STUDIES ON LIPID ARTIFICIAL TEARS

Prof. Dr. Juan Torrent-Burgués

Dep. Enginyeria Química. UPC

Abstract

The use of artificial tears is related with dry eye problems or ocular irritations. It exist different types of artificial tears. One type of them is the lipid artificial tears which tray to repair or improve the lipid layer present in the outermostpart of the tear film. Several lipid artificial tears are present in the market and commercialised by several companies. In the composition of some of these lipid tears occurs as a principal item a phospholipid component that is lecithin of soya, which is composed mainly by phospholipids as phosphocholine or also named phosphatidylcholine (PC).

The film formation on the water/air interface (Langmuir film technique) has been applied to study the behaviour of Meibomian lipids. The Langmuir technique has been applied previously by the author to study the behaviour of lipid and phospholipid films. In this work Langmuir films have been performed from lipid artificial tears and the corresponding surface pressure-area isotherms registered. Three commercial lipid artificial tears, and presented in dispensers for spray applications, have been used, INNOXA, OPTICALM and OPTREX.

Introduction

The use of artificial tears is related with dry eye problems or ocular irritations [Behrens 2006, DEWS 2007, DEWS 2011]. It exist different types of artificial tears [Muruhe 1998a,b,Moshirfar 2014] and several studies have been reported on them [Benelli 2011, Doughty 2009, Ridder 2005, Nilforoushan 2005, Grene 1992, McCann 2012, Wang 2010, Urzua 2012, Nepp 2001]. Annex I presents more information on it. One type of them is the lipid artificial tears which tray to repair or improve the lipid layer present in the outermostpart of the tear film, and some studies have been reported in literature [Scaffidi 2007, Benelli 2011, Korb 2005, Peters 2002]. In these studies the artificial tears are used as eye drops.

Several lipid artificial tears are present in the market and commercialised by several companies (brands). In the composition of some of these lipid tears occurs as a principal item a phospholipid component that is lecithin of soya, which is composed mainly by phospholipids as

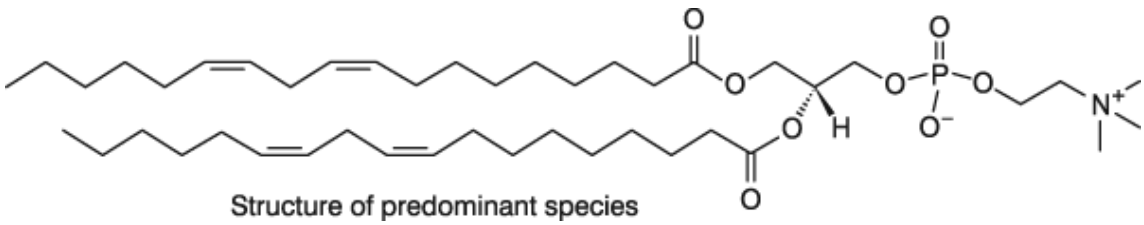
phosphocholine or also named phosphatidylcholine (PC). Lecithin of soya is obtained from soya grains by mechanical extraction or chemically using hexane. It has a great content of PC, specially refined lecithin, but also other lipids are present as phosphatidylserine (PS) and phosphatidylinositol (PI). The fatty acid chains present in these PC are mainly palmitic or stearic, in C1, and oleic or linoleic, in C2. For example, POPC is palmitoyloleoyl-phosphatidylcholine (M=760.1), or DLPC dilinoleoil phosphatidylcholine (M=782.08), but an average soy PC is that reported with M=775.04 [Avanti Polar Lipids]. Refined lecithin is used mostly for pharmaceutical applications and research.

In commercial lipid artificial tears others components are also present and have been detailed for three of them in the next section, which have been used in the present study.

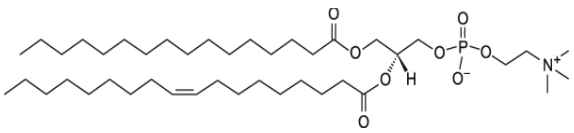
The film formation on the water/air interface (Langmuir film technique) has been applied to study the behaviour of Meibomian lipids [Kaercher 1993a, 1995b, Hagedorn-Jones 2015, Petrov 2007, Mudgil 2011] and specially to study the interaction of them with lachrymal proteins [Miano 2005, Mudgil 2006a, 2008b, Millar 2009].

