications(**)	Método/ Method
Osmolalidad/Osmolality	2018-02-06	mOsm/Kg	282	NA	USP 40 <785>

(**) Según Norma / Acoordinng to Standard:

(*) Métodos acreditados/Methods Accredited: ONAC, Certificado/Certificate: 10-LAB-053 Fecha/Date: 2014-09-05 ISO/IEC 17025:2005

NOTA: Este resultado corresponde, exclusivamente a la muestra recibida y analizada en el laboratorio/This result correspond only to the sample received and analyzed by the laboratory

Luz Elena Osorio C

Luz E. Osorio Castaño
T.P. 01345801606001664
Química Farmacéutica U de A
Coordinadora
Fecha / Date: 2018-02-07

Fecha de Impresión/printing date: 2018-02-07

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Veracidad a toda ¡Prueba!

Resultado viscosidad

Equipo

Kinexus Pro (www.malvern.com)



Muestra

Código CECOLTEC	Nombre de la muestra	Lote
C1178 - CF1	Biofocus (abbol)	7A5975
C1178 - CF2	Azarga (Alcon a Novrtis company)	65963
C1178 - CF3	Simbrinza (Alcon a Novrtis company)	17G12DE
C1178 - CF4	Oloftal (tecnoquimicas)	7J360
C1178 - CF5	Brimoftal (tecnoquimicas)	7M396B
C1178 - CF6	Agglad ofteno (sophia)	4015466
C1178 - CF7	Lumigan (al ergan)	E79821
C1178 - CF8	Ganfort (alle gan)	E79942
C1180 - CF1	Dorzopt	1076238 SL C
C1184 - CF1	Alap 0,2% (procaps)	1164658 SL C
C1184 - CF2	Krytan tek ofteno (sophia)	4016194
C1184 - CF3	Trusopt (MSD)	M040389

Condiciones de la medida

Sistema de medida: Plato - Plato 40
Tratamiento:

Tasa de cizalladura: 5,000 s-1 a 20,000 s-1
Muestreo: 15 puntos.
Gap: 0.1 mm
Temperatura: 25 °C ± 0.01 °C

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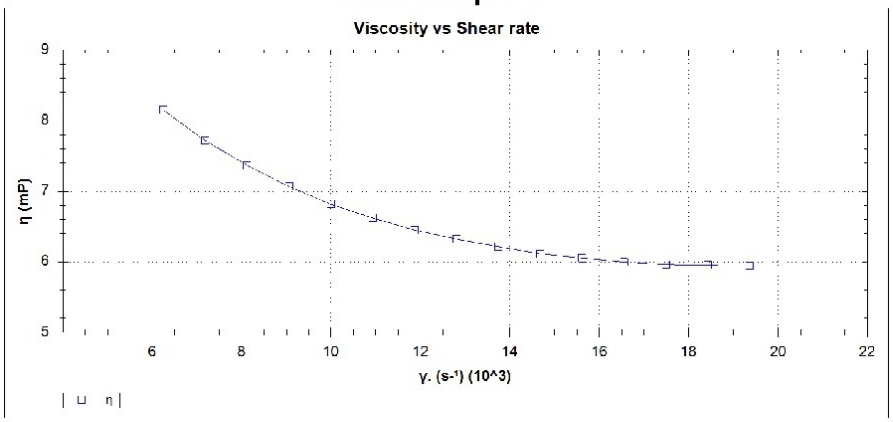
cecoltec
EL ALIADO PRECISO

Trusopt (MSD) M040389

Tabla de datos

t[s]	T [C°]	Esfuerzo [Pa]	Tasa de cizalladura [s^{-1}]	Viscosidad [mP]
15	25	50.88	6240.00	8.154
22.5	25	55.41	7178.00	7.719
30	25	59.83	8118.00	7.369
37.5	25	63.99	9056.00	7.066
45	25	68.12	9994.00	6.816
52.5	25	72.38	10930.00	6.621
60	25	76.54	11870.00	6.449
67.5	25	80.97	12810.00	6.323
75	25	85.42	13740.00	6.215
82.5	25	89.77	14680.00	6.115
90	25	94.54	15620.00	6.053
97.5	25	99.27	16560.00	5.996
105	25	104.3	17490.00	5.960
112.5	25	109.7	18430.00	5.951
120	25	115.1	19370.00	5.942

Grafico reporte



Viscosidad final

Valor	Unidad
6.583	mP

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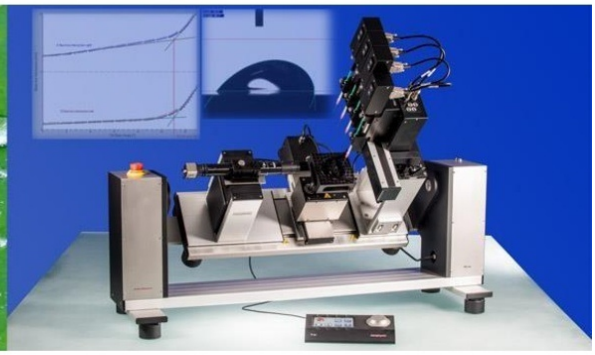
cecoltec
EL ALIADO PRECISO

Informe de resultado tensión superficial

Equipo

Dataphysics OCA15





Características del equipo:

Medida	Rango
Ángulo de contacto [°]	0 – 180 ° ± 0.1°
Tensión superficial e interfacial [Dinas/cm]	0.01 2000 [Dinas/cm] ± 0.01 [Dinas/cm]

Condiciones de medición:

Técnica usada: Gota - péndulo
Jeringa utilizada:Halmilton de 1 mL
Temperatura: 25 ° C
Dosificación: 1 uL/ seg

cecoltec
EL ALIADO PRECISO

Muestras

Código Cecoltec	Nombre de la muestra	Lote
C1178 - TS1	Biofocus (abbot)	7A5975
C1178 - TS2	Azarga (Alcon a Novrtis comoany)	65963
C1178 - TS3	Simbrinza (Alcon a Novrtis company)	17G12DE
C1178 - TS4	Oloftal (tecnoquimicas)	7J360
C1178 - TS5	Brimoftal (tecnoquimicas)	7M396B
C1178 - TS6	Agglad ofteno (soohia)	4015466
C1178 - TS7	Lumigan (allergan)	E79821
C1178 - TS8	Ganfort (allergan)	E79942
C1180- TS1	Dorzopt	1076238 SL C
C1184 - TS1	Alap 0,2% (procaps)	1164658 SL C
C1184 - TS2	Krytan tek ofteno (sophia)	4016194
C1184 - TS3	Trusopt (MSD)	M040389

Resultados

Muestra	Medida 1 (Dinas/cm)	Medida 2 (Dinas/cm)	Medida 3 (Dinas/cm)	Medida 4 (Dinas/cm)	Medida 5 (Dinas/cm)	Promedio (Dinas/cm)	Desviación
C1178 - TS1	51.13	51.09	51.37	51.18	51.5	51.25	0.16
C1178 - TS2	47.76	47.45	47.42	48.22	47.85	47.74	0.29
C1178 - TS3	52.94	53.8	52.86	52.96	53.15	53.14	0.34
C1178 - TS4	50.22	50.17	50.58	51.86	51.32	50.83	0.66
C1178 - TS5	53.81	52.21	53.49	52.28	52.4	52.84	0.67
C1178 - TS6	48.31	48.7	48.75	48.79	48.78	48.67	0.18
C1178 - TS7	63.46	63.25	63.31	63.89	63.83	63.55	0.26
C1178 - TS8	64.88	64.33	64.9	64.89	65	64.80	0.24
C1180- TS1	44.32	43.71	44.08	44.3	44.65	44.21	0.31
C1184 - TS1	63.28	63.32	63.62	63.19	63.27	63.34	0.15
C1184 - TS2	78.94	78.26	77.42	78.58	78.77	78.39	0.54
C1184 - TS3	49.87	49.26	49.77	49.28	49.6	49.56	0.25

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MSD

Trusopt®

DORZOLAMIDA CLORHIDRATO

MUESTRA MEDICA
PROHIBIDA SU VENTA

FRASCO OCUMETER PLUS ®

Solución Oftálmica
Estéril al 2%

5 mL

MUESTRA MEDICA
PROHIBIDA SU VENTA

Lot.: M040389

Vence: 07 2018

5187127
040314-1
3519

Cada mL contiene:
Dorzolamida Clorhidrato
Equivalente a Dorzolamida 20 mg

18

Fabricado y empacado por
MERCK SHARP & DOHME
Chibret, Francia

Importado y Distribuido por:
MERCK SHARP & DOHME COLOMBIA S.A.S.
Bogotá, Colombia.
Reg. San. INVIMA 2007 M-006524-R1

3 556610 000031

Vía de administración: Conjuntival.
DOSIS: Úsese según criterio médico.
Venta bajo fórmula médica.
Para mayor información ver inserto adjunto.

CONTRAINDICACIONES Y ADVERTENCIAS:
Hipersensibilidad a los componentes del producto.
Consérvese a menos de 30°C, protegido de la luz.
Manténgase fuera del alcance de los niños.

MSD

Trusopt®

DORZOLAMIDA CLORHIDRATO

Solución Oftálmica
Estéril al 2%

5 mL

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Laboratorio de Análisis S.A.S.

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info@tecnimicro.net
www.tecnimicro.net
Carrera 42 # 10-37
Medellín - Colombia

REPORTE DE ANÁLISIS/ANALYSIS REPORT

Muestra/Sample #: 257564

Empresa / Company: ESPECIALIDADES OFTALMOLOGICAS S.A. **Telf. / Phone:** 448 19 18

Sede / Headquarters: Sede principal Carrera 37 A No. 2 Sur 104, Loma Alejandria, Poblado, Medellí

Producto / Product: GANFORT

Muestra / Sample: Lote: E79942; Laboratorio: Allergan

Fecha de Recepción / Reception date: 2018-02-06 **Temp. de Recepción / Temp. Reception:** 26,1°C

Cantidad / Amount: 3 Unidades/ 3 units

Contenedor / Container: Plástico preformado

Enviada por /Send by: Tatiana María Gómez Gaviria

Aspecto / Aspect: Líquido translúcido, homogéneo, libre de partículas extrañas/ Translucent, homogeneous liquid free of foreign particles.

Olor / Smell: Inobjetable/Unobjectionable

Color / Color: Incoloro/Colorless

Análisis Fisicoquímico/ Physicochemical Analysis	Fecha/ Date	Unidad/ Unit	Resultado/ Result	Especificaciones(**)/ Specifications(**)	Método/ Method
Osmolalidad/Osmolality	2018-02-06	mOsm/Kg	283	NA	USP 40 <785>

(**) Según Norma / Acoordinng to Standard:

(*) Métodos acreditados/Methods Accredited: ONAC, Certificado/Certificate: 10-LAB-053 Fecha/Date: 2014-09-05 ISO/IEC 17025:2005

NOTA: Este resultado corresponde, exclusivamente a la muestra recibida y analizada en el laboratorio/This result correspond only to the sample received and analyzed by the laboratory

Luz Elena Osorio C

Luz E. Osorio Castaño
T.P. 01345801606001664
Química Farmacéutica U de A
Coordinadora
Fecha / Date: 2018-02-07

Fecha de Impresión/printing date: 2018-02-07

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Resultado viscosidad

Equipo

Kinexus Pro (www.malvern.com)



Muestra

Código CECOLTEC	Nombre de la muestra	Lote
C1178 - CF1	Biofocus (abbol)	7A5975
C1178 - CF2	Azarga (Alcon a Novrtis company)	65963
C1178 - CF3	Simbrinza (Alcon a Novrtis company)	17G12DE
C1178 - CF4	Oloftal (tecnoquimicas)	7J360
C1178 - CF5	Brimoftal (tecnoquimicas)	7M396B
C1178 - CF6	Agglad ofteno (sophia)	4015466
C1178 - CF7	Lumigan (al ergan)	E79821
C1178 - CF8	Ganfort (alle gan)	E79942
C1180 - CF1	Dorzopt	1076238 SL C
C1184 - CF1	Alap 0,2% (procaps)	1164658 SL C
C1184 - CF2	Krytan tek ofteno (sophia)	4016194
C1184 - CF3	Trusopt (MSD)	M040389

Condiciones de la medida

Sistema de medida: Plato - Plato 40
Tratamiento:

Tasa de cizalladura: 5,000 s-1 a 20,000 s-1
Muestreo: 15 puntos.
Gap: 0.1 mm
Temperatura: 25 °C ± 0.01 °C

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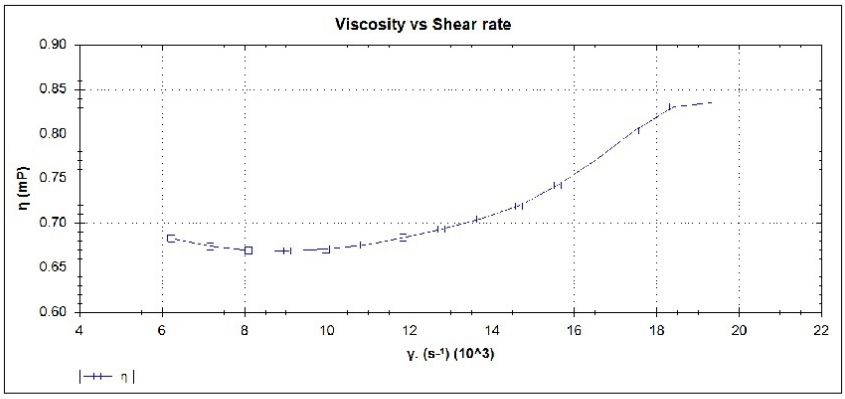
cecoltec
EL ALIADO PRECISO

Ganfort (allergan) E79942

Tabla de datos

t[s]	T [C°]	Esfuerzo [Pa]	Tasa de cizalladura [s^{-1}]	Viscosidad [mP]
15	25	4.247	6217.00	0.6831
22.5	25	4.824	7155.00	0.6743
30	25	5.416	8092.00	0.6693
37.5	25	6.042	9030.00	0.6691
45	25	6.687	9967.00	0.6709
52.5	25	7.365	10900.00	0.6754
60	25	8.098	11840.00	0.6838
67.5	25	8.859	12780.00	0.6932
75	25	9.669	13720.00	0.7049
82.5	25	10.54	14660.00	0.7195
90	25	11.58	15590.00	0.7426
97.5	25	12.75	16530.00	0.7713
105	25	14.05	17470.00	0.8041
112.5	25	15.29	18410.00	0.8306
120	25	16.16	19340.00	0.8354

Grafico reporte



Viscosidad final

Valor	Unidad
0.7218	mP

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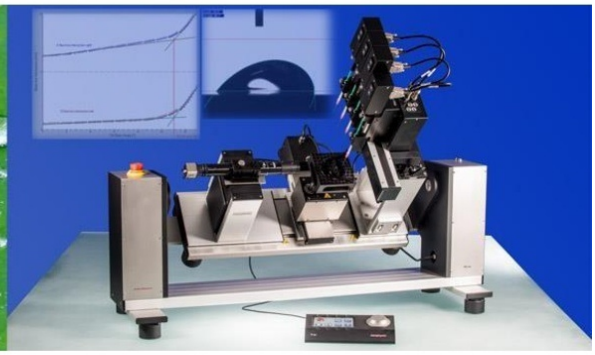
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EL ALIADO PRECISO

Informe de resultado tensión superficial

Equipo

Dataphysics OCA15





Características del equipo:

Medida	Rango
Ángulo de contacto [°]	0 – 180 ° ± 0.1°
Tensión superficial e interfacial [Dinas/cm]	0.01 2000 [Dinas/cm] ± 0.01 [Dinas/cm]

Condiciones de medición:

Técnica usada: Gota - péndulo
Jeringa utilizada:Halmilton de 1 mL
Temperatura: 25 ° C
Dosificación: 1 uL/ seg

cecoltec
EL ALIADO PRECISO

Muestras

Código Cecoltec	Nombre de la muestra	Lote
C1178 - TS1	Biofocus (abbot)	7A5975
C1178 - TS2	Azarga (Alcon a Novrtis comoany)	65963
C1178 - TS3	Simbrinza (Alcon a Novrtis company)	17G12DE
C1178 - TS4	Oloftal (tecnoquimicas)	7J360
C1178 - TS5	Brimoftal (tecnoquimicas)	7M396B
C1178 - TS6	Agglad ofteno (soohia)	4015466
C1178 - TS7	Lumigan (allergan)	E79821
C1178 - TS8	Ganfort (allergan)	E79942
C1180- TS1	Dorzopt	1076238 SL C
C1184 - TS1	Alap 0,2% (procaps)	1164658 SL C
C1184 - TS2	Krytan tek ofteno (sophia)	4016194
C1184 - TS3	Trusopt (MSD)	M040389

Resultados

Muestra	Medida 1 (Dinas/cm)	Medida 2 (Dinas/cm)	Medida 3 (Dinas/cm)	Medida 4 (Dinas/cm)	Medida 5 (Dinas/cm)	Promedio (Dinas/cm)	Desviación
C1178 - TS1	51.13	51.09	51.37	51.18	51.5	51.25	0.16
C1178 - TS2	47.76	47.45	47.42	48.22	47.85	47.74	0.29
C1178 - TS3	52.94	53.8	52.86	52.96	53.15	53.14	0.34
C1178 - TS4	50.22	50.17	50.58	51.86	51.32	50.83	0.66
C1178 - TS5	53.81	52.21	53.49	52.28	52.4	52.84	0.67
C1178 - TS6	48.31	48.7	48.75	48.79	48.78	48.67	0.18
C1178 - TS7	63.46	63.25	63.31	63.89	63.83	63.55	0.26
C1178 - TS8	64.88	64.33	64.9	64.89	65	64.80	0.24
C1180- TS1	44.32	43.71	44.08	44.3	44.65	44.21	0.31
C1184 - TS1	63.28	63.32	63.62	63.19	63.27	63.34	0.15
C1184 - TS2	78.94	78.26	77.42	78.58	78.77	78.39	0.54
C1184 - TS3	49.87	49.26	49.77	49.28	49.6	49.56	0.25

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ALLERGAN
Ganfort® UD
SOLUCION OFTALMICA
PARA UNA SOLA APLICACION
LIBRE DE PRESERVANTES
Bimatoprost 0,3 mg/mL/ Timolol 5,0 mg/mL
MUESTRA MEDICA
PROHIBIDA SU VENTA
Para un solo uso
5 viales unidosis estériles de 0,4 mL
Composición:
Cada mL contiene:
Bimatoprost 0,3 mg , Timolol maleato 6,8 mg (equivalente a Timolol base 5,0 mg), Cloruro de sodio, fosfato de sodio dibasico heptahidratado, ácido cítrico monohidrato, ácido clorhídrico o hidróxido de sodio para ajustar el pH, Agua purificada.
Posología: Según prescripción médica
Viales para un solo uso, descartar el sobrante después de su uso
Condiciones de Almacenamiento:
Ganfort® UD debe ser almacenado a una temperatura no mayor a 30°C.
Almacenar los viales en el sobre protegido de la luz.
Cierre doblando el extremo del sobre.
Vía de Administración:
Tópica oftálmica (conjuntival).
Lote: E79942
Vence: ENE 2019
6


Para un solo uso
5 viales unidosis estériles de 0,4 mL
Bimatoprost 0,3 mg/mL/ Timolol 5,0 mg/mL
SOLUCION OFTALMICA
PARA UNA SOLA APLICACION
LIBRE DE PRESERVANTES
Ganfort® UD
MUESTRA MEDICA
PROHIBIDA SU VENTA
952690CO
ALLERGAN
Ganfort® UD
SOLUCION OFTALMICA
PARA UNA SOLA APLICACION
LIBRE DE PRESERVANTES
Bimatoprost 0,3 mg/mL/ Timolol 5,0 mg/mL
MUESTRA MEDICA
PROHIBIDA SU VENTA
Para un solo uso
5 viales unidosis estériles de 0,4 mL
Contraindicaciones y Advertencias:
Ver inserto adjunto
Manténgase fuera del alcance de los niños
Importado y Distribuido por
Allergan de Colombia S.A.
Bogotá D.C.
Registro Sanitario
No. INVIMA 2014M-0015449
Fabricado por :
Allergan Pharmaceuticals Ireland, Westport, Co. Ireland
® Marca Registrada de Allergan, Inc.
65778CO10

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Medellín - Colombia

REPORTE DE ANÁLISIS/ANALYSIS REPORT

Muestra/Sample #: 257560

Empresa / Company: ESPECIALIDADES OFTALMOLOGICAS S.A. **Telf. / Phone:** 448 19 18

Sede / Headquarters: Sede principal Carrera 37 A No. 2 Sur 104, Loma Alejandria, Poblado, Medelli

Producto / Product: OLOFTAL

Muestra / Sample: Lote: 6P450B; Laboratorio: Tecnoquímicas S.A.

Fecha de Recepción / Reception date: 2018-02-06 **Temp. de Recepción / Temp. Reception:** 26,1°C

Cantidad / Amount: 1 Unidad/ 1 unit

Contenedor / Container: Frasco gotero con tapa/ Dropper bottle with lid

Enviada por /Send by: Tatiana María Gómez Gaviria

Aspecto / Aspect: Líquido translúcido, homogéneo, libre de partículas extrañas/ Translucent, homogeneous liquid free of foreign particles.

Olor / Smell: Inobjetable/Unobjectionable

Color / Color: Incoloro/Colorless

Análisis Fisicoquímico/ Physicochemical Analysis	Fecha/ Date	Unidad/ Unit	Resultado/ Result	Especificaciones(**)/ Specifications(**)	Método/ Method
Osmolalidad/Osmolality	2018-02-06	mOsm/Kg	283	NA	USP 40 <785>

(**) Según Norma / Acoordinng to Standard:

(*) Métodos acreditados/Methods Accredited: ONAC, Certificado/Certificate: 10-LAB-053 Fecha/Date: 2014-09-05 ISO/IEC 17025:2005

NOTA: Este resultado corresponde, exclusivamente a la muestra recibida y analizada en el laboratorio/This result correspond only to the sample received and analyzed by the laboratory

Luz Elena Osorio C

Luz E. Osorio Castaño
T.P. 01345801606001664
Química Farmacéutica U de A
Coordinadora
Fecha / Date: 2018-02-07

Fecha de Impresión/printing date: 2018-02-07

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Veracidad a toda ¡Prueba!

Resultado viscosidad

Equipo

Kinexus Pro (www.malvern.com)



Muestra

Código CECOLTEC	Nombre de la muestra	Lote
C1178 - CF1	Biofocus (abbol)	7A5975
C1178 - CF2	Azarga (Alcon a Novrtis company)	65963
C1178 - CF3	Simbrinza (Alcon a Novrtis company)	17G12DE
C1178 - CF4	Oloftal (tecnoquimicas)	7J360
C1178 - CF5	Brimoftal (tecnoquimicas)	7M396B
C1178 - CF6	Agglad ofteno (sophia)	4015466
C1178 - CF7	Lumigan (al ergan)	E79821
C1178 - CF8	Ganfort (alle gan)	E79942
C1180 - CF1	Dorzopt	1076238 SL C
C1184 - CF1	Alap 0,2% (procaps)	1164658 SL C
C1184 - CF2	Krytan tek ofteno (sophia)	4016194
C1184 - CF3	Trusopt (MSD)	M040389

Condiciones de la medida

Sistema de medida: Plato - Plato 40
Tratamiento:

Tasa de cizalladura: 5,000 s-1 a 20,000 s-1
Muestreo: 15 puntos.
Gap: 0.1 mm
Temperatura: 25 °C ± 0.01 °C

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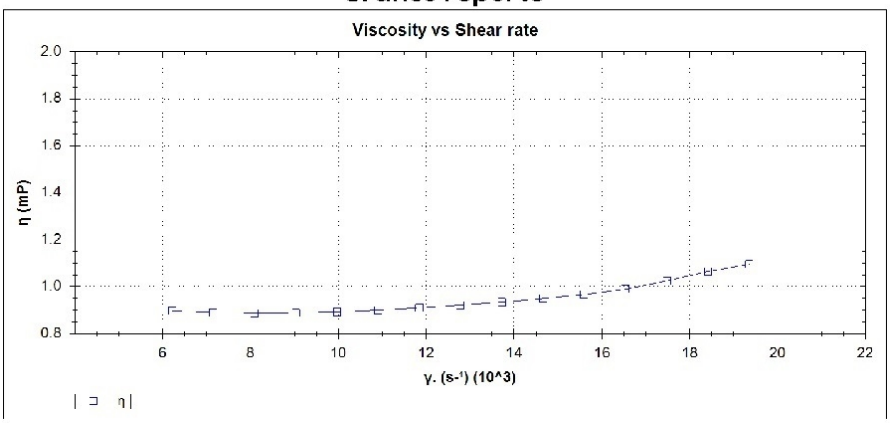
cecoltec
EL ALIADO PRECISO

Oloftal (tecnoquimicas) **7J360**

Tabla de datos

t[s]	T [C°]	Esfuerzo [Pa]	Tasa de cizalladura [s^{-1}]	Viscosidad [mP]
15	25	5.584	6217.00	0.8982
22.5	25	6.369	7155.00	0.8902
30	25	7.183	8092.00	0.8877
37.5	25	8.024	9030.00	0.8886
45	25	8.904	9967.00	0.8933
52.5	25	9.819	10900.00	0.9004
60	25	10.78	11840.00	0.9104
67.5	25	11.79	12780.00	0.9222
75	25	12.82	13720.00	0.9345
82.5	25	13.92	14660.00	0.9497
90	25	15.06	15590.00	0.9661
97.5	25	16.35	16530.00	0.9893
105	25	17.91	17480.00	1.025
112.5	25	19.61	18410.00	1.065
120	25	21.2	19350.00	1.096

Grafico reporte



Viscosidad final

Valor	Unidad
0.9477	mP

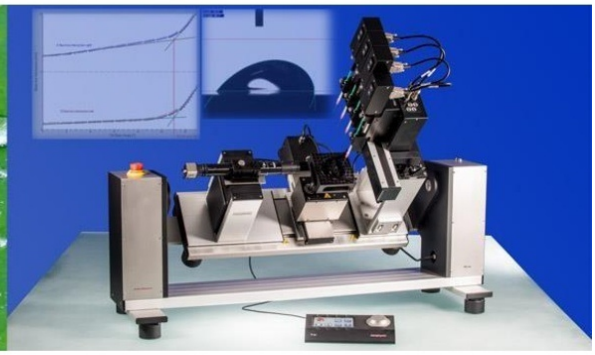
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EL ALIADO PRECISO

Informe de resultado tensión superficial

Equipo

Dataphysics OCA15





Características del equipo:

Medida	Rango
Ángulo de contacto [°]	0 – 180 ° ± 0.1°
Tensión superficial e interfacial [Dinas/cm]	0.01 2000 [Dinas/cm] ± 0.01 [Dinas/cm]

Condiciones de medición:

Técnica usada: Gota - péndulo
Jeringa utilizada:Halmilton de 1 mL
Temperatura: 25 ° C
Dosificación: 1 uL/ seg

cecoltec
EL ALIADO PRECISO

Muestras

Código Cecoltec	Nombre de la muestra	Lote
C1178 - TS1	Biofocus (abbot)	7A5975
C1178 - TS2	Azarga (Alcon a Novrtis comoany)	65963
C1178 - TS3	Simbrinza (Alcon a Novrtis company)	17G12DE
C1178 - TS4	Oloftal (tecnoquimicas)	7J360
C1178 - TS5	Brimoftal (tecnoquimicas)	7M396B
C1178 - TS6	Agglad ofteno (soohia)	4015466
C1178 - TS7	Lumigan (allergan)	E79821
C1178 - TS8	Ganfort (allergan)	E79942
C1180- TS1	Dorzopt	1076238 SL C
C1184 - TS1	Alap 0,2% (procaps)	1164658 SL C
C1184 - TS2	Krytan tek ofteno (sophia)	4016194
C1184 - TS3	Trusopt (MSD)	M040389

Resultados

Muestra	Medida 1 (Dinas/cm)	Medida 2 (Dinas/cm)	Medida 3 (Dinas/cm)	Medida 4 (Dinas/cm)	Medida 5 (Dinas/cm)	Promedio (Dinas/cm)	Desviación
C1178 - TS1	51.13	51.09	51.37	51.18	51.5	51.25	0.16
C1178 - TS2	47.76	47.45	47.42	48.22	47.85	47.74	0.29
C1178 - TS3	52.94	53.8	52.86	52.96	53.15	53.14	0.34
C1178 - TS4	50.22	50.17	50.58	51.86	51.32	50.83	0.66
C1178 - TS5	53.81	52.21	53.49	52.28	52.4	52.84	0.67
C1178 - TS6	48.31	48.7	48.75	48.79	48.78	48.67	0.18
C1178 - TS7	63.46	63.25	63.31	63.89	63.83	63.55	0.26
C1178 - TS8	64.88	64.33	64.9	64.89	65	64.80	0.24
C1180- TS1	44.32	43.71	44.08	44.3	44.65	44.21	0.31
C1184 - TS1	63.28	63.32	63.62	63.19	63.27	63.34	0.15
C1184 - TS2	78.94	78.26	77.42	78.58	78.77	78.39	0.54
C1184 - TS3	49.87	49.26	49.77	49.28	49.6	49.56	0.25

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Oloftal®
Olopatadina 0,2%
Vision
Solución oftálmica estéril
5 mL
Oloftal®
Olopatadina 0,2%
Composición: Cada mL de Solución Oftálmica Estéril de Oloftal® contiene Olopatadina Clorhidrato equivalente a Olopatadina base 2 mg; excipientes c.s. (Cada mL contiene 34 gotas). Posología: Según prescripción médica. Vía de administración: Tópica oftálmica. Contraindicaciones y advertencias: Hipersensibilidad a cualquiera de los componentes de este producto, embarazo, lactancia, niños menores de 3 años de edad.
El cloruro de benzalconio como preservante, puede depositarse en los lentes de contacto blandos, estos deben retirarse y colocarse como mínimo 15 minutos después.
Evite contaminar el contenido y la punta del gotero. Evítese el congelamiento y manténgase en posición vertical.
EL PRODUCTO DEBE SER UTILIZADO HASTA 28 DÍAS DESPUÉS DE ABIERTO. ALMACENAR A TEMPERATURA INFERIOR A 30 °C. MANTÉNGASE FUERA DEL ALCANCE DE LOS NIÑOS. VENTA BAJO FÓRMULA MÉDICA.
Fabricado por Tecnofar TQ S.A.S., Villa Rica - Colombia
Comercializado por Tecnoquímicas S.A., Cali - Colombia
Colombia: Reg. San. No. INVIMA 2011 M-0012476
7 702057 080718
Cualquier inquietud comuníquese con la línea 01 8000 523339.
0815-3T
Oloftal®
Olopatadina 0,2%
MUESTRA MÉDICA
Prohibida su venta
Vision
Solución oftálmica estéril
5 mL
L. 6P450B
F. OC 16
V. OC 18
7
8185217
Oloftal®
Olopatadina 0,2%
MUESTRA MÉDICA
Prohibida su venta
Vision
Solución oftálmica estéril
5 mL


Oloftal®
Olopatadina 0,2%
Oloftal®
Olopatadina 0,2%
Vision
Solución oftálmica estéril
MUESTRA MÉDICA PROHIBIDA SU VENTA
5 mL
Oloftal®
Olopatadina 0,2%
Vision
Solución oftálmica estéril
5 mL
L. 7J360
F. AGO 2017
V. AGO 2019
3
8185033

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REPORTE DE ANÁLISIS/ANALYSIS REPORT

Muestra/Sample #: 257725

Empresa / Company: ESPECIALIDADES OFTALMOLOGICAS S.A. **Telf. / Phone:** 448 19 18

Sede / Headquarters: Sede principal Carrera 37 A No. 2 Sur 104, Loma Alejandria, Poblado, Medellí

Producto / Product: ALAP

Muestra / Sample: Lote: 1164658 SL C; Laboratorio: Procaps

Fecha de Recepción / Reception date: 2018-02-07 **Temp. de Recepción / Temp. Reception:** 26,1°C

Cantidad / Amount: 1 unidad/1 unit

Contenedor / Container: Frasco gotero con tapa/ Dropper bottle with lid

Enviada por /Send by: Tatiana María Gómez Gaviria

Aspecto / Aspect: Líquido translúcido, homogéneo, libre de partículas extrañas/ Translucent, homogeneous liquid free of foreign particles.

Olor / Smell: Inobjetable/Unobjectionable.

Color / Color: Incoloro/Colorless.

Análisis Fisicoquímico/ Physicochemical Analysis	Fecha/ Date	Unidad/ Unit	Resultado/ Result	Especificaciones(**)/ Specifications(**)	Método/ Method
Osmolalidad/Osmolality	2018-02-07	mOsm/Kg	308	NA	USP 40 <785>

(**) Según Norma / Acoordinng to Standard:

(*) Métodos acreditados/Methods Accredited: ONAC, Certificado/Certificate: 10-LAB-053 Fecha/Date: 2014-09-05 ISO/IEC 17025:2005

NOTA: Este resultado corresponde, exclusivamente a la muestra recibida y analizada en el laboratorio/This result correspond only to the sample received and analyzed by the laboratory

Luz Elena Osorio C

Luz E. Osorio Castaño
T.P. 01345801606001664
Química Farmacéutica U de A
Coordinadora
Fecha / Date: 2018-02-08

Fecha de Impresión/printing date: 2018-02-08

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Veracidad a toda ¡Prueba!

Resultado viscosidad

Equipo

Kinexus Pro (www.malvern.com)



Muestra

Código CECOLTEC	Nombre de la muestra	Lote
C1178 - CF1	Biofocus (abbol)	7A5975
C1178 - CF2	Azarga (Alcon a Novrtis company)	65963
C1178 - CF3	Simbrinza (Alcon a Novrtis company)	17G12DE
C1178 - CF4	Oloftal (tecnoquimicas)	7J360
C1178 - CF5	Brimoftal (tecnoquimicas)	7M396B
C1178 - CF6	Agglad ofteno (sophia)	4015466
C1178 - CF7	Lumigan (al ergan)	E79821
C1178 - CF8	Ganfort (alle gan)	E79942
C1180 - CF1	Dorzopt	1076238 SL C
C1184 - CF1	Alap 0,2% (procaps)	1164658 SL C
C1184 - CF2	Krytan tek ofteno (sophia)	4016194
C1184 - CF3	Trusopt (MSD)	M040389

Condiciones de la medida

Sistema de medida: Plato - Plato 40
Tratamiento:

Tasa de cizalladura: 5,000 s-1 a 20,000 s-1
Muestreo: 15 puntos.
Gap: 0.1 mm
Temperatura: 25 °C ± 0.01 °C

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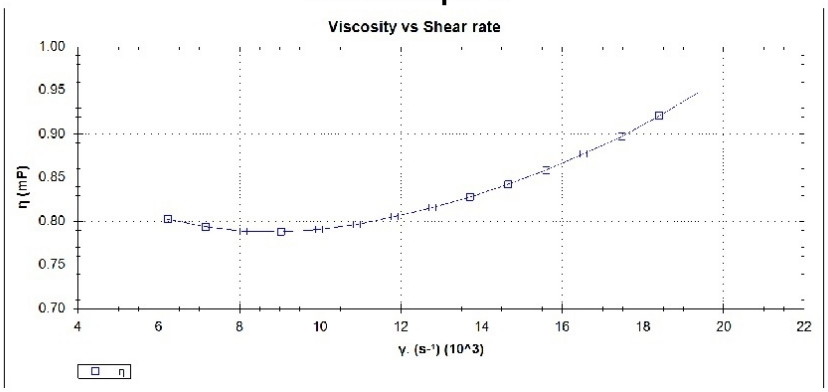
cecoltec
EL ALIADO PRECISO

Alap 0,2% (procaps) 1164658 SL C

Tabla de datos

t[s]	T [C°]	Esfuerzo [Pa]	Tasa de cizalladura [s^{-1}]	Viscosidad [mP]
15	25	4.991	6217.00	0.8028
22.5	25	5.681	7155.00	0.7940
30	25	6.383	8092.00	0.7888
37.5	25	7.118	9030.00	0.7883
45	25	7.882	9967.00	0.7908
52.5	25	8.686	10900.00	0.7965
60	25	9.543	11840.00	0.8059
67.5	25	10.43	12780.00	0.8158
75	25	11.36	13720.00	0.8281
82.5	25	12.35	14660.00	0.8428
90	25	13.39	15590.00	0.8589
97.5	25	14.51	16530.00	0.8777
105	25	15.67	17470.00	0.8972
112.5	25	16.96	18410.00	0.9212
120	25	18.33	19350.00	0.9472

Grafico reporte



Viscosidad final

Valor	Unidad
0.8391	mP

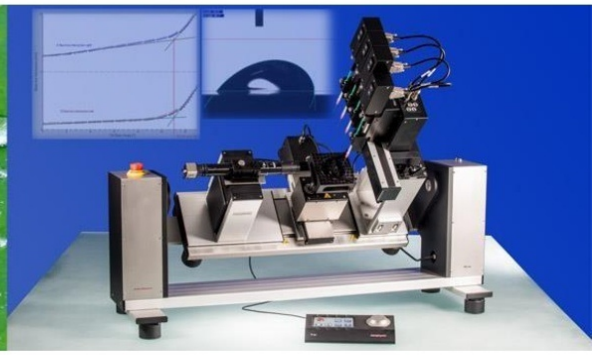
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EL ALIADO PRECISO

Informe de resultado tensión superficial

Equipo

Dataphysics OCA15





Características del equipo:

Medida	Rango
Ángulo de contacto [°]	0 – 180 ° ± 0.1°
Tensión superficial e interfacial [Dinas/cm]	0.01 2000 [Dinas/cm] ± 0.01 [Dinas/cm]

Condiciones de medición:

Técnica usada: Gota - péndulo
Jeringa utilizada:Halmilton de 1 mL
Temperatura: 25 ° C
Dosificación: 1 uL/ seg

cecoltec
EL ALIADO PRECISO

Muestras

Código Cecoltec	Nombre de la muestra	Lote
C1178 - TS1	Biofocus (abbot)	7A5975
C1178 - TS2	Azarga (Alcon a Novrtis comoany)	65963
C1178 - TS3	Simbrinza (Alcon a Novrtis company)	17G12DE
C1178 - TS4	Oloftal (tecnoquimicas)	7J360
C1178 - TS5	Brimoftal (tecnoquimicas)	7M396B
C1178 - TS6	Agglad ofteno (soohia)	4015466
C1178 - TS7	Lumigan (allergan)	E79821
C1178 - TS8	Ganfort (allergan)	E79942
C1180- TS1	Dorzopt	1076238 SL C
C1184 - TS1	Alap 0,2% (procaps)	1164658 SL C
C1184 - TS2	Krytan tek ofteno (sophia)	4016194
C1184 - TS3	Trusopt (MSD)	M040389

Resultados

Muestra	Medida 1 (Dinas/cm)	Medida 2 (Dinas/cm)	Medida 3 (Dinas/cm)	Medida 4 (Dinas/cm)	Medida 5 (Dinas/cm)	Promedio (Dinas/cm)	Desviación
C1178 - TS1	51.13	51.09	51.37	51.18	51.5	51.25	0.16
C1178 - TS2	47.76	47.45	47.42	48.22	47.85	47.74	0.29
C1178 - TS3	52.94	53.8	52.86	52.96	53.15	53.14	0.34
C1178 - TS4	50.22	50.17	50.58	51.86	51.32	50.83	0.66
C1178 - TS5	53.81	52.21	53.49	52.28	52.4	52.84	0.67
C1178 - TS6	48.31	48.7	48.75	48.79	48.78	48.67	0.18
C1178 - TS7	63.46	63.25	63.31	63.89	63.83	63.55	0.26
C1178 - TS8	64.88	64.33	64.9	64.89	65	64.80	0.24
C1180- TS1	44.32	43.71	44.08	44.3	44.65	44.21	0.31
C1184 - TS1	63.28	63.32	63.62	63.19	63.27	63.34	0.15
C1184 - TS2	78.94	78.26	77.42	78.58	78.77	78.39	0.54
C1184 - TS3	49.87	49.26	49.77	49.28	49.6	49.56	0.25

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31 x 25 x 60
COMPOSICIÓN: cada mL de solución contiene: olopatadina clorhidrato equivalente a olopatadina base 2 mg. Excipientes c.s.p.
VÍA DE ADMINISTRACIÓN: conjuntival.
DOSIFICACIÓN: según criterio médico. 1 mL = 28 gotas.
CONTRAINDICACIONES Y ADVERTENCIAS: hipersensibilidad a cualquiera de los componentes de este producto. Embarazo, lactancia, niños menores de tres (3) años de edad. Para evitar contaminación no toque ni ponga la punta del dispensador en contacto con la zona afectada.
MUESTRA MÉDICA PROHIBIDA SU VENTA
3 mL
SOLUCIÓN OFTÁLMICA
PROCAPS
Alap® 0,2%
OLOPATADINA
PROCAPS
4


SOLUCIÓN OFTÁLMICA
PROCAPS
Alap® 0,2%
OLOPATADINA
CYAN
MAGENTA
AMARILLO
NEGRO
P 173 C
C 0,M 0 Y 0 K 0
Elaborado por Pharmayect S.A.
Bogotá - Colombia
Para PROCAPS S.A. Barranquilla - Colombia
Línea Soluciones Terapéuticas Visión Care
Director Técnico:
Dr. Alberto De La Hoz Durán Q.F. U. de C.
Registro Sanitario No.
INVIMA 2008 M-0009401 Colombia
Registro Sanitario No.
PF-40614 Guatemala
El Salvador inscrito en la DNM
bajo el No. F04152408201
Perú:
Importado por UNIMED DEL PERÚ S.A.
Calle Los Libertadores 155, pisos 6 y 7
San Isidro. Lima - Perú. R.U.C. 20253768119
Director Técnico: Q.F. Rosalio Reyes.
Registro Sanitario No. Perú
Ecuador:
Importado y distribuido por: RODOQUIM PHARMACEUTICAL S.A. (Quito-Ecuador).
Registro Sanitario No. Ecuador.
Producto de uso delicado. Administrar bajo prescripción y vigilancia médica.
VENTA BAJO FÓRMULA O RECETA MÉDICA.
MANTÉNGASE FUERA DEL ALCANCE DE LOS NIÑOS.
ALMACENAR A TEMPERATURA INFERIOR A 30 °C. EN SU ENVASE Y EMPAQUE ORIGINAL.
UNA VEZ ABIERTO SE CONSERVA DURANTE 30 DÍAS A TEMPERATURA INFERIOR A 30 °C. EN SU ENVASE Y EMPAQUE ORIGINAL.
MUESTRA MÉDICA PROHIBIDA SU VENTA
3 mL
SOLUCIÓN OFTÁLMICA
PROCAPS
Alap® 0,2%
OLOPATADINA

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Laboratorio de Análisis S.A.S.

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info@tecnimicro.net
www.tecnimicro.net
Carrera 42 # 10-37
Medellín - Colombia

REPORTE DE ANÁLISIS/ANALYSIS REPORT

Muestra/Sample #: 257563

Empresa / Company: ESPECIALIDADES OFTALMOLOGICAS S.A. **Telf. / Phone:** 448 19 18

Sede / Headquarters: Sede principal Carrera 37 A No. 2 Sur 104, Loma Alejandria, Poblado, Medelli

Producto / Product: LUMIGAN

Muestra / Sample: Lote: E79821; Laboratorio: Allergan

Fecha de Recepción / Reception date: 2018-02-06 **Temp. de Recepción / Temp. Reception:** 26,1°C

Cantidad / Amount: 15 Unidades/ 15 units

Contenedor / Container: Plástico preformado

Enviada por /Send by: Tatiana María Gómez Gaviria

Aspecto / Aspect: Líquido translúcido, homogéneo, libre de partículas extrañas/ Translucent, homogeneous liquid free of foreign particles.

Olor / Smell: Inobjetable/Unobjectionable

Color / Color: Incoloro/Colorless

Análisis Fisicoquímico/ Physicochemical Analysis	Fecha/ Date	Unidad/ Unit	Resultado/ Result	Especificaciones(**)/ Specifications(**)	Método/ Method
Osmolalidad/Osmolality	2018-02-06	mOsm/Kg	290	NA	USP 40 <785>

(**) Según Norma / Acoordinng to Standard:

(*) Métodos acreditados/Methods Accredited: ONAC, Certificado/Certificate: 10-LAB-053 Fecha/Date: 2014-09-05 ISO/IEC 17025:2005

NOTA: Este resultado corresponde, exclusivamente a la muestra recibida y analizada en el laboratorio/This result correspond only to the sample received and analyzed by the laboratory

Luz Elena Osorio C

Luz E. Osorio Castaño
T.P. 01345801606001664
Química Farmacéutica U de A
Coordinadora
Fecha / Date: 2018-02-07

Fecha de Impresión/printing date: 2018-02-07

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Veracidad a toda ¡Prueba!

Resultado viscosidad

Equipo

Kinexus Pro (www.malvern.com)



Muestra

Código CECOLTEC	Nombre de la muestra	Lote
C1178 - CF1	Biofocus (abbol)	7A5975
C1178 - CF2	Azarga (Alcon a Novrtis company)	65963
C1178 - CF3	Simbrinza (Alcon a Novrtis company)	17G12DE
C1178 - CF4	Oloftal (tecnoquimicas)	7J360
C1178 - CF5	Brimoftal (tecnoquimicas)	7M396B
C1178 - CF6	Agglad ofteno (sophia)	4015466
C1178 - CF7	Lumigan (al ergan)	E79821
C1178 - CF8	Ganfort (alle gan)	E79942
C1180 - CF1	Dorzopt	1076238 SL C
C1184 - CF1	Alap 0,2% (procaps)	1164658 SL C
C1184 - CF2	Krytan tek ofteno (sophia)	4016194
C1184 - CF3	Trusopt (MSD)	M040389

Condiciones de la medida

Sistema de medida: Plato - Plato 40
Tratamiento:

Tasa de cizalladura: 5,000 s-1 a 20,000 s-1
Muestreo: 15 puntos.
Gap: 0.1 mm
Temperatura: 25 °C ± 0.01 °C

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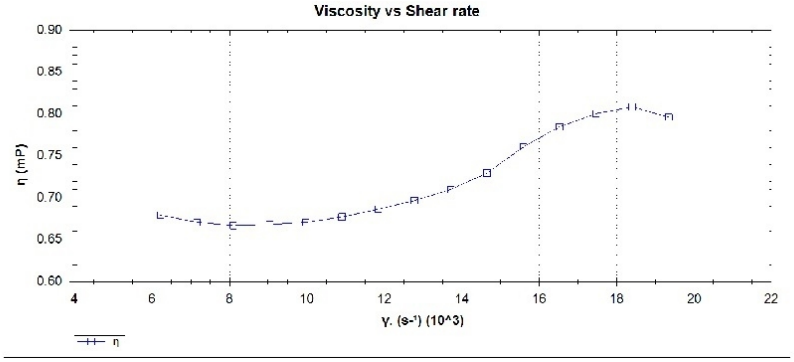
cecoltec
EL ALIADO PRECISO

Lumigan (allergan) E79821

Tabla de datos

t[s]	T [C°]	Esfuerzo [Pa]	Tasa de cizalladura [s^{-1}]	Viscosidad [mP]
15	25	4.224	6217.00	0.6795
22.5	25	4.801	7155.00	0.671
30	25	5.399	8092.00	0.6671
37.5	25	6.034	9030.00	0.6683
45	25	6.686	9967.00	0.6708
52.5	25	7.387	10900.00	0.6774
60	25	8.129	11840.00	0.6864
67.5	25	8.906	12780.00	0.6969
75	25	9.742	13720.00	0.7101
82.5	25	10.7	14660.00	0.7298
90	25	11.87	15590.00	0.7609
97.5	25	12.98	16530.00	0.7851
105	25	13.99	17470.00	0.8007
112.5	25	14.88	18410.00	0.8085
120	25	15.41	19340.00	0.7964

Grafico reporte



Viscosidad final

Valor	Unidad
0.7206	mP

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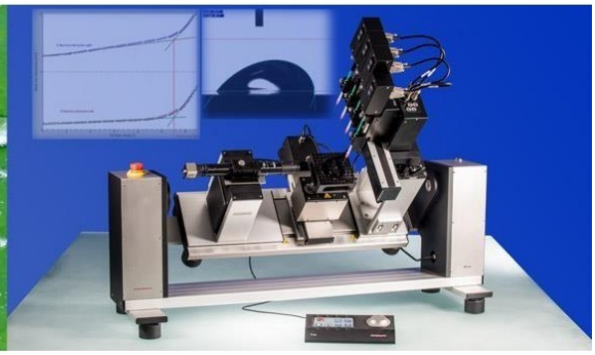
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EL ALIADO PRECISO

Informe de resultado tensión superficial

Equipo

Dataphysics OCA15





Características del equipo:

Medida	Rango
Ángulo de contacto [°]	0 – 180 ° ± 0.1°
Tensión superficial e interfacial [Dinas/cm]	0.01 2000 [Dinas/cm] ± 0.01 [Dinas/cm]

Condiciones de medición:

Técnica usada: Gota - péndulo
Jeringa utilizada:Halmilton de 1 mL
Temperatura: 25 ° C
Dosificación: 1 uL/ seg

cecoltec
EL ALIADO PRECISO

Muestras

Código Cecoltec	Nombre de la muestra	Lote
C1178 - TS1	Biofocus (abbot)	7A5975
C1178 - TS2	Azarga (Alcon a Novrtis comoany)	65963
C1178 - TS3	Simbrinza (Alcon a Novrtis company)	17G12DE
C1178 - TS4	Oloftal (tecnoquimicas)	7J360
C1178 - TS5	Brimoftal (tecnoquimicas)	7M396B
C1178 - TS6	Agglad ofteno (soohia)	4015466
C1178 - TS7	Lumigan (allergan)	E79821
C1178 - TS8	Ganfort (allergan)	E79942
C1180- TS1	Dorzopt	1076238 SL C
C1184 - TS1	Alap 0,2% (procaps)	1164658 SL C
C1184 - TS2	Krytan tek ofteno (sophia)	4016194
C1184 - TS3	Trusopt (MSD)	M040389

Resultados

Muestra	Medida 1 (Dinas/cm)	Medida 2 (Dinas/cm)	Medida 3 (Dinas/cm)	Medida 4 (Dinas/cm)	Medida 5 (Dinas/cm)	Promedio (Dinas/cm)	Desviación
C1178 - TS1	51.13	51.09	51.37	51.18	51.5	51.25	0.16
C1178 - TS2	47.76	47.45	47.42	48.22	47.85	47.74	0.29
C1178 - TS3	52.94	53.8	52.86	52.96	53.15	53.14	0.34
C1178 - TS4	50.22	50.17	50.58	51.86	51.32	50.83	0.66
C1178 - TS5	53.81	52.21	53.49	52.28	52.4	52.84	0.67
C1178 - TS6	48.31	48.7	48.75	48.79	48.78	48.67	0.18
C1178 - TS7	63.46	63.25	63.31	63.89	63.83	63.55	0.26
C1178 - TS8	64.88	64.33	64.9	64.89	65	64.80	0.24
C1180- TS1	44.32	43.71	44.08	44.3	44.65	44.21	0.31
C1184 - TS1	63.28	63.32	63.62	63.19	63.27	63.34	0.15
C1184 - TS2	78.94	78.26	77.42	78.58	78.77	78.39	0.54
C1184 - TS3	49.87	49.26	49.77	49.28	49.6	49.56	0.25

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94576CO

LUMIGAN® UD

Bimatoprost 0,12 mg/vial

Solución oftálmica

Vial de dosis única

Uso oftálmico

Dosis única

Estéril, libre de preservantes

30 viales x 0,4 mL

LOT: E79821

FAB: DIC 2016

EXP: JUN 2018

ALLERGAN

¡MUESTRA MÉDICA
PROHIBIDA SU VENTA

Cada vial de 0,4 mL contiene: Bimatoprost 0,12 mg
(Cada mL contiene 0,3 mg de Bimatoprost)
Excipientes c.s.p. 1 Vial

Contraindicaciones y advertencias: ver inserto adjunto.

Descarte el envase unidosis inmediatamente después de uso.

Una vez abierta la bandeja, los envases unidosis deben utilizarse dentro de los 30 días siguientes.

Posología: según prescripción médica

Mantener fuera de la vista y del alcance de los niños.

Venta bajo prescripción médica.

Dosis única

Mantener a temperatura menor a 30°C.

Fabricado por:
Allergan Pharmaceuticals
Ireland, Westport, Ireland
Importado y Distribuido por:
Allergan de Colombia S.A.
Bogotá D.C., Colombia
Registro Sanitario
INVIMA 2015M-0016118

7 707236 675769

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www.tecnimicro.net
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Medellín - Colombia

REPORTE DE ANÁLISIS/ANALYSIS REPORT

Muestra/Sample #: 257565

Empresa / Company: ESPECIALIDADES OFTALMOLOGICAS S.A. **Telf. / Phone:** 448 19 18

Sede / Headquarters: Sede principal Carrera 37 A No. 2 Sur 104, Loma Alejandria, Poblado, Medellí

Producto / Product: KRITAN TEK OFTENO PF

Muestra / Sample: Lote: 4016194; Laboratorio: Sophia

Fecha de Recepción / Reception date: 2018-02-06 **Temp. de Recepción / Temp. Reception:** 26,1°C

Cantidad / Amount: 1 Unidad/ 1 unit

Contenedor / Container: Frasco gotero con tapa/ Dropper bottle with lid

Enviada por /Send by: Tatiana María Gómez Gaviria

Aspecto / Aspect: Producto translúcido, homogéneo, libre de partículas extrañas/ Translucent, homogeneous product, free of foreign particles.

Olor / Smell: Inobjetable/Unobjectionable

Color / Color: Incoloro/Colorless

Análisis Fisicoquímico/ Physicochemical Analysis	Fecha/ Date	Unidad/ Unit	Resultado/ Result	Especificaciones(**)/ Specifications(**)	Método/ Method
Osmolalidad/Osmolality	2018-02-06	mOsm/Kg	313	NA	USP 40 <785>

(**) Según Norma / Acoordinng to Standard:

(*) Métodos acreditados/Methods Accredited: ONAC, Certificado/Certificate: 10-LAB-053 Fecha/Date: 2014-09-05 ISO/IEC 17025:2005

NOTA: Este resultado corresponde, exclusivamente a la muestra recibida y analizada en el laboratorio/This result correspond only to the sample received and analyzed by the laboratory

Luz Elena Osorio C

Luz E. Osorio Castaño
T.P. 01345801606001664
Química Farmacéutica U de A
Coordinadora
Fecha / Date: 2018-02-07

Fecha de Impresión/printing date: 2018-02-07

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Veracidad a toda ¡Prueba!

Resultado viscosidad

Equipo

Kinexus Pro (www.malvern.com)



Muestra

Código CECOLTEC	Nombre de la muestra	Lote
C1178 - CF1	Biofocus (abbol)	7A5975
C1178 - CF2	Azarga (Alcon a Novrtis company)	65963
C1178 - CF3	Simbrinza (Alcon a Novrtis company)	17G12DE
C1178 - CF4	Oloftal (tecnoquimicas)	7J360
C1178 - CF5	Brimoftal (tecnoquimicas)	7M396B
C1178 - CF6	Agglad ofteno (sophia)	4015466
C1178 - CF7	Lumigan (al ergan)	E79821
C1178 - CF8	Ganfort (alle gan)	E79942
C1180 - CF1	Dorzopt	1076238 SL C
C1184 - CF1	Alap 0,2% (procaps)	1164658 SL C
C1184 - CF2	Krytan tek ofteno (sophia)	4016194
C1184 - CF3	Trusopt (MSD)	M040389

Condiciones de la medida

Sistema de medida: Plato - Plato 40
Tratamiento:

Tasa de cizalladura: 5,000 s-1 a 20,000 s-1
Muestreo: 15 puntos.
Gap: 0.1 mm
Temperatura: 25 °C ± 0.01 °C

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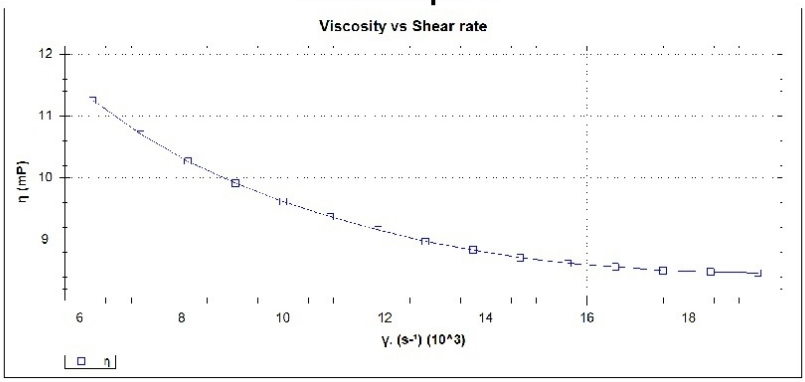
cecoltec
EL ALIADO PRECISO

Krytan tek ofteno (sophia) 4016194

Tabla de datos

t[s]	T [C°]	Esfuerzo [Pa]	Tasa de cizalladura [s^{-1}]	Viscosidad [mP]
15	25.01	70.29	6243.00	11.260
22.5	25.01	76.93	7181.00	10.710
30	25	83.38	8119.00	10.270
37.5	25	89.84	9056.00	9.920
45	25	96.14	9994.00	9.620
52.5	25	102.5	10930.00	9.376
60	25	108.8	11870.00	9.164
67.5	25	115	12810.00	8.977
75	25	121.5	13740.00	8.839
82.5	25	127.9	14680.00	8.713
90	25	134.7	15620.00	8.625
97.5	25	141.8	16560.00	8.566
105	25	148.8	17490.00	8.506
112.5	25	156.4	18430.00	8.483
120	25	164	19370.00	8.469

Grafico reporte



Viscosidad final

Valor	Unidad
9.3	mP

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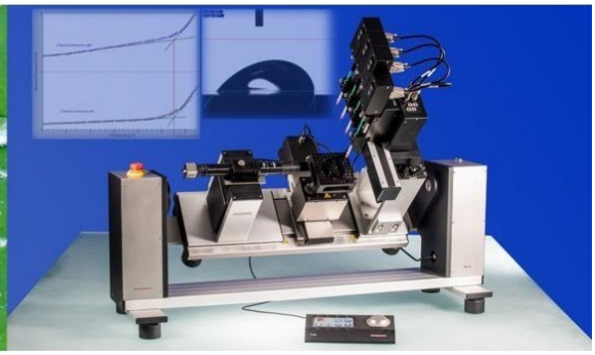
cecoltec
EL ALIADO PRECISO

Informe de resultado tensión superficial

Equipo

Dataphysics OCA15





Características del equipo:

Medida	Rango
Ángulo de contacto [°]	0 – 180 ° ± 0.1°
Tensión superficial e interfacial [Dinas/cm]	0.01 2000 [Dinas/cm] ± 0.01 [Dinas/cm]

Condiciones de medición:

Técnica usada: Gota - péndulo
Jeringa utilizada:Halmilton de 1 mL
Temperatura: 25 ° C
Dosificación: 1 uL/ seg

cecoltec
EL ALIADO PRECISO

Muestras

Código Cecoltec	Nombre de la muestra	Lote
C1178 - TS1	Biofocus (abbot)	7A5975
C1178 - TS2	Azarga (Alcon a Novrtis comoany)	65963
C1178 - TS3	Simbrinza (Alcon a Novrtis company)	17G12DE
C1178 - TS4	Oloftal (tecnoquimicas)	7J360
C1178 - TS5	Brimoftal (tecnoquimicas)	7M396B
C1178 - TS6	Agglad ofteno (soohia)	4015466
C1178 - TS7	Lumigan (allergan)	E79821
C1178 - TS8	Ganfort (allergan)	E79942
C1180- TS1	Dorzopt	1076238 SL C
C1184 - TS1	Alap 0,2% (procaps)	1164658 SL C
C1184 - TS2	Krytan tek ofteno (sophia)	4016194
C1184 - TS3	Trusopt (MSD)	M040389

Resultados

Muestra	Medida 1 (Dinas/cm)	Medida 2 (Dinas/cm)	Medida 3 (Dinas/cm)	Medida 4 (Dinas/cm)	Medida 5 (Dinas/cm)	Promedio (Dinas/cm)	Desviación
C1178 - TS1	51.13	51.09	51.37	51.18	51.5	51.25	0.16
C1178 - TS2	47.76	47.45	47.42	48.22	47.85	47.74	0.29
C1178 - TS3	52.94	53.8	52.86	52.96	53.15	53.14	0.34
C1178 - TS4	50.22	50.17	50.58	51.86	51.32	50.83	0.66
C1178 - TS5	53.81	52.21	53.49	52.28	52.4	52.84	0.67
C1178 - TS6	48.31	48.7	48.75	48.79	48.78	48.67	0.18
C1178 - TS7	63.46	63.25	63.31	63.89	63.83	63.55	0.26
C1178 - TS8	64.88	64.33	64.9	64.89	65	64.80	0.24
C1180- TS1	44.32	43.71	44.08	44.3	44.65	44.21	0.31
C1184 - TS1	63.28	63.32	63.62	63.19	63.27	63.34	0.15
C1184 - TS2	78.94	78.26	77.42	78.58	78.77	78.39	0.54
C1184 - TS3	49.87	49.26	49.77	49.28	49.6	49.56	0.25

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33547
KRYTAN
TEK
Ofteno
PF
LIBRE DE CONSERVADORES
MUESTRA MÉDICA
PROHIBIDA SU VENTA
IMPORTADO Y DISTRIBUIDO POR:
DISTRIBUIDO POR NOVOFARMA SERVICE S.A.,
Registro Sanitario:
REGISTRO SANITARIO
COLOMBIA: INVIMA 2017M-0017885
Dorzolamida 2% - Timolol 0.5%
Tartrato de Brimonidina 0.2%
Solución Oftálmica Estéril
Caja con Frasco Gotero con 5 mL
OPHIA
Lote:
Elab:
Cad:
4016194
18/ABR/17
18/ABR/19 L21


KRYTAN
TEK
Ofteno
PF
LIBRE DE CONSERVADORES
Dorzolamida 2% - Timolol 0.5%
Tartrato de Brimonidina 0.2%
Solución Oftálmica Estéril
Caja con Frasco Gotero con 5 mL
OPHIA
COMPOSICIÓN:
Cada mL (30gotas) contiene:
Clorhidrato de Dorzolamida 22.25 mg
equivalente a 20.00 mg (2.0%) de Dorzolamida
Maleato de Timolol 6.8 mg
equivalente a 5.00 mg (0.5%) de Timolol
Tartrato de Brimonidina 2.00 mg (0.2%)
Vehículo csp 1.00 mL
Excipientes:
Hidroxipropilmetilcelulosa, Manitol, Ácido Cítrico Monohidratado, Citrato de Sodio Dihidratado y Agua para preparación de inyectables.
Cada gota contiene 0.66556 mg de Dorzolamida, 0.16529 de Timolol y 0.06615 mg de Tartrato de Brimonidina.
VÍA DE ADMINISTRACIÓN:
Tópica Oftálmica.
INDICACIÓN Y DOSIS: Lo que el médico señale.
Producto de uso delicado, administrese por prescripción y bajo vigilancia médica. Venta bajo receta médico. Conservese el Frasco bien tapado a temperatura ambiente a no más de 25°C. Desechar el contenido del Frasco luego de 30 días de abierto. No se deje al alcance de los niños. Este producto no debe ser administrado durante el embarazo o cuando se sospeche su existencia, ni durante la lactancia. Para evitar contaminación, no toque ni ponga en contacto la punta del dispensador con cualquier superficie.
Para mayor información sobre indicaciones, dosis, contraindicaciones y advertencias, leer instructivo anexo.
Reg. No. 07M42007 SSA IV
Elaborado
LABORATORIOS SOPHIA, S.A. DE C.V.
Av. Pinzon del Norte No. 5255,
Col. Guadalajara Technology Park,
C.P. 45010, Zapopan, Jalisco, México.
Responsable Sanitario:
Q.F.B. José Rubén Torrero Montaño
www.sophia.com.mx
7

TECNIMICRO
Laboratorio de Análisis S.A.S.

PBX (4) 403 11 00
info@tecnimicro.net
www.tecnimicro.net
Carrera 42 # 10-37
Medellín - Colombia

REPORTE DE ANÁLISIS/ANALYSIS REPORT

Muestra/Sample #: 257562

Empresa / Company: ESPECIALIDADES OFTALMOLOGICAS S.A. **Telf. / Phone:** 448 19 18

Sede / Headquarters: Sede principal Carrera 37 A No. 2 Sur 104, Loma Alejandria, Poblado, Medellí

Producto / Product: AGGLAD OFTENO

Muestra / Sample: Lote: 4015466; Laboratorio: Sophia

Fecha de Recepción / Reception date: 2018-02-06 **Temp. de Recepción / Temp. Reception:** 26,1ºC

Cantidad / Amount: 1 Unidad/ 1 unit

Contenedor / Container: Frasco gotero con tapa/ Dropper bottle with lid

Enviada por /Send by: Tatiana María Gómez Gaviria

Aspecto / Aspect: Líquido translúcido, homogéneo, libre de particulas extrañas/ Translucent, homogeneous liquid free of foreign particles.

Olor / Smell: Inobjetable/Unobjectionable

Color / Color: Incoloro/Colorless

Análisis Fisicoquímico/ Physicochemical Analysis	Fecha/ Date	Unidad/ Unit	Resultado/ Result	Especificaciones(**)/ Specifications(**)	Método/ Method
Osmolalidad/Osmolality	2018-02-06	mOsm/Kg	332	NA	USP 40 <785>

(**) Según Norma / Acoordinng to Standard:

(*) Métodos acreditados/Methods Accredited: ONAC, Certificado/Certificate: 10-LAB-053 Fecha/Date: 2014-09-05 ISO/IEC 17025:2005

NOTA: Este resultado corresponde, exclusivamente a la muestra recibida y analizada en el laboratorio/This result correspond only to the sample received and analyzed by the laboratory

Luz Elena Osorio C

Luz E. Osorio Castaño
T.P. 01345801606001664
Química Farmacéutica U de A
Coordinadora
Fecha / Date: 2018-02-07

Fecha de Impresión/printing date: 2018-02-07

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Veracidad a toda ¡Prueba!

Resultado viscosidad

Equipo

Kinexus Pro (www.malvern.com)



Muestra

Código CECOLTEC	Nombre de la muestra	Lote
C1178 - CF1	Biofocus (abbol)	7A5975
C1178 - CF2	Azarga (Alcon a Novrtis company)	65963
C1178 - CF3	Simbrinza (Alcon a Novrtis company)	17G12DE
C1178 - CF4	Oloftal (tecnoquimicas)	7J360
C1178 - CF5	Brimoftal (tecnoquimicas)	7M396B
C1178 - CF6	Agglad ofteno (sophia)	4015466
C1178 - CF7	Lumigan (al ergan)	E79821
C1178 - CF8	Ganfort (alle gan)	E79942
C1180 - CF1	Dorzopt	1076238 SL C
C1184 - CF1	Alap 0,2% (procaps)	1164658 SL C
C1184 - CF2	Krytan tek ofteno (sophia)	4016194
C1184 - CF3	Trusopt (MSD)	M040389

Condiciones de la medida

Sistema de medida: Plato - Plato 40
Tratamiento:

Tasa de cizalladura: 5,000 s-1 a 20,000 s-1
Muestreo: 15 puntos.
Gap: 0.1 mm
Temperatura: 25 °C ± 0.01 °C

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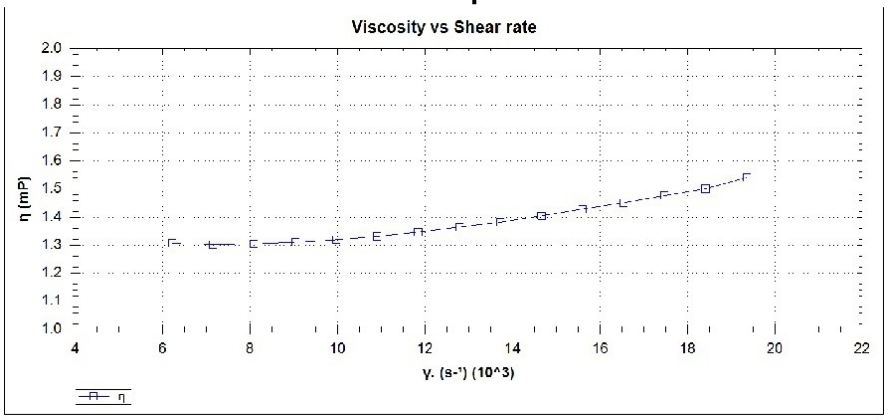
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Agglad ofteno (sophia) 4015466

Tabla de datos

t[s]	T [C°]	Esfuerzo [Pa]	Tasa de cizalladura [s^{-1}]	Viscosidad [mP]
15	25	8.122	6217.00	1.306
22.5	25	9.319	7155.00	1.302
30	25	10.56	8092.00	1.305
37.5	25	11.83	9030.00	1.31
45	25	13.15	9967.00	1.319
52.5	25	14.52	10900.00	1.331
60	25	15.95	11840.00	1.347
67.5	25	17.45	12790.00	1.365
75	25	18.97	13730.00	1.382
82.5	25	20.6	14660.00	1.405
90	25	22.29	15600.00	1.429
97.5	25	24	16540.00	1.451
105	25	25.8	17480.00	1.476
112.5	25	27.65	18420.00	1.501
120	25	29.82	19360.00	1.54

Grafico reporte



Viscosidad final

Valor	Unidad
1.3846	mP

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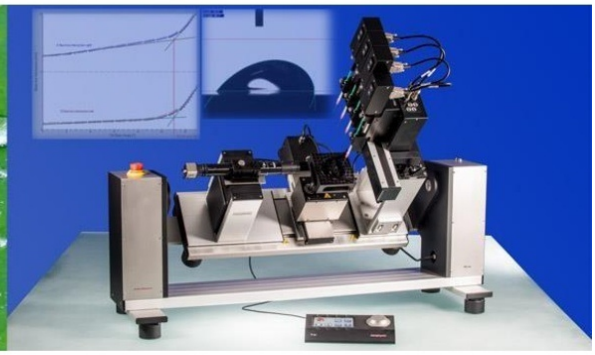
cecoltec
EL ALIADO PRECISO

Informe de resultado tensión superficial

Equipo

Dataphysics OCA15





Características del equipo:

Medida	Rango
Ángulo de contacto [°]	0 – 180 ° ± 0.1°
Tensión superficial e interfacial [Dinas/cm]	0.01 2000 [Dinas/cm] ± 0.01 [Dinas/cm]

Condiciones de medición:

Técnica usada: Gota - péndulo
Jeringa utilizada:Halmilton de 1 mL
Temperatura: 25 ° C
Dosificación: 1 uL/ seg

cecoltec
EL ALIADO PRECISO

Muestras

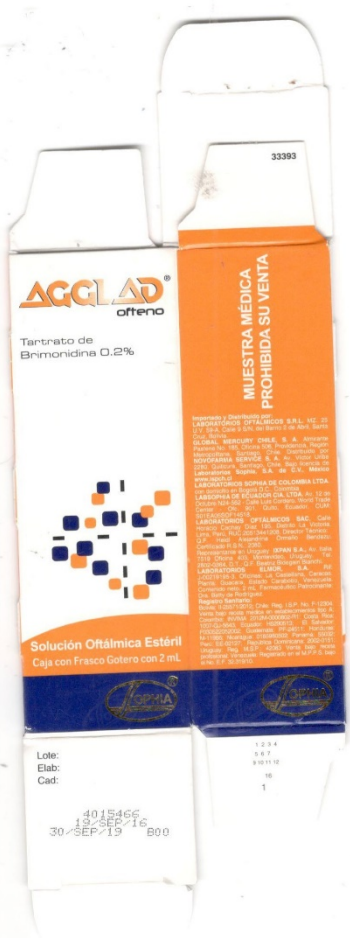
Código Cecoltec	Nombre de la muestra	Lote
C1178 - TS1	Biofocus (abbot)	7A5975
C1178 - TS2	Azarga (Alcon a Novrtis comoany)	65963
C1178 - TS3	Simbrinza (Alcon a Novrtis company)	17G12DE
C1178 - TS4	Oloftal (tecnoquimicas)	7J360
C1178 - TS5	Brimoftal (tecnoquimicas)	7M396B
C1178 - TS6	Agglad ofteno (soohia)	4015466
C1178 - TS7	Lumigan (allergan)	E79821
C1178 - TS8	Ganfort (allergan)	E79942
C1180- TS1	Dorzopt	1076238 SL C
C1184 - TS1	Alap 0,2% (procaps)	1164658 SL C
C1184 - TS2	Krytan tek ofteno (sophia)	4016194
C1184 - TS3	Trusopt (MSD)	M040389

Resultados

Muestra	Medida 1 (Dinas/cm)	Medida 2 (Dinas/cm)	Medida 3 (Dinas/cm)	Medida 4 (Dinas/cm)	Medida 5 (Dinas/cm)	Promedio (Dinas/cm)	Desviación
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C1178 - TS2	47.76	47.45	47.42	48.22	47.85	47.74	0.29
C1178 - TS3	52.94	53.8	52.86	52.96	53.15	53.14	0.34
C1178 - TS4	50.22	50.17	50.58	51.86	51.32	50.83	0.66
C1178 - TS5	53.81	52.21	53.49	52.28	52.4	52.84	0.67
C1178 - TS6	48.31	48.7	48.75	48.79	48.78	48.67	0.18
C1178 - TS7	63.46	63.25	63.31	63.89	63.83	63.55	0.26
C1178 - TS8	64.88	64.33	64.9	64.89	65	64.80	0.24
C1180- TS1	44.32	43.71	44.08	44.3	44.65	44.21	0.31
C1184 - TS1	63.28	63.32	63.62	63.19	63.27	63.34	0.15
C1184 - TS2	78.94	78.26	77.42	78.58	78.77	78.39	0.54
C1184 - TS3	49.87	49.26	49.77	49.28	49.6	49.56	0.25

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AGGLAD®
ofteno
Tartrato de
Brimonidina 0.2%
Solución Oftálmica Estéril
Caja con Frasco Gotero con 2 mL
33393
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Calle 80 No 69 - 43 Bogotá D.C., Colombia.
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Lote:
Elab:
Cad:
4015466
19/SEP/16
30/SEP/19 B00
1 2 3 4
5 6 7
9 10 11 12
16
1


Solución Oftálmica Estéril
Tartrato de
Brimonidina 0.2%
AGGLAD®
ofteno
AGGLAD®
ofteno
Tartrato de
Brimonidina 0.2%
Composición:
Cada mL (22 gotas) contiene:
Tartrato de
Brimonidina ..... 2.0 mg (0.2%)
Vehículo csp ..... 1.0 mL
Excipientes: Ácido cítrico monohidratado, alcohol polivinílico, citrato de sodio dihidratado, cloruro de sodio, cloruro de benzalconio como conservador csp. al 50%).
0.10 mg/mL. Cada gota contiene aproximadamente 0.09 mg de Tartrato de Brimonidina.
Vía de Administración:
Tópica Oftálmica.
Indicación y Dosis: La que el médico señale.
Producto de uso delicado; administrese por prescripción y bajo vigilancia médica. Venta bajo receta médica. Consérvese el frasco bien tapado a temperatura ambiente a no más de 30°C. Desechar el contenido del frasco luego de 30 días de abierto. No se deje al alcance de los niños. Este producto no debe ser administrado durante el embarazo o cuando se sospeche su existencia, ni durante la lactancia. Para evitar contaminación, no toque ni ponga en contacto la punta del dispensador con cualquier superficie.
Para mayor información sobre indicaciones, dosis, contraindicaciones y advertencias, leer instructivo anexo.
Reg. No. 526M2000 SSA IV
Elaborado por:
LABORATORIOS SOPHIA, S.A. DE C.V.
Av. Paseo del Norte No. 5255,
Col. Guadalajara Technology Park,
C. P. 45010, Zapopan, Jalisco, México.
Responsable Sanitario:
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www.sophia.com.mx
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www.tecnimicro.net
Carrera 42 # 10-37
Medellín - Colombia

REPORTE DE ANÁLISIS/ANALYSIS REPORT

Muestra/Sample #: 257557

Empresa / Company: ESPECIALIDADES OFTALMOLOGICAS S.A. **Telf. / Phone:** 448 19 18

Sede / Headquarters: Sede principal Carrera 37 A No. 2 Sur 104, Loma Alejandria, Poblado, Medelli

Producto / Product: BIOFOCUS

Muestra / Sample: Lote: 7A5975; Laboratorio: Abbot

Fecha de Recepción / Reception date: 2018-02-06 **Temp. de Recepción / Temp. Reception:** 26,1°C

Cantidad / Amount: 1 Unidad/ 1 unit

Contenedor / Container: Frasco gotero con tapa/ Dropper bottle with lid

Enviada por /Send by: Tatiana María Gómez Gaviria

Aspecto / Aspect: Líquido translúcido, homogéneo, libre de partículas extrañas/ Translucent, homogeneous liquid free of foreign particles.