The Langmuir technique has been applied previously by the author to study the behaviour of lipid and phospholipid films [Torrent 2011a, 2012b]. In this work Langmuir films have been performed from lipid artificial tears and the corresponding surface pressure-area isotherms registered. Three commercial lipid artificial tears, and presented in dispensers for spray applications, have been used, INNOXA, OPTICALM and OPTREX, which composition is shown in table 1.

At the knowledgement of the author, it is the first time that a Langmuir film study is peformed on lipid artificial tears dispensed as sprays.



Dilinoleilphosphatidylcholine (DLPC) present in Soy PC (Avanti Polar Lipids).



palmitoyloleoylphosphatidylcholine (POPC)

Experimental section

a) Materials

Commercial lipid tears are those of INNOXA, OPTICALM and OPTREX. Bellow their composition is indicated (Table 1).

Table 1

INNOXA (OPTIMYST)

Composition in 1 mL:

Lecithin of soya	10 mg
NaCl	8 mg
Ethanol	8 mg
Fenoxiethanol	5 mg
Vitamin A-palmitate	0.25 mg
Vitamin E	0.02 mg
Purified water	

Manufacturer: Optima Pharmazeutische GmbH

Distributor: Omega Pharma España

OPTICALM (LIPOMYST)

Composition in 1 mL:

Lecithin of soya	10 mg
NaCl	2.8 mg
Ethanol	8 mg
Vitamin A-palmitate	0.25 mg
Vitamin E	0.02 mg
Purified water	

Manufacturer: Medena AG

Distributor: Omega Pharma

OPTREX

Composition in 1 mL:

Lecithin of soya	10 mg
NaCl	8 mg
Ethanol	8 mg
Fenoxiethanol	5 mg
Vitamin A-palmitate	0.25 mg
Vitamin E	0.02 mg
Purified water	

Manufacturer: Optima Medical Swiss AG

Distributor: Reckitt Benckiser Healthcare

b) Equipment

The isotherm experiments have been done in a NIMA trough, model 1232D1D2, with two movable barriers and using a Wilhelmy plate to measure surface pressure. The linear velocity of barriers was 2.5 cm/min, which mean 50 cm^2/min in the trough used. The Brewster angle microscopy images were captured with a MicroBAM microscope from NIMA-Nanofilm, with lateral resolution of 8 μm.

Results

Several isotherms for Langmuir films of lipid artificial tears have been done.

a)

A first set of experiments was done without control of the volume used, because the tear solution was directly sprayed onto water using the commercial set. The temperature was 22-23ºC (22.5ºC).

Nevertheless, each spray dispense around 0.1 mL solution (10 mL content/100 sprays). As the PC concentration is high (10 mg/1 mL) the amount of sprayed PC is very high, around 1 mg. This amount has intended to be reduced placing a foil in front of the spray, but in most of the trials the amount extending on water is still high and a non-zero value of the surface pressure occurs at the beginning of the isotherm. A way to reduce the excess of PC is suctioning the layer spread till the value of surface pressure is zero. For that, this set of experiments was mainly to determine the shape of the isotherms.

Two experiments with the BAM were also made.

Experiments:

- Water subphase:

Innoxa prova 1 (with BAM), Innoxa prova 2, Innoxa prova 3, Innoxa prova 4

Innoxa (with BAM), Innoxab1, Innoxab2

Optical1, Optical2

Optrex 1, Optrex 2, Optrex 3, Optrex 4, Optrex 5, Optrex 6

- NaCl 0.9% aqueous subphase:

Optrex 7, Optrex 8, Optrex 9, Optrex 10

Optical 3, Optical 4, Optical 5, Optical 6

Innoxab3, Innoxab4, Innoxab5

b)

Another set of experiments was with control of the volume used. In this case, the desired volume was taken with a microsyringe and extended onto the subphase. The temperature was 23-24ºC (23ºC).