Olor / Smell: Inobjetable/Unobjectionable

Color / Color: Incoloro/Colorless

Análisis Fisicoquímico/ Physicochemical Analysis	Fecha/ Date	Unidad/ Unit	Resultado/ Result	Especificaciones(**)/ Specifications(**)	Método/ Method
Osmolalidad/Osmolality	2018-02-06	mOsm/Kg	298	NA	USP 40 <785>

(**) Según Norma / Acoordinng to Standard:

(*) Métodos acreditados/Methods Accredited: ONAC, Certificado/Certificate: 10-LAB-053 Fecha/Date: 2014-09-05 ISO/IEC 17025:2005

NOTA: Este resultado corresponde, exclusivamente a la muestra recibida y analizada en el laboratorio/This result correspond only to the sample received and analyzed by the laboratory

Luz Elena Osorio C

Luz E. Osorio Castaño
T.P. 01345801606001664
Química Farmacéutica U de A
Coordinadora
Fecha / Date: 2018-02-07

Fecha de Impresión/printing date: 2018-02-07

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Resultado viscosidad

Equipo

Kinexus Pro (www.malvern.com)



Muestra

Código CECOLTEC	Nombre de la muestra	Lote
C1178 - CF1	Biofocus (abbol)	7A5975
C1178 - CF2	Azarga (Alcon a Novrtis company)	65963
C1178 - CF3	Simbrinza (Alcon a Novrtis company)	17G12DE
C1178 - CF4	Oloftal (tecnoquimicas)	7J360
C1178 - CF5	Brimoftal (tecnoquimicas)	7M396B
C1178 - CF6	Agglad ofteno (sophia)	4015466
C1178 - CF7	Lumigan (al ergan)	E79821
C1178 - CF8	Ganfort (alle gan)	E79942
C1180 - CF1	Dorzopt	1076238 SL C
C1184 - CF1	Alap 0,2% (procaps)	1164658 SL C
C1184 - CF2	Krytan tek ofteno (sophia)	4016194
C1184 - CF3	Trusopt (MSD)	M040389

Condiciones de la medida

Sistema de medida: Plato - Plato 40
Tratamiento:

Tasa de cizalladura: 5,000 s-1 a 20,000 s-1
Muestreo: 15 puntos.
Gap: 0.1 mm
Temperatura: 25 °C ± 0.01 °C

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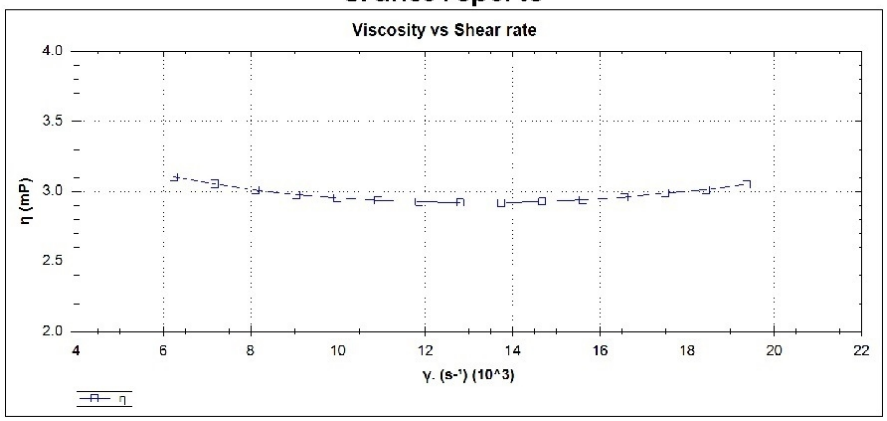
cecoltec
EL ALIADO PRECISO

Biofocus (abbot) **7A5975**

Tabla de datos

t[s]	T [C°]	Esfuerzo [Pa]	Tasa de cizalladura [s^{-1}]	Viscosidad [mP]
15	25	19.34	6228.00	3.105
22.5	25	21.89	7165.00	3.054
30	25	24.39	8103.00	3.01
37.5	25	26.92	9041.00	2.978
45	25	29.49	9979.00	2.956
52.5	25	32.08	10920.00	2.937
60	25	34.73	11860.00	2.929
67.5	25	37.38	12800.00	2.921
75	25	40.1	13730.00	2.919
82.5	25	43.01	14680.00	2.93
90	25	45.91	15610.00	2.94
97.5	25	48.98	16550.00	2.959
105	25	52.29	17490.00	2.99
112.5	25	55.53	18430.00	3.013
120	25	59.11	19370	3.052

Grafico reporte



Viscosidad final

Valor	Unidad
2.9795	mP

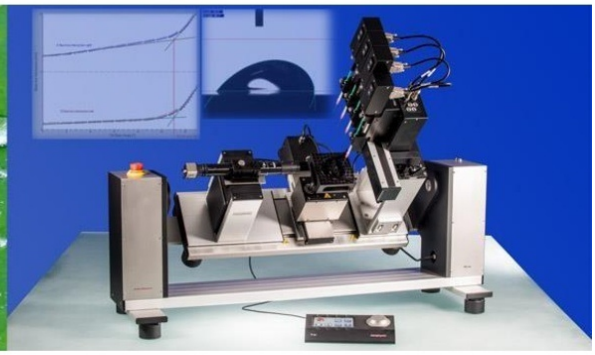
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EL ALIADO PRECISO

Informe de resultado tensión superficial

Equipo

Dataphysics OCA15





Características del equipo:

Medida	Rango
Ángulo de contacto [°]	0 – 180 ° ± 0.1°
Tensión superficial e interfacial [Dinas/cm]	0.01 2000 [Dinas/cm] ± 0.01 [Dinas/cm]

Condiciones de medición:

Técnica usada: Gota - péndulo
Jeringa utilizada:Halmilton de 1 mL
Temperatura: 25 ° C
Dosificación: 1 uL/ seg

cecoltec
EL ALIADO PRECISO

Muestras

Código Cecoltec	Nombre de la muestra	Lote
C1178 - TS1	Biofocus (abbot)	7A5975
C1178 - TS2	Azarga (Alcon a Novrtis comoany)	65963
C1178 - TS3	Simbrinza (Alcon a Novrtis company)	17G12DE
C1178 - TS4	Oloftal (tecnoquimicas)	7J360
C1178 - TS5	Brimoftal (tecnoquimicas)	7M396B
C1178 - TS6	Agglad ofteno (soohia)	4015466
C1178 - TS7	Lumigan (allergan)	E79821
C1178 - TS8	Ganfort (allergan)	E79942
C1180- TS1	Dorzopt	1076238 SL C
C1184 - TS1	Alap 0,2% (procaps)	1164658 SL C
C1184 - TS2	Krytan tek ofteno (sophia)	4016194
C1184 - TS3	Trusopt (MSD)	M040389

Resultados

Muestra	Medida 1 (Dinas/cm)	Medida 2 (Dinas/cm)	Medida 3 (Dinas/cm)	Medida 4 (Dinas/cm)	Medida 5 (Dinas/cm)	Promedio (Dinas/cm)	Desviación
C1178 - TS1	51.13	51.09	51.37	51.18	51.5	51.25	0.16
C1178 - TS2	47.76	47.45	47.42	48.22	47.85	47.74	0.29
C1178 - TS3	52.94	53.8	52.86	52.96	53.15	53.14	0.34
C1178 - TS4	50.22	50.17	50.58	51.86	51.32	50.83	0.66
C1178 - TS5	53.81	52.21	53.49	52.28	52.4	52.84	0.67
C1178 - TS6	48.31	48.7	48.75	48.79	48.78	48.67	0.18
C1178 - TS7	63.46	63.25	63.31	63.89	63.83	63.55	0.26
C1178 - TS8	64.88	64.33	64.9	64.89	65	64.80	0.24
C1180- TS1	44.32	43.71	44.08	44.3	44.65	44.21	0.31
C1184 - TS1	63.28	63.32	63.62	63.19	63.27	63.34	0.15
C1184 - TS2	78.94	78.26	77.42	78.58	78.77	78.39	0.54
C1184 - TS3	49.87	49.26	49.77	49.28	49.6	49.56	0.25

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Biofocus®
0,004 % Travoprost
0,5 % Timolol
Solución Oftálmica Estéril
5 mL
30 x 30 x 73
Biofocus® - Solución Oftálmica Estéril
Composición: Cada mL de solución oftálmica estéril contiene Travoprost 0,04 mg y Timolol maleato equivalente a timolol 5 mg.
Contraindicaciones y advertencias:
Hipersensibilidad a los componentes.
embarazo. Puede inducir cambios en la pigmentación ocular (iris) o en la piel de los párpados. Puede inducir crecimiento de pelos en la región de la bronquial que incluye asma bronquial o historia de asma bronquial, o enfermedad pulmonar obstructiva crónica severa. Bradicardia sinusal, segundo o tercer grado de bloqueo aurículo-ventricular, falla cardíaca evidente, shock cardiogénico, falla cardíaca congestiva, asma o hipersensibilidad bronquial, obstrucción severa enfermedad pulmonar obstructiva crónica severa. Hipersensibilidad a otros betabloqueantes.
Después de abierto el producto puede ser usado máximo por 30 días y luego debe desechar su contenido.
Vía de administración: Conjuntival.
Conservar a temperatura inferior a 30°C en su envase y empaque original.
Mantenga fuera del alcance de los niños.
0,004 % Travoprost
0,5 % Timolol

2011541
Biofocus®
0,004 % Travoprost
0,5 % Timolol
Solución Oftálmica Estéril
5 mL
MUESTRA MÉDICA
PROHIBIDA SU VENTA
Venta bajo fórmula médica.
Psicotrópico según prescripción médica.
Contenido: Frasco por 5 mL
Cada mL contiene aprox. 34 gotas.
Fabricado por:
Laboratorios Syntheon S.A.S
Carrera 7 44 C No 20 C - 73
Bogotá D.C. - Colombia.
REG. SAN. INVIMA 2015M-0016333
Abbott
L 785975
V 07. 2019

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Medellín - Colombia

REPORTE DE ANÁLISIS/ANALYSIS REPORT

Muestra/Sample #: 257726

Empresa / Company: ESPECIALIDADES OFTALMOLOGICAS S.A. **Telf. / Phone:** 448 19 18

Sede / Headquarters: Sede principal Carrera 37 A No. 2 Sur 104, Loma Alejandria, Poblado, Medellí

Producto / Product: DORZOPT

Muestra / Sample: Lote: 1168398 SL D; Laboratorio: Procaps

Fecha de Recepción / Reception date: 2018-02-07 **Temp. de Recepción / Temp. Reception:** 26,1°C

Cantidad / Amount: 1 unidad/1 unit

Contenedor / Container: Frasco gotero con tapa/ Dropper bottle with lid

Enviada por /Send by: Tatiana María Gómez Gaviria

Aspecto / Aspect: Líquido translúcido, homogéneo, libre de partículas extrañas/ Translucent, homogeneous liquid free of foreign particles.

Olor / Smell: Inobjetable/Unobjectionable.

Color / Color: Incoloro/Colorless.

Análisis Fisicoquímico/ Physicochemical Analysis	Fecha/ Date	Unidad/ Unit	Resultado/ Result	Especificaciones(**)/ Specifications(**)	Método/ Method
Osmolalidad/Osmolality	2018-02-07	mOsm/Kg	283	NA	USP 40 <785>

(**) Según Norma / Acoordinng to Standard:

(*) Métodos acreditados/Methods Accredited: ONAC, Certificado/Certificate: 10-LAB-053 Fecha/Date: 2014-09-05 ISO/IEC 17025:2005

NOTA: Este resultado corresponde, exclusivamente a la muestra recibida y analizada en el laboratorio/This result correspond only to the sample received and analyzed by the laboratory

Luz Elena Osorio C

Luz E. Osorio Castaño
T.P. 01345801606001664
Química Farmacéutica U de A
Coordinadora
Fecha / Date: 2018-02-08

Fecha de Impresión/printing date: 2018-02-08

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Veracidad a toda ¡Prueba!

Resultado viscosidad

Equipo

Kinexus Pro (www.malvern.com)



Muestra

Código CECOLTEC	Nombre de la muestra	Lote
C1178 - CF1	Biofocus (abbol)	7A5975
C1178 - CF2	Azarga (Alcon a Novrtis company)	65963
C1178 - CF3	Simbrinza (Alcon a Novrtis company)	17G12DE
C1178 - CF4	Oloftal (tecnoquimicas)	7J360
C1178 - CF5	Brimoftal (tecnoquimicas)	7M396B
C1178 - CF6	Agglad ofteno (sophia)	4015466
C1178 - CF7	Lumigan (al ergan)	E79821
C1178 - CF8	Ganfort (alle gan)	E79942
C1180 - CF1	Dorzopt	1076238 SL C
C1184 - CF1	Alap 0,2% (procaps)	1164658 SL C
C1184 - CF2	Krytan tek ofteno (sophia)	4016194
C1184 - CF3	Trusopt (MSD)	M040389

Condiciones de la medida

Sistema de medida: Plato - Plato 40
Tratamiento:

Tasa de cizalladura: 5,000 s-1 a 20,000 s-1
Muestreo: 15 puntos.
Gap: 0.1 mm
Temperatura: 25 °C ± 0.01 °C

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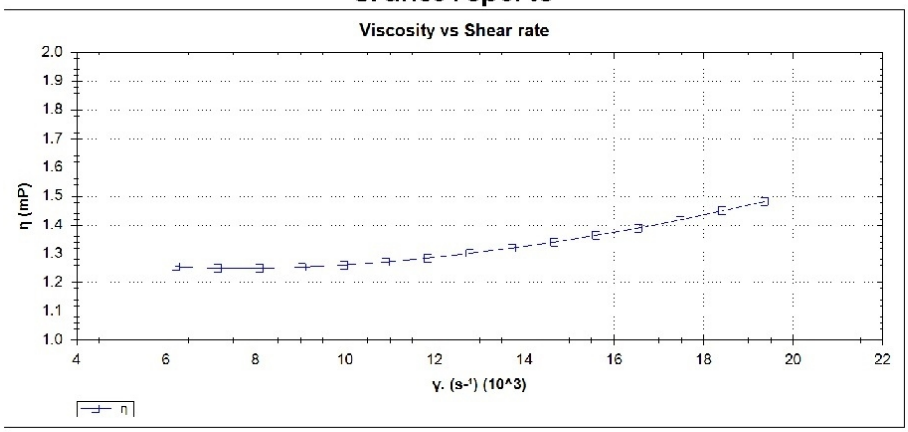
cecoltec
EL ALIADO PRECISO

Dorzopt 1076238 SL C

Tabla de datos

t[s]	T [C°]	Esfuerzo [Pa]	Tasa de cizalladura [s^{-1}]	Viscosidad [mP]
15	25	7.805	6217.00	1.255
22.5	25	8.935	7155.00	1.249
30	25	10.11	8092.00	1.249
37.5	25	11.32	9030.00	1.253
45	25	12.56	9967.00	1.26
52.5	25	13.87	10900.00	1.272
60	25	15.22	11840.00	1.285
67.5	25	16.64	12780.00	1.302
75	25	18.12	13730.00	1.32
82.5	25	19.65	14660.00	1.34
90	25	21.29	15600.00	1.365
97.5	25	22.98	16540.00	1.389
105	25	24.78	17480.00	1.418
112.5	25	26.69	18410.00	1.45
120	25	28.69	19360.00	1.482

Grafico reporte



Viscosidad final

Valor	Unidad
1.3259	mP

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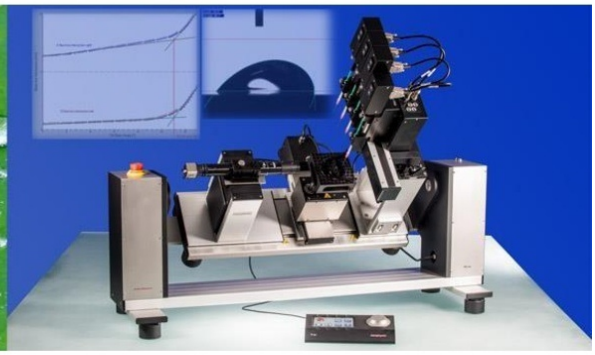
cecoltec
EL ALIADO PRECISO

Informe de resultado tensión superficial

Equipo

Dataphysics OCA15





Características del equipo:

Medida	Rango
Ángulo de contacto [°]	0 – 180 ° ± 0.1°
Tensión superficial e interfacial [Dinas/cm]	0.01 2000 [Dinas/cm] ± 0.01 [Dinas/cm]

Condiciones de medición:

Técnica usada: Gota - péndulo
Jeringa utilizada:Halmilton de 1 mL
Temperatura: 25 ° C
Dosificación: 1 uL/ seg

cecoltec
EL ALIADO PRECISO

Muestras

Código Cecoltec	Nombre de la muestra	Lote
C1178 - TS1	Biofocus (abbot)	7A5975
C1178 - TS2	Azarga (Alcon a Novrtis comoany)	65963
C1178 - TS3	Simbrinza (Alcon a Novrtis company)	17G12DE
C1178 - TS4	Oloftal (tecnoquimicas)	7J360
C1178 - TS5	Brimoftal (tecnoquimicas)	7M396B
C1178 - TS6	Agglad ofteno (soohia)	4015466
C1178 - TS7	Lumigan (allergan)	E79821
C1178 - TS8	Ganfort (allergan)	E79942
C1180- TS1	Dorzopt	1076238 SL C
C1184 - TS1	Alap 0,2% (procaps)	1164658 SL C
C1184 - TS2	Krytan tek ofteno (sophia)	4016194
C1184 - TS3	Trusopt (MSD)	M040389

Resultados

Muestra	Medida 1 (Dinas/cm)	Medida 2 (Dinas/cm)	Medida 3 (Dinas/cm)	Medida 4 (Dinas/cm)	Medida 5 (Dinas/cm)	Promedio (Dinas/cm)	Desviación
C1178 - TS1	51.13	51.09	51.37	51.18	51.5	51.25	0.16
C1178 - TS2	47.76	47.45	47.42	48.22	47.85	47.74	0.29
C1178 - TS3	52.94	53.8	52.86	52.96	53.15	53.14	0.34
C1178 - TS4	50.22	50.17	50.58	51.86	51.32	50.83	0.66
C1178 - TS5	53.81	52.21	53.49	52.28	52.4	52.84	0.67
C1178 - TS6	48.31	48.7	48.75	48.79	48.78	48.67	0.18
C1178 - TS7	63.46	63.25	63.31	63.89	63.83	63.55	0.26
C1178 - TS8	64.88	64.33	64.9	64.89	65	64.80	0.24
C1180- TS1	44.32	43.71	44.08	44.3	44.65	44.21	0.31
C1184 - TS1	63.28	63.32	63.62	63.19	63.27	63.34	0.15
C1184 - TS2	78.94	78.26	77.42	78.58	78.77	78.39	0.54
C1184 - TS3	49.87	49.26	49.77	49.28	49.6	49.56	0.25

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MUESTRA MÉDICA
PROHIBIDA SU VENTA
3 mL
SOLUCIÓN
OFTÁLMICA
PROCAPS
Dorzopt®
DORZOLAMIDA + TIMOLOL
31 x 25 x 60
COMPOSICIÓN: cada mL contiene:
dorzolamida clorhidrato equivalente a
dorzolamida base...20 mg
timolol maleato equivalente a
timolol base.....5 mg
Excipientes: manitol, cloruro de benzalconio
(solución al 50%), citrato c.s.p.
VÍA DE ADMINISTRACIÓN: Colombia:
conjuntival. Perú y otros países: oftálmica.
DOSIFICACIÓN: según criterio médico.
1mL= 25 gotas.
CONTRAINDICACIONES Y
ADVERTENCIAS: asma bronquial o
enfermedad pulmonar obstructiva
crónica severa, bradicardia sinusal,
bloqueo atrioventricular de 2° y 3°
grado, insuficiencia cardiaca evidente,
shock cardiogénico. Hipersensibilidad
a cualquiera de sus componentes,
insuficiencia cardiaca, renal y hepática.
Lactancia. Para evitar contaminación
no toque ni ponga en contacto la punta
del dispensador con la zona afectada.
Producto de uso delicado. Administrar
bajo prescripción y vigilancia médica.
PROCAPS
1
L 11663299 SL D
V 10 2019
200009941
SOLUCIÓN
OFTÁLMICA
PROCAPS
Dorzopt®
DORZOLAMIDA 20mg + TIMOLOL 5mg
MUESTRA MÉDICA
PROHIBIDA SU VENTA
3 mL
SOLUCIÓN
OFTÁLMICA
PROCAPS
Dorzopt®
DORZOLAMIDA 20mg + TIMOLOL 5mg
CYAN
MAGENTA
AMARILLO
NEGRO
7.375 C
536 C
Elaborado por: Pharmayect S.A.
Bogotá - Colombia
Para Procaps S.A. Barranquilla - Colombia
Dir. Técnico: Dr. Alberto De La Hoz Durán
Q. F. U. de C.
Línea Soluciones Terapéuticas Visión Care.
Registro Sanitario No.
INVIMA 2013-M-0002597-R1 Colombia
Costa Rica: Registro Sanitario No.
3101-CU-9111.
Venta bajo fórmula o receta médica.
Manténgase fuera del alcance de los niños.
Almacenar a temperatura inferior a 30°C.
Una vez abierto este producto se conserva
durante 4 semanas a temperatura ambiente
inferior a 30°C. Solamente para uso
oftálmico.

Resultados de análisis producto GAAP ofteno®

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REPORTE DE ANÁLISIS/ANALYSIS REPORT

Muestra/Sample #: 260962

Empresa / Company: ESPECIALIDADES OFTALMOLOGICAS S.A. **Telf. / Phone:** 448 19 18

Sede / Headquarters: Sede principal Carrera 37 A No. 2 Sur 104, Loma Alejandria, Poblado, Medellín

Producto / Product: GAAP OFTENO

Muestra / Sample: Lote: 4016594; Fabricante: Sophia

Fecha de Recepción / Reception date: 2018-03-08 **Temp. de Recepción / Temp. Reception:** 27,0°C

Cantidad / Amount: 1 Unidad x 3 ml / 1 unit x 3 ml

Contenedor / Container: Frasco gotero con tapa/ Dropper bottle with lid

Enviada por /Send by: Tatiana María Gómez Gaviria

Aspecto / Aspect: Líquido translúcido, homogéneo, libre de particulas extrañas/ Translucent, homogeneous liquid free of foreign particles.

Olor / Smell: Inobjetable. / Unobjectionable.

Color / Color: Incoloro. / colorless.

Análisis Fisicoquímico/ Physicochemical Analysis	Fecha/ Date	Unidad/ Unit	Resultado/ Result	Especificaciones(**)/ Specifications(**)	Método/ Method
Osmolalidad/Osmolality	2018-03-09	mOsm/Kg	349	NA	USP 40 <785>

(**) Según Norma / Acoordinng to Standard:

(*) Métodos acreditados/Methods Accredited: ONAC, Certificado/Certificate: 10-LAB-053 Fecha/Date: 2014-09-05 ISO/IEC 17025:2005

NOTA: Este resultado corresponde, exclusivamente a la muestra recibida y analizada en el laboratorio/This result correspond only to the sample received and analyzed by the laboratory

Luz Elena Osorio C

Luz E. Osorio Castaño
T.P. 01345801606001664
Química Farmacéutica U de A
Coordinadora
Fecha / Date: 2018-03-09

Fecha de Impresión/printing date: 2018-03-09

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Equipo

Empresa	OPHTHA
Fabricante (solo MP)	No aplica
Fecha de recepción	08/03/2018
Fecha del análisis	08/03/2018
Analista	Natalia Jaramillo
N ° de serie	Kinexus Pro MAL1023074
Especificación	Informativa



Muestra

Código CECOLTEC	Nombre de la muestra
C1202 - CF1	GAAP ofteno Lote 4016594

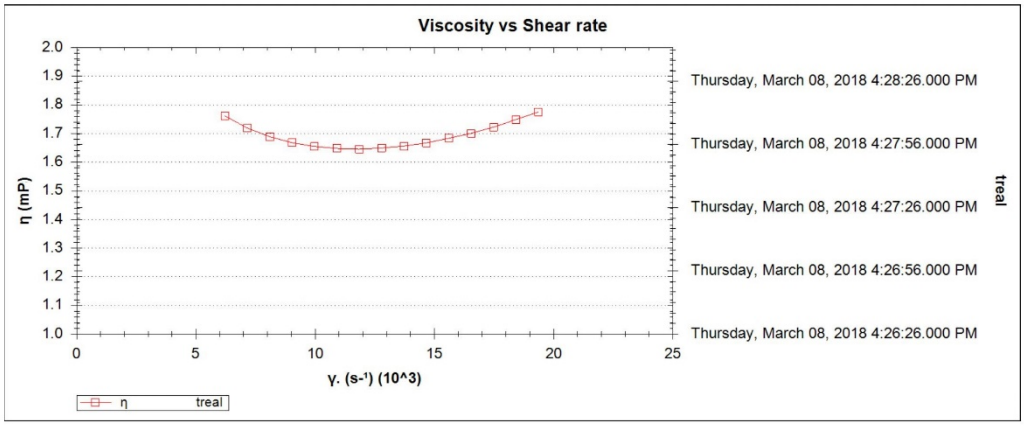
Condiciones de la medida

Sistema de medida:
Tratamiento: Barrido de tasa de cizallamiento
Tasa de cizalladura: 5000 s-1 hasta 20000 s-1
Muestreo: 15 Puntos
Gap: 0.1 mm
Temperatura: 25 °C ± 0.01 °C

Tabla de datos

t[s]	T [C°]	Esfuerzo [Pa]	Tasa de cizalladura [s^{-1}]	Viscosidad [mP]
7.5	25	10.34	5341.00	1.937
15	25	10.95	6217.00	1.762
22.5	25	12.3	7154.00	1.719
30	25	13.67	8092.00	1.689
37.5	25	15.06	9030.00	1.668
45	25	16.5	9968.00	1.655
52.5	25	17.99	10910.00	1.648
60	25	19.5	11850.00	1.646
67.5	25	21.1	12790.00	1.65
75	25	22.74	13730.00	1.657
82.5	25	24.45	14660.00	1.667
90	25	26.27	15600.00	1.684
97.5	25	28.14	16540.00	1.701
105	25	30.12	17480.00	1.723
112.5	25	32.22	18420.00	1.749
120	25	34.37	19360.00	1.776

Grafico reporte



Viscosidad final

Valor	Unidad	Desviación STD
1.692	mP	0.0436

Revisión

Cumple ☐ No cumple ☐ No aplica X

cecoltec
EL ALIADO PRECISO

Informe de resultado tensión superficial

Equipo

Dataphysics OCA15





Características del equipo:

Medida	Rango
Ángulo de contacto [°]	0 – 180 ° ± 0.1°
Tensión superficial e interfacial [Dinas/cm]	0.01 200 [Dinas/cm] ± 0.01 [Dinas/cm]

Condiciones de medición:

Técnica usada: Gota - péndulo
Jeringa utilizada:Halmilton de 1 mL
Temperatura: 25 ° C
Dosificación: 1 uL/ seg

cecoltec
EL ALIADO PRECISO

Muestras

Código Cecoltec	Nombre de la muestra	Lote
C1202 – TS1	GAAP ofteno	Lote 4016594

Resultados

# Medida	GAAP ofteno Lote 4016594 C1202-TS1
1 [Dinas/cm]	67,64
2 [Dinas/cm]	67,54
3 [Dinas/cm]	67,77
4 [Dinas/cm]	67,66
5 [Dinas/cm]	67,61
Promedio [Dinas/cm]	67,644
Desviación estándar	0,057

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Composición:
Cada mL (20 gotas) contiene:
Latanoprost.....0.05 mg (0.005%)
Vehículo csp.....1.0 mL
Excipientes: Hialuronato de sodio, hidroxipropilbetaciclodextrina, ácido bórico, borato de sodio decahidratado, edetato disódico dihidratado, cloruro de benzalconio como conservador (sol. al 50%). 0.2 mg/mL. Cada gota contiene aproximadamente 0.0025 mg de Latanoprost.
Vía de Administración: Tópica Oftálmica.
Indicación y Dosis: La que el médico señale.
Producto de uso delicado, administrese por prescripción y bajo vigilancia médica. Venta bajo receta médica. Consérvese el frasco bien tapado a temperatura ambiente a no más de 30°C. Desechar el contenido del frasco luego de 30 días de abierto. No se deje al alcance de los niños. Este producto no debe ser administrado durante el embarazo o cuando se sospeche su existencia, ni durante la lactancia. Para evitar contaminación, no toque ni ponga en contacto la punta del dispensador con cualquier superficie.
Para mayor información sobre indicaciones, dosis, contraindicaciones y advertencias, leer instructivo anexo.
Reg. No. 285M2004 SSA IV
Elaborado por:
LABORATORIOS SOPHIA, S.A. DE C.V.
Av. Paseo del Norte No. 5255,
Col. Guadalajara Technology Park,
C. P. 45010,
Zapopan, Jalisco, México.
Responsable Sanitario:
Q.F.B. José Rubén Tornero Montaño.
www.sophia.com.mx
GAAP
OFTENO
Latanoprost 0.005%
Solución Oftálmica Estéril
Caja con Frasco Gotero con 3 mL
MEDICAMENTO ESENCIAL*
SOPHIA
SOPHIA
1
Lote:
Elab:
Cad:
4016594
18/JUL/17
18/JUL/19
C19


33446
GAAP
OFTENO
Latanoprost 0.005%
Importado y Distribuido por:
LABORATORIOS OFTALMICOS S.R.L.
U.V. 59-A, Calle 9 S/N, del Barrio 2 de Abril,
Cruz, Bolivia.
GLOBAL MERCURY CHILE, S. A.
Pasteur No. 183, Oficina 506, Providencia,
Metropolitana, Santiago, Chile. Distribuido
MEDICINA SERVICE S. A.
2280, Quito, Pichincha, Ecuador.
Laboratorios Sophia, S.A. de C.V.
www.sophia.t
LABORATORIOS SOPHIA DE COLOMBIA LTD
con domicilio en Bogotá D.C., Colombia.
REIPROM FARMA, S.A.
Cruz N° 1E2I-09 y Av. Alshuajira, Quito, Ecuador.
LABORATORIOS OFTÁLMICOS SAC.
Huaylas-Cochez Diaz 195, Distrito La Victoria, Lim
Perú. RUC N°
Director Técnico: Q.F. Heidi Alejandrina Ormeñ
Bendezu.
Representante en Uruguay: DIPAN S.A.
7319 oficina 403, Montevideo, Uruguay.
(802)-0264, D.T.: Q.F. Beatriz Bolognani Bianchi.
LABORATORIOS ELMOR, S.A.
Número: La Castellana, Caracas. Planta: Guacara
Estado Carabobo, Venezuela. Contenido neto:
3 mL. Oftalmológico Farmacéutico Patrocinante
Dra. Nelly de Rodríguez.
Registro Sanitario:
Bolivia: 9-31532005. Chile: Reg. I.S.P.
F-10625. Venta bajo receta médica
establecimientos tipo A. Colombia:
2015M-0004006-R1 "Leyenda solo para Colombia
Costa Rica: 1007-Q2-13854. Ecuador: H074061
Salvador: F03501063005. Guatemala
FF-34844-14. Honduras: Nicaragua
018203405. Panamá: 62410. Perú:
República Dominicana: 2006-1940. Uruguay
M.S.P.: 42058 Control médico: receta
Venezuela: Registrado en el M.P.P.S. bajo el N
E.F. 34.036
SOPHIA
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Lote:
Elab:
Cad:
4016594
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18/JUL/19
C19

Anexo 5. Capítulo general Productos oftálmicos-pruebas de calidad.

⟨771⟩ PRODUCTOS OFTÁLMICOS—PRUEBAS DE CALIDAD

INTRODUCCIÓN

Los productos oftálmicos son productos estériles que están destinados a la aplicación en cualquier estructura ocular, incluyendo los espacios adyacentes a una estructura ocular y espacios circundantes inmediatos.

Las vías de administración de los productos oftálmicos se dividen en tres categorías generales: tópicos, inyecciones intraoculares e inyecciones extraoculares. Los medicamentos tópicos están destinados a la administración en un componente de la superficie ocular, tal como el párpado, la conjuntiva o la córnea y pueden producir efectos sistémicos o locales. Las inyecciones intraoculares y las extraoculares se administran a través del tejido conjuntivo externo. Las vías oftálmicas de administración incluyen, entre otras: las vías tópica, subconjuntival, subtenoniana, subretiniana, subcoroidal, intracorneal, intraescleral, supracoroidal, intravítrea, intracameral, yuxtaescleral y retrobulbar (ver la *Figura 1*). Los productos oftálmicos se administran en el ojo mediante una amplia variedad de formas farmacéuticas, incluyendo, entre otras: soluciones, suspensiones, ungüentos, geles, emulsiones, tiras, inyecciones, insertos e implantes.

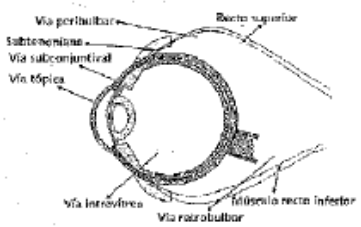


Figura 1. Algunas vías de administración en el ojo.

Este capítulo provee listas de los requisitos de pruebas de calidad de productos comunes y consolidadas en un formato coherente y conciso. Este capítulo es aplicable, en parte o en su totalidad, cuando se haga referencia al mismo en una monografía de un medicamento (ver *Advertencias Generales, 3.10 Aplicabilidad de las Normas*). El capítulo incluye las pruebas de calidad para la vía de administración específica. Las pruebas de calidad listadas pueden ser usadas por los fabricantes, según corresponda, en el desarrollo de nuevas monografías para medicamentos que se van a presentar ante la *USP–NF*.

[NOTA—Todas las referencias a los capítulos superiores a ⟨1000⟩ son únicamente para propósitos informativos y pueden usarse como un recurso útil. Estos capítulos no son de cumplimiento obligatorio a menos que se exija su aplicación explícitamente.]

FORMAS FARMACÉUTICAS OFTÁLMICAS

Este capítulo trata las características específicas de las formas farmacéuticas que se administran a cualquier estructura en el ojo. Ver el capítulo *Formas Farmacéuticas* ⟨1151⟩ para información adicional sobre la descripción y la fabricación de formas farmacéuticas.

Los productos oftálmicos tienen requisitos idénticos o similares a los productos inyectables e implantes. Para mayor información sobre los requisitos de estas formas farmacéuticas, ver el capítulo *Medicamentos Inyectables y en Implantes* ⟨1⟩.

Dependiendo de la formulación, el sistema de envase–cierre y el proceso de esterilización, pueden ocurrir cambios por degradación y/o cambios morfológicos durante la etapa de esterilización del proceso de fabricación, los cuales deben minimizarse. Las temperaturas requeridas para la esterilización por autoclave pueden ocasionar daños irreversibles a ciertas formas farmacéuticas, tales como suspensiones, semisólidos, emulsiones, entre otras, mientras que la filtración es aplicable solo a formulaciones que contienen partículas con tamaños de partículas <0,2 µm. Una alternativa es fabricar el producto a partir de ingredientes estériles en un ambiente aséptico.

Para productos multidosis, se requiere un conservante antimicrobiano adecuado y se debe demostrar su efectividad durante la vida útil del producto.

Soluciones

[NOTA—En esta sección se incluyen aquellos productos sólidos que, al reconstituirlos de acuerdo con las instrucciones en la etiqueta, dan lugar a una solución.]

El tiempo de contacto de las soluciones oftálmicas tópicas con la córnea se incrementa con la viscosidad de las formulaciones. Diversos polímeros sintéticos, incluidos, entre otros, el alcohol polivinílico, la polivinilpirrolidona, el polietilenglicol, el ácido poliacrílico y muchos derivados de celulosa, tales como la hipromelosa y la hidroxietilcelulosa se usan comúnmente como mejoradores de la viscosidad debido a su compatibilidad fisiológica y a sus propiedades fisicoquímicas satisfactorias.

Otra forma de incrementar el tiempo de contacto con la córnea implica el uso de polímeros que proveen a la formulación líquida una consistencia semisólida sólo cuando se coloca en el área conjuntiva o en la córnea. De esta forma, a la instilación simple de la solución le sigue una permanencia prolongada como resultado de las propiedades viscoelásticas del hidrogel formado. El "hidrogel" o los "geles de base acuosa" son redes tridimensionales de cadenas de polímeros que contienen agua dentro de la red. La red puede ser una estructura entrecruzada física o químicamente (un enlace covalente) entre cadenas de polímeros. El contenido de agua de los hidrogeles puede ajustarse modulando la composición y la conformación de los polímeros, tales como el balance hidrofílico/hidrofóbico de las cadenas de polímeros y los grupos laterales y el grado de entrecruzamiento. El fenómeno de gelificación in situ es ocasionado por un cambio en la conformación de los polímeros que puede ser desencadenado por estímulos externos, tales como la temperatura, el pH, el contenido iónico y el fluido lagrimal al momento de la administración en el ojo. Además, algunos polímeros pueden interactuar, mediante enlaces no covalentes, con la mucina conjuntival y mantener la formulación en contacto con los tejidos de la córnea.

Las soluciones pueden inyectarse no sólo por la vía intravítrea, sino también por otras vías, tales como las vías subconjuntival, subtenoniana, retrobulbar, supracoroidal y subretiniana.

Suspensiones

[NOTA—En esta sección se incluyen aquellos productos sólidos que, al reconstituirlos de acuerdo con las instrucciones en la etiqueta, dan lugar a una suspensión.]

Se puede considerar el uso de suspensiones acuosas u oleosas por una variedad de razones, tales como las siguientes: 1) medicamentos poco solubles en agua; 2) medicamentos con baja estabilidad acuosa; y 3) en casos en los que es necesario incrementar el tiempo de contacto con el ojo e incrementar la humectación del ojo. El tamaño de partícula del medicamento a menudo se reduce a niveles <10 µm en un intento por evitar la producción excesiva de lágrimas.

Después de la instilación tópica, se espera que las partículas se mantengan en el fondo de saco y que el fármaco se disuelva o se libere lentamente a partir de las estructuras poliméricas mediante difusión, disolución, degradación polimérica o intercambio iónico.

Las suspensiones pueden inyectarse no sólo por la vía intravítrea, sino también por otras vías, tales como subconjuntival, subtenoniana, retrobulbar, supracoroidal y subretiniana.

Ungüentos

Los ungüentos oftálmicos son productos semisólidos que por lo general están destinados a aplicación en la conjuntiva, la cómea o el párpado. Tienen un mayor tiempo de contacto en comparación con muchas soluciones. Una base para ungüento oftálmico adecuada no provoca irritación en el ojo y permite la difusión del fármaco a través de las secreciones que bañan el ojo.

La mayoría de las bases oleosas y exentas de agua para ungüento oftálmico están compuestas de petrolato blanco y petrolato líquido (aceite mineral) o la base para ungüento oftálmico es una modificación de la fórmula a base de petrolato. Están diseñadas para fundirse a la temperatura corporal. También se pueden usar otros tipos de bases lipofílicas para ungüento. Un vehículo anhidro puede presentar ventajas para los medicamentos sensibles a la humedad.

Geles

Los productos semisólidos de tipo gel son una alternativa a los ungüentos tradicionales y se basan en el efecto de incrementar la viscosidad para prolongar la retención del fármaco en el ojo. Se pueden usar varios tipos de agentes gelificantes, tales como derivados del ácido poliacrílico, carbómero e hipromelosa.

Emulsiones

Las emulsiones oftálmicas tópicas por lo general se preparan disolviendo o dispersando el fármaco en una fase oleosa, agregando agentes emulsionantes y de suspensión adecuados, y mezclando con agua vigorosamente para formar una emulsión uniforme de aceite en agua. Cada fase por lo general se esteriliza antes o durante la carga en el vaso de mezclado. Se puede usar homogenización de alto corte para reducir el tamaño de las gotitas de aceite a tamaños submicrónicos, lo cual puede mejorar la estabilidad física de las micelas de aceite evitando que se fusionen. La forma farmacéutica resultante debe contener gotitas de aceite pequeñas suspendidas de manera uniforme.

La justificación más común para desarrollar una emulsión oftálmica es la limitada solubilidad en agua de los fármacos. Los fármacos pueden agregarse a la fase en la que sean solubles al inicio del proceso de fabricación, o el fármaco puede ser agregado después de preparar la emulsión mediante un proceso adecuado de dispersión.

La estabilidad física de la emulsión puede medirse mediante técnicas de dispersión de luz que caracterizan la distribución del tamaño de glóbulos en la fase oleosa. Se pueden agregar surfactantes adecuados para mejorar la estabilidad de la emulsión.

Tiras

Las tiras oftálmicas pueden tener diferentes usos oftálmicos que incluyen, entre otros, el uso como una herramienta de diagnóstico para visualizar defectos o aberraciones en el epitelio de la córnea o para medir la cantidad de producción de lágrimas. Se fabrican con papel de filtro y pueden contener compuestos, tales como fluoresceína sódica. Se envasan de forma individual para preservar la esterilidad hasta el momento de su uso.

Inyectables

Aunque los inyectables se consideran una forma farmacéutica para propósitos de nomenclatura, no se tratan como tales en este capítulo. Referirse a las formas físicas apropiadas, tales como solución, suspensión u otras, para obtener información general.

Insertos

Los insertos oftálmicos y los sistemas oculares son formas farmacéuticas sólidas de tamaño y forma apropiados que se colocan en el fondo del saco conjuntival, en el punto lagrimal (*Figura 2*) o en la córnea. Los insertos a menudo pueden retirarse, si se presentan efectos adversos y proveer la liberación prolongada del fármaco durante cierto periodo. Los insertos pueden ser erosionables (solubles) o no erosionables (insolubles). La liberación de fármacos a partir de los insertos solubles implica dos etapas: 1) la liberación rápida de una porción del fármaco a medida que el fluido lagrimal penetra en el sistema; y 2) la liberación lenta a medida que se forma una capa de gel en la superficie del inserto. Los escudos de colágeno fabricados a partir de colágeno de la esclerótica porcina o de tejido dérmico bovino—y los dispositivos obtenidos por moldeo, extrusión o compresión (minitabletas) de polímeros gelificantes—pertenecen a esta categoría de insertos solubles. Los polímeros bioerosionables (p.ej., derivados de gelatina entrecruzada y poliésteres) pueden usarse para preparar insertos erosionables; estas matrices actúan como depósitos o interactúan con las moléculas del fármaco a través de enlaces lábiles.

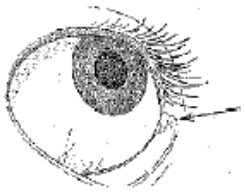


Figura 2. Punto lagrimal.

Los insertos solubles pueden tener el fármaco incorporado en matrices erosionables, tales como hidroxipropilcelulosa, ácido hialurónico, carbómero o ácido poliacrílico. Los insertos solubles pueden colocarse en el fondo de saco inferior y por lo general se disuelven dentro de las 12–24 horas. Los productos poliméricos erosionables se disuelven gradualmente mientras liberan el fármaco y por lo tanto el paciente no tiene que retirar el inserto polimérico erosionable después de usarlo.

Los insertos insolubles pueden tener una estructura de matriz o un depósito. Su mecanismo de acción se basa en la difusión de un fluido en el dispositivo, disolviendo el medicamento y la creación de una solución saturada que se libera al medio desde el inserto mediante difusión. Estos insertos insolubles deben ser retirados después de cierto periodo.

Implantes

Los implantes se inyectan o implantan en el segmento anterior (intracameral, subconjuntival, subtenoniano u otras partes del segmento anterior) o en las cavidades intravítreas, y los implantes pueden presentarse en diversas formas, tales como un disco o una varilla delgada. Los implantes pueden fabricarse con polímeros no biodegradables o biodegradables.

Entre los tipos de implantes (polímero) sólidos no biodegradables se encuentran los implantes de tipo depósito que se anclan a la esclerótica, en los que el fármaco es liberado a través de un polímero semipermeable no biodegradable. Los implantes tipo depósito pueden fabricarse a partir de una variedad de materiales, incluido el alcohol polivinílico–etilenvinilacetato. Los polímeros biodegradables pueden usarse para formar implantes sólidos inyectables.

Productos de Combinación de Medicamento–Dispositivo

Una combinación de medicamento oftálmico–dispositivo es un producto que en la mayoría de los casos está constituido por dos componentes. Uno es una forma farmacéutica que contiene los fármacos y el otro es un dispositivo que activará o facilitará la penetración de los fármacos a partir de la forma farmacéutica en una región particular del ojo. Algunos ejemplos de los dispositivos son aquellos que generan ondas (calor o luz).

Este capítulo se aplica sólo al componente de la forma farmacéutica del producto de combinación de medicamento oftálmico–dispositivo. Las reglamentaciones apropiadas de la FDA con respecto a los dispositivos médicos deben usarse para el componente del dispositivo.

CALIDAD DEL MEDICAMENTO

Los procedimientos y los criterios de aceptación para el análisis de productos oftálmicos se dividen en dos categorías: 1) aquellos que evalúan los atributos generales de calidad, p.ej., identificación, potencia, pureza (e impurezas), esterilidad y partículas; y 2) aquellos que evalúan el desempeño in vitro del producto, es decir, disolución o liberación de los fármacos a partir del producto. Las pruebas de calidad evalúan la integridad de la forma farmacéutica, mientras que las pruebas de desempeño evalúan la liberación de fármacos y otros atributos que se relacionan con el desempeño in vivo. En conjunto, las pruebas de calidad y de desempeño aseguran la identidad, contenido, calidad, pureza y eficacia del medicamento. Este capítulo trata las pruebas de calidad para productos oftálmicos. Las pruebas de desempeño (disolución/liberación de fármacos) se tratan en el capítulo *Productos Oftálmicos—Pruebas de Desempeño* ⟨1771⟩.

Pruebas Universales

En este capítulo, la división de las pruebas de calidad del producto en pruebas universales y en pruebas específicas no sigue de manera estricta la guía de la ICH *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* (disponible en inglés en www.ich.org). En este capítulo, pruebas universales se refiere a las pruebas que son aplicables a todos los productos oftálmicos, independientemente del tipo de forma farmacéutica.

DESCRIPCIÓN

Se debe proveer una descripción cualitativa del medicamento. Los criterios de aceptación deben contener la apariencia final aceptable, que incluya la transparencia y el color de la forma farmacéutica y del envasado. Si el color cambia durante el almacenamiento, puede ser apropiado un procedimiento cuantitativo. Esta no es una prueba farmacopeica, aunque forma parte de la especificación del fabricante del medicamento.

IDENTIFICACIÓN

Las pruebas de identificación se tratan en las *Advertencias y Requisitos Generales 5.40*. Las pruebas de identificación deben establecer la identidad del fármaco o fármacos presentes en el artículo y deben discriminar entre compuestos con estructuras estrechamente relacionadas potencialmente presentes. Las pruebas de identidad deben ser específicas para los fármacos [p.ej., espectroscopía en el infrarrojo (IR, por sus siglas en inglés)]. Los métodos espectrofotométricos en el infrarrojo cercano (NIR, por sus siglas en inglés) o Raman pueden ser aceptables para la identificación del medicamento. Los procedimientos de identificación de uso más amplio para fármacos contenidos en formas farmacéuticas son los procedimientos cromatográficos que incluyen una comparación con los estándares apropiados (ver los capítulos *Cromatografía* ⟨621⟩ y *Prueba de Identificación por Cromatografía en Capa Delgada* ⟨201⟩). La identificación mediante un solo tiempo de retención cromatográfico no constituye una prueba específica.

VALORACIÓN

Se debe usar una prueba específica e indicadora de la estabilidad para determinar la concentración (contenido) del medicamento. Para casos en los que se justifique el uso de una valoración no específica, se deben usar otros procedimientos analíticos para lograr la especificidad general. Se debe usar un procedimiento específico cuando exista evidencia de interferencia de excipientes con la prueba de valoración no específica. Se encuentra disponible información adicional sobre valoraciones específicas en los capítulos *Antibióticos—Valoraciones Microbiológicas* ⟨81⟩, ⟨621⟩ y *Cromatografía Iónica* ⟨1065⟩.

IMPUREZAS

Pueden estar presentes impurezas del proceso, subproductos sintéticos y otras impurezas orgánicas e inorgánicas en el fármaco y en los excipientes usados en la fabricación del medicamento. Estas impurezas son controladas por las monografías de fármacos y excipientes. Se deben monitorear las impurezas orgánicas que surgen de la degradación del fármaco en el medica-

mento y aquellas impurezas que surgen durante el proceso de fabricación del medicamento. Todos los artículos cumplen con los requisitos de los capítulos *Impurezas Elementales—Límites* ⟨232⟩ y *Disolventes Residuales* ⟨467⟩.

pH

Ver el capítulo *pH* ⟨791⟩. Las lágrimas normales tienen un pH de aproximadamente 7,4. El ojo puede tolerar productos en un intervalo de valores de pH desde aproximadamente 3,0 hasta aproximadamente 8,6, dependiendo de la capacidad de amortiguación de la formulación. El valor de pH de la formulación debe ser aquél en el que el producto sea más estable. Las formulaciones que se centran en los extremos del intervalo de pH aceptable tendrán una mejor aceptación por parte del paciente si las formulaciones tienen una baja capacidad de amortiguación.

OSMOLARIDAD

Ver el capítulo *Osmolalidad y Osmolaridad* ⟨785⟩. Los productos oftálmicos pueden ser tolerados en un intervalo bastante amplio de tonicidad (cloruro de sodio al 0,5%–5%, equivalente a aproximadamente 171–1711 mOsm/kg). Las soluciones hipotónicas se toleran mejor que las soluciones hipertónicas. Se deben tomar precauciones para asegurar que el producto mantiene su osmolaridad durante la vida útil. Se debe tener en cuenta cualquier posible contribución o interferencia del sistema de envase.

PARTÍCULAS Y MATERIA EXTRAÑA

Todos los productos oftálmicos deben ser inspeccionados con respecto a la integridad del envase y, en la medida de lo posible, para determinar la presencia de partículas extrañas y observables (partículas visibles). Estas partículas indeseables surgen de dos fuentes: extrínsecas (es decir, materia extraña); e intrínsecas o materia relacionada con el producto. La materia extrínseca no puede asociarse con el producto o el proceso. La incorporación de partículas intrínsecas ocurre durante el montaje del producto o resulta de cambios con el paso del tiempo. Una tercera categoría, la materia inherente, describe un estado físico o partículas que son un atributo esperado del producto.

Se requiere una inspección del cien por ciento para los productos inyectables en envases transparentes a fin de eliminar los envases finales con partículas visibles. Cuando sea difícil realizar una inspección del 100% del producto inyectable en el envase final, como en el caso de los envases opacos, se pueden usar métodos alternativos para determinar la aceptabilidad. El capítulo *Partículas Visibles en Inyectables* ⟨790⟩ provee guías adicionales para los métodos de inspección general y una definición de "esencialmente exento de partículas visibles" para el cumplimiento de las partidas.

Son dos las categorías aplicables para la administración de productos en tejidos oculares. La administración intraocular incluye a todos los productos oftálmicos que atraviesan (penetran) el tejido conjuntivo, tales como la córnea y la esclerótica. La administración extraocular de productos oftálmicos incluye a todos los demás componentes y espacios. Para el contenido de partículas subvisibles, se deben seguir las guías de la USP. Los productos para uso intraocular deben cumplir con el capítulo *Partículas en Soluciones Oftálmicas* ⟨789⟩. Los productos para uso extraocular deben cumplir con el capítulo *Partículas en Inyectables* ⟨788⟩. Los aspectos a tener en cuenta para la evaluación del producto y los antecedentes para ambos métodos subvisibles se encuentran en el capítulo *Métodos para la Determinación de Partículas en Inyectables y Soluciones Oftálmicas* ⟨1788⟩.

ESTERILIDAD

Las formas farmacéuticas oftálmicas deben cumplir con los requisitos del capítulo *Pruebas de Esterilidad* ⟨71⟩. Si los ingredientes específicos usados en la formulación no se prestan para las técnicas de esterilización de rutina, se pueden usar ingredientes que cumplen con los requisitos de esterilidad descritos en el capítulo ⟨71⟩ usando una técnica de fabricación aséptica. El envase primario para los productos oftálmicos deberá ser estéril al momento de llenado y de cierre. Es obligatorio que los envases primarios para los productos oftálmicos estén sellados y que sean a prueba de alteración intencional de modo que se asegure la esterilidad al momento del primer uso.

CONSERVANTES ANTIMICROBIANOS

Se deben agregar agentes antimicrobianos a los productos que se envasan en envases que permiten retirar o administrar dosis múltiples, a menos que prevalezca una de las siguientes condiciones: 1) se proveen instrucciones distintas en la monografía individual; 2) la sustancia contiene un radionucleído con una media vida física de <24 horas; y 3) el medicamento, sin agentes adicionales, tiene la suficiente capacidad microbicida para cumplir con los requisitos del capítulo *Pruebas de Eficacia Antimicrobiana* ⟨51⟩. Las sustancias deben cumplir con los requisitos de los capítulos ⟨51⟩ y *Agentes Antimicrobianos—Contenido* ⟨341⟩. Se deben establecer criterios de aceptación para el contenido de conservantes antimicrobianos en productos de unidades múltiples.

ENDOTOXINAS BACTERIANAS

Todos los medicamentos oftálmicos inyectados deben prepararse de manera que minimicen las endotoxinas bacterianas según se definen en el capítulo *Prueba de Endotoxinas Bacterianas* ⟨85⟩. Los límites son no más de 0,5 UE/mL para los productos de irrigación oftálmica y no más de 2,0 UE/dosis/ojo para los medicamentos inyectados o implantados. Por lo general, esta prueba no es requerida para los productos oftálmicos de aplicación tópica. Este capítulo no trata los límites de endotoxina para los dispositivos que se inyectan o implantan.

UNIFORMIDAD DE UNIDADES DE DOSIFICACIÓN

Esta prueba es aplicable a las formas farmacéuticas envasadas en envases unitarios. Incluye tanto la masa de la forma farmacéutica y el contenido del fármaco en la forma farmacéutica. La prueba puede realizarse mediante uniformidad de contenido o variación de peso (ver el capítulo *Uniformidad de Unidades de Dosificación* ⟨905⟩).

CONTENIDO DE LOS ENVASES

Se debe determinar el contenido de los envases de los productos oftálmicos (ver el capítulo *Llenado Mínimo* ⟨755⟩).

SUSTANCIAS LIXIVIABLES Y SUSTANCIAS EXTRAÍBLES

El sistema de envase no debe interactuar física ni químicamente con el producto de ninguna manera que altere el contenido, la calidad o la pureza del medicamento. El sistema de envase debe cumplir con los requisitos de los capítulos *Tapones Elastoméricos para Inyectables* ⟨381⟩, *Envases—Vidrio* ⟨660⟩, *Materiales Plásticos de Construcción* ⟨661.1⟩ y *Sistemas de Envases Plásticos para Uso Farmacéutico* ⟨661.2⟩. Se puede encontrar información adicional sobre los sistemas de envase en los capítulos *Evaluación de Sustancias Extraíbles Relacionadas con Envases Farmacéuticos y Sistemas de Administración* ⟨1663⟩ y *Evaluación de Sustancias Lixiviables Relacionadas con Envases Farmacéuticos y Sistemas de Administración* ⟨1664⟩. La evaluación de posibles sustancias lixiviables y sustancias extraíbles, y el establecimiento de criterios de aceptación para estos compuestos deben tener en cuenta la evaluación de riesgos del producto, su indicación y su sistema de envase.

Además, se debe tener en cuenta que una evaluación de riesgos del impacto de las sustancias extraíbles/sustancias lixiviables, en una vía de administración tópica o intraocular es una actividad desafiante. Las evaluaciones toxicológicas o de seguridad de las sustancias lixiviables o de las sustancias extraíbles en los componentes de envases primarios o secundarios por lo regular no están disponibles para vías de administración oftálmicas. Una evaluación de riesgos puede incluir la evaluación de la toxicología y la seguridad a partir de otras vías de administración y una evaluación de la Ingesta Diaria Total de las sustancias extraíbles/sustancias lixiviables que se están evaluando. La preponderancia de dichas evaluaciones conlleva a una estimación del riesgo de las sustancias extraíbles/sustancias lixiviables mediante la administración ocular al paciente.

INTEGRIDAD DEL ENVASE–CIERRE

El sistema de envase debe cerrarse o sellarse de manera tal que se prevenga la contaminación o la pérdida de contenidos y debe demostrar que es a prueba de alteración intencional. La validación de la integridad del envase debe demostrar la ausencia de penetración de contaminación microbiana o de impurezas químicas o físicas (ver el capítulo *Evaluación de la Integridad del Envase—Productos Estériles* ⟨1207⟩).

Pruebas Específicas

VISCOSIDAD

Un incremento en la viscosidad aumenta el tiempo de residencia en el ojo. Sin embargo, la difusión del fármaco desde la formulación hacia el ojo podría verse inhibida debido a la alta viscosidad del producto. Los ungüentos oftálmicos están diseñados para tener una viscosidad muy alta a fin de prolongar el tiempo de residencia en el ojo. La inclusión de la evaluación de la viscosidad en la especificación del producto debe basarse en el tipo de forma farmacéutica y en si los cambios en la viscosidad del producto afectarán su desempeño. Esta no es una prueba farmacopeica, aunque forma parte de la especificación del fabricante del medicamento. Ver los capítulos *Viscosidad—Métodos Capilares* ⟨911⟩, *Viscosidad—Métodos Rotatorios* ⟨912⟩ y *Viscosidad—Método de Bola Rodante* ⟨913⟩.

CONTENIDO DE ANTIOXIDANTES

Si el medicamento presenta antioxidantes, se deben establecer pruebas para determinar el contenido de los mismos, a menos que se pueda detectar la degradación por oxidación usando otro método de prueba, tal como un análisis de impurezas. Se

deben establecer criterios de aceptación para el contenido de antioxidantes, los cuales deben basarse en los niveles de antioxidantes necesarios para mantener la estabilidad del producto en todas las etapas a lo largo del uso propuesto y de su vida útil.

CAPACIDAD DE RESUSPENSIÓN/CAPACIDAD DE REDISPERSIÓN

Se debe tener en consideración el establecimiento de una buena estabilidad física de una suspensión. Si las partículas sedimentan y eventualmente producen un residuo en la parte inferior del envase, deben ser redispersadas rápidamente al momento de su uso para lograr la uniformidad de la dosificación.

TAMAÑO DE PARTÍCULA Y DISTRIBUCIÓN DEL TAMAÑO DE LA PARTÍCULA

Se debe evaluar el potencial de cualquier cambio en el tamaño de la partícula de las suspensiones y de las emulsiones oftálmicas mediante el análisis de estabilidad (ver el capítulo *Medición del Tamaño de Partícula por Difracción de Luz* ⟨429⟩).

TAMAÑO DE LAS GOTAS

Para los medicamentos oftálmicos dispensados como gotas, los tamaños de las gotas por lo general están entre 20 y 70 µL. El tamaño de las gotas puede controlarse por peso o por volumen y por lo regular se evalúa durante el desarrollo del producto.

SUSTANCIAS AGREGADAS

Se pueden agregar sustancias adecuadas a los ungüentos oftálmicos para aumentar su estabilidad, a menos que se prohíba su uso en la monografía individual correspondiente, y siempre y cuando sean inocuas en las cantidades administradas y no interfieran con la eficacia terapéutica o con las respuestas a las valoraciones y las pruebas especificadas. Por lo regular, deben evaluarse durante el desarrollo del producto. Se prohíbe el uso de ingredientes cuyo único objetivo sea otorgar color, olor o sabor.

⟨776⟩ MICROSCOPÍA ÓPTICA

La microscopía óptica para la caracterización de partículas por lo general es una técnica adecuada para partículas con un tamaño de 1 µm o mayor. El límite inferior está determinado por la resolución del microscopio. El límite superior es menos estricto y está determinado por las dificultades que presenta para caracterizar partículas de mayor tamaño. Además de la microscopía óptica, existen diversas técnicas alternativas para la caracterización de partículas. La microscopía óptica es una técnica sumamente recomendable para caracterizar partículas que no son esféricas, método que también puede constituir la base de otros métodos de calibración más rutinarios y más rápidos.

APARATO

Emplear un microscopio estable y protegido de vibraciones. Es necesario que el aumento del microscopio (resultado del aumento del objetivo, ocular y de otros componentes adicionales) sea suficiente para caracterizar adecuadamente hasta la partícula más pequeña de la muestra en análisis. Buscar para cada intervalo de aumento, el mayor valor de apertura numérica del objetivo. En algunos casos, se recomienda usar los filtros polarizadores con analizadores y placas de retardo adecuadas. Con objetivos acromáticos se recomienda emplear un filtro cromático de poca transmisión espectral, de preferencia apocromáticos, y son necesarios para obtener los colores que correspondan en la microfotografía. Con la lámpara y los accesorios colocados debajo de la platina del microscopio se deben emplear condensadores corregidos al menos por aberración esférica. La apertura real del diafragma del condensador y la presencia de aceites de inmersión afectan la apertura numérica del condensador de los accesorios ubicados por debajo de la platina y es necesario que ésta coincida con la del objetivo en las condiciones de uso.

AJUSTE

Es de suma importancia que todos los elementos del sistema óptico estén alineados con precisión y que el enfoque sea el adecuado. Enfocar los elementos según las recomendaciones del fabricante del microscopio. Se recomienda alinear el eje con precisión.

Anexo 6. TFOS DEWS II, The Ocular Surface. Tear Film Report.

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TFOS DEWS II Tear Film Report

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ABSTRACT

The members of the Tear Film Subcommittee reviewed the role of the tear film in dry eye disease (DED). The Subcommittee reviewed biophysical and biochemical aspects of tears and how these change in DED. Clinically, DED is characterized by loss of tear volume, more rapid breakup of the tear film and increased evaporation of tears from the ocular surface. The tear film is composed of many substances including lipids, proteins, mucins and electrolytes. All of these contribute to the integrity of the tear film but exactly how they interact is still an area of active research. Tear film osmolarity increases in DED. Changes to other components such as proteins and mucins can be used as biomarkers for DED. The Subcommittee recommended areas for future research to advance our understanding of the tear film and how this changes with DED. The final report was written after review by all Subcommittee members and the entire TFOS DEWS II membership.

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1. Overview of the tear film in health

A stable preocular tear film is a hallmark of ocular health, largely because it forms the primary refracting surface for light entering the visual system and it protects and moisturizes the cornea. The three layered model of the tear film proposed by Wolff [1,2] has had an overwhelming allure because it is simple and logical: a mucin layer covering the ocular surface and lowering the supposed hydrophobicity of the epithelial cells; an aqueous layer to nurse the exposed ocular epithelium by providing lubricity, some nutrients, antimicrobial proteins and appropriate osmolarity; and a lipid layer to prevent loss of the aqueous layer through overspill and evaporation. There is a continual return to this three layered model, despite Doane stating over 20 years ago that the three layered structure "is a considerable simplification of reality" [3]. This has generally limited novel perspectives that might lead to a clearer understanding of the dynamics, structure and function of the tear

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film and the changes that occur to cause dry eye. The precorneal tear film behaves as a single dynamic functional unit [4] with different compartments.

Laxity of terminology means that there is ready acceptance of information that may not be entirely correct. For instance, "tear osmolarity is approximately 302 mOsm/L" is often accepted terminology, but in reality such a value is for tears sampled from within the lower tear meniscus. While it may represent the osmolarity of the tear film spread over the ocular surface, there is no evidence of this. A consequence of being aware of where the samples being measured are coming from and how they are collected may lead to a more cautious approach to extrapolating data to the tear film that covers the ocular surface and, ultimately, a better understanding of its composition, structure and spatial distribution. Optical coherence tomography (OCT) has allowed non-invasive measurements of both the upper and lower menisci in terms of height, area, and curvature of the surface and while the upper and lower meniscus in an individual appear to be identical in these parameters, none of these parameters correspond to central tear film thickness [5], but lower meniscus height seems to correspond to the volume of mucoaqueous tears [6,7].

When the eyes are open the tears are distributed in three compartments, which are the fornical compartment (which occupies the fornix and retrotarsal space), the tear menisci and the preocular tear film. The fornical compartment is assumed to be narrowest in the region of the lid wiper of the lid margin, which is directly apposed to the globe. The preocular tear film overlies the exposed conjunctiva and cornea [8]. The precorneal tear film follows the contours of the cornea, and is usually highly stable [9]. The pre-bulbar film follows the varying contours of the bulbar conjunctiva. The preocular tear film is the whole tear component that is spread over the exposed surface of the eye. Results from studies using ultrahigh resolution OCT has resolved the debate over the thickness of the tear film. It is extraordinarily thin, 2–5.5 μm thick over the corneal region (precorneal tear film), and these data concur with estimates of tear film thickness using interferometry techniques [8–10]. The tear film is so thin that the roughness of the corneal surface (~0.5 μm) cannot be ignored [11]. Neither the tear film thickness over the conjunctival region, nor the roughness of the conjunctival surface has been measured. Water has a high surface tension and therefore to form such a thin film of water without it collapsing onto the surface or forming lenses, the surface on which it spreads has to have similar properties to water and the surface tension of the water at the air interface has to be lowered [12,13].

The apical surfaces of the corneal and conjunctival epithelia have transmembrane mucins [14], which increase the adhesion tension for water, facilitating the spread of the tears across the ocular surface. Transmembrane mucins attached to the microplicae of the epithelial cells extend up to 500 nm (0.5 μm) into the tear film [15,16]. They also constitute a line of defense for the epithelial cells against infection and injury [17,18].

Much remains to be learned about the mucoaqueous component of the preocular tear film and whether it is the same within all compartments. In addition to oxygen, metabolites and electrolytes, the tear film contains antimicrobial peptides, proteins and soluble immunoglobulins that protect the ocular surface from infection. The sensitivity of modern proteomics techniques has allowed the identification of more than 1500 proteins [19], and more than 200 peptides originating from several of those proteins [20]. The nature of the vast majority of these proteins and peptides reflects that tears are also a mechanism for removal of cellular debris that occurs due to the turnover of ocular epithelial cells. In addition, sensitive lipid studies also show that tears contain a lipid profile similar in ratio to meibomian lipids, but with a relative abundance of phospholipids [21].

Shortly after a blink, the mucoaqueous component of the preocular tear film is believed to become physically isolated from the upper and lower menisci, such that diffusion between these compartments does not occur [22,23]. This isolation has been observed as a black line at the ocular margins in fluorescein-labeled tears.

The tear film lipid layer is approximately 40 nm thick [24], lowers the surface tension at the air interface of the preocular tear film and results in spreading of the tear film over the ocular surface. A feature of the preocular tear film is that it resists evaporation, and it is purported that the tear film lipid layer is responsible for this [25–27,67]. The complete nature of the tear film lipid layer is unknown, but it is likely it has surfactant molecules at the mucoaqueous interface and lipophilic molecules at the air interface. Unlike the aqueous component of the preocular tear film, which appears to be isolated shortly after a blink, the lipid layer of the tear film appears to be continuous over the menisci and indeed continues to move upwards over the ocular surface following a blink. Observations using various interference techniques at different magnifications show that the lipid layer is variable in thickness across the ocular surface. This movement and continuum from the meibomian gland orifices, and direct observation of secretions from the meibomian glands onto the ocular surface, indicate that the tear film lipid layer is almost entirely derived from meibomian gland secretions. It is unknown if lipids from the tear film lipid layer move into the mucoaqueous compartment of the preocular tear film, or if lipids from other ocular tissues (origin unknown) transverse the mucoaqueous compartment and adsorb to the tear film lipid layer. By examining the shear rheology of films of meibomian lipids *in vitro* and comparing them with other lipids, there is evidence that meibomian lipid films spread over a mucoaqueous subphase, causing the subphase to resist collapse as it thins [28]. Dilatational rheology studies also confirmed that the viscoelastic films of tear lipids, meibum and contact lens lipid extracts are predominantly elastic, which may enhance their capability to stabilize the air/tear surface [29–31].

2. Biophysical measurements of the tear film

2.1. Tear film structure and dynamics

There is evidence that, in the above described three layer structure of the tear film, the mucin layer has a decreasing gradient of concentration from the epithelium towards the aqueous layer [32]. It is also commonly considered that the aqueous and mucin layers are a single layer of mucoaqueous gel (referred to hereafter as the mucoaqueous layer) [33].

The tear film lipid layer is derived from meibum secreted from the lid margins and is spread onto the tear film with each blink, driven by surface tension forces. It plays an important role in stabilizing the tear film and in the past has been thought to play a key role in retarding tear evaporation [25–27,67]. The lipid layer can be investigated with interferometry techniques. The color and brightness of the interference images are analyzed to yield lipid layer thickness [24,34–37]. The thickness of the lipid layer has been reported to be from 15 to 157 nm, with a mean of 42 nm [24].

Evidence from reflection spectra of the precorneal tear film suggested the tear film has a thickness of approximately 2 μm [9]. OCT techniques find the thickness of the tear film to range from 2 to 5.5 μm [10,38–42].

To elucidate the structure of the tear film, studies have made use of multiple methods. These include combining a wavefront sensor with OCT [43], using fluorescein tear breakup time (TBUT) and Schirmer test [43], applying fluorescein and assessing using a

rotating Scheimpflug camera (Pentacam, Oculus, Germany) [44], simultaneously recording videos of fluorescence and imaging tear film lipid layer [45], and using dual thermal-fluorescent imaging [46].

The bulk of the tear volume and flow is via secretion from the lacrimal gland [47,48], with a smaller portion secreted by the conjunctiva [49]. In animal studies, tears can be produced by the accessory lacrimal glands in the conjunctiva even after removal of the main gland [50]. Both parasympathetic and sympathetic nerves innervate the main lacrimal glands [51,52] and a few sensory nerves have also been identified [51]. The nerves are located in close proximity to acinar, ductal, and myoepithelial cells as well as being close to blood vessels [51,52]. Stimulation of the lacrimal gland and secretion occur via the cornea –trigeminal nerve–brainstem–facial nerve–lacrimal gland reflex arc. Afferent sensory nerves of the cornea and conjunctiva are activated by stimulation of the ocular surface. Efferent parasympathetic and sympathetic nerves are then activated to stimulate secretion from acinar and tubular cells in the lacrimal gland [53].

Tears have been classified into four broad types - basal, reflex, emotional and closed-eye. (see review by Craig et al.) [54]. Basal tears (sometimes referred to as open-eye tears) are tears that constitutively coat the eye and are deficient in dry eye. Reflex tears are produced upon stimulation of the ocular surface (for example by onion vapor) or stimulation of the reflex arc (for example by nasal stimulation of the sneeze reflex). Emotional tears are also produced upon stimulation, but in this case via emotions such as sadness. Closed-eye tears are those that can be collected from the ocular surface immediately after a period of sleep. Basal, reflex and emotional tears are produced mainly from the lacrimal glands via the neural arc [55], but differ in their constitution, for example, the concentration of various proteins change [54]. Secretion from the lacrimal gland is greatly reduced during sleep, and so the constitution of closed-eye tears is somewhat different to that of other types with, for example, an increased amount of serum-derived proteins leaking from the conjunctival blood vessels [54].