Experiments:

- Water subphase:

ginnoxa1, ginnoxa2

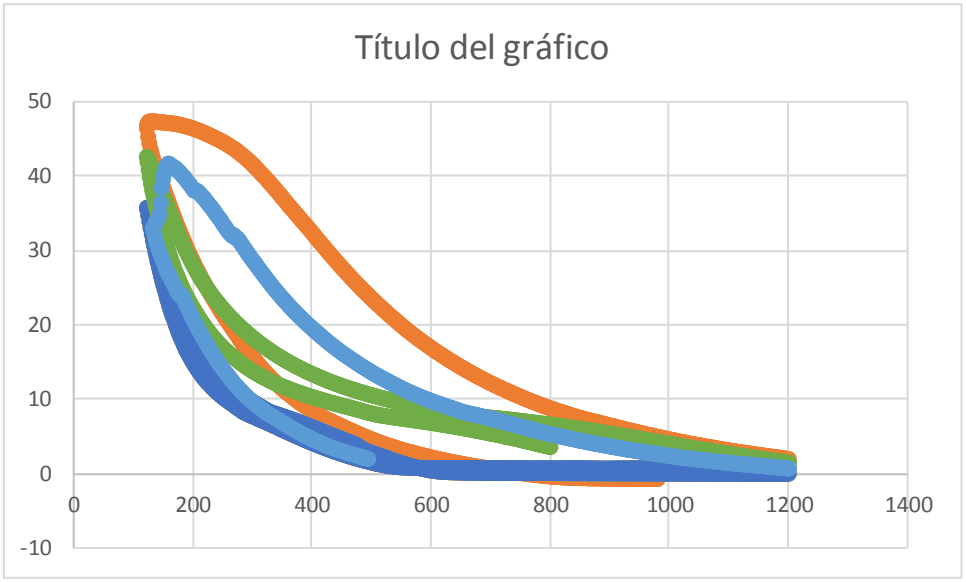
goptical1, goptical2, goptical3

goptrex1

Results and discussion

a.1) Langmuir films, surface pressure-area isotherms for INNOXA artificial tear solution.

INNOXA



innoxaprova1	blaufluix
innoxaprova2	verd
innoxaprova3	blaufort
innoxaprova4	marro

1) Blue light Innoxa 1 5-3-13

v=50 cm^2/min cycle with hysteresis (it has been spreading over). 22-23ºC. BAM but nothing is seen.

Isotherm shows a slow increase, a low slope at the beginning of the rise, below P of 10 mN/m. Then a higher slope is presented until P of 40 mN/m. The hysteresis shown by the isotherm is due to an overflow during the compression, at high compression.

2) Green Innoxa 2 19-3-13

v=50 cm^2/min cycle with small hysteresis. 21-22ºC.

Isotherm shows a slow increase, a low slope at the beginning of the rise, below P of 10 mN/m. Then a higher slope is presented until P of 40 mN/m. There is practically no hysteresis.

3) Blue dark Innoxa 3 19-3-13

v=50 cm^2/min cycle with small hysteresis. 21-22ºC. Little spray.

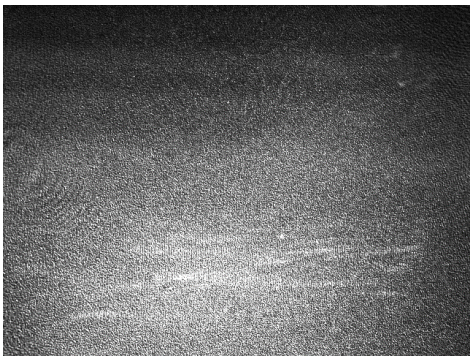
Isotherm shows a slow increase, a low slope at the beginning of the rise, below P of 10 mN/m. Then a higher slope is presented until P of 35 mN/m. There is practically no hysteresis. The lower values of area are due to the lower amount of sprayed substance.

4) Brown Innoxa 4 12-11-13

v=50 cm^2/min with hysteresis, as number 1. Stored at fridge but opened since several days.

Isotherm shows a slow increase, a low slope at the beginning of the rise, below P of 10 mN/m. Then a higher slope is presented until P of 40 mN/m or higher. In respect to Innoxa 1, more substance has been sprayed in this case.

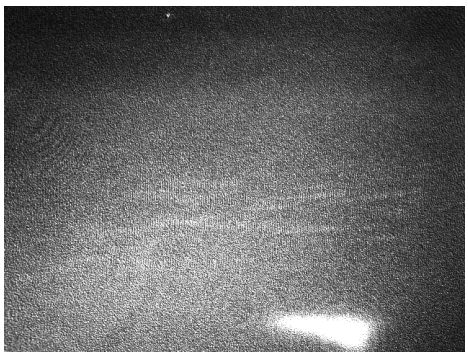
BAM images for Langmuir films of INNOXA (INNOXA 1).



P=0

P=9.6 some islands appear

P=24 big islands are shown

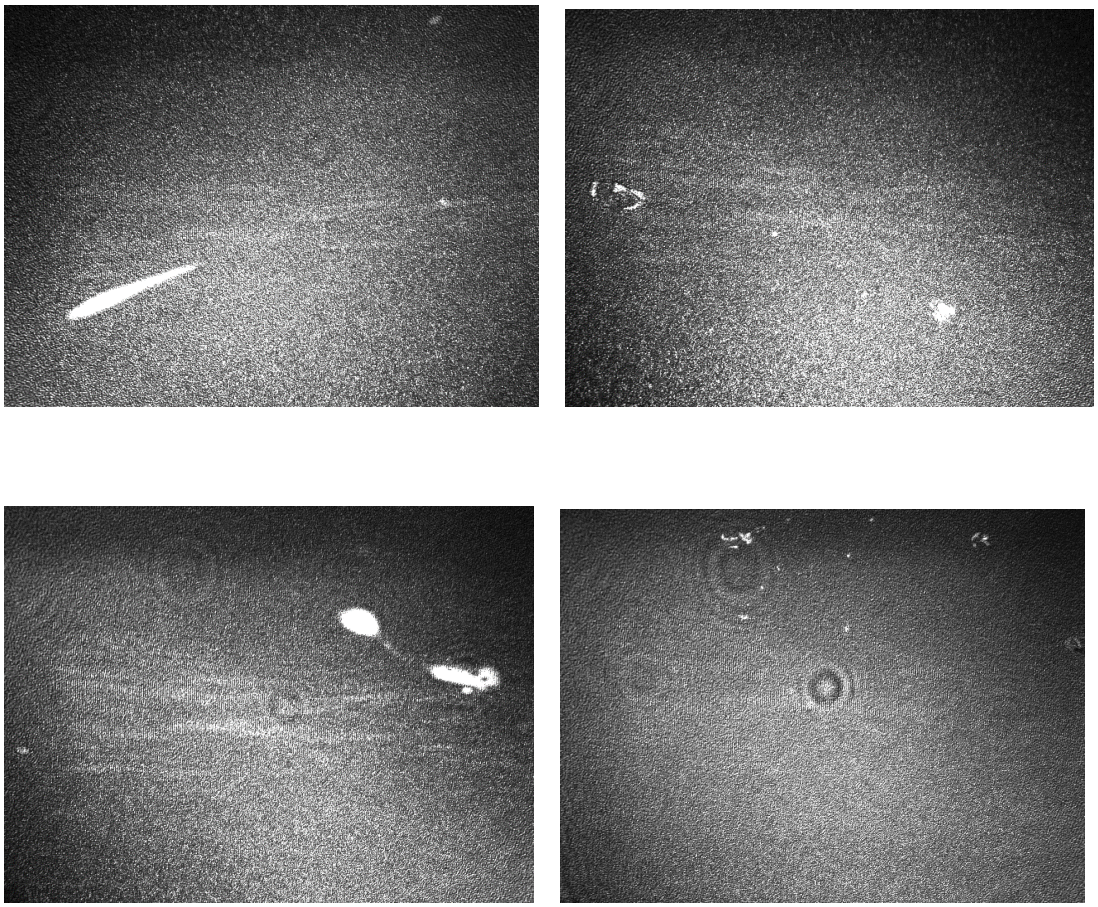


P=40 a big island, bright

Decompression P=3 few islands remain

Perhaps big islands are collapsed lipids. In fact, the formed films are practically not seen, due probably they present a similar index with water.

BAM images of INNOXA sprayed on a water pool of 9 cm diameter. T=22.5ºC.