A two-step process of tear film deposition through a blink has been proposed [56]. In the first step, the upper lid pulls a layer of tears over the cornea by capillary action; in the second step, the lipid layer drifts upward, which may drag up aqueous tears along with it. The upward drift of the lipid layer can be observed using interferometry imaging approaches [57]. After the blink, tear film redistribution occurs due to the negative hydrostatic pressure within the nascent menisci. This draws liquid from the forming tear film and eventually causes the precorneal portion to separate from the menisci. The boundary can be observed as a black line of reduced fluorescence in the fluorescein-stained tear film, indicating where the aqueous layer is thin but the lipid layer remains intact [58,59].

Tears flow from the supply region towards the puncta, located on the lids near the nasal canthi, to facilitate their turnover and removal [60,61]. Tear turnover rate has been estimated to be 16 ± 5%/min [62–64]. Between blinks, thinning of the tear film occurs, which can be observed using several different approaches [40,57,65,66]. Most of the observed tear thinning between blinks is due to evaporation [25–27,57,65,67,68].

Tear production, turnover and volume can be estimated by several methods, but there is limited correlation between different tests [69]. Accordingly, a combination of tests should provide a more reliable diagnosis and increase the specificity and sensitivity of dry eye diagnosis [70]. The phenol red thread test (Hamano test) [71] is a measurement of tear volume or change in tear volume with time, by observation of the amount of wetting of a phenol red dye impregnated cotton thread placed over the inferior eyelid. The Schirmer test [72] is a measure of tear production and is undertaken by observing the wetting of a standardized paper strip. Historically, the Schirmer I test is performed without anesthesia and thus measures predominantly reflex tearing. A variation on the Schirmer I test involves use of topical anesthesia and claims to reflect the basal secretion of tears, although a contribution from reflex tearing cannot be discounted [626]. Tear volume can also be measured by fluorophotometric assessment, and demonstrates an apparent normal human volume of approximately 8 ± 3 μl [47,62]. Tear meniscus height (TMH) is linearly proportional to the lacrimal secretory rate [47]. Differences in TMH and radius of curvature can be used to aid diagnosis of dry eye [7,73,74]. Tear clearance rate is the rate at which the preocular tear film or an instilled marker of the tears is removed from the tear film by dilution or drainage from the tear volume [75]. Tear clearance rate measurement is seldom performed in the clinical setting. Tear dynamics can be estimated by dividing the value of the Schirmer test with anesthesia by the tear clearance rate, giving the Tear Function Index [76]. This value has been shown to have greater sensitivity for detecting dry eye than either one of these tests alone [76].

2.2. Tear film stability on eye and ocular surface wettability

A stable precorneal tear film has long been viewed as one of the hallmarks of ocular health, largely because it provides the primary refracting surface for light entering the visual system as well as creating a protective and lubricated environment for the tissues of the palpebral and bulbar surfaces. Unlike some other species, whose tears can remain stable for many minutes [77], the human tear film tends to collapse or "break up" in under half a minute or so, unless it is re-established by the act of blinking. While all individuals will manifest this behavior if blinking is prevented for long enough, rapid appearance of regions of localized drying is viewed as evidence for tear film disorder, particularly in dry eye, and so observations of stability are commonly and frequently performed as a diagnostic aid.

Experiments have shown that tear film thinning and breakup occur mainly as a result of evaporation from the tear film, rather than due to fluid flow, whether that be tangentially within the film itself, or radially across the ocular surface [78,79]. Using reflectivity and tear fluorescein as respective indicators for lipid and mucoaqueous layer thickness, King-Smith et al. suggested a lack of correspondence between dry eye and both lipid layer thickness and thinning rate [45]. Further, thinning rate was not affected by apparent thickening of the lipid layer with lipid emulsion-based eye drops [24], suggesting that the lipid was a poor barrier to evaporation [45]. Perhaps it is the whole healthy preocular tear film that resists evaporation from the ocular surface, and hence thinning? Measurement of TBUT may provide a better indicator of the ability of the preocular tear film to prevent evaporative losses.

Acquiring a TBUT is a relatively simple task, but interpreting the result is not straightforward because of its inherent variability [80,81]. A number of approaches to improving repeatability have been suggested, including taking multiple readings and averaging or selecting a subset of values [82,83], minimizing the amount of fluorescein instilled [84–86] and, most significantly, eliminating the use of fluorescein altogether. This last approach, via a number of different methods, provides a non-invasive breakup time (NIBUT) value. Tear film additives are avoided, the examination environment should ideally introduce no additional sources of heat, air movement, humidity etc., and head posture and blinking behavior are standardized. Inevitably however, the extent to which these conditions are achieved varies somewhat between methods.

Early efforts in acquiring a NIBUT projected a grid pattern [87,88] or keratometry mires [89,90] onto the surface of the tear film and viewed their distortion in time after a blink. While it is still

possible to use keratometer-based methods in clinical situations, a degree of subjectivity is involved in judging when the image distortion first occurs. Increasing sophistication in both image capture and computational capability has led to a refinement of the technique, using both automated detection and more detailed targets. In most cases, these targets are identical to those originally developed and used for measuring corneal shape (keratoscopes) and consist of multiple concentric rings whose angular subtense is sufficient to cover more or less all of the visible cornea. The image of this target is reflected from the anterior surface of the tear film and captured for subsequent analysis [91–98]. Typically, multiple, sequential images are acquired during the inter-blink period and image analysis software utilized to automatically detect the onset of areas of breakup.

Although repeatability has not been reported for all the devices using this approach, the available data are in reasonable agreement that they operate with a coefficient of variation of around 10% [92,94], which is roughly three times better than traditional TBUT measurement [92]. Despite this improvement, the range of values reported for normal individuals is broad, being from about 4 to 19 s (Table 1). It may be that this reflects the different algorithms being used to extract breakup data among the various instruments, a suspicion that is strengthened by the observation that the corresponding dry eye breakup times are consistently about half those given for normal eyes. Thus, while inter-instrument comparisons are likely to be difficult to interpret, data derived from a given instrument type appear reasonably reliable and offer quite good sensitivity and specificity in distinguishing dry-eyed individuals from normals (Table 1). Further details may be obtained from the Tear Film and Ocular Surface Society's Dry Eye Workshop II (TFOS DEWS II) Diagnostic Methodology report [99].

Ocular surface thermography has been used to measure NIBUT, on the principle that breakup is associated with evaporative cooling and therefore thinning areas in the tear film show up as cool spots in the thermograph [46]. The technique is suggested to be reliable [100], although test-retest confidence intervals have not been made available so far. While data are limited to a single study, NIBUT derived from this method appear similar to those from the lower end of the videokeratoscopy range. Again, dry-eyed subjects yield breakup times that are about half those of normals, with levels of sensitivity and specificity being similar to those from videokeratoscopy (Table 1).

All the systems discussed so far are commercially available and so could feasibly be used in routine clinical practice. The following discussion deals with instruments that are more complex and/or unlikely to be applicable outside a research setting. Recently, lateral shearing interferometry has been used to monitor changes in tear film stability. This instrument uses an optical wedge to laterally shift the wavefront reflected from the tear film surface and rotate it so that it can be made to interfere with itself [101,102]. Information about the shape of the reflecting surface is contained in this wavefront and can be extracted from the resulting interference pattern. Note that this differs from colored fringe methods, such those of Guillon [103], or the interferometer developed by Doane [104], both of which rely on interference between light reflected from different surfaces within the tear film, such as the front and back of the lipid layer. Using fast Fourier transformation, images derived with the shearing technique can be processed to generate a surface stability index parameter (M2). Sequential image acquisition allows M2 to be followed over the blink cycle, in real time, at a resolution determined by the video frame rate. It is claimed that this method is relatively insensitive to eye movements and the degree of dryness of the surface being measured [105] and is better able to discriminate dry eyed subjects from normal than either dynamic area high speed videokeratoscopy or wavefront sensing [106].

Another technique that may be developed for clinical application is the use of double pass methods. The basis for double pass methods is that the view of the retina obtained using a double pass optical system, in which the image forming light traverses all the optical surfaces of the eye twice (once on entry and again on exit), will be affected by scattering from all these surfaces, including the tear film. Thus, analysis of double-pass retinal images on the time scale of the blink cycle may provide an indirect measure of tear film stability. Deteriorations in image quality metrics such as intensity distribution index [107], Strehl ratio, modulation transfer function cut-off frequency and objective scattering index [108] are observed in dry eye. More data are needed to establish the diagnostic ability of this approach for discriminating dry eye.

2.3. Vision quality

An association between dry eye and compromised visual acuity postulated by Rieger [110] is poorly documented using high contrast letter acuity [111]. However, based on the measurement of "functional visual acuity", whereby acuity is measured after suspension of blinking for several seconds, dry eyed subjects do significantly worse than normals [111]. Delayed blinking generates subtle wavefront aberrations that more rapidly give rise to higher order aberrations after the blink in dry eye individuals [112]. In an effort to directly link tear film changes to visual loss, a three channel optical system that allowed concurrent measurement of letter contrast acuity, TBUT and refractive aberrations was constructed. Although the data reported were for contact lens wearing eyes only, progression of TBUT was clearly associated with both visual performance reduction and declining optical quality [113].

Table 1
Summary of non-invasive breakup time (NIBUT) measurements in normal and dry-eyed subjects, together with discrimination diagnostic metrics. NIBUT = non-invasive breakup time; AUC = area under the curve of a receiver operating characteristic graph plotting sensitivity vs. 1-specificity.

Author (Reference)	NIBUT Normal (sec)	NIBUT Dry Eye (sec)	AUC	Sensitivity	Specificity	Instrument	Principle
Hong et al. 2013[94]	4.3 ± 0.3 n = 41	2.0 ± 0.2 n = 44	0.83	84.1	75.6	Oculus keratograph	Videokeratoscopy
Gumus et al. 2011[97]	4.9 ± 1.6 n = 25	2.4 ± 2.5; Mild n = 23 1.2 ± 1.8; Moderate n = 11 0.4 ± 0.5; Severe n = 11		82.2	88.0	Tomey RT7000	Videokeratoscopy
Downie 2015 [92]	19.4 ± 5.3 n = 17	7.9 ± 4.9 n = 28	0.92	81.5	94.4	Medmont E300	Videokeratoscopy
Koh et al. 2016[95]	9.7 ± 6.7 n = 31	4.6 ± 1.3 n = 49				Keratograph M5	Videokeratoscopy
Su et al. 2016[109]	4.5 ± 0.9 n = 31	2.1 ± 1.1 n = 42	0.88	80.0	89.0	IT-85, United Integrated Services Co	Thermography

2.4. Tear osmolarity

Tear film osmolarity has been described as a single measurement that gives insight into the balance between tear production, evaporation, drainage and absorption [114]. In the 1995 National Eye Institute/Industry Workshop [115], tear hyperosmolarity was included as a global feature of dry eye and in the 2007 TFOS DEWS definition and classification report [116] tear film hyperosmolarity was identified as one of the two core mechanisms of dry eye and included in the definition. This section will mainly focus on new knowledge gained since the 2007 reports.

The terms tear film osmolarity and osmolality have frequently been employed interchangeably, with osmolarity being the more common term, and is the term used throughout this manuscript [117,118]. Both refer to the amount of osmotically active particles, although with small differences [119] that are clinically irrelevant. Previously, tear film osmolarity was primarily measured via freezing point depression or vapor pressure osmometry, but a series of factors have limited their usage in clinical settings [118–121]. Clinical evaluation of tear osmolarity has increased with the introduction of a new osmometer that collects a 50 nL tear sample and analyzes its electrical impedance (TearLab, San Diego, CA, USA).

Mean tear film osmolarity values in normal participants range from 270 to 315 mOsm/L [122–137], with an overall average of 300 mOsm/L, which is similar to the value stated by Tomlinson et al., who reviewed studies between 1978 and 2004 [138]. There seems to be no statistical or clinically relevant effect on tear osmolarity of age [128,139–141], race [140,142,143], hormonal fluctuation in women with a regular menstrual cycle [131,144], or oral contraceptive pill use [131,144]. Vehof et al. investigated the influence of genetic factors on dry eye in female twins and found an estimated heritability of 40% for osmolarity [145]. Variation between normal right and left eyes is 6.9 ± 5.9 mOsm/L [146]. Data on the effect of sex on tear osmolarity remain equivocal, with Lemp et al. [128] and Versura et al. [126] reporting no significant effect of sex, which is in agreement with a previous review of the literature [54], whilst Fuerst et al. [140] show significantly higher tear film osmolarity in men (311.8 vs. 302.3 mOsm/L). An increase in tear osmolarity has been observed after sleep deprivation, exposure to high altitude and religious fasting [135,147,148]. In accordance with previous studies, prolonged eye closure has been found to lead to tear hyperosmolarity but data about diurnal variations are equivocal [130,134,139,142,149]. Some authors [130,142] show a shift towards lower values mid-day, followed by an increase, whilst others [134,139,149] show no significant effect of time. There is a positive relationship between plasma osmolarity and tear osmolarity and both are raised in patients with dry eye disease or with systemic dehydration [150–152].

The concentration of electrolytes in the mucoaqueous layer mainly determines the osmolarity of the normal tear film, and secretion mechanisms and contribution to tear film osmolarity have been previously summarized [117,119]. Various mathematical models, as summarized and furthered by Braun et al., have stated that the osmolarity across the ocular surface is different to that measured in the tear meniscus [153]. During the blink interval the tear film thins over the cornea, mainly due to evaporation, leading to a hyperosmotic shift [153,154]. The level of hyperosmotic shift depends on the thinning rate, which is driven by the evaporation rate [154]. In the event of a low thinning rate, such as 1 μm/min, tear film osmolarity over the ocular surface will increase from 300 mOsm/L to 332 mOsm/L over a 25 s period, but will increase to 1830 mOsm/L in the case of a rapid thinning rate of 20 μm/min [153]. During tear film breakup, local spikes of tear osmolarity around 1900 mOsm/L have been predicted [153]. Those rates are significantly higher than those observed in the tear meniscus, partly due to the mixing of the tear fluid from the ocular surface with that in the meniscus during the blink and secretion of new tears. In the non-dry eye, the predicted osmolarity difference between the tear film over the ocular surface and in the tear meniscus is fairly small, but is predicted to increase in dry eye, particularly when there is increased evaporation with reduced TMH [68]. The peak in tear film osmolarity during tear film breakup is supported by studies investigating ocular comfort sensations. A slow increase in ocular discomfort has been demonstrated during tear thinning, with a sharp increase at tear film breakup or before a blink [155,156]. Liu et al. evaluated the subjective response during tear film breakup and tried to match the experienced sensation by instilling hyperosmolar drops [157]. The detection threshold for NaCl drops was 454 ± 14 mOsm/kg, with overall discomfort increasing as osmolarity increased. On average, a salt solution with 809 mOsm/kg was needed to evoke the same ocular response as during TBUT, ranging from 696 to 972 mOsm/kg [157]. The link between tear evaporation, tear thinning and tear film osmolarity is further supported in clinical studies showing a significant correlation between increased evaporation, tear film osmolarity and decreased tear stability, or automated measures of tear film surface quality breakup time being a clinical marker for tear hyperosmolarity in moderate to severe dry eye [92,158].

As summarized in the 2007 TFOS DEWS report, tear hyperosmolarity in dry eye has been attributed to increased evaporation or a higher impact of evaporation in low volume [116,159]. Mean tear film osmolarity values for dry eye in studies until 2008 ranged between 311 and 360 mOsm/L, with an average of 326.9 mOsm/L [119,138]. Table 2 summarizes the values obtained in studies since 2009 that aimed to establish osmolarity values in dry eye or investigated the feasibility of osmolarity measurements in the diagnosis or treatment success of dry eye. Using different degrees of dry eye severity and etiologies, mean values range between 297 and 337 mOsm/L, with an overall mean of 315. Higher tear film osmolarity values have been reported with increased dry eye severity grade [126,128,160–164]. For example, normal, mild/moderate, and severe dry eyes have average tear osmolarity values of 302 ± 8 mOsm/L, 315 ± 11 mOsm/L and 336 ± 22 mOsm/L, respectively [162]. Suzuki et al. and Sullivan et al. found a significant correlation between dry eye severity scores and measured tear film osmolarity ($r = 0.47$ and $r = 0.74$, respectively) [160,162]. Despite similar outcomes, it must be noted that the criteria for dry eye severity were not uniform among studies, with authors using different cut-off values, different calculation of scores and different decisions about the inclusion of tear film osmolarity as a diagnostic factor for dry eye severity, which could have introduced selection bias [116].

Although there can be large within-subject fluctuations [130,137,141,149], Eperjesi et al. proposed that changes of 33 mOsm/L or higher can be considered clinically relevant [141]. The instability of osmolarity readings has been attributed to compromised homeostasis of the dry eye tear film. Differences between readings can be considered a marker for tear film instability [128,133,146]. Such interpretation may be supported by studies showing higher variability between measurements or eyes with higher osmolarity values or more severe dry eye [128,133,137,139,165].

Despite a general shift in tear film osmolarity with dry eye, there is a large overlap in osmolarity values between normal and dry eye participants. Sensitivity and specificity measurements of osmolarity for dry-eye diagnosis using a threshold of 294 mOsm/L were 67% and 46% respectively [143], 40% and 100% using a threshold of >310 mOsm/L and Sjögren syndrome patients [166]. For a more in-depth analysis of statistical measures of performance and potential

Table 2
Tear film osmolarity values in dry eye and non-dry eye subjects.

Author	Testing Method	Measurement from one eye, combined eyes, or worst eye	Non-Dry Eye (mOsm/L)	Dry Eye (mOsm/L)	Change %	Dry Eye Group Definition
Khanal et al., 2009 [123]	Freezing point depression	NK	308.39 ± 9.29	330.01 ± 13.34 325.57 ± 14.76	6.6 5.3	Aqueous deficient; TFOS DEWS Evaporative dry eye; TFOS DEWS
Messmer et al., 2010 [122] [a]	Electrical impedance	One eye	307.1 ± 11.3	308.9 ± 14.0	0.6[b]	≥3 of the following criteria were fulfilled:(1) ocular surface disease index (OSDI) > 15; (2) staining of the cornea in the typical interpalpebral area; (3) staining of the conjunctiva in the typical interpalpebral area; (4) tear film breakup time < 7 s; (5) Schirmer test < 7 mm in 5 min; (6) the presence of blepharitis or meibomitis.
Suzuki et al., 2010 [160] [a]	Freezing point depression	One eye	–	309.7 ± 22.3		Modified TFOS DEWS Grades 1-4
Tomlinson et al., 2010 [125] [a]	Electrical impedance	One eye	308 ± 6.2	321 ± 7.2	4.1	NIBUT <10 s, Schirmer I test <5 mm, and positive symptoms
	Freezing point depression		310 ± 7.2	323 ± 14.7	4.0	
Versura et al., 2010 [126]	Electrical impedance	Worst eye	295.5 ± 9.8	298.1 ± 10.6	0.9[b]	Mild; OSDI 13–21, meibomian gland dysfunction variably present
				306.7 ± 9.5	3.7	Moderate; OSDI 23–32, MGD variably present, TBUT ≤ 10 s, Schirmer ≤ 10 mm
				314.4 ± 10.1	6.0	Severe; OSDI 33–100, MGD frequent, TBUT ≤ 5 s, Schirmer ≤ 5 mm, moderate to marked corneal and conjunctival staining
Jacobi et al., 2011 [127] [a]	Electrical impedance	One eye	301 (298–304)	320 (301–324)	5.9	TFOS DEWS Grade 3
Lemp et al., 2011 [128]	Electrical impedance	Worst eye	300.8 ± 7.8	315 ± 10.4	4.5	Mild/Moderate; modified TFOS DEWS classification system
				336.7 ± 22.2	10.7	Severe; modified TFOS DEWS classification system
Utine et al., 2011 [164]	Electrical impedance	Both eyes	294.9 ± 8.3	301.9 ± 11.4	2.3	Primary Sjögren syndrome
Li et al., 2012 [130]	Electrical impedance	Both eyes	298 ± 14.2	304 ± 10.8	2.0[b]	OSDI >12 and a TBUT of <10 s or Schirmer test score of <5 mm
Sullivan et al., 2012 [161]	Electrical impedance	Both eyes	–	307.1 ± 9.9		Mild/Moderate; modified TFOS DEWS classification system
				324.3 ± 19.8		Severe; modified TFOS DEWS classification system
Szalai et al., 2012 [129] [a]	Electrical impedance	Both eyes	303.5 ± 12.9	296.8 ± 16.5	−2.3[b]	Non-Sjögren syndrome; at least 2 of the following 3 objective dry eye tests: Schirmer I value < 10 mm per 5 min, TBUT <10 s, fluorescein corneal staining >4 bright spots
				303.4 ± 17.2	0[b]	Sjögren syndrome
Bunya et al., 2013 [167]	Electrical impedance	Both eyes		314.5 ± 18.0		Severe Sjögren syndrome
Chen et al., 2013 [131]	Electrical impedance	Both eyes	301.6 ± 14.2	–		
Hassan et al., 2013 [132]	Electrical impedance	Both eyes	303.62 ± 12.29	–		
Keech et al., 2013 [133]	Electrical impedance	Both eyes	304.0 ± 8.4	334.0 ± 25.6	9.0	Symptomatic participants; OSDI ≥20
Amparo et al., 2014 [168] [a]	Electrical impedance	Worst eye	–	312.8 ± 20.3		A previous diagnosis of dry-eye disease
Berchicci et al., 2014 [169]	Electrical impedance	Both eyes	–	314 ± 22.1		Graft-Versus-Host Disease
Garcia et al., 2014 [134]	Freezing point depression	Both eyes	270 ± 4.4	–		
Koktekir et al., 2014 [135]	Electrical impedance	Both eyes	285.6 ± 8.2	–		
Bunya et al., 2015 [137]	Electrical impedance	Both eyes	312 (299–326)	307 (296–325) 314 (306–321)	−1.6[b] 0.6	Blepharitis Sjögren syndrome
Downie 2015 [92]	Freezing point depression	Both eyes	296.2 ± 9.9	325.0 ± 17.8	8.9	OSDI score of ≥18, tear osmolarity ≥ 316 mOsm/L and at least one (of three) consecutive fluorescein TBUT of <10 s, in at least one eye
Na et al., 2015 [170]	Electrical impedance	Both eyes	296	300	1.0	Graft-Versus-Host Disease
Schargus et al., 2015 [171]	Electrical impedance	Worst eye	300 ± 16.5	337 ± 36	11.0	Ocular Graft-Versus-Host Disease
Tukenmez-Dikmen et al., 2015 [163] [a]	Electrical impedance	Both eyes	–	308.1 ± 8.5 318.9 ± 12.8		TFOS DEWS Grade 1&2 TFOS DEWS Grade 3&4

[a] Do not provide information on the use of artificial tears prior to measurements. All other studies stipulated that no artificial tears were to be used, with washout periods ranging from no use at the visit to 1 month.
[b] Results were not statistically different between control and dry-eye groups.

selection bias of subjects included, please refer to the TFOS DEWS II Diagnostic Methodology report [99]. Future studies are required to establish consistent cut-off values for dry eye, which are ideally derived from a study population where osmolarity was not a diagnostic criterion and where the sensitivity and specificity are tested in an independent cohort.

2.5. Tear ferning

Assessment of ferning patterns has been proposed as a simple and economical test of dry eye [172–178]. Normal individuals commonly display dense, uniform, closely branching ferns (Fig. 1) that change with altered tear functionality and chemical composition.

Collection of tears from the lower temporal tear meniscus with a capillary tube is most commonly used [124,126,178–190], with a low coefficient of variance [191]. It should be borne in mind that the composition of tears collected from the meniscus may not be reflective of that over the entire ocular surface, and thus the ferning pattern obtained may differ with differing collection sites. A tear sample of 1–4 μL is expelled onto a clean glass slide, allowed to dry at stable room temperature (20–26 °C) and humidity (≤50%), observed using white light microscopy and photographed within 10–15 min. Factors shown to influence the ferning pattern are tear volume [173], room temperature and humidity during drying [190], covering the tear sample during drying [174], time between collection and assessment [174], and oil on glass slides [191].

Many authors [124,126,177,179,181–183,186,188,190,192–198] grade tear fern patterns using the 1 (complete, uninterrupted ferning pattern with no spaces between ferns) to 4 (complete absence of ferning) scale of Rolando (Fig. 1) [172]. The scale displays good intra- and inter-observer agreements, particularly when collapsing grades for normal (grade 1 or 2) and abnormal (3 and 4) patterns [185,199]. However, representation of only a portion of the entire ferning pattern [185], and usage of full grades [199] may have increased the repeatability of the scale.

Tear ferning patterns are independent of sex [175,181], hormonal fluctuations in women with a regular menstrual cycle [182,197], races on the Asian continent [181] and time of day during waking [180]. Degradation of tear fern patterns, indicating abnormal tear functionality, occur upon eye opening after wakening [179], with contact lens wear [186] and with increasing age, independent of dry eye status [124,181,198,200]. The effect of reflex tearing on ferning patterns remains equivocal, with Norn [191] demonstrating no effect on ferning patterns when reflex tearing was provoked by inhalation of ammonium chloride, but an improvement in ferning patterns after exposure to draught, which was hypothesized to result from reflex tearing [201].

Ferning in dry eye tears is less regular, with increasing space between ferns and shortening of ferns, culminating in an absence of ferning. Over 90% of keratoconjunctivitis sicca patients fell into ferning classes 3 and 4 [172,202] Sjögren syndrome patients exhibited 87.8% and 83.3% respectively with grades of 3–5 [176]. However, another study with Sjögren syndrome patients found only 59% and 48% showed class 3 and 4 ferning patterns [177]. 50% of post-menopausal women with dry eye symptoms fell into class 2 [124]. Using average grades, mean and median values range between 2.0 and 2.9 for participants with dry eye [126,176,182,195]. Using the 5-point Masmali scale, the authors reported a median value of 2.3, with 72.5% of samples graded between 2.0 and 3.0 [178]. Classifying ferning into normal and abnormal patterns or comparison of mean values between dry eye and non-dry eye participants can be analytically effective with this scale. Overall good sensitivity (80–90%) and specificity (75–89%) has been demonstrated for Sjögren syndrome [186], but more studies are needed to establish sensitivity and specificity and cut-off values in other forms of dry eye before this relatively simple approach is translated into private practice.

2.6. pH

Mean tear pH values range between 6.8 and 8.2, with individual values ranging between 5.2 and 8.6 [203–216]. Yamada et al. [215] compared the pH values of collected tears to those measured on the

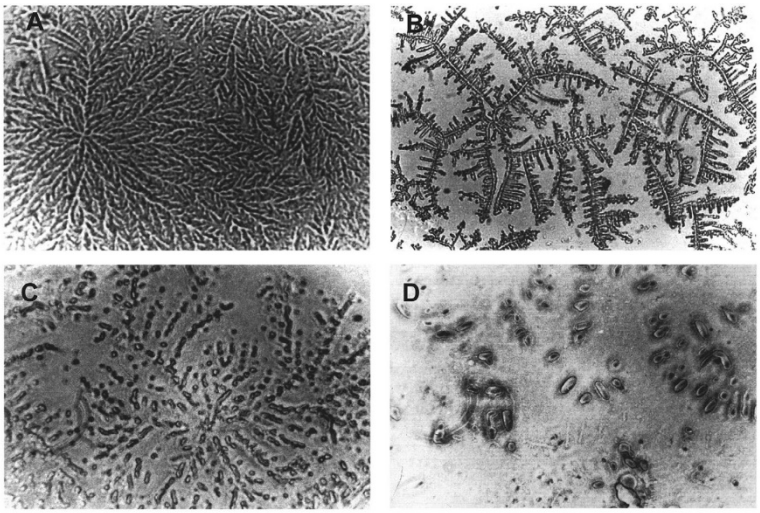


Fig. 1. Examples of tear ferning patterns for Rolando's grade 1 (A), 2 (B), 3 (C), 4 (D). From Maragou et al., 1996. Clin Rheumatol. 15: 125-32 [177].

eye and found an alkaline shift of 0.1 pH units in collected tears, which was thought to be caused by interaction of the tear fluid with air. As with all physical measures of the tear film, the collection site may influence the result obtained. Tears collected for pH assessment are typically those from the lower meniscus and may not be reflective of the pH over the ocular surface.

There seems to be no effect of sex [205,212], but age [210,212], time of day [204,210], eye closure [204,210], prolonged eye opening [208,210,213], blinking [208] and reflex tearing [208] have been shown to affect pH values. An alkaline shift of approximately 0.2 pH units can be observed between 10 and 50 year olds or between groups of under and over 40 year olds [210,212]. Slight acidification of the tear film by approximately 0.2 pH units can be observed after eye closure overnight or for 1 h [204,210]. Blinking causes a slight acidic shift, but overall the tear film shifts from acidic to alkaline throughout the day, with a difference of usually no more than 0.6 pH units [204,208,210]. An alkaline shift of 2.5 ± 0.6 pH units/min has also been observed with prolonged eye opening, with a maximum value of 9.3, however, the tear film reaches equilibrium after 30–60 s [208]. It is important to remember that pH is measured on a logarithmic scale such that for every one unit change in pH there is a 10-fold change in the concentration of hydrogen ions.

Investigations in dry eye using pH indicator paper showed no significant difference in pH mean values between a dry eye and control group (7.46 ± 0.24 and 7.45 ± 0.23 respectively), although 12% of participants with dry eye displayed a pH value over 7.7, compared with only 4% in the control group [214]. Norn [205], using a micro-electrode inserted into the inferior conjunctival fornix, found tears in participants with keratoconjunctivitis sicca to be significantly more alkaline compared to non-dry eye participants when both eyes were measured (0.2 pH unit shift), but not when only one was assessed (0.05 pH unit shift). Reporting a systemic error, with the second eye measured showing an alkaline trend, the authors judged their observation in dry eye to be unreliable [205]. Using a similar method, Khurana et al. reported a small alkaline shift of 0.1 pH units in participants with dry eye compared to non-dry eye ones [214]. Various methods have been used to measure tear film pH, each having their own limitations. To date, there is limited evidence for a change in pH values with DED.

2.7. Tear evaporation

Inter-blink tear evaporation may contribute to dry eye. Tear evaporation rate has been considered an indicator of tear lipid layer stability [217–220], with higher tear evaporation rates associated with increased tear thinning, ocular dryness and discomfort [220–222]. An early study on humans measured the evaporation rate using an instrument adapted from dermatology [223], but this technique involved touching the corneal surface, which is a stimulus for reflex tearing and likely resulted in an overestimation of evaporation rates. Non-invasive analysis in an environment with relative humidity between 30 and 40% revealed a tear film evaporation rate of 0.4–50 $\times$ 10^{-7} g/cm^2/sec (Table 3) [25–27,67,123,224–242]. This very large range of evaporation rates may derive from use of different assays. Measurements undertaken with ventilated chambers may better mimic natural air flow on the ocular surface than closed preocular chambers [243], although fast measurement (<10 s) closed chamber devices may be appropriate. Currently there is no commercially available instrument dedicated to detection of tear film evaporation. Thus, researchers have either used in-house designed systems or modifications of closed chamber dermatological units [25,158,239].

The effect of age and sex on tear evaporation rates is equivocal. Some studies have shown that older age groups (>45 years) have 1.5 times higher evaporation rates than younger adults and women have evaporation rates approximately 1.4 times higher than men [244–246], but other studies have failed to show any impact of age or sex [240,247]. Subjects who blink more than normal (likely being a consequence of evaporation) or have a larger exposed ocular surface have increased tear evaporation rates [246,248]. Low humidity increases evaporation [249–251], with tear evaporation rates of healthy individuals increasing by >40% with a 10% reduction in relative humidity [249]. Increased tear evaporation rates in low humidity (5%) environments has been associated with reduced lipid layer thickness and tear film stability [251]. Meta analyses point to a 2–3 fold increase in tear evaporation rate as a diagnostic cut-off for DED, with a sensitivity of 45.5–61.2% and a specificity of 79.8–90.6% [252].

3. Biophysical studies of tears

3.1. Tear film evaporation and the lipid layer

Goggle-based chambers detect very low but dispersed tear evaporation rates of 0.14 ± 0.07 μL/min in the healthy eye, but 0.26 ± 0.16 μL/min for patients with meibomian gland dysfunction (MGD) [252]. Tear film thinning kinetics measured by interferometry suggests a higher tear evaporation rate of 1.137 μL/min in the healthy eye, which is a value similar to that of water [25,252]. The thickness of the lipid layer may not affect the evaporation rate unless it is very thin (less than 24 nm) or completely absent [24–27,67]. Nonetheless, increased expression of meibum in normal eyes correlates with reduced evaporation in both healthy individuals and patients with DED [233,253]. An abnormal tear film lipid layer is associated with increased evaporation [24–27,67]. Evaporation rates differ substantially between different studies, likely due to challenges in controlling environmental factors such as air flow and humidity [254]. Whether only evaporation from the ocular surface is being measured is also not always clear.

Such *in vivo* variability makes *in vitro* studies attractive [255]. Meibum films with physiological thickness do not retard evaporation in *in vitro* studies [255]. Evaporation found in studies using meibum films is in the range of 6–8% [225,256,257], or less in studies using artificial tear film lipid layers of up to 100 nm thick [253,254,257,258]. Only non-physiologically thick, 4 μm or ≥ 17 μm, meibum films can reduce the evaporation of water in laboratory experiments, but then by only 7 or 23% respectively [225,254]. Straight chain alcohols and acids and pure wax esters used alone can retard evaporation [259–261]. Monolayers of tear film-like wax esters can retard evaporation when used at temperatures 3 °C lower than their bulk melting temperature [258,260,261]. However, meibum has a much more complex composition, structure and thermotropic behavior compared to the model films, and the melting temperature of meibum (~30 °C) [262–264] is lower than the ocular surface temperature (35 °C). Recently *in vitro* studies with the Interfacial Dewetting and Drainage Optical Platform (i-DDrOP) on silicone hydrogel (SiHy) contact lenses have shown that the mucoaqueous subphase beneath thinner parts of meibomian films thins and dewets faster compared to that seen below thicker “islands” in the meibomian layer [265]. Therefore, it might be possible that meibum may locally be an effective barrier to evaporation. Suppression of tear evaporation by the lipid layer is thus poorly understood.

Three evaporation suppression hypotheses have been proposed: (1) the effect is based on a certain organization of the lipid layer, as proposed previously [266]; (2) the lipid layer is not solely the structure that is responsible for the retardation of evaporation, but specific protein or mucin (or a combination) interactions are also needed [267]. However, whole tears collected by capillary tube,

Table 3
Evaporation of tears from normal eyes.

Technique used	Evaporation rate (mean ± SD) (× 10^{-7} g/cm^2/sec)	Relative humidity (%)	Reference
Open chamber with no temperature and humidity control	26.9 (±NR)	NR	Hamano et al., 1981 [226]
Closed ventilated chamber using resistance hygrometry	50 ± 16.6	50%	Cedarstaff & Tomlinson 1983 [227]
Temperature and humidity sensors interconnected with constant humidity	4.1 ± 0.4	30%	Rolando & Refojo 1983 [228]
Closed chamber modified dermatologic evaporimeter with two sensors placed at a known distance from ocular surface	12.5 ± 1.8	NR	Trees & Tomlinson 1990 [229]
Closed chamber, temperature and humidity sensor	15.6 ± 3.8	40%	Tsubota & Yamada 1992 [230]
Closed chamber humidity sensor	14.7 ± 6.7	30%	Mathers 1993 [217]
Closed chamber humidity sensor	0.4 (±NR)	50%	Craig & Tomlinson 1997 [67]
Ventilated chamber with constant airflow of known water content	4.1 ± 1.4	NR	Goto et al. 2003 [232]
Closed chamber humidity sensor	10.8 ± 5.3	NR	Thai et al. 2004 [236]
Closed chamber humidity sensor	15.1 ± 7.3	30%	Guillon & Maissa 2008 [237]
Closed chamber humidity sensor	5.8 ± 2.8	NR	Khanal et al., 2009 [123]
Quartz crystal humidity sensor	5.0 ± 2.8	18%	Kojima et al., 2011 [234]
Closed chamber humidity sensor	0.04 ± 0.01 (µl/min/cm^2)	30%	Arciniega et al., 2011 [233]
Infrared thermography in a controlled adverse environmental chamber	26 ± 11.1	45%	Petznick et al., 2013 [235]
Ventilated chamber with constant airflow of known water content	7.7 ± 6.0	30-50% (in room)	Hirayama et al., 2013 [238]
Closed chamber humidity sensor	55.6 (95% CI: 40.8–75.8) (g/m^2/h)	56%	Rohit et al., 2014 [239]
Flow Evaporimeter	26 (±NR)	40%	Peng et al., 2014 [25]
Ocular thermography	66.1 ± 21.1 (W/min)	NR	Yeo et al., 2016 [240]
Closed chamber humidity sensor	79 ± 33 (g/m^2/h)	45%	Alghamdi et al., 2016 [241]

NR = Not Reported.

apparently with all tear lipid and protein species and at least some mucins [17,19,21,268–272], evaporate *in vitro* with water-like rates; (3) water evaporation from the ocular surface is not at all controlled by lipids and the lipid layer has other functions [257]. A thick duplex film enriched with unsaturated and branched chain lipids, as found in meibum, is a much less effective barrier to evaporation than tightly packed lipid monolayers [273].