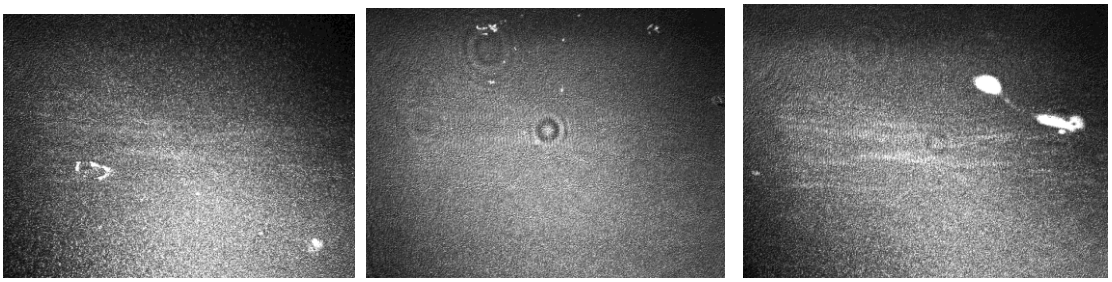
Again

Perhaps big islands are collapsed lipids. In fact, the formed films are practically not seen, due probably they present a similar index with water.

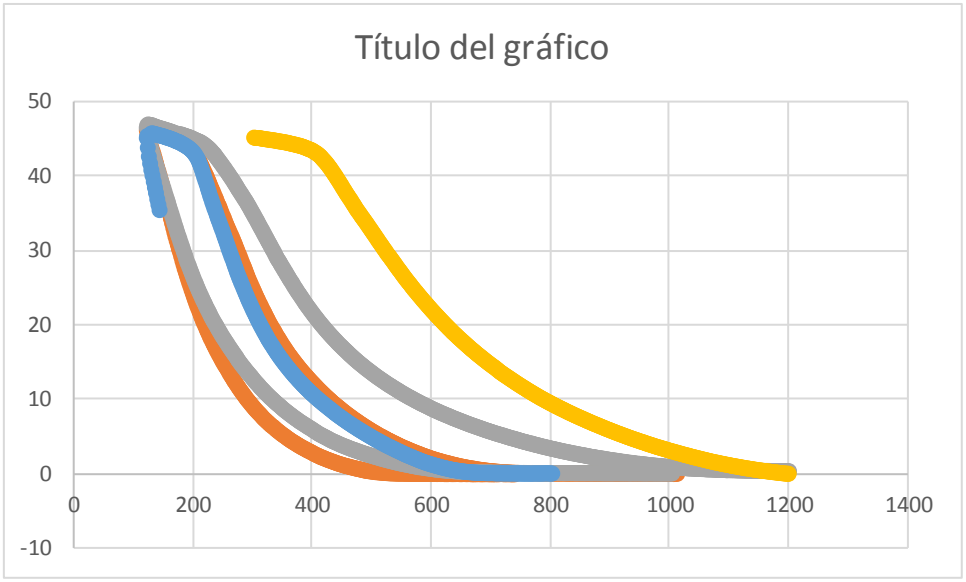
New experiments with INNOXA, OPTICALM, OPTREX without control of volume

Innoxa (with BAM)

BAM images of INNOXA films (5-3-15)



Isotherms for Innoxab1 and Innoxab2 (water subphase, t=22.5ºC, v=50 cm^2/min), innoxab4 and innoxab5 (NaCl 0.9% subphase, t=23ºC, v=50 cm^2/min). Innoxab1 and innoxab2 show hysteresis, and a collapse pressure around 45 mN/m. The isotherm shape is similar to those of innoxa1 and innoxa4 (pg 7). The presence of NaCl 0.9% in the subphase does not change the isotherm shape and collapse pressure.



innoxab1	gris	grey	
innoxab2	marro	brown	
innoxab4	groc	yellow	
innoxab5	blau	Blue	Very similar to 2