If tears do evaporate at the same rate as water, eventually the concentration of secretory mucins and proteins in the lipid layer would increase, and approximate mucin near the surface of the cornea [274]. A dense polymer network of mucin has a high hydration "water holding" property and might suppress further tear evaporation [275]. It is also possible that mucins, together with proteins and polar lipids from tears, enhance spreading and structure of the tear film lipid layer. Thus all tear film key constituents may contribute to increased evaporative resistance.

3.2. Clinical observation and harvesting of tear film lipids

The tear film lipid layer is derived predominantly from meibum from the meibomian glands and spreads upward over the mucoaqueous layer [8] with blinking. Thinning of the lipid layer superiorly may create a rise in surface tension as a driving force for spreading [8]. Spreading may initially involve interaction between polar lipids and the mucoaqueous layer [276]. Polar lipids then carry nonpolar lipids [277]. In the normal eye, spreading of the lipid layer can be observed clinically by interference video microscopy as an upwardly moving front of horizontally disposed, colored fringes (Fig. 2). Fringes reflect topographic variations in thickness of the lipid layer and are thereby reflective of its intermolecular organization. The lipid layer is compressed during the down stroke of the blink and restored in the upstroke, with only a moderate disturbance of its organization between consecutive blinks [4,26]. Spreading is rapid at first (about 10 mm s^{-1}), although lagging behind the upper lid [278]. Spreading slows and stabilizes after one second or more, with the interference pattern showing remarkable stability over the remainder of the blink [34,278]. Spreading is slower and less laterally arranged in dry eye patients [34,278], with reduced stability of the lipid layer fringes [279], suggesting that intermolecular stability is lost.

The dynamic nature of the lipid layer allows it to respond to the shear stress induced by the changing area of the air-tear interface during blinking. The lipid layer must be compressible during the down-sweep [280,281], but must spread rapidly after the up-sweep of the lid [26]. Polar lipids decrease the surface tension of the air-tear interface and increase the spreading rate of the lipid layer. Non-polar lipids increase the compressibility and stability of the lipid layer [281]. Imbalances in composition show as impaired viscoelastic properties.

Human meibum comprises ~90% of the tear film lipid layer, and is often investigated as the archetype for the tear film lipid layer. Commercially available clinical devices (such as Yoshitomi's meibomian gland pressure forceps, or Arita's meibum collector) [120,282] ensure collection of ≤0.5 mg meibum per donor, thus allowing for multiple repetitions of experiments. The different meibum collection procedures (by glass microcapillary tube, Dacron swab, cytology micro brush, or spatula) and inherent intra- and inter-individual variability may contribute to variations in the amount and composition of the meibum samples [283–285].

The most representative tear film lipid layer mimic might be the lipid extract of whole human tears. However, to-date only one study has used it for *in vitro* analysis of surface tension [286], which is not surprising considering the difficulties in collecting a sufficient sample for reproducible experiments. Lipids extracted from deposits adsorbed on worn contact lenses have been used [287],

although they contain higher amounts of phospholipids than meibum. Schirmer strips can be used to collect lipids [288]. The tear film contains ~8% of amphiphilic (polar) lipids [289–291] that may be released from the lipid-binding protein lipocalin [292] from the mucoaqueous layer upon organic solvent extraction. These phospholipids are at very low levels in meibum [21,272], but as surfactants, if they are not bound to lipocalin, may have a significant role at the tear interface [255,285,293].

3.3. Surface tension of tears

The tear film lipid layer lowers the tear surface tension, thus sustaining the tear film's high area-to-volume aspect ratio. Tear surface tension of healthy individuals is 43.6 ± 2.7 mN/m [294], rising to 53.0–55.5 mN/m after delipidation, which is remarkably close to the upper boundary of values observed in samples collected from patients with dry eye, of 49.6 ± 2.2 mN/m [286].

Supplementing delipidated tears with meibum lipids does not restore the surface tension [286,295]. Normal surface tension may thus rely on lipids and perhaps some proteins and glycoproteins from the mucoaqueous layer, such as lipocalin, lysozyme, and mucin, that are thought to intercalate with the lipid layer [272,276,296]. Increased surface tension in dry eye implicates abnormally enhanced protein content at the air/tear interface as a consequence of a compromised lipid layer. Proteins appear to take hours to penetrate a normal meibum lipid layer [297–300].

Data on the thermotropic phase transitions (via spectroscopy, differential scanning calorimetry and X-ray diffraction studies) [262,264,301–303] and interfacial and bulk rheology [29,301,302] of tear lipids *in vitro* and *in vivo*, suggest a thick viscoelastic duplex structure composed of a monomolecular layer of amphiphilic polar lipids at the mucoaqueous surface and a generally unstructured shear thinning lipophilic suspension at the lipid-air interface. The lipophilic suspension consists of lipid lamellar-crystallite particulates immersed in a continuous liquid phase with no long-range order. An alternative hypothesis rebrands the old folded trilayer model of McCulley and Shine and views the tear film lipid layer as a lamellar sandwich [304]. Lamellar models demand an ordered, almost rigid solid [302], which conflicts with the need for rapid reorganization during blinking.

Due to the abundance (≥90%) of non-polar lipids, both meibum and contact lens extracts do not spread as monolayers at the air/water surface, but instead form thick (10 nm to >100 nm) duplex films. They are thick enough to display bulk properties with two separate interfaces, but thin enough to neglect the effects of gravity) [257,285,288,301,302,305]. Uniform spreading of meibum is enhanced by polymers that contain polyanionic polysaccharide moieties, such as hyaluronic acid and secretory mucin glycoproteins [296,305], that form polymer interfacial gel-like networks due to hydrogen bonding of the polymer moieties with each other and with the phospholipid head groups. As a consequence, film viscosity is enhanced, and a more uniform 2-dimensional (2D) distribution of lipids and water is achieved [257,296,305].

Films of meibum and contact lens lipid extracts are non-collapsible, which helps them to withstand the dramatic area changes during the blink. In some studies, meibum layers show almost full surface pressure (π)/area reversibility (i.e. very low π/area hysteresis), which point to meibum's capacity to rapidly reorganize during area cycling (as a model for the interblink period) [29,296,305–307]. Interestingly, meibum films expand and thin at lower temperatures (23-25 °C), but shrink and thicken at physiological (≈35 °C) temperatures [29,263,301,305,308]. Such behavior agrees with the liquid suspension model of the non-polar lipids of the lipid layer. The non-polar lipid oily cap might act as a lipophilic solvent [29,301,309–311] to accommodate polar lipids, which may form inverse micelles within it, during temperature-induced interface/bulk redistribution of the polar layer and during film compression. In other words, it may prevent expulsion of polar lipids into the aqueous phase such that polar lipids can promptly return to the mucoaqueous interface at film expansion.

Meibum interfacial properties and structure are largely insensitive to changes in osmolarity [312,313]. However, both meibum and contact lens lipid extracts are sensitive to the presence of (glyco)proteins (lactoferrin, lysozyme, mucin, lipocalin, serum albumins, lactoglobulin, lactoferrin, secretory IgA, keratin, lung surfactant proteins) [297–300,307,314] and pharmaceutical agents (hyaluronic acid, benzalkonium chloride, SofZia, Polyquad, whole eye drops and lens care solutions) [305,315–317] in the film

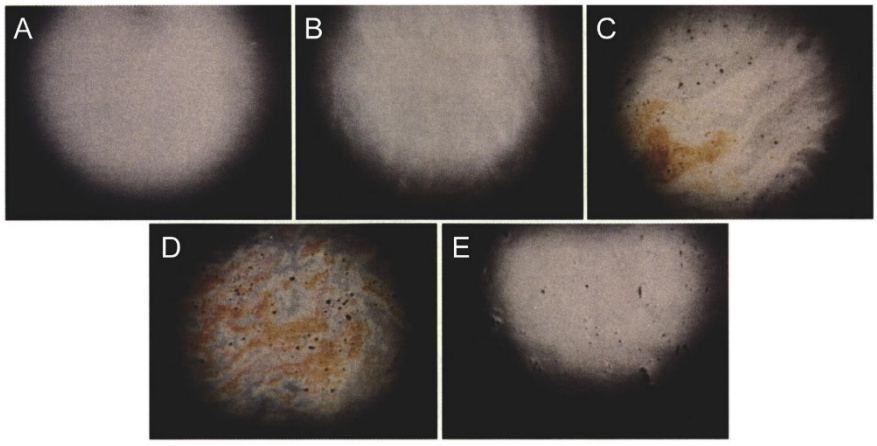


Fig. 2. Tear film lipid layer interferometry grading patterns. From Yokoi et al., Correlation of tear lipid layer interference patterns with the diagnosis and severity of dry eye. Am J Ophthalmol. 1996; 122: 818-24 [35]. A = Grade 1 (gray uniform), B = Grade 2 (gray non-uniform), C = Grade 3 (few colors non-uniform), D = Grade 4 (many colors non-uniform), E = Grade 5 (partly exposed corneal surface).

subphase. However, even in sub-physiologically "diluted" (5–10 mN/m vs. ~30 mN/m) meibum films, the kinetics of the penetration of such substances is much slower (>1 h) than the physiological time scale [297–300].

An alternative mechanism has been proposed, whereby the proteins or pharmaceuticals dissolved in the mucoaqueous subphase do not have to insert into the meibum or contact lens lipid extracts films. Instead, they need only to interact with polar lipid head groups aligned at the mucoaqueous interface. This is a rapid interaction that immediately alters the structure and dynamic interfacial properties of the layers [287,305,311]. These data, along with studies evaluating the impact of lipid (or lipophilic) inclusions directly into meibum layers, demonstrate that non-surface active or lipophilic substances are well tolerated by tear lipid films [318–322], while polar surface active ingredients can disrupt the film's structural integrity and surface properties [314–317]. Interactions between the tear film lipid layer and pharmaceutical agents are of particular pharmacokinetic importance as they may impart long term effects at the ocular surface, in light of the much slower *in vivo* turnover rate of the tear film lipid layer compared to the mucoaqueous layer (0.93 ± 0.36%/min vs. 10.3 ± 3.7%/min respectively) [323].

Shear rheology experiments have demonstrated the viscoelastic nature of meibum films, which were able to stabilize tear film-mimicking films and to reduce the critical film thickness for dewetting [28]. The protective effect of meibum layers was stronger than that of Newtonian arachidonic acid and primarily viscous dipalmitoylphosphatidylcholine films, in line with the classic paradigm that viscoelastic surfactants are particularly effective at stabilizing thin films [324].

Meibum and contact lens lipid extract films also display viscoelastic behavior in dilatational rheology studies [29–31], with predominantly elastic properties, thereby enabling resistance to deformation during tear film breakup. Whereas films of meibum collected from healthy donors are continuous, thick and predominantly elastic, films from patients with meibomian gland dysfunction are discontinuous, patchy and show viscoelasticity compromised at time scales (ie at low frequencies) encompassing the durations of blink and interblink intervals found *in vivo* [29]. The *in vitro* data correlate well with the impaired spreading and heterogeneous structure of the tear film lipid layer of patients with MGD seen *in vivo* [29]. Similar characteristic differences in the viscoelastic properties are reported between films of contact lens lipid extracts from Caucasians versus dry eye-susceptible Asians [30,325]. More attention should be paid to the capacity of the lipid layer to elastically stabilize the air/tear interface.

3.4. Tear film lipid layer bulk properties

Differential scanning calorimetry reveals that the phase transitions in meibum start at 10–15 °C and end at 35–36 °C, with a melting temperature (Tm) of ~30 °C [264,302]. Thus, it is reasonable to assume that in the meibomian gland orifices meibum is both disorganized and liquid to facilitate excretion. When exposed to the cooler (33-35 °C) ocular surface, meibum solidifies to a partially melted liquid crystalline state, thereby enhancing lipid layer in-plane elasticity, and via denser 2D molecular packing, ensuring a barrier to water evaporation.

Combining differential scanning calorimetry with small- and wide-angle X-ray diffraction points to meibum as a liquid suspension consisting of lipid lamellar-crystallite particulates immersed in a continuous liquid phase, with no long-range order at physiological temperature [262,264,301–303]. Hot stage cross-polarized light microscopy confirms such a view and reveals that in meibum from patients with MGD there is an increased presence of non-lipid, non-melting, chloroform-insoluble inclusions of protein, including cytokeratin [262]. Spectroscopy studies also confirmed that MGD meibum contains more protein and relatively less methyl groups (CH_3) and *cis* double bonds (*cis*=CH) compared to normal meibum [303]. The increased content of non-melting proteinaceous particles that are poorly miscible with lipid can account for the impaired spreading and discontinuous structure of meibum films *in vitro* and for their worsened viscoelasticity and evaporation suppression capability *in vitro* and *in vivo* [29–31].

Bulk shear rheology evaluation suggests that meibum is a shear thinning liquid of extremely high viscosity [302]. At 35 °C, the shear viscosity of bovine and human meibum is approximately 10^5 greater than that of water and 3–4 orders of magnitude more viscous than mineral oil. However, such high bulk viscosity is inconsistent with the high mobility of fluorescent probes reported in meibum layers [296] and with the rapid reorganization of meibum films during area cycling [29,296,305–307]. More research needs to be performed to resolve this issue.

Research on the bulk rheology of non-stimulated (or mildly stimulated) tears is relatively old, but in light of the new findings on the tear lipidome, there is a need for reappraisal. Human reflex tears collected after cold air stimulation are non-Newtonian and shear thinning [326]. Their viscosity at rest is ~9 cP and when shear is applied it rapidly drops to 1 cP (at shear rates $\geq$ 100 s^{-1}) [327,328]. This indicates that the tear constituents, and particularly the compounds dissolved in the mucoaqueous layer, when at rest form a "transient" intermolecular network via weak non-covalent interactions (hydrogen-bonding, hydrophobic and/or electrostatic interactions etc.). Thus, they increase the mucoaqueous layer viscosity in the open eye, which raises its resistance to thinning and enhances tear film stability. At blink, the high shear applied by the eyelid breaks these weak interactions, the intermolecular network disintegrates and the aqueous can flow like water, thus preventing any damage that high viscosity may cause to the underlying corneal epithelium. The exact nature of the compounds involved in the transient intermolecular network remains unclear. Pure monocomponent solutions of mucin or tear proteins in physiological concentrations are low viscosity and/or Newtonian fluids. Also, if the lipocalin-bound lipids are extracted, then tears become a low viscosity Newtonian fluid. This suggests that lipid/protein interactions, lipocalin and possibly lysozyme and lactoferrin play important roles in the shear thinning property of tears.

An interesting study found that when whole human tears are subjected to shear (at rates of 2–160 sec^{-1}), dry eye tears need >10 times longer relaxation times compared to normal tears (2.8 ± 0.14 s vs. 0.26 ± 0.12 s) in order to equilibrate after the shear is ceased [328]. This suggests that a longer period should be needed for dry eye tear film, compared to a healthy one, to stabilize at the ocular surface after a blink. This demonstrates the potential importance of elasticity for tear film stability.

4. Biochemical properties of tears

4.1. The tear lipidome

In the normal eye, clear oil can be expressed from the meibomian orifices, which are located anteriorly to the mucocutaneous junction of the lid rim [329], by pressing on the glands through the lids. Expressibility is greatest nasally and least temporally [330]. An average amount of meibum stored in the meibomian glands is in the range of several hundred micrograms per eyelid [26]. The lid reservoir contains at least 30 times the amount of lipid present on the surface of the tear film (approximately 300 μg vs. 10 μg, respectively) [331,332]. Comparison of the lipids from meibum and whole tears [21,255,333] showed that the classes and ratios of lipids

in whole tear samples were very similar to the classes and ratios of lipids and ratios in meibum. The only exception was phospholipids, the majority of which may be from another source.

Tears from the meniscus and meibum have been extensively studied to determine if changes in one or more components can be correlated with dry eye. Overcoming the technical difficulties involved with collection and processing small volumes without contamination has formed a major part of this journey, and therefore these studies have included developing techniques for collecting, identifying and quantifying both specific families of lipids and individual lipids. Techniques for analyzing meibum and tear lipid components have been extensively reviewed in previous publications [159,276,284,309,334]. Techniques employed to measure lipid composition each have limitations. Mass spectrometry (MS) is excellent for identifying lipid species, but until recently, has been weak in quantification. Nuclear magnetic resonance (NMR) is quantitative, however, single signals may derive from many different species of lipids. Only by a process of elimination can individual lipids be attributed to particular spectra.

Meibum is composed of approximately 95% non-polar lipids and 5% amphipathic lipids. Collection methods can alter the composition of the amphipathic lipids [282]. In humans, the non-polar component is composed of 30–50 mol% (ie the fraction of the wax esters compared to the total amount of lipid expressed as moles) of wax esters [284,309,334], 30–45 mol% of cholesterol esters [21,335,336] and a small percentage of triglycerides (~2%) [309]. The wax esters generally have an oleic acid component (C18:1) and the alcohol components vary from C18-C30. A feature of the cholesteryl esters is that they have very long acyl chains, predominantly C22:1-C34:1 [21,272]. In both cases, the acid groups can have odd numbers of carbons (such as C25) and this is unusual because fatty acids are normally synthesized using acetic acid (2C) as the building block. Other lipids found in meibum include free cholesterol, which makes up <0.5 mol% and phospholipids, which make up <0.01 mol% of meibum [21]. The predominant amphipathic lipid family found in meibum is the (O-acyl)-ω-hydroxy fatty acids (OAHFAs), which comprise about 4 mol% of total meibum [21,336,337]. The amount of OAHFAs and the low level of phospholipids imply that OAHFAs are the major surfactants in the tear film lipid layer, and although this has not been shown, it gathers support from *in vitro* experiments where OAHFAs have been shown to readily spread over large surface areas of an mucoaqueous subphase [320].

The range of mol% of total lipids for each major lipid class means that to correlate one of these main classes of non-polar lipids with dry eye requires a very large change relative to normal. In this regard, it should be noted that an earlier finding that normal, but not dry eye subjects, did not have cholesteryl esters [338] has not been confirmed in more recent studies [333,336].

Particular genetic profiles that correlate with particular ratios of lipids in tears or meibum have not been studied, but if there were such correlations, ethnicity does not appear to be a factor, because a population study of Asians found similar lipid ratios [336] to those found in other studies [21,272]. The ratios of lipids in meibum do not vary with age [339], but there are changes in certain polar lipids (not identified) in meibum with sex and age [340]. Whether or not the ratio changes for an individual as they develop dry eye has not been studied, although there is a relatively large variation in mol% lipid types among individuals [341]. Recently, using NMR spectroscopy, squalene was detected in meibum [318,342]. Squalene is of interest because it illustrates an example of a lipid that might play a protective role rather than a role in the formation of the tear film lipid layer. Squalene is anti-inflammatory and antibacterial and could have antioxidant properties by scavenging free radicals produced by UV rays [343].

A recent development in the field has been to compare meibum and the lipids of whole tears from the meniscus [21,341]. This centers on the concept that the lipid layer of the tear film might contain not only lipids derived from meibomian glands, but also lipids that have migrated from the mucoaqueous layer. To put this in perspective, the upper limits of total lipid concentration reported in whole tears collected from the meniscus are 380–580 pmol/μL (~0.5 mmol/L) [291,344], of which non-polar lipids comprise ~85mol%, OAHFAs ~4mol% and phospholipids ~10mol%. For individual subjects, main lipid classes in whole tears were in the same ratios as those found in meibum, except for phospholipids that derive from the meniscus, irrespective of the analytical technique used. The relative amount of phospholipid varies markedly between individuals from 1 to 30 mol% of total lipids; lysophosphatidylcholine is the most abundant species [341]. However, over a 3-day period, the ratios for an individual were the same [341].

Whether phospholipids contribute to lipid layer performance is an area of debate. Some argue for insufficient available phospholipid [309], with most of the intact phosphatidylcholine (but not lysophosphatidylcholine) bound to lipocalin. Others suggest that there is sufficient phospholipid in stimulated tears to form a monolayer [292]. Assuming 0.5 mmol/L (5×10^{-4} mol/L) total lipid and 10mol% phospholipid (5×10^{-5} mol/L) in whole tears and a total tear volume of 10 μL (10^{-5} L), then the total number of phospholipid molecules [345] available for lipid layer adsorption would be 3×10^{14} (5×10^{-5} x 10^{-5} x 6×10^{23}). If one assumes a lipid layer surface area of 2 cm^2 (or 2×10^{16} $Å^2$), ~70 $Å^2$ (2×10^{16} $Å^2$/ 3×10^{14}) should be available per surface phospholipid, which is identical to the area occupied by a single phosphatidylcholine molecule [345]. This calculation is based on the understanding that all phospholipids in 10 μL of tears have adsorbed to the tear film lipid layer and none is bound to lipocalin in the mucoaqueous layer. There is a strong case for a 'perched tear film', and if this were the case then the true ocular surface tear volume would be about 0.06 μL. Overall, it appears that phospholipids are insufficient to form a layer. The countering argument is that phospholipids collected from tears of the meniscus were already part of the lipid layer at higher concentration and so there are more than ample phospholipids to form a layer at the ocular surface.

Several studies have investigated whether the collection technique of whole tears from the meniscus affected the lipid profiles obtained [288,290,291]. Rohit and co-workers compared flushed & reflex tears with basal tears and found a relative mol% increase of phospholipids and free cholesterol [291], pointing to a preference for basal tears, and suggested care to avoid reflex tearing during collection. Moreover, reflex or flush tears contain very low levels of several lipids. Others found lipid profiles from capillary-collected basal tears and flushed tears to be almost identical [290], and that tears collected by Schirmer strips had similar profiles to these but with a greater amount of total lipid (~7.5 times). Two studies examined the lipid profile on different regions of the Schirmer strips that were used to collect tear samples. Using an IR method, Borchman and colleagues estimated that in the first 5 mm of the Schirmer strip, only 5% of the lipids were from the meibomian glands and also noticed that the lipid profile did not change over the first 15 mm [288]. Contrary to these findings, Lam and co-workers using a MS method, showed that the first 5 mm was composed of 15% phospholipids and approximately 80% was made up of meibomian lipids [290]. They also noticed that in the next 5 mm of the strip, the quantity of meibomian lipids halved, with few other lipids being detected and no signal for phospholipids. These results suggest that the use of Schirmer strips to collect tears may be not reliable.

In another study of mixed purpose, the main lipid classes found in meibum of wearers of contact lenses with and without dry eye

were compared. The opportunity was also taken to compare the effect of different collection techniques (microcapillary tube, Dacron swab, cytology micro-brush, spatulas) and extraction techniques (immediate and following storage) [283] on the lipid profiles obtained. A cytology micro-brush was the most efficient at recovering phospholipids (50%), followed by the spatula (40%), microcapillary tube (38%), and Dacron swab (23%), and the authors concluded that the choice of collection device and extraction method plays a significant role in the detection of meibum lipids, particularly phospholipids [283]. This study also showed that contact lens wearers not suffering from dry eye were more likely to have inorganic phosphates present in their meibum samples compared with samples from contact lens wearers who had dry eye [283]. Another study that compared lipid composition of meibum collected using cotton buds, the meibomian gland evaluator and meibomian gland forceps demonstrated that the use of the evaluator resulted in smaller polar lipid quantities than the cotton bud approach [282]. There were no significant differences between techniques for nonpolar lipids [282].

Several studies have evaluated the impact of age on the composition of meibum and lipids from whole tears from the meniscus and compared these with subjects suffering from MGD [288,303,339,346–350]. Interestingly, Lam et al. found OAHFAs to increase with age [333], which is unexpected because they also found that OAHFAs decreased with dry eye [336]. There was no difference in meibum phospholipid between males and females [351], but another study has shown a difference in polar (not identified) between the sexes [340]. Studies using NMR have shown that there was an increase in order of the molecules in MGD relative to age-matched controls and a corresponding decrease in lipid order with age [303]. An investigation of the meibum from Asians with different severities of dry eye showed that there was no overall difference in the ratios of the different classes of lipids between dry eye patients and normal subjects [336]. The proportion of total lipids that were triacyl glycerols was higher in the mildest category of dry eye compared with more severe categories, and the relative percentage of OAHFAs to total lipids progressively fell with increasing severity of dry eye. This was the only class of lipids to do so [336]. Some changes in the relative percentage of individual species of lipids to total lipid detected were found, but the trends were not consistent in direction across the dry eye categories.

Recently, several studies have profiled lipids in whole tears from the meniscus of patients with different severities of DED [21,289–292,333,344,351,352]. Beyond the relative ease of tear collection versus meibum, marked levels of phospholipids are detectable in tears, ratios of lipids in whole tears from the meniscus reflect lipid-species ratios in meibum, and all meibum lipids have been identified in the tears. Table 4 summarizes recent studies (adapted from Millar and Schuett) [255]. Lam et al. observed a decrease in low molecular weight wax esters and a tendency of medium molecular weight wax esters to be more unsaturated although total tear lipids were unchanged in dry eye patients versus control subjects [290]. Another study by the same group used HPLC/MS/MS to determine correlations between structure-specific human amphipathic tear lipids and dry eye [333]. They found that several amphipathic lipids, cholesteryl sulfates, glucosylceramides, ganglioside mannoside 3, and lysophosphatidylcholines, were positively correlated with increased Schirmer I results, and that phosphatidic acids and phosphatidylglycerols showed a negative correlation. Small amounts of cholesteryl sulfate in meibum and tears from patients suffering with dry eye syndrome have been detected [290,333]. However, its role in meibum or the tear film needs further investigation. These components are commonly associated with epithelia, where they are believed to have a secondary messenger role [353]. It is possible that the cholesteryl sulfate detected in Lam et al.'s samples [290] may have originated from meibomian ductal cells.

In summary, tear lipid profiles from studies to date are variable, warranting investigation of the source(s) of variation (collection methods, analysis techniques or a combination of both) and close collaboration among different tear and meibum lipid laboratories worldwide. An initial step would be comparative analysis of a common shared sample towards comprehensive procedural standardization of all analytical and collection steps.

4.2. Mucins

Mucins are large high molecular weight glycoproteins that contain one or more protein domains, rich in serines and threonines, which are extensively glycosylated via O-glycan attachments. These important glycan chains constitute a significant part (50–80%) of the weight of the mucin [354,355]. Mucins, the building blocks of mucus, in general are present at apical epithelial surfaces of the respiratory, gastrointestinal, and reproductive tracts, as well as the ocular surface. Mucins provide a variety of protective functions, including but not limited to, lubrication, barrier formation and hydration. Fig. 3 demonstrates the role of mucins in the tear film structure.

At least 20 mucin genes (MUC) have been identified in humans [356], the products of which are classified into two types: secretory mucins and transmembrane mucins. The secretory mucins are further subdivided into large gel-forming mucins and small soluble (or non-gel forming) mucins [356]. The gel forming mucins are MUC2, MUC5AC, MUC5B, MUC6 and MUC19, the small soluble mucins are MUC7, MUC8 and MUC9, and 10 others have been characterized as transmembrane [356]. Ocular surface mucins are synthesized by corneal and conjunctival epithelia and lacrimal glands, where they contribute to the epithelial barrier and prevent binding of pathogens to the ocular surface, and are present in the tears where they maintain hydration [17,18,271,357–359]. The role of mucins in ocular surface health and DED is a subject of great interest, that has been reviewed a number of times in recent years [15,359–362].

Gel-forming mucins can be incredibly large, up to 40 MDa, thanks to their ability to multimerize through disulfide bonding of cysteine rich domains that flank the large central tandem repeat region [355]. The source of gel-forming mucins on the ocular surface are goblet cells of the conjunctiva, with MUC5AC being the most abundantly expressed [271,359] (though mRNA for others have also been found [363,364]). The abundance of MUC5AC present on the ocular surface is determined by the number of conjunctival goblet cells and the stimulation of its secretion by these cells. Gel-forming mucins are important for hydration of the ocular surface, and have also been suggested to play an important role in not only tear structure, but also in preventing debris and pathogens from binding to the ocular surface and damaging cells [18] by clearing them from the ocular surface through entrapment in the mucus layer and blinking [17,359].

Several studies have demonstrated decreased levels of MUC5AC in dry eye, yet it is important to note that altered levels of MUC5AC (and gel forming mucins in general), both decreased and increased, can negatively impact ocular surface health. As such, mucin production must be tightly regulated for ocular surface homeostasis. In patients with moderate DED a decrease in the total number of goblet cells, as well as empty goblet cells, has been observed by impression cytology [365]. MUC5AC has also been shown by impression cytology to be lower in dry eye patients with severe symptoms compared to mild and moderate symptoms [366], which was associated with increased inflammation, and (along with decreased levels of MUC16) in patients with an unstable tear film or

Table 4
Concentration of lipids in tears (adapted from Millar and Schuett) [255].

Lipid	Saville et al., 2010 [289]	Saville et al., 2011 [351]	Rantamaki et al., 2011 [352]	Dean and Glasgow 2012 [292]	Brown et al., 2013 [21]	Rohit et al., 2014 [291]			Lam et al., 2014 [290]	Lam et al., 2014 [333]	Lam et al., 2014 [344]
						Basal	Reflex	Flush			
Collection method	Cap[a]	Cap	Cap	Cap (reflex)	Cap	Cap	Cap	Cap	Sch	Sch	Sch
Mol %											
Cholesterol-Ester					39	54.8	35.7	33	44.8	43	33
Wax Ester					43	29.1	18.6	30	35.2	30	46
Cholesterol						8.2	17.2	~20	5.9	8	8
OAHFA					4.4	~2.5	<1	<1	2.5	2	1.1
Trigylceride					2.1				2.8	1	2
Phospholipids:											
Phospholipid total					12						
Phosphatidylcholine					1.6				2.5	2	3
Lysophosphatidyl-choline					8				0.5	0.8	1.7
Phosphatidyl-ethanolamine					0.8				0.7	1	1.2
Lysophosphatidyl-ethanolamine									1.3	1.6	2
Phosphatidylserine					0.5				0.1	0.5	0.3
Sphingomyelin					1.1				1.5	3	
Ceramide											
	Concentration										
	pmol/μl	ng/ng tear	μM	ng/ml		pmol/μl					μmol/ml
Cholesterol-Ester						178.1	27.9	13.5			
Wax Ester						81.8	15.5	8.3			
Cholesterol						16.6	9.8	5.9			
OAHFA						4.3	0.4	0.1			
Trigylceride			1.5			1.6	0.1	0.2			
Phospholipids:											
Phospholipid total		11	29.6								
Phosphatidylcholine	6		20.9	194		1.6	1.1	0.5			
Lysophosphatidyl-choline						3.5	9.5	3.2			
Phosphatidyl-ethanolamine			5.2			0.1	0.1	0			
Lysophosphatidyl-ethanolamine						1.5	1.2	0			
Phosphatidylserine			0.1								
Sphingomyelin	5		0.9			1.9	1.6	0.6			
Ceramide			0.9								
Total lipid (pmol/μL)						~380	~100	~40			0.58

[a] Cap = collected by capillary tubes; Sch = collected by Schirmer strips.

aqueous deficiency compared to control eyes [367]. Consistent with these findings, very recently, goblet cell deficiency, and thus decreased MUC5AC expression, was observed in subjects (office workers using visual display terminals) with DED, particularly so in moderate to severe cases [368]. In patients with atopic kerato-conjunctivitis, the number of goblet cells and MUC5AC mRNA levels were significantly diminished [369]; a concomitant increase in MUC16 was also observed and the authors speculated that MUC16 compensates for lack of MUC5AC. In Sjögren syndrome patients, decreased MUC5AC mRNA and protein in tears and decreased MUC19 mRNA and protein has also been reported [270,364]. In summary, there is an abundance of data demonstrating DED is associated with decreased levels of MUC5AC.

MUC7 is currently the only small soluble mucin to be detected in ocular tissue, but it has not been detected in tears [271,363,370,371]. MUC7 is small (~180 kDa) [372] compared to gel-forming mucins, and exists as a monomer with a typical rigid structure 'bottle-brush' shape provided by water-binding O-glycans [361,373]. While MUC7 is expressed in the acinar cells of the lacrimal gland and in human conjunctiva, it is not known which cell type is responsible for synthesis and secretion in the conjunctiva, nor is it known what stimulates MUC7 secretion in ocular tissues [271,363,370,371]. As MUC7 has not been detected in the tears, its putative role in the tear film is not well understood. It is reasonable to speculate, based on MUC7 having the expected O-linked glycans of a mucin, that it would contribute to hydration of the ocular surface. However, no studies to date clearly demonstrate the function of MUC7 on the ocular surface. MUC7 expression, as assessed by mRNA levels in conjunctival impression cytology, has been reported to not be different between normal and patients with dry eye [374].

Transmembrane mucins expressed in the most superficial cell layer of the corneal and conjunctival stratified epithelia include MUC1, MUC4, and MUC16 [15,17,375]. MUC20 is one of the more highly expressed mucins in the human conjunctiva and is predominant along the plasma membranes of intermediate cell layers [376,377]. Transmembrane mucins have large extracellular domains, a hydrophobic membrane-spanning domain, and a short cytoplasmic domain. The extracellular domain comprises the tandem repeats rich in serine and threonine, which are subject to *O*-linked glycosylation [354], and can extend up to 200–500 nm above the ocular surface [362]. Soluble forms of MUC1, MUC4, and MUC16 have been detected in tears [271]. MUC16 has recently been localized to mucin granules of goblet cells as well, though its function remains to be determined [16]. In general, the transmembrane mucins play important protective roles on the ocular

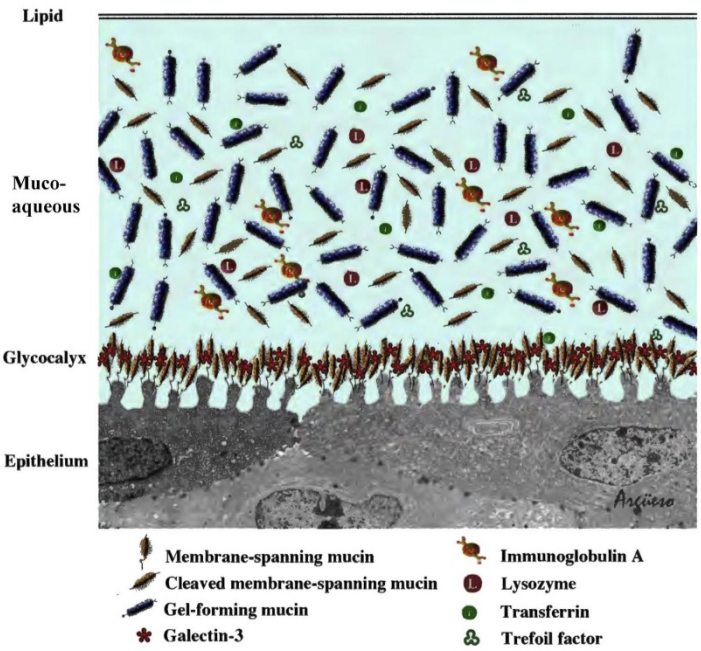


Fig. 3. The tear film structure showing the mucins and galectin of the glycocalyx, soluble mucins and proteins in the mucoaqueous layer and the surface lipid layer. Adapted from Craig et al., 2013 [54].

surface. These include, consistent with those mentioned above, hydration of the ocular surface, and anti-adhesive properties between the cells of the conjunctiva and ocular surface [361], as well as contributing to tear film stabilization [15]. The cytoplasmic domain can associate with cytoskeletal components and also have numerous phosphorylation sites that suggest it may function in cell signaling [378,379]. A direct comparison between MUC 1 and MUC16 barrier function in the same epithelium suggested that transmembrane mucin barriers vary in the context of other transmembrane mucins, and that MUC16 provides a major barrier when present [380]. Messenger RNA transcripts of the transmembrane mucins MUC13, MUC15, MUC17 have been identified in human conjunctiva [381], but neither their presence in tears nor their functions have yet been elucidated.

Transmembrane mucins also contribute to the highly organized protective epithelial barrier on the apical glycocalyx of the ocular surface epithelia cells though binding to galectin-3 (a multivalent β-galactoside-binding lectin) [382]. Indeed, galectin-3 co-localizes with MUC1 and MUC16 on the apical surface of epithelial cells, in a carbohydrate-dependent manner, and plays a key role in maintaining mucosal barrier function. The concentration of galectin-3 protein in tears (but not conjunctival epithelium expression) was found to be significantly higher in patients with dry eye and associated with epithelial dysfunction in dry eye, and the data demonstrate proteolytic cleavage of galectin-3 that may contribute to impaired ocular surface barrier function [383].

Changes in transmembrane mucin have been observed in patients with DED, but remain controversial. In post-menopausal women with non-Sjögren syndrome dry eye, increased MUC1 and MUC16 mRNA and protein levels have been reported relative to controls [384]. Similarly, increased MUC1 and MUC16 mRNA and soluble protein levels have been observed in Sjögren syndrome [385,386]. Conversely, decreased levels of MUC1 and MUC4 mRNA levels were reported in conjunctival epithelia of dry eye patients, and those authors suggested MUC1 mRNA levels could be used as a diagnostic biomarker for dry eye [374]. Such alterations could be the result of dry eye-related inflammatory mediators (eg IL-1, IL-6, IFN-γ, TNF-α) regulating the expression of transmembrane mucin, although, to date, studies examining this hypothesis have been *in vitro* only [387–389]. In patients with complete androgen insensitivity syndrome who have DED [390], MUC1 mRNA and protein as well as the gel forming MUC5AC levels were decreased compared to those in control patients [376].

Altered glycosylation of ocular mucins has been observed in dry eye. Differential regulation of genes involved in glycosylation, as well as altered distribution of the responsible enzymes, has been observed in the conjunctiva of patients with DED [376,391]. Alteration of MUC16 sialylation, as shown by using the monoclonal antibody H185, has been detected in patients with dry eye symptoms [392,393]. Upregulated sialylation of MUC1 in mild-to-moderate dry eye and a decrease in severe dry eye has also been observed [394]. Indeed, altered sialylation of mucins in DED appears to depend on disease severity; whereas increased sialylation has been noted in the earlier stages of disease development, it is eventually lost with disease progression [395,396]. Increased sialylation on the cell surface would increase negative charge and enhance cell repulsion, as well as hydration through attraction of water. Additional work is required on the glycosylation of mucins and mucin-like molecules in DED.

A mucin-like glycoprotein called lubricin, or proteoglycan 4, is

present on the ocular surface, where it provides lubrication and plays a protective role [397]. Lubricin was originally discovered in synovial fluid and on the surface of cartilage, and was found to also be present at the epithelial surface of human cornea and conjunctiva, though it is yet to be detected in tears [397]. Lack of lubricin on a mouse eye is associated with increased ocular surface damage, as demonstrated by an increase in corneal fluorescein staining [397], though to date no studies exist demonstrating alterations in lubricin expression with dry eye. *In vitro*, lubricin reduces friction at a human cornea-eyelid biointerface, as well as tissue-contact lens biomaterial interfaces [398–400]. Recently, recombinant human lubricin was found to demonstrate improvement in both the signs and symptoms of DED compared to a control drop based on hyaluronate) [401]. Another heavily *O*-linked glycoprotein found in tears is Deleted in Malignant Brain Tumors-1 (also known as gp-340) and this has two isoforms [402]. The role of this protein in the tear film is unknown, although gp340 has been shown to be identical with the salivary agglutinin that strongly binds to bacteria and can activate the complement system [403,404] so may be involved in host defense.

In conclusion, mucins are critical to ocular surface health and deregulation of their synthesis is an important factor in ocular surface disease. Decreased MUC5AC expression and alteration in mucin glycosylation in dry eye is a consistent finding among most studies, while changes in transmembrane mucin expression is more variable (see Stephens & McNamara [360] for summary tables). Additional work is required to elucidate the role of individual mucins in disease, with the potential confounding factor of compensatory and/or complementary responses. Such work will likely benefit from the use of new, sophisticated genomic, glycomic and proteomic methods.

4.3. The tear proteome

The mucoaqueous layer contains salts and numerous proteins derived from the lacrimal gland and conjunctiva. A much expanded understanding of the tear proteome [405,406] has been achieved over the past decade and this section will concentrate on research conducted within this time frame. Techniques that have been used for proteomic analysis include unbiased tandem mass spectrometric (MS/MS) sequencing [19,268,269,407–414], candidate immunocapture [368,415–421] and other approaches (Table 5), from which a select group of putative disease biomarkers have emerged (Tables 6 and 7).

MS/MS runs are fed by trypsinized tear protein fragments that are first subjected to reverse-phase C-18 (without or with cation exchange [269,407]) separation. In some cases, tear proteins were first partitioned by 1- or 2-D sodium dodecyl sulfate polyacrylamide gel electrophoresis [269,408,409,414], which offers the advantage of separating monomers from polymers, or were collected into normal or dry eye pools for differential labeling by mass [407] or by fluorescence [408]. In other cases, tear proteins were first adsorbed onto protein chips, disks or tips bearing C-8, C-18 or cation ion exchange chemistry [410,422], or abundant albumin was first immunodepleted from tears [409], the latter an acknowledgement of the limited dynamic range of MS/MS, by which changes in less abundant tear proteins are overlooked.

Although well-suited for discovery, MS/MS coupled with chromatography is currently not practical as a quantitative, high throughput tear diagnostic, despite some success in a few academic studies. For this reason, candidate immunological approaches have been explored (Table 6) [270,368,415,417,420,421,423–436]. These include antibody array (16 inflammatory cytokines [437]), sandwich ELISA (for MMP-9 [415,418,421], MUC5AC [368], IL-1β and IL-6 [415]), direct ELISA (lacritin [416,438]), and bead adsorption [439] (13 inflammatory cytokines, EGF, vascular endothelial growth factor (VEGF) [417,419], TGFβ1 and 2 [420]). An expanded selection of quantitative immunoassays built on validated biomarkers (Tables 6 and 7) should be the way of the future. Investigators should be careful to control for non-specific tear matrix effects [437,440], and independently validate commercial immunoassays where possible (one commercial lacritin ELISA displayed no reactivity for purified recombinant lacritin [405]).

Currently, almost 1800 proteins are known to constitute the human tear proteome. Before the original TFOS DEWS report in 2007, 491 proteins had been identified [268]. In 2012, Zhou et al. [19] reported 1543 proteins, of which 1304 were new. Over half are indicated to be 'intracellular' or associated with the 'plasma membrane' by Gene Ontology, but those that selectively decrease or increase in ocular surface diseases and thus are potential biomarkers are to date largely 'extracellular' according to Gene Ontology [270,368,407,408,410,411,425,428,430,431,434,441–448].

Other technical considerations include the method of tear collection, whether topical anesthesia is employed to reduce reflex tearing [442], sampling from open versus closed eyes [268,437] and the optimal collection point on the eye. Capture of tears by microcapillary tubes is most common in proteomic studies [268,269,408,409,418–421,432,437,450], although others collect tears onto Schirmer strips [269,407,410–412,442], using sponges [409,415,429] or via micropipette tip [368,417,450]. Posa et al. [456] and Grus et al. [442] note that microcapillary tubes and Schirmer strips are equally effective, whereas Green-Church et al. [269] suggest that the tear film collection method impacts proteins present in the sample. However, Schirmer strips are preferred by patients for comfort and perceived safety. Schirmer strips also appear to retain proteins <40 kDa [442]. Most studies fail to mention the use of anesthesia, whether tears are from open or closed eyes, and the site of collection by tubes and sponges (sampling is slightly more common from the lateral [417–419,450] versus medial [420] canthus). Noting whether anesthesia has been used is important, with relative levels of 15 tear proteins, possibly more, differing between basal and reflex tears [457]. Previous studies have shown that certain tear proteins such as lysozyme, lactoferrin, and lipocalin-1 are regulated, in that their concentration remains approximately the same during changes to the amount of tears being produced (for example during reflex tearing) [457]. Other proteins, such as sIgA, are constitutive or have a constant level of production, such that their concentration decreases during increases in tear fluid production [458]. Some proteins appear in the tear film via leakage from conjunctival blood vessels [459,460]. The concentration of sIgA could be used to normalize protein levels that might be affected by collection of reflex vs. non-reflex tears [461], and this is an area worthy of further study, although sIgA is deregulated in some pathological conditions. Indeed, it is currently not known whether most of the proteins within the proteome are constitutive, regulated or derived from serum (or elsewhere). A correct normalization process usually involves a “normalizer protein” or “housekeeping protein” [462]. A strict definition of a housekeeping protein is a constitutive protein that should be expressed under normal and pathological conditions at relatively constant levels. Such a protein has yet to be described in tears. A publication of cerebral spinal fluid proteomics indicates that the preferable way to quantify proteins is to first match the samples on total protein amount and then normalize the data based on the median intensities [463]. This technique has yet to be used in tear film biochemistry studies.

Human tear biomarkers might predict, diagnose and even, in

Table 5
Mass spectrometric approaches.

Name	Abbreviation	Approach
Surface-Enhanced Laser Desorption/Ionization Time-Of-Flight Mass Spectrometry	SELDI-TOF-MS	Peptides are initially screened by differential binding chemistry (ie hydrophobic, anion, cation exchange), then are ionized and masses determined.
Matrix-Assisted Laser Desorption/Ionization Time-Of-Flight Mass Spectrometry	MALDI-TOF MS	Peptides are separated by liquid chromatography, or 2D or 1D polyacrylamide gel electrophoresis, then ionized and masses determined.
Isobaric Tag for Relative and Absolute Quantitation	iTRAQ	Stable isotope tagging to differentiate peptides from different sources, ie. normal vs. dry eye.
Tandem Mass Spectrometry	MS/MS	Ionized peptides are separated by mass, selected ions are fragmented, further separated and sequence derived.

some cases, be therapeutic for ocular surface disease. Nine early candidate biomarkers were identified primarily by immunoassay (see Tables 5 and 6 for expanded details):

a) epidermal growth factor (EGF): reduced in Sjögren syndrome and aqueous deficient dry eye (ADDE) [430,464], augmented in evaporative dry eye due to MGD [417].
b) interleukin 1α (IL-1α): increased in Sjögren syndrome dry eye and MGD [433].
c) interleukin 6 (IL-6): increased in Sjögren syndrome dry eye [432,465].
d) lactoferrin (LTF): reduced in Sjögren syndrome and non-Sjögren syndrome dry eye [466].
e) lipocalin 1 (LCN1): a putative auto-antigen for Sjögren syndrome [467] that is decreased in MGD [468].
f) matrix metalloproteinase 9 (MMP-9): increased in Sjögren syndrome dry eye, but unchanged from normal in MGD [433].
g) MUC5AC: reduced in Sjögren syndrome dry eye [270,469].
h) plasmin activity from plasminogen (PLG): increased in Sjögren syndrome dry eye [434].
i) group IIA phospholipase A2 (PLA2G2A): increased in dry eye [470,471].

Seven more have been identified by unbiased MS/MS analysis of 2-D gel protein bands that differed in quantity between normal and blepharitis tears [443]. Selectively down-regulated biomarkers were albumin (ALB), immunoglobulin kappa variable 3–20 (IGKV3-20), serpin peptidase inhibitor clade A member 1 (SERPINA1), prolactin-induced protein (PIP), cystatin S (CST4), lacritin (LACRT) and lysozyme [443].

Topping the 'extracellular' list of deficient or augmented biomarkers in unbiased MS/MS screens (Table 6) in decreasing order of replications (respectively ≥6, 5, 4, 3, 2) listed alphabetically are (≥6) lacritin, lactoferrin, lipocalin 1, prolactin-inducible protein, proline rich 4 (PRR4) and S100 calcium binding protein A8 (S100A8); next (5) are cystatin S (CST4), lysozyme (LYZ) and secretoglobin family member 2A member 1; followed by (4) albumin (ALB) and S100 calcium binding protein A9 (S100A9); and (3) alpha-2-glycoprotein 1 (AZGP1), apolipoprotein A-II (APOA2), beta 2 microglobulin (B2M), haptoglobin (HP), orosomucoid 1 (ORM1), polymeric immunoglobulin receptor (PIGR), proline rich lacrimal 1 (PROL1), secretoglobin family member 1D member 1, serpin peptidase inhibitor clade A member 1; and finally (2) actin beta (ACTB), complement component 3 (C3), deleted in malignant brain tumors 1 (DMBT1), enolase 1 (alpha; EN01), secretoglobin family member 2A member 2, transferrin (TF). Thirty-four other 'extracellular' proteins are deficient or augmented in single unbiased MS/MS screens - many from Sjögren syndrome.

Among intracellular proteins (Table 7) [407,409,411,424,425,429,430,433,444,446,464,470,472] in decreasing order of replications (respectively 4, 3, 2) are annexin A1 (ANXA1), followed by annexin A11 (ANXA11), glutathione S-transferase pi 1 (GSTP1), peroxiredoxin (PRDX5), S100 calcium binding protein A4 (S100A4), S100 calcium binding protein A6 (S100A6) and S100 calcium binding protein A11 (S100A11). Seven others are deregulated in single unbiased MS/MS screens to date. The surprisingly large representation of intracellular proteins in tears is presumed to be due to normal shedding of ocular surface epithelial cells [268], but why so few are more abundant in diseased tears is unknown. The classification of proteins by gene ontology, whilst useful, is a fairly blunt technique as, for example, secretory phospholipase A2 group IIA is classified as an intracellular protein when it is known to be secreted onto mucosal surfaces [470,473].

Not detected by MS/MS, but apparent by candidate immunoscreening or activity assays (Table 6) [415,417,420,421,423,424,426,427,429,432,433,449,450] were several growth factors and cytokines. VEGF levels were increased in MGD [417]. Elevated in ADDE were soluble epidermal growth factor receptor, colony stimulating factor 3 (CSF3), transforming growth factor activity, and soluble tumor necrosis factor superfamily member 1B (TNFRSF1B) [429]. Levels of twelve chemokines were augmented in ADDE or MGD [424,427,429]. Fifteen interleukins or interleukin-associated molecules were for the most part increased in ADDE but two decreased and one increased in MGD [415,417,423,425,427,429]. There was disagreement over whether interferon gamma (IFNG) is increased or decreased in ADDE (although it is clearly increased in animal dry eye models) [423,427,429,474,475]. MMP-9 was increased in ADDE, post-LASIK dry eye, blepharitis, and conjunctivochalasis [415,421,433]. Five intracellular or plasma membrane tear proteins were detected only by candidate immuno-screening: transforming growth factor alpha (TGFA), phospholipase A2 group IIA (PLA2G2A), aquaporin 5 (AQP5), interleukin 1 alpha (IL1A) and interleukin 33 (IL33) - all increased in ADDE. AQP5 and IL1A were also increased in Sjögren syndrome, and the latter also in MGD [410,417,423,425,427,429,430,432,433,464,476,477]. It is noteworthy that of extracellular biomarkers most are immune-related (34 proteins), or fall under the category of protease/inhibitor/antimicrobial (14 proteins), or carrier/binding/protein steroid associated (11 proteins), or cytoprotective/anti-apoptotic (6 proteins). Intracellular ones are most commonly associated with cell communication/signal transductions (6 proteins), metabolism/energy pathways (4 proteins) or regulation of transcription/nucleic acid metabolism (4 proteins).

To date, half of the candidate biomarkers (Tables 5 and 6) lack immunological validation. Once confirmed, dry eye versus normal protein concentrations are needed, for which there should be good agreement among different laboratories. Initial values have been documented for several members of the interleukin family (IL1A, IL1B, IL-2, IL-4, IL-5, IL-6, IL-10), CXCL8 [415,424,425,427], TNF-α and IFN-γ [427,432], MMP-9 [415] and MMP-9 activity [421,433], LTF and EGF [425,430,433,450], ENO1, S100A4 [407], LYZ, TF, LCN1, ALB, AZGP1 [450], CALCA, NPY, NGF, CCL3, CCL4, and CCL5 [424,426]. Values for IL1B, IL-6, MMP-9 and TNF-α vary greatly. Most have not been subjected to replication by others. If the assumption that biomarkers repeatedly deficient or augmented in

Table 6
Human 'extracellular' tear proteins reported to decrease or increase with ocular surface pathology. Right column: # articles detecting a significant change from normal by: unbiased mass spectrometric screening ('US') and/or a candidate immuno-detection or activity detection approach [CA]; NP, not performed. 'Extracellular', in whole or part by Gene Ontology.

Gene Symbol	Protein	Change from Normal & Pathology	Known Function(s)	# Articles US/[CA]
		Angiogenesis		
VEGF	vascular endothelial growth factor A	↑ADDE [449], ↑MGD [417]	angiogenesis, endothelial cell migration	0/[2]
ZG16B	zymogen granule protein 16B	↓ADDE, ↓MGD↓, ADDE/MGD [414]	angiogenesis, pancreatic adhesion, proliferation	1/[NP]
		Calcium		
AHSG	alpha-2-HS-glycoprotein	↑SSDE [411]	calcification inhibitor	1/[NP]
ANXA2	annexin A2	↑SSDE [411]	osteoclast formation and bone resorption	1/[NP]
ANXA5	annexin A5	↓SSDE [411]	promotes Ca^{2+} channel activity	1/[NP]
CALCA	calcitonin related polypeptide alpha	↓ADDE [426]	Ca^{2+} regulation	0/[1]
CALR	calreticulin	↑SSDE [411]	Ca^{2+} binding protein in ER and nucleus; SS assoc.	1/[NP]
NPY	neuropeptide Y	↓SSDE [426]	promotes Ca^{2+} signaling	0/[1]
		Carbohydrate		
ENO1	enolase 1, (alpha)	↑ADDE [407,414] ↑ADDE/MGD [414]	glycolytic enzyme	2/[1]
		Carrier/Binding Protein/Steroid Associated		
ALB	albumin	↑ADDE [444,450], ↓BL [443], ↑CLDE [408], ↑FK [441], ↑MGD [451]	carrier protein	4/[2]
AZGP1	alpha-2-glycoprotein 1	↓ADDE [447,450], ↓MGD [409], ↑FK [441]	zinc-binding, lipid degradation, cell adhesion	3/[1]
DMBT1	deleted in malignant brain tumors 1	↓ADDE, ↓ADDE/MGD [414], ↑CLDE [408]	scavenger receptor, binds surfactant protein D	2/[NP]
HP	haptoglobin	↑ADDE [447], ↑CDK [445], ↑FK [441]	hemoglobin binding, turnover to diminish iron loss	3/[NP]
LCN1	lipocalin-1	↓↑ADDE [409,423,424,447,450], ↓FK [441], ↓MGD [451], ↓SSDE [411,428]	hydrophobic protein binding, cysteine protease inhibitor	9/[3]
SCGB1D1	secretoglobin family 1D member 1[a]	↓↑ADDE [410,447], ↓CLDE [408], ↓MGD [451]	in complex that binds steroids, including androgen	3/[1]
SCGB1D2	secretoglobin, family 1D, member 2	↓MGD [451]	in complex that binds steroids, including androgen	0/[1]
SCGB2A1	secretoglobin, family 2A, member 1[b]	↓↑ADDE [409,410,414,424,447], ↓ADDE/MGD [414]	possibly binds steroids, including androgen	5/[NP]
SCGB2A2	secretoglobin, family 2A, member 2	↓ADDE [447], ↑CLDE [408]	cell migration?	2/[NP]
TCN1	transcobalamin I	↓ADDE [447]	binds and helps move vitamin B12 into cells	1/[NP]
TF	transferrin	↓ADDE [414,450], ↑ADDE/MGD [414], ↑SSDE [411]	iron binding and transport to proliferating cells	2/[1]
		Cell Adhesion/Motility/Structure		
ACTB	beta actin	↑MGD [409], ↑SSDE [411]	cell structure, motility	2/[NP]
CFL1	cofilin 1	↑SSDE [411]	cytoskeleton organization	1/[NP]
LGALS3	lectin, galactoside-binding, soluble 3	↑ADDE [446]	cell adhesion, T cell regulation, antimicrobial	1/[NP]
LGALS7B	galectin 7	↓MGD [409]	cell - cell and cell matrix communication	1/[NP]
MIF	macrophage migration inhibitory factor	↑SSDE [411]	chemo attractant and cell communication	1/[NP]
		Cell Growth		
EGF	epidermal growth factor	↓↑ADDE [424], ↑MGD [417,431],↑ NK [431], ↓↑SSDE [430,431,451]	mitogen: growth & differentiation	1/[6]
EGFR	soluble epidermal growth factor receptor	↑ADDE [429]	transmembrane receptor kinase	0/[1]
GCSF	granulocyte colony stimulating factor	↑ADDE [449]	colony-stimulating factor	0/[1]
GMCSF	granulocyte monocyte colony stimulating factor	↑ADDE [449]	colony-stimulating factor	0/[1]
LACRT	lacritin	↓ADDE [447], ↓ADDE/MGD [414], ↓BL [443], ↓CDK [445], ↓CLDE [408], ↓FK [441], ↓SSDE [411,428,452]	basal tearing, cell survival, wound healing	8/[1]
NGF	nerve growth factor (beta polypeptide)	↑ADDE [426]	neuronal differentiation and growth	0/[1]
		Cytoprotective/Anti-Apoptotic		
CASP14	caspase 14	↓SSDE [411]	apoptosis induction	1/[NP]
CLU	clusterin	↑SSDE [411]	inhibits apoptosis	1/[NP]
MUC5AC	mucin 5AC	↓ADDE [368], ↓↑SSDE [270,411]	mucus/gel-forming, cytoprotective, hydrophilic	1/[2]
PIP	prolactin-inducible protein	↓ADDE [407,409,424,447],↓BL [443], ↑CLDE [408,453], ↓SSDE [411]	inhibitor of T-cell apoptosis, aspartyl protease	8/[NP]
PROL1	proline rich, lacrimal 1	↓ADDE [414,447], ↓ADDE/MGD [414], ↓MGD [414], ↓TAO [446]	possible ocular protective function	3/[NP]
PRR4	proline rich 4 (lacrimal)	↓ADDE [410,414,442,447], ↓MGD [414] ↓CLDE [408], ↓SSDE [411,428], ↓TAO [446]	possible ocular protective function	8/[NP]
		Immune		
C3	complement component 3	↑ADDE [447], ↑SSDE [411]	complement activation	2/[NP]
C4A	complement component 4A	↑SSDE [411]	cleaved to a trimer for complement activation	1/[NP]
CCL2	chemokine (C-C motif) ligand 2	↑ADDE [429,449]	monocyte, basophil specific chemotaxis	0/[2]

(*continued on next page*)

Table 6 (*continued*)

Gene Symbol	Protein	Change from Normal & Pathology	Known Function(s)	# Articles US/[CA]
CCL3	chemokine (C-C motif) ligand 3	↑ADDE [424], ↑SSDE [424]	inflammatory response	0/[1]
CCL4	chemokine (C-C motif) ligand 4	↑ADDE [424], ↑SSDE [424]	inflammatory, chemokinetic	0/[1]
CCL5	chemokine (C-C motif) ligand 5	↑ADDE [424], ↑SSDE [424]	chemoattractant, histamine release	0/[1]
CCL11	chemokine (C-C motif) 11	↑ADDE [449]	Eosinophil chemotaxis	0/[1]
CCL15	chemokine (C-C motif) ligand 15	↑ADDE [429]	neutrophil, monocyte, and lymphocyte chemotaxis	0/[1]
CSF3	colony stimulating factor 3 (granulocyte)	↑ADDE [429]	production, different, function of granulocytes, macrophages	0/[1]
CX3CL1	chemokine (C-X3-C motif) ligand 1	↑ADDE [429], ↑MGD [417]	neutrophil chemotaxis	0/[2]
CXCL5	chemokine (C-X-C motif) ligand 5	↑ADDE [429]	inflammatory cytokine, neutrophil activation	0/[1]
CXCL8	chemokine (C-X-C motif) ligand 8	↑ADDE [427,449]	inflammatory mediator	0/[2]
CXCL9	chemokine (C-X-C motif) ligand 9	↑SSDE [436]	T cell chemotaxis	0/[1]
CXCL10	chemokine (C-X-C motif) ligand 10	↑SSDE [436], ↑MGD [417]	T cell, monocyte chemotaxis	0/[2]
CXCL11	chemokine (C-X-C motif) ligand 11	↑ADDE [436], ↑SSDE [436]	T cell chemotaxis	0/[1]
ELANE	neutrophil elastase	↑SSDE [411]	phagocytosis and leukocyte migration	1/[NP]
IL1B	interleukin 1 beta	↑ADDE [423,427,429,449],↑CCH [415]	pro inflammatory response	0/[5]
IL1RN	interleukin 1 receptor antagonist	↑ADDE [435,449], ↑MGD [417]	cytokine activity	0/[3]
IL1R1	interleukin 1 receptor, type I (soluble)	↑ADDE [429]	immune mediator	0/[1]
IL2	interleukin 2	↑ADDE [427]	T, B cell proliferation	0/[1]
IL4	interleukin 4	↓ADDE [427,429]	immune response, growth factor	0/[2]
IL5	interleukin 5	↑ADDE [423,427]	B cell, eosinophil growth & differentiation	0/[2]
IL6	interleukin 6	↑ADDE [423,425,427,429,432], ↑CCH [415], ↑MGD [425], ↑SSDE [411,425]	B cell, nerve cell differentiation	1/[7]
IL6R	interleukin 6 receptor alpha	↑ADDE [429]	regulation of immune response, hematopoiesis., acute-phase reaction	0/[1]
IL6ST	interleukin 6 signal transducer	↑ADDE [429]	shared interleukin transducing receptor subunit	0/[1]
IL-9	interleukin 9	↑ADDE [449]	Cell proliferation, anti-apoptosis	0/[1]
IL10	interleukin 10	↑ADDE [427]	inflammation, immunoregulation	0/[1]
IL12	interleukin 12	↑ADDE [449], ↓ADDE [429]	activated T, NK cell mitogen	0/[2]
IL15	interleukin 15	↑ADDE [449]	cell proliferation of natural killer cells	0/[1]
IL16	interleukin 16 (lymphocyte chemoattractant factor)	↑ADDE [429]	$CD4^+$ lymphocyte, monocyte, eosinophil migration	0/[1]
IL17A	interleukin 17A	↓ADDE [429]	proinflammatory response	0/[1]
IFNG	interferon, gamma	↓↑ADDE [423,427,429]	immune-regulatory, antiviral	0/[3]
JCHAIN	joining chain of multimeric IgA and IgM	↑CDK [445]	linkage of IgA or IgM monomers	1/[NP]
IG	Immunoglobulin G	↑RA + SS [454]	Immunoglobulin	0/[1]
ORM1	orosomucoid 1	↑ADDE [407,414], ↑ADDE/MGD [414], ↑SSDE [411]	modulator of acute-phase immune activity	3/[NP]
ORM2	orosomucoid 2	↑SSDE [411]	modulator of acute-phase immune activity	1/[NP]
PEBP1	Phosphatidyl-ethanolamine binding protein 1	↑ADDE [414], ↑ADDE/MGD [414]	modulates NF-kB in Sjögren syndrome	1/[NP]
SERPING1	serpin peptidase inhibitor clade A member 1	↑SSDE [411]	complement activation regulator	1/[NP]
TGFB activator	transforming growth factor beta 1 & 2 activation	↑SSDE [420]	suppress IL-2 T cell growth	0/[1]
TNF	tumor necrosis factor	↑ADDE [423,427,432],↑SSDE [432]	autoimmune, pyrogen, mitogen, differentiation	0/[3]
TNFRSF1B	soluble TNF receptor superfamily member 1B	↑ADDE [429]	part of TNF receptor heterocomplex	0/[1]
		Lipid/Cholesterol		
APOA2	apolipoprotein A-II	↑FK [441], ↑SSDE [411]	in high density lipoprotein particles	2/[NP]
		Other/Unknown		
B2M	beta-2-microglobulin	↑ADDE [410], ↓CLDE [408]	loss associated with hypercatabolic hypoproteinemia	2/[NP]
POTEI	POTE ankyrin domain family member I	↑TAO [446]	?	1/[NP]
SMR3B	submaxillary gland androgen regulator protein 3B	↓ADDE [442]	?	1/[NP]
SOD1	superoxide dismutase 1	↑SSDE [411]	Antioxidant	1/[NP]
		Phosphatase/Kinase/GTPase/Other Enzyme Phosphatase		
F2	coagulation factor II (thrombin)	↑SSDE [428]	fibrinogen to fibrin conversion	1/[NP]
MMP9	matrix metallopeptidase 9	↑ADDE [415],↑BL [415],↑CCH [415], ↑MGD [433], ↑PLDE [421],↑SSDE [433]	matrix collagen IV and V degradation	0/[3]
S100A8	S100 calcium binding protein A8 (calgranulin A)	↑ADDE [407,409,410,414,424,442,446], ↑SSDE [411], ↑MGD [414,448], ↓TAO [446]	cytokine & inhibitor of casein kinase/ Inflammation	9/[NP]
S100A9	S100 calcium binding protein A9 (calgranulin B)	↑ADDE [407,409,414,424], ↑ADDE/MGD [414] ↑SSDE [423], ↑MGD [414,448]	possible inhibitor of casein kinase	6/[NP]
		Protease inhibitor/Antimicrobial		
AZU1	azurocidin 1 (cationic antimicrobial protein 37)	↑SSDE [411]	antibacterial and monocyte chemoattractant	1/[NP]
CST1	cystatin SN	↑ADDE [423], ↓MGD [409]	cysteine protease inhibitor	1/[1]
CST4	cystatin S	↓ADDE [447], ↓BL [443], ↓FK [441], ↓MGD [409], ↓SSDE [428]	cysteine protease inhibitor/antimicrobial	5/[NP]
CTSB	cathepsin B	↓SSDE [428]	lysosomal cysteine protease	1/[NP]
CTSS	cathepsin S	↑SSDE [455]	lysosomal cysteine protease	0/[1]

Table 6 (*continued*)

Gene Symbol	Protein	Change from Normal & Pathology	Known Function(s)	# Articles US/[CA]
DCD	dermcidin	↑SSDE [411]	C-terminal antibacterial, N-terminal prosurvival	1/[NP]
IGHA1	immunoglobulin heavy constant alpha 1	↓SSDE [411]	microbial and foreign antigen defense	1/[NP]
IGKV3-20	immunoglobulin kappa variable 3-20	↓BL [443]	microbial and foreign antigen defense	1/[NP]
IGLC2	immunoglobulin lambda constant 2	↓ADDE [447]	microbial and foreign antigen defense	1/[NP]
LTF	lactoferrin	↓ADDE [409,424,444,450], ↑FK [441], ↓MGD [451], ↓SSDE [411,430,433]	iron metabolism, antibacterial	6/[4]
LYZ	lysozyme	↓ADDE [407,447,450], ↓BL [443], ↓SSDE [411]	hydrolase, antibacterial	5/[NP]
PIGR	polymeric immunoglobulin receptor	↓ADDE [447], ↓CDK [445], ↓SSDE [411]	antibacterial, polymeric Ig transcellular transport	3/[NP]
PLG	plasminogen	↑SSDE [434]	activates urokinase-type plasminogen activator, collagenase	1/[NP]
S100A7	s100 calcium binding protein A7 (psoriasin)	↑SSDE [411]	chemotactic, antibacterial	1/[NP]
SERPINA1	serpin peptidase inhibitor clade A member 1	↑ADDE [423,442], ↓BL [443], ↑FK [441]	serine protease inhibitor, anti-inflammatory	3/[1]

ADDE = aqueous deficient dry eye; BL = blepharitis; CCH = conjunctivochalasis; CDK = climatic droplet keratopathy; CLDE = contact lens-related dry eye; FK = Fusarium keratitis; MGD = meibomian gland dysfunction; NK = neurotrophic keratopathy; PLDE = post-LASIK dry eye; RA + SS = rheumatoid arthritis with Sjögren syndrome; SSDE = Sjögren syndrome-associated dry eye; TAO = thyroid-associated orbit pathology.

[a] Also known as lipophilin A.

[b] Also known as mammaglobin B, mammaglobin 2 & lipophilin C.

unbiased MS/MS screens may indeed be the most promising, then future priority could be given to the extracellular biomarkers that have been commonly found by MS/MS screening and, with the exception of LTF and LYZ, have not been subjected to this kind of analysis.

Poor efficacy of anti-inflammatory agents for dry eye highlights the need for new therapeutic strategies [478]. Some biomarkers - all extracellular ones deficient in dry eye - have shown benefits for ocular surface homeostasis and/or tearing in preclinical and, in some cases, clinical situations. Albumin [479], lactoferrin [480] and lacritin [481] each have prosurvival and wound healing activities [479,482]. When applied topically, albumin was reported to provide symptom relief in most dry eye patients with graft versus host disease [483]. Lactoferrin can promote healing of damaged human corneal epithelial cells in culture [484]. In a mouse corneal alkali injury model, topical lactoferrin protected corneal epithelial cells from hydrogen peroxide oxidative damage [485], and when fed to one year old mice, reportedly reduced inflammation of both lacrimal glands and the conjunctiva, and reduced oxidative stress [486]. A lactoferrin supplement was recently reported to increase tearing in a randomized double blind placebo controlled dry eye study in humans [487], and to restore tearing and TBUT in a randomized controlled study of cataract surgery-induced dry eye [488]. Topical lacritin reduced corneal staining in the Aire$^{-/-}$ mouse model of dry eye [489] and promoted the health of cultured human corneal epithelial cells exposed to interferon gamma and tumor necrosis factor [481] or to benzalkonium chloride [490]. Normal human tears immunodepleted of lacritin lacked cell survival activity. Spiking lacritin, but not the truncation mutant C-25, into ADDE tears restored cell survival activity [481]. Topical lacritin, but not C-25, promoted basal tearing when applied topically to eyes of normal rabbits [491]. Topical lacritin (discovered out of an unbiased screen for factors that promote basal tearing) [438] also restored tearing in Aire$^{-/-}$ dry eye mice [489]. Tear film stability is enhanced by interaction of lysozyme with the tear protein vitelline membrane outer layer protein 1 homolog (VMO1) [492].

A successful biomarker(s) should facilitate the prognosis, diagnosis and monitoring of ocular surface disease in patients. It should also aid in the development of new therapeutics. Several individual biomarkers have been proposed, including lysozyme and lactoferrin [159], and MMP-9 [421]. Grouping biomarkers into an optimized panel may offer superior sensitivity and sensitivity (Table 8) [407,409,410,421,442,450,493], as revealed by Receiver Operating Characteristic (ROC) curve analysis which plots true positive (sensitivity) and false positive (specificity) rates respectively on y- and x-axes. The Area Under the upward rising Curve (AUC) is a measure of test accuracy, with a perfect test having an AUC value of 1, but is surprisingly lacking for several assayed biomarkers (Table 8). However, all these markers require further validation in independent studies and cohorts of participants from different geographic populations, age and etiology of DED. Panels in their present form require mass spectrometry, an approach currently not appropriate for day-to-day patient analysis. Evolution of panels into an integrated immunological assay holds considerable promise.

Biomarkers should help identify and screen out individuals at risk of developing DED prior to refractive eye surgery, that itself can promote extended dryness. To date, biomarker analysis has been carried out after LASIK [421,494] but not before. Prophylactic treatment for at risk individuals might also be possible, for example treatments that promote natural basal tearing, ocular surface homeostasis and corneal sensory innervation. Similarly, diagnosis of the type [409] and severity [407,410,430,432,444,450] of dry eye, or other ocular surface pathology [446], should become much more precise. One can also imagine a precision medicine approach to dry eye, whereby deficiency of one or several functionally-relevant tear proteins is topically corrected. Follow up of patients may also be more accurate, such as monitoring of tear MMP-9 after surgery for conjunctivochalasis [418], or for monitoring the increase of tear lacritin, lysozyme and prolactin-inducible protein, and decrease of enolase 1 (alpha), S100A6 and S100A11 coincident with reduced ocular surface inflammation one year after switching patients from preserved latanoprost to preservative-free tafluprost for glaucoma [495].

Currently, the only commercial options to investigate tear film biomarkers are Inflammadry® (MMP-9) and TearScan™ Lactoferrin Diagnostic Test Kit. Inflammadry detects ~40 ng/ml or more MMP-9, with indicated sensitivity and specificity values respectively of 85 and 94%, and negative and positive predictive values respectively of

Table 7
Human 'intracellular' tear proteins reported to decrease or increase with ocular surface pathology. Right column: # articles detecting a significant change from normal by unbiased mass spectrometric screening ('US') and/or a candidate immuno-detection or activity detection approach ('CA'); NP, not performed. Designated as 'intracellular' or associated with the 'plasma membrane' by Gene Ontology.

Gene Symbol	Protein	Change from Normal & Pathology	Known Function(s)	# Articles with Change from Normal: US/[CA]
		Regulation of transcription/Nucleic acid metabolism		
BAZ2B	bromodomain adjacent to zinc finger domain 2B	↑ADDE [444]	likely transcription regulator activity	1/[NP]
MDN1	midasin AAA ATPase1	↑TAO [446]	ribosome maturation	1/[NP]
RREB1	ras responsive element binding protein 1[a]	↑ADDE [444]	zinc finger transcription factor	1/[NP]
SMARCA4	Transcription activator BRG1	↑ADDE [446], ↓TAO [446]	transcription regulation	1/[NP]
		Cell communication/Signal transduction		
ANXA11	annexin A11	↑ADDE [409], ↑SSDE [411]	calcium-dependent phospholipid binding protein	2/[NP]
PLAA	phospholipase A2-activating protein	↑ADDE [409]	secosteroid 1α,25-dihydroxy vitamin D3 signaling	1/[NP]
S100A6	S100 calcium binding protein A6[b]	↑ADDE [409], ↑SSDE [411]	calcium binding/epithelial integrity, growth	2/[1]
S100A11	S100 calcium binding protein A11[c]	↑ADDE [407], ↑SSDE [411]	calcium ion binding	2/[NP]
S100A12	S100 calcium-binding protein A12[d]	↑SSDE [411]	proinflammatory, calcium binding	1/[NP]
TGFA	transforming growth factor alpha	↑ADDE [429]	targets EGFR to stimulate cell differentiation and proliferation	0/[1]
		Cell growth and/or maintenance		
S100A4	S100 calcium binding protein A4	↑ADDE [407,409]	calcium binding possibly in cell motility, invasion	2/[1]
		Cytoprotective/Anti-Apoptotic		
ALDH3A1	aldehyde hydrogenase 3A1	↑ADDE/MGD [414]	promotes survival of corneal epithelial cells	1/[NP]
HSPB1	heat shock protein family B (small) member 1	↑ADDE [446]	stress resistance, organization of actin	1/[NP]
		Metabolism/Energy pathways		
ANXA1	annexin A1	↑ADDE [409,424,446],↑SSDE [411]	inhibits phospholipase a2, anti-inflammatory	4/[NP]
GSTP1	glutathione S-transferase pi 1	↑ADDE [409], ↑CCH [472]	links reduced glutathione to electrophilic & hydrophobic molecules	2/[NP]
PRDX5	peroxiredoxin 5	↑ADDE [409], ↑CCH [472]	antioxidant, reduces hydrogen peroxide and alkyl hydroperoxide	2/[NP]
PLA2G2A	phospholipase A2 group IIA	↑ADDE [470]	hydrolysis of phosphoglycerides	0/[1]
		Transport		
AQP5	aquaporin 5	↑ADDE [430], ↑SSDE [430]	tear, saliva, pulmonary secretion; water channel protein	0/[1]
		Immune response		
IL1A	interleukin 1 alpha	↑ADDE [425,433], ↑MGD [433], ↑SSDE [433,464]	hematopoiesis, immune response, inflammation	0/[3]
IL33	interleukin 33	↑ADDE [429]	Th2 cell mat; mast/natural killer cell, basophil, eosinophil activator	0/[1]

ADDE = aqueous deficient dry eye; CCH = conjunctivochalasis; MGD = meibomian gland dysfunction; SSDE = Sjögren syndrome-associated dry eye; TAO = thyroid-associated orbitopathy.
[a] Also known as zinc finger motif enhancer-binding protein 1.
[b] Also known as calcyclin.
[c] Also known as calgizzarin.
[d] Also known as calgranulin C.

73% and 97% [493]. Clinical studies suggest specificity and sensitivity of 80% in patients with pseudoexfoliation syndrome [496], positive agreement of 81% and a negative agreement of 98% in dry eye patients [497], and 57% detection of MMP-9 in post-LASIK dry eye patients [421]. However, in a population with no previous diagnosis of DED and who were classified as having mild dry eye in the study, the Inflammadry assay was positive for only 11% of subjects with symptoms of dry eye [498], and in a study of symptomatic (DEQ-5 $\geq$6) subjects, only 39% tested positive with the Inflammadry test [499]. These data suggest that the Inflammadry test is better at detecting moderate to severe dry eye subjects. The lactoferrin assay has indicated sensitivity and specificity values, respectively, of 83 and 98%, and precision of <9% coefficient of variation. Both are semi-quantitative assays.

Proteomics and biomarker cell biology are progressively transforming ocular surface clinical research. From proteomics, new immunoassays will enhance prognosis and diagnosis. From cell biology, new therapeutics should emerge. Proteomic discovery will continue to be challenged by the nine orders of magnitude between the most (mg/mL) and least (pg/mL) abundant proteins [500]. Development of multiplexed systems that allow simultaneous quantification of several biomarkers in a single tear sample (commercially available only thus far for cytokines, interleukins and metalloproteinases - although development work is underway) [446,501–503], and coordinated clinical validation studies are needed. More information is needed on biomarker dynamic range, cut-off definition, specificity, sensitivity, positive predictive value and negative predictive value, and linkage of biomarker detection to treatment.

Lagging behind immunoassay and discovery is an appreciation for the biology of biomarkers. Are there disease modifications, such as glycosylation, methylation, acetylation or covalent cross-linking, and disease-upregulated slice variants? N-glycosylation in climatic droplet keratopathy was the subject of one MS/MS study [445] and Perumal et al. [504] discovered different methylated isoforms of proline-rich protein 4 in tears for which disease or functional implications are unknown. Cross-linking by tissue transglutaminase (TGM2) in tears may play an important disease role, as conjunctival expression of TGM2 is elevated both in Sjögren syndrome and MGD [505], and substrates include S100A7, annexin A1, alpha-2-HS-glycoprotein, enolase 1, actin, beta-2-microglobulin, plasminogen [506], and lacritin [507]. Notably, TGM2 constitutively inactivates

Table 8
Diagnostic power of individual and panels of biomarkers for dry eye discrimination relative to normal controls.

Biomarker (reference)	Dry Eye	Number of subjects (dry-eye/ normal)	AUC	CA (%)	Sensitivity (%)	Specificity (%)	PPV	NPV	Technique	Reference
Individual										
ALB	ADDE	160/45	0.729	–	42.5	90.9	97.1	–	Protein LabChip Bionalyzer	Versura et al., 2013 [450]
ANXA1	ADDE	63/43	–	89.7	92.0	85.6	–	–	2D-PAGE/ MALDI-TOF MS	Soria et al., 2013 [409]
ANXA11	ADDE	63/43	–	76.0	84.0	61.6	–	–	2D-PAGE/ MALDI-TOF MS	Soria et al., 2013 [409]
AZGP1	ADDE	160/45	0.759	–	56.9	87.5	81.8	–	Protein LabChip Bionalyzer	Versura et al., 2013 [450]
CST4	ADDE	63/43	–	67.7	90.2	27.2	–	–	2D-PAGE/ MALDI-TOF MS	Soria et al., 2013 [409]
ENO1	ADDE	56/40	0.850	–	77.0	88.5	–	–	ITRAQ	Zhou et al., 2009 [407]
LCN1	ADDE	160/45	0.843	–	65.5	94.9	97.1	–	Protein LabChip Bionalyzer	Versura et al., 2013 [450]
LTF	ADDE	160/45	0.812	–	44.2	93.2	94.5	–	Protein LabChip Bionalyzer	Versura et al., 2013 [450]
LYZ	ADDE	160/45	0.826	–	57.8	96.6	97.9	–	Protein LabChip Bionalyzer	Versura et al., 2013 [450]
MMP9	ADDE	143/63	–	–	85.0	94.0	97.0	73.0	Immunocapture	Sambursky et al., 2013 [493]
	ADDE	146/91	–	–	81.0	98.0	–	–	Immunocapture	Sambursky et al., 2014 [497]
	PLDE	14/34	–	–	57.1	–	–	–	Immunocapture	Chan et al., 2015 [421]
PIP	ADDE	56/40	0.810	–	71.7	87.1	–	–	ITRAQ	Zhou et al., 2009 [407]
PLAA	ADDE	63/43	–	92.3	94.2	88.0	–	–	2D-PAGE/ MALDI-TOF MS	Soria et al., 2013 [409]
PRDX5	ADDE	63/43	–	75.1	91.6	45.6	–	–	2D-PAGE/ MALDI-TOF MS	Soria et al., 2013 [409]
S100A6	ADDE	63/43	–	90.6	93.8	84.8	–	–	2D-PAGE/ MALDI-TOF MS	Soria et al., 2013 [409]
TF	ADDE	160/45	0.885	–	70.8	96.7	98.1	–	Protein LabChip Bionalyzer	Versura et al., 2013 [450]
Panel										
PRR4, S100A8, SERPINA1, SMR3B plus two unknowns (3700 and 3916 Da)	ADDE	88/71	0.93	–	90.0	90.0	–	–	SELDI-TOF-MS	Grus et al., 2005 [442]
ENO1, PIP, LCN1, S100A9	ADDE	56/40	0.96	–	91.0	90.0	–	–	iTRAQ	Zhou et al., 2009 [407]
ANXA1, ANXA11, CST4, PLAA, S100A6	ADDE	63/43	1.00	94.6	96.0	92.0	–	–	2D-PAGE/MALDI-TOF MS	Soria et al., 2013 [409]
B2M, PRR4 (4043 & 4078 Da) S100A8, SCGB1D1, SCGB2A1	ADDE	40/39	1.00	–	100.0	100.0	–	–	SELDI-TOF-MS	Boehm et al., 2013 [410]
	MGD	40/39	1.00	–	100.0	100.0	–	–		

ALB = albumin; ANXA1 = annexin A1; ANXA11 = annexin A11; AZGP1 = alpha-2-glycoprotein 1; CST4 = cystatin S; ENO1 = Enolase 1; LCN1 = Lipocalin 1; LTF = lactoferrin; LYZ = lysozyme; MMP9 = matrix metalloproteinase 9; PIP = prolactin-induced protein; PLAA = phospholipase A2 activating protein; PRDX5 = peroxiredoxin 5; S100A6 = S100 calcium-binding protein A6; TF = transferrin; PRR4 = proline-rich protein 4; S100A8 = S100 calcium-binding protein A8; SERPINA1 = serpin family A member 1; S100A9 = S100 calcium-binding protein A9; B2M = beta-2 microglobulin; SCGB1D1 = secretoglobin family 1D member 1; SCGB2A1 = secretoglobin family 2A member 1. ADDE = aqueous deficient dry eye; MGD - meibomian gland dysfunction.

lacritin's C-terminal 'business end' necessary for cell targeting [507], and more higher order protein complexes have been noted in dry eye [508], the latter also perhaps from mis-folding as a potential new direction in dry eye research.

4.4. Lipid-protein-mucin interactions

Secreted mucins may have an active role in lipid organization at the surface of the tear film [296,509] and phospholipid transfer protein functions to scavenge lipophilic substances from ocular mucins [510], but data supporting a direct interaction between mucins and lipids are lacking. In the epithelial glycocalyx, the transmembrane mucins MUC1 and MUC16 bind galectin-3 to promote ocular surface barrier function [382]. This interaction is dependent on the surface recognition carbohydrate residues and the capacity of galectin-3 to form surface lattices [511]. The altered mucin glycosylation observed in DED could lead to loss of galectin-3 binding affinity and release of cellular galectin-3 into the tear film. This hypothesis is supported by increased shed galectin-3 levels in dry eye tears concomitant with a galectin-3 proteolytic cleavage product with the potential to impair proper barrier function [383]. Clusterin, a cytoprotective chaperone, inhibits MMP-9 [512] and interacts with galectin-3 to ameliorate ocular surface barrier disruption by a sealing mechanism on the ocular surface [513]. Elevated levels of MMP-9 have been linked to epithelial barrier disruption.

The dominant lipid binding protein in tears is lipocalin-1 [255,514,515]. Lipocalin-1 (previously known as tear prealbumin) can bind a broad range of lipid ligands such as fatty acids, cholesterol and phosphatidyl lipids, but has a low affinity for

lysophospholipids [515,516]. Lipocalin stabilizes the tear film by both scavenging lipids from the hydrophobic ocular surface into the mucoaqueous layer [517], and by interacting with tear polar lipids to reduce surface tension [286]. Whether lipocalin-1 is altered in ADDE is uncertain (Table 6). It is increased in tears of intolerant contact lens wearers [518], but decreased in tears of patients with MGD [468] and Sjögren syndrome [519] (Table 6).

Other proteins known to interact with lipids in the tear film include the tear surfactant proteins B and C [520], apolipoprotein D [521], lysozyme [299], keratins [300], secretoglobins (also known as lipophilins, mammaglobins, lacryglobin and uteroglobins) [522–524] and phospholipid transfer protein [525]. Of these, only levels of lysozyme are altered in dry eye (down in ADDE and Sjögren syndrome dry eye, and in blepharitis – see Table 6).

Some soluble tear proteins interact with the epithelial cell surface to help promote ocular surface health. Lacritin is a multifunctional tear protein that in its monomeric form [507] binds cell surface heparan sulfate proteoglycan syndecan-1 [526] to promote basal tear secretion [438]. Binding of lacritin to syndecan-1 is dependent on heparanase modification of heparan sulfate to expose both a 3-O-sulfate site in cleaved heparan sulfate and the core protein sequence GAGAL [527]. Tear levels of active lacritin monomer are reduced in all forms of dry eye (Table 6) and in blepharitis [443]. Further, the levels of heparan sulfotransferases are downregulated in conjunctival cells from dry eye patients [376], which could influence heparanase cleavage and/or lacritin binding of syndecan-1 [527]. Vitelline membrane outer layer 1 homolog has been shown to interact with lysozyme and stabilize the tear film [492], but the relevance of this interaction to DED has not been yet established.

4.5. The tear metabolome

The aim of metabolomics is to identify, determine, interpret, and quantify the complex time-related concentration, activity, and flux of endogenous metabolites in cells, tissues, and other biosamples [528]. The mucoaqueous layer of the tear film contains electrolytes (such as sodium, potassium, calcium, magnesium, chlorine, phosphate, bicarbonate), protein fragments as peptides, and metabolites (such as amino acids, urea, glucose, lactate). Because the levels of the latter are low (confounded by low volumes of sample), the tear metabolome is poorly characterized [529].

The main analytical techniques implemented in metabolomics analysis are proton nuclear magnetic resonance spectroscopy (^{1}H NMR) [530,531], MS, gas chromatography, and liquid chromatography-MS (LC-MS) [532,533]. Following information-dependent acquisition, directed liquid chromatography/tandem mass spectrometry (LC-MS/MS) coupled to peak mining can be performed, using isotope pattern matching [534]. NMR and GC-MS (gas chromatography mass spectrometry) offer high reproducibility and straightforward identification of metabolites. NMR is nondestructive, requires minimal sample preparation and offers the benefit of obtaining quantitative data simultaneously. However, it is the least sensitive of the above techniques and may be biased toward the detection of high-abundance metabolites.

The analysis includes extraction of metabolites, chromatographic separation and acquisition of data. Post-acquisition data processing typically comprises peak detection and alignment, followed by chemometric analysis to identify the marker ions. Metabolites are then identified through database searches, and their identities are confirmed by comparison of retention time and tandem mass spectra with pure standards [535]. However, no analytical platform can resolve and detect all the metabolites in a sample [534].

The study of tear metabolite profiling is of particular interest, as metabolomics provides an insight into the dynamic biochemical processes occurring in biological systems [536]. The most comprehensive description of human tear metabolome has been published by Chen et al., [534] who identified 60 metabolites representing diverse compound classes, of which 16 had been previously reported. To date, 85 metabolites have been identified in the tears of normal human subjects, 41 previously reported [537–546] and 44 newly reported by Chen et al. [534].

Healthy and dry eye tears display differences. Reduced levels of carnitine in dry eye patients appear to associate with low retention of water in the mucoaqueous layer. This may contribute to hyperevaporation associated with hyperosmolarity [542]. Nakatsukasa et al. [537] have identified 23 amino acids in healthy subjects and found reduced levels of taurine, methionine, and arginine in the severe dry eye patients, in comparison with those in healthy individuals, relative to a change to total amino acid concentration. The concentration of diadenosine polyphosphates increases in tears from dry eye subjects and those with Sjögren syndrome [547,548].

Most recently, differences between the metabolomic profiles of reflex tears in patients with mild-to-moderate and moderate DED and healthy subjects have been analyzed using ^{1}H NMR spectroscopy [530]. Differences between tear metabolite levels were found for cholesterol, N-acetylglucosamine, glutamate, creatine, amino-n-butyrate, choline, acetylcholine, arginine, phosphoethanolamine, glucose, and phenylalanine (Table 9). The healthy subjects had elevated concentration of glycoproteins, lipids, cholesterol, leucine, glycerol, and glutamate in comparison with dry eye patients. In the dry eye samples, an increase in glucose and lactate and a decrease in formic acid and N-acetylglucosamine levels were found. Increased levels of serotonin have been correlated with dry eye signs and symptoms and higher concentrations of this neurotransmitter have been found in symptomatic ADDE tears compared to tears of symptomatic dry eye patients with normal tear production [549].

Finally, the effect of antioxidants and polyunsaturated fatty acid oral treatments on the profile of reflex tear metabolites has been demonstrated [531]. The metabolomics methods have some limitations for the study of human tears and further studies are required to broaden our knowledge of the tear metabolome. However, it is clear that the metabolome reflects the status of local and systemic biological processes, opening new routes of identification of potential biomarkers for disease diagnosis and treatment monitoring.

5. Translational dry eye animal models of tear film

There are several genetic, surgically or dry chamber/drug-induced models of DED in different species [489,550–554]. The most characterized model is the desiccating stress murine model without or with prior injection of scopolamine to block parasympathetic stimulation of tear secreting machinery [555–574]. In this dry eye mouse desiccating stress model, the levels of several tear cytokines and chemokines and some others molecules increase as a result of dry eye induction (Table 10). These changes are similar to those found in human tears (although not always evaluated with the same techniques; see Table 6) [407,409–411,415,424,425,427,429,432,442,444,446,447,450]. Some, such as IL-17, do not always behave similarly [429]. The regulatory effects of cytokines and chemokines in tears have been observed after depletion of antigen presenting cells in mice [566]. It should be noted that the most commonly expressed mRNAs in mouse and human lacrimal gland differ substantially [575].

Zhou et al. [576] have reported on similarities to human dry eye tear protein expression in a rabbit model of Sjögren syndrome-associated dry eye induced autoimmune dacryoadenitis

(Table 10). The expression of S100A6, S100A9, and serum albumin was upregulated in this model, whereas TF, PIP, polymeric immunoglobulin receptor (pIgR) and Ig gamma chain C region were downregulated. In this animal model, the changes in the expression of S100A6, TF, PIP, and pIgR were verified. The protein pIgR may be unique to Sjögren syndrome, while the remaining proteins were also found in the tears of non-Sjögren syndrome dry eye patients [407,409,448].

The Harderian gland, that releases secretions onto the ocular surface and fills the orbit of all animals with the exception of primates, is a potential complicating factor that is largely often overlooked. Butovich et al. [577] have compared the mouse, canine, rabbit, and human meibum lipidomes using HPLC and GLC. This study demonstrated that mouse and human meibomian lipidomes are most closely matched, and the canine lipidome is the second closest. Thus, the rabbit is not the best model of the human tear film for studying the lipidome biochemistry and biophysics [577].

Some progress has also been made in the search for appropriate dry eye models with respect to severity. Three rabbit dry eye models for mild (lacrimal gland and nictitating membrane removal), moderate (conjunctival burn with 50% trichloroacetic acid), and severe manifestations of dry eye (combination of both methods), have been developed [578]. However, there is a lack of studies analyzing tear instability in these models [579].

6. Non-pathophysiological factors impacting the tear film

6.1. Contact lenses

Contact lens wear increases the risk of developing dry eye from between 2.01 and 2.96 times [580–582]. Contact lenses compartmentalize the tear film into two layers; the outer pre-lens tear film layer in front of the lens, and the inner post-lens tear film layer, which lies between the lens and the cornea [583,584]. With lens wear, the tear film undergoes extensive biophysical and biochemical changes, which have the potential to influence tear function and/or contact lens tolerance.

In 2013 TFOS published the outcomes of a workshop on Contact Lens Discomfort, including a subcommittee report of Contact Lens Interactions With the Tear Film [54]. The following were associated with worsening of comfort during lens wear: increases in the rapidity of tear film breakup time on the cornea or over the surface of a contact lens; higher contact lens water content; the grade of tear ferning (grade 0 vs. grades 1 or 2); increased tear evaporation rate during contact lens wear; reduced tear flow rate and tear volume; impaired tear film lipid layer; mucin degradation on contact lenses; increases in the concentrations of lipocalin-1, secretory phospholipase A2 (and activity), and lipid aldehyde products. The following section will concentrate on references published since that report.

In cross-sectional studies there are no statistically significant differences in tear film osmolarity between contact lens wearers and non-lens wearers [131,585]. The concentration of phospholipase A2 levels in tears has been associated with an increased concentration of malondialdehyde, which is also a by-product of phospholipid degradation and shorter TBUT over a contact lens [586].

The limited thickness of the post-lens tear film (1–2 μm) has clinical implications, as the stagnation of tears beneath a contact lens is believed to be one of the major causes of complications seen with contact lens wear, including mucin ball formation and ocular surface staining [587]. Technological limitations have not allowed for the accurate and non-invasive determination of fluid circulation between the pre- and post-lens tear film, a phenomenon commonly referred to as tear exchange or tear turnover. Fluorophotometry studies on tear exchange have demonstrated that tear exchange occurs in 30 min with soft lenses [588,589], which is longer than that with rigid lenses or no lens wear [590]. This large difference probably relates to lens size and material stiffness, and therefore lens movement with the blink. Silicone hydrogel materials were reported to improve tear exchange by 5% compared to hydrogels [589] due to the slightly higher modulus, which improves lens movement. Good tear exchange may minimize the risk of adverse sequelae via timely flushing of debris and metabolic by-products from the ocular surface. Innovations in soft lens designs, in an attempt to increase tear exchange, have not proven clinically effective thus far [587].

A thicker lipid layer during contact lens wear is associated with increased stability of the tear film, increased interblink period and decreased tear evaporation rate [586]. Using interferometry, the lipid layer thickness over soft contact lenses was estimated to be around 15 nm [586]. Reduced pre-lens TBUT values have been associated with increased symptoms of discomfort in hydrogel contact lens wearers [586]. A prospective, randomized, crossover study, showed that a daily disposable silicone hydrogel contact lens manufactured from delefilcon A permitted significantly longer NIBUT compared to lenses made from narafilcon A and filcon II-3, in addition to inducing significantly less corneal staining after 16 h of wear [595]. However, the study found no improvement in comfort with any particular contact lens [595]. Use of a liposomal eye spray has been reported to improve pre-lens TBUT [586]. Recently, a prospective, randomized, double blind study reported a favorable

Table 9
Metabolite differences in the tears of dry eye tears in comparison to control subjects.

Metabolites	Change in dry eye tears	Reference
Cholesterol/lipids	↓	Galbis-Estrada et al., 2014 [530]
N-Acetylglucosamine	↓	Galbis-Estrada et al., 2014 [530]
Glutamate	↓	Galbis-Estrada et al., 2014 [530]
Carnitine	↓	Galbis-Estrada et al., 2014 [542]
Taurine	↓	Nakatsukasa et al., 2011 [537]
Methionine	↓	Nakatsukasa et al., 2011 [537]
Arginine	↓	Nakatsukasa et al., 2011 [537]
Serotonin	↑	Chhadva et al., 2015 [549]
Total creatine	↑	Galbis-Estrada et al., 2014 [530]
Arginine + phosphoetanolamine	↑	Galbis-Estrada et al., 2014 [530]
Phenylalanine	↑	Galbis-Estrada et al., 2014 [530]
Choline/acetylcholine	↑	Galbis-Estrada et al., 2014 [530]
Choline	↑	Galbis-Estrada et al., 2014 [530]
Glucose	↑	Galbis-Estrada et al., 2014 [530]
Amino-n-butyrate	↑	Galbis-Estrada et al., 2014 [530]
Diadenosine polyphosphates (Ap4A and Ap5A)	↑	Carracedo et al., 2010 [547] Peral et al., 2006 [548]

Table 10
Animal tear proteins that appear to decrease or increase in induced dry eye.

Dry Eye	Animal	Model	Tear Change from Normal & Induced DE	Technology for Tear Analysis	Reference
Aqueous deficient dry eye (lacrimal insufficiency)	Rabbit	Induced autoimmune dacryoadenitis (IAD)	↑S100A6, ↑S100A9, ↑ALB, ↓TF, ↓PIP, ↓pIgR, ↓Ig γ chain C region	iTRAQ + nanoLC-nanoESI-MS/MS	Zhou et al., 2013 [576]
Combined lacrimal insufficiency and evaporative dry eye models	Mice	Desiccating stress (DS) model and scopolamine	↑IL-17	Immunobead assay	De Paiva et al., 2009 [555], Dursun et al., 2002 [568]
			↑IL-1β, TNF-α, IL-2, IL-6, CCL5, CXCL10, IFN-γ, IL-17, IL-10	Luminex	Schaumburg et al., 2011 [566]
			↑IL-1α, TNF-α, IL-2, IL-12, IFN-γ, IL-4 and IL-10 (mouse strain dependent)	Immunobead assay	Corrales et al., 2007 [574]
			↑IL-1β, MMP9	ELISA, Zymography	Luo et al., 2004 [591]
			↑ SP-D	Western immunoblot	Heimer et al., 2013 [592]
			↑ MMP1, MMP3, MMP9	Activity assay	Corrales et al., 2006 [573]
Aqueous deficient	Mice	IL-2r alpha (CD25) knockout mice (develop Sjögren syndrome-like disease)	↑ IL-1α and IFN-γ	Luminex	De Paiva et al., 2010 [554]
Preganglionic parasympathetic denervation	Rabbit	Parasympathetic denervation	↑CGRP after cyclosporine treatment	ELISA	Toshida et al., 2009 [593], Toshida et al., 2007 [594]

S100A6 = S100 calcium-binding protein A6; S100A9 = S100 calcium-binding protein A9; ALB = albumin; TF = transferrin; PIP = prolactin-induced protein; pIgR = polymeric immunoglobulin receptor; Ig = immunoglobulin; IL = interleukin; TNF = tumor necrosis factor; CCL = C-C motif chemokine ligand; CXCL = C-X-C motif chemokine ligand; IFN = interferon; MMP-9 = matrix metallopeptidase 9; SP-D = surfactant protein-D; CGRP = calcitonin gene-related peptide.

effect of Omega 3 fatty acid supplements in improving tear film stability, tear film breakup time and wear comfort in contact lens wearers [596].

The hypothesis that inflammation may be involved in contact lens discomfort has not been supported by two studies examining levels of cytokines in tears of contact lens wearers. One study examining tear cytokine concentrations of symptomatic and asymptomatic lens wearers found no difference in the concentration of 11 cytokines in tears, including IL-1β, IL-6 and IL-8 [597]. The other study found no change in the concentration of 14 cytokines in tears over the course of a day wearing contact lenses, even though comfort was significantly reduced [440]. The latter study did find the concentration of VEGF was correlated with ocular comfort, but the change in VEGF concentration was more pronounced when contact lenses were not worn rather than during lens wear.

Although previous studies evaluating transmembrane mucins during contact lens wear reported conflicting results, using fluorescein-labeled wheat germ agglutinin (F-WGA) as a marker, Fukui et al. [598] reported less fluorescence intensity in soft contact lens wearers. Observing a positive correlation between tear film breakup time and F-WGA fluorescence, the authors suggested that a decrease or compositional alteration of ocular surface glycocalyx could be a factor in contact lens-induced dryness. Disturbance of the glycocalyx during contact lens wear may be due to slower epithelial turnover and consequently decreased quality of surface mucin, contact lens-induced friction and resultant inflammation, or restricted tear exchange resulting in restricted delivery of secreted mucins on the corneal surface [598].

What is still unclear is the natural history of contact lens discomfort. Are people who experience contact lens discomfort normal before lens wear and at risk of developing symptoms of dry eye even on contact lens removal entirely as a result of wearing lenses? Or are those people predisposed to dry eye (perhaps having subclinical signs or symptoms) and contact lens wear tips them towards dry eye?

6.2. Hormonal factors

Low androgen levels have been reported to be consistently associated with dry eye [599]. Biophysical and biochemical changes in the tear film in postmenopausal women have been investigated in a few studies. Tear osmolarity in postmenopausal women with dry eye symptoms were shown to be significantly higher than those without symptoms [124], and sex hormone levels correlated with tear osmolarity [600,601]. Tear ferning tests were also reported to have higher grades in postmenopausal women with dryness complaints than asymptomatic postmenopausal women [124]. As for the biochemical changes, although tear film levels of lipocalin and lysozyme do not seem to change in postmenopausal women with dry eye [602], in one study lactoferrin levels were reported to significantly decrease [603]. The effect of hormone replacement therapy is controversial; some studies suggested it improves tear function tests and increases goblet cell density [604,605], whereas, others reported hormone replacement therapy (particularly estrogen alone) to be associated with a higher risk of dry eye [606]. A further, more exhaustive discussion on this topic is provided in the TFOS DEWS II Sex, Gender, and Hormones report [607].

Thyroid eye disease may be associated with tear function abnormalities. Increased dryness symptoms, decreased tear film breakup time, decreased corneal sensitivity, and increased ocular surface staining have been reported both during the active and inactive phases of Graves' ophthalmopathy [608,609]. Increased tear osmolarity [610,611] and increased levels of inflammatory mediators such as IL-1β, IL-6, IL-8 and plasminogen activator inhibitor-1 have also been found in the tear film of patients with active Graves' ophthalmopathy [609,612].

6.3. Environmental factors

The use of visual display units (VDU) is also a factor that is associated with dryness symptoms, even in young subjects. Up to 27.4% of VDU users reportedly have high tear osmolarity levels [613]. Kojima et al. [614] reported that long-term VDU users (using digital devices more than 4 h per day) exhibited a significantly reduced TMH and increased symptom scores compared to short-term VDU users and controls. VDU-related dryness has been attributed to reduction in spontaneous blink rate [615–618], predominance of incomplete blinks [615], the presence of MGD [619], lipid layer instability and decreased TBUT [614,615]. In normal subjects, NIBUT has been shown to decrease significantly after 30 min of playing a computer game [93]. The resultant tear film hyperosmolarity was suggested to be reliable in diagnosing dry eye

in VDU users, and osmolarity levels were shown to correlate with tear function tests and tear film breakup levels [620]. Frequent breaks from VDU use, blinking awareness training and moist cool air devices were reported to provide relief of ocular dryness and improvement of tear stability for these subjects [238,621].

In vitro and *in vivo* studies have shown that increasing the ambient temperature increases the tear evaporation rate, TBUT, lipid layer thickness, and ocular surface temperature [254,622]. High altitude exposure, with cold and dry air, leads to a decrease in TBUT and an increase in tear film osmolarity [148]. Controlled environmental chamber studies provide a way of controlling the environmental temperature and humidity independently or together. One controlled environmental chamber study showed that, after 2 h exposure in the chamber, TBUT decreased, corneal staining and tear MMP-9 levels increased in both symptomatic (mild to moderate dry eye) and asymptomatic control subjects exposed to 5% (low) humidity in a desiccating environment [419]. The authors concluded that acute adverse changes in environmental conditions could lead to significant functional deterioration in subjects with or without dry eye symptoms [419]. In another study, changing the humidity from 40% (normal) to 5% (low) significantly increased tear evaporation rate, decreased lipid layer thickness, increased tear instability, and reduced tear production [251]. Exposing non-adapted contact lens wearers to a controlled environmental chamber for 20 min increased tear osmolarity, evaporation rates, visual symptoms and tear instability significantly for hydrogel wearers compared to silicone hydrogel wearers [234]. Another factor that may impact the tear film, leading to signs and symptoms of dry-eye, is air pollution [623]. Exposure to traffic-derived air pollution reduces the goblet cell numbers in the conjunctiva [624]. Further details can be found in the TFOS DEWS II Iatrogenic Dry Eye report [625].

In conclusion, several factors, including contact lens wear and environmental conditions (such as VDU use, ambient temperature and humidity) significantly affect tear film stability and function. However, it is yet to be established if any of these changes can lead to the development of chronic DED.

7. Conclusions and new frontiers

A two layered tear film model of the tear film's structure is preferred over the traditional three layered model, with a mucoaqueous gel layer lying beneath, but at least partly integrated with, an overlying lipid layer. The mucoaqueous layer makes up the bulk of the thin (2–6 μm) tear film, but most data on thickness is from the precorneal tear film and there is virtually no data on the preconjunctival and other compartment tear films. The lipid layer is very thin, at approximately 42 nm.

Tears are distributed over the ocular surface by the combined actions of the lids, capillary movement and upward drift of the lipid layer. Tear film thinning and breakup occurs mainly as a result of evaporation of water from the tear film, and breakup times are usually twice as rapid as normal, for people with DED. The development of lateral shearing interferometry or double pass methods may improve discrimination of TBUT between normal and dry eye subjects.

It is important that future studies be clear about how, and from which compartment, tears are collected, and the type of tears (reflex, basal, or after sleep). Most studies that have measured tear film osmolarity have used tears from the lower tear film meniscus and have shown increases in tear osmolarity with dry eye. However, it is likely that the osmolarity of the lower meniscus does not accurately reflect the osmolarity over the rest of the ocular surface. Development of techniques to measure tear film osmolarity over the cornea, ideally before and after the tear film ruptures, may provide important insight into diagnosis, improve discrimination of the type of DED present, assist with development of new treatments, and provide more accurate tests for monitoring treatments for DED. Tear evaporation rates increase with dry eye by approximately two-fold. However, the lack of commercially available, reliable evaporimeters to measure this in the clinic limits its use to specialized facilities. The development of evaporimeters that can be used in clinical settings and take into account variations in ambient humidity and temperature would be extremely valuable.

Mucins help to stabilize and spread tears by binding, via their high levels of glycosylation, to water. The lipid layer reduces the surface tension of tears, allowing the thin film to avoid collapse. The lipid layer is probably responsible for reducing evaporation of tears, but how this occurs and the role of proteins and mucins in this process requires further investigation. Also, further investigation is needed to understand how proteins and mucins form the mucoaqueous gel.

The traditional belief that the tear film lipid layer can reduce water evaporation from the mucoaqueous layer has been recently questioned, by experiments *in vitro* that have shown that meibum or artificial lipid mixtures can only reduce evaporation of underlying water by $\leq$ 8%. It may be that intercalating proteins and mucins in the tear film lipid layer are needed to reduce evaporation. However, if this is the case, then results showing the importance of the ability of the tear film lipid layer to reduce the surface tension of tears and that the presence of proteins in this layer disrupts this system are difficult to reconcile. Also, proteins in meibum impair its spreading and worsen its viscoelasticity. Clearly, more studies in these areas are needed.

The tear lipidome has been explored in great detail since the publication of the first TFOS DEWS report in 2007. At least five, probably more, lipid classes are present, with each class having many different types due to the large number of possible fatty acids than can be esterified within each class. The majority of lipids in meibum and the tear film lipidome are wax and cholesterol esters. Debates regarding the presence of phospholipids in meibum have largely been settled and experiments show very low levels of this lipid class in meibum. However, the presence of relatively high levels of phospholipids in the tear film lipidome then begs the questions of where these originate from, and indeed if they are really in the tear film lipid layer or are extracted from lipid-binding proteins in tears such as lipocalin (and thereby sequestered away from the tear film lipid layer). Studies have shown that dry eye may be related to changes in the tear film lipidome, especially to changes in the concentration of OAHFAs, but more work is required to confirm these findings. Multi-laboratory and multi-national testing of common pooled meibum and tear lipid extracts is required to provide baseline lipidome data that can then be used as a gold standard to examine the effects of dry eye and its treatments.

There are various mucins found in tears, with the major soluble mucin being MUC5AC and the transmembrane mucins being MUC1, MUC4 and MUC16. However, mRNA for other mucins has been found in ocular surface epithelial cells, and so may be present in tears, although perhaps in low concentrations. There are changes to the concentration of MUC5AC, MUC1, MUC4 and MUC16 in tears of dry eye subjects, but not all studies agree on the magnitude or direction of the changes. However, decreased MUC5AC expression and alteration in mucin glycosylation in dry eye is a consistent finding among most studies. Further studies using the latest glycomic, proteomic and genomic techniques will be beneficial in helping to determine the role of changes to mucin in DED.

There has been an explosion in the number of proteins known to be present in the tear film proteome, with approximately 1800 proteins being present. The use of non-biased MS methods to evaluate changes to proteins, along with more traditional immuno-

assays, has helped to show that several proteins change from normal levels in dry eye tears. These proteins can be used as biomarkers, which might help to predict, diagnose and even, in some cases, be therapeutic for dry eye. However, MS is not appropriate for converting into point-of-care analysis, whereas immunological techniques may be. To date, many candidate biomarkers found by MS have yet to be validated by immunological techniques. Furthermore, validating the biomarkers in separate populations is often lacking, resulting in a lack of data on sensitivity and specificity. Data that have been generated on specificity and sensitivity of protein biomarkers show that panels of at least four proteins are superior to individual proteins. More information is needed on biomarker dynamic range, cut-off definition, specificity, sensitivity, positive predictive value and negative predictive value, and linkage of biomarker detection to treatment. Also, testing application of biomarkers in animal models to demonstrate whether they can alleviate dry eye signs is lacking for many.

Investigations into the tear film metabolome have been small and sporadic, but much could be learned from more research in this area. The metabolome is a measure of endogenous metabolites in tears. Due to the fact that these metabolites can be many and varied, sophisticated laboratory techniques are needed during the discovery phase, and so development of assays appropriate for point-of-care use will need to be made for any metabolites that can be used as biomarkers. Changes to amino acids or their derivatives in the tear film of dry eye subjects have been found to be possible markers of the disease.

This subcommittee also examined the effect of non-pathophysiological factors impacting the tear film. Epidemiological evidence pointing to the high risk of having dry eye if the person has been a contact lens wearer has focused attention in this area, as had the publication of the TFOS report of Contact Lens Discomfort in 2013 [54]. Recent data does not support an underlying inflammatory response being associated with contact lens discomfort, but there are clearly changes to the tear lipid layer and mucins during contact lens wear. Whether these changes are transient or more permanent has not been investigated. Furthermore, it is unclear whether those people who have increased discomfort or dryness symptoms during contact lens wear were predisposed to becoming dry eye patients even if they did not wear lenses, or whether lens wear accelerated their path toward DED. With our increasing use of electronic means to communicate, the associated dry eye symptoms that can occur and how to manage or treat these is an area worthy of research in the future.

The tear film is clearly required for a healthy ocular surface. There are several changes to the tear film that occur in dry eye. How biochemical changes relate to biophysical changes, and how these relate to clinical manifestations of tear film stability and volume are not currently known, although progress is being made in many of these areas. The development of a holistic model of tear film structure and function, and changes that occur during dry eye will likely be forthcoming in response to current and future research.

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