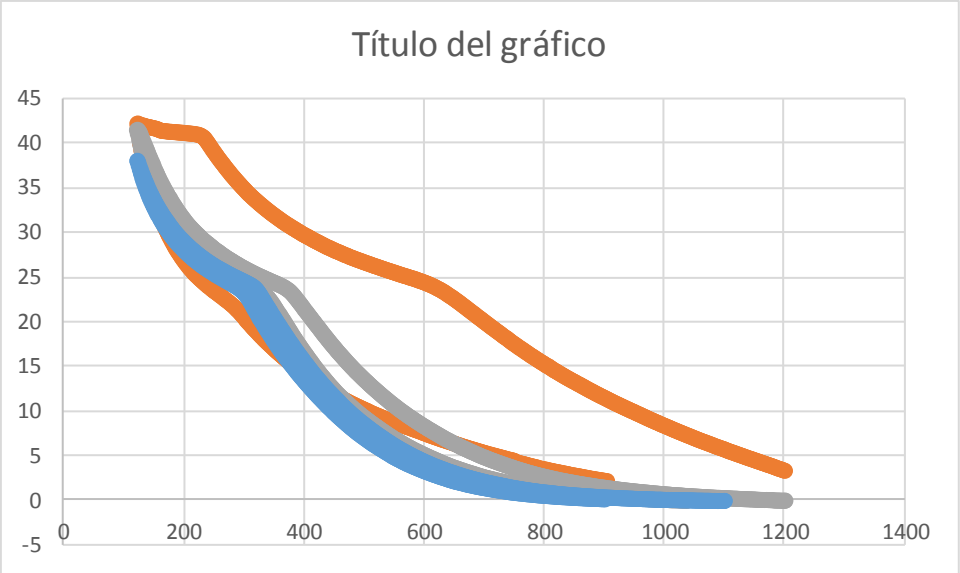
All of them present
similar shape

Opticalm

Optical1 and Optical2 (water subphase, t=22.5ºC, v=50 cm^2/min), Optical 3, Optical 4, Optical 5 and Optical 6 (NaCl 0.9% subphase, t=22.5-23ºC, v=50 cm^2/min). Isotherm optical1 shows a not null value of pressure at the beginning, a slow increase with and inflexion point around 25 mN/m, and a collapse pressure around 42 mN/m. Also presents an important hysteresis. Isotherm optical2 also shows inflexion at 25 mN/m, collapse at 42 mN/m, but little hysteresis since no plateau is attained by the isotherm. No hysteresis or not significant hysteresis is observed when reversing below the collapse pressure.

The influence of the saline suphase is small and does not affect the isotherm shape.

When spraying with optical, the surface pressure attains significant values and must be reduced eliminating material by suction. It seems that the PC concentration is higher in optical tears.



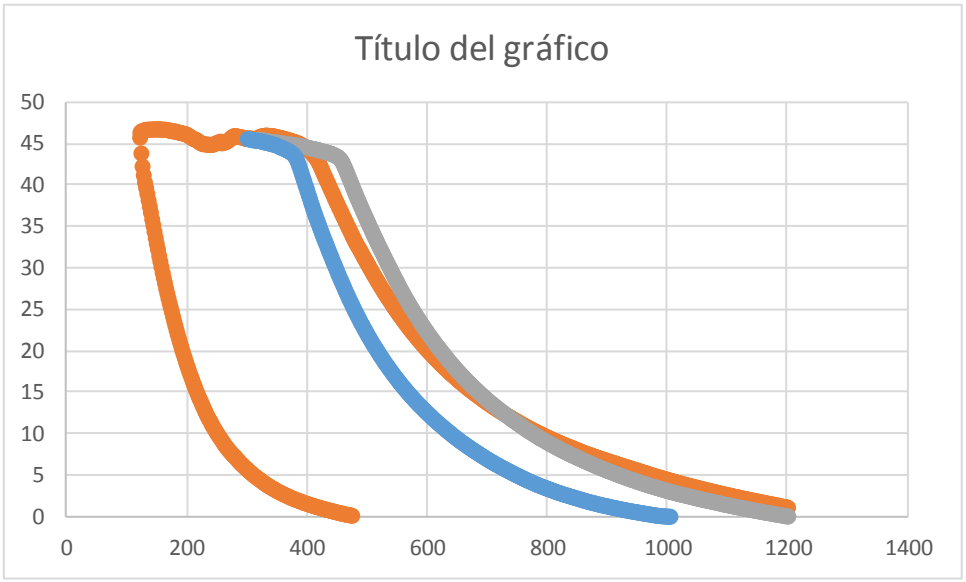
opticalm1	marro
opticalm2	gris
opticalm6	blau

Optrex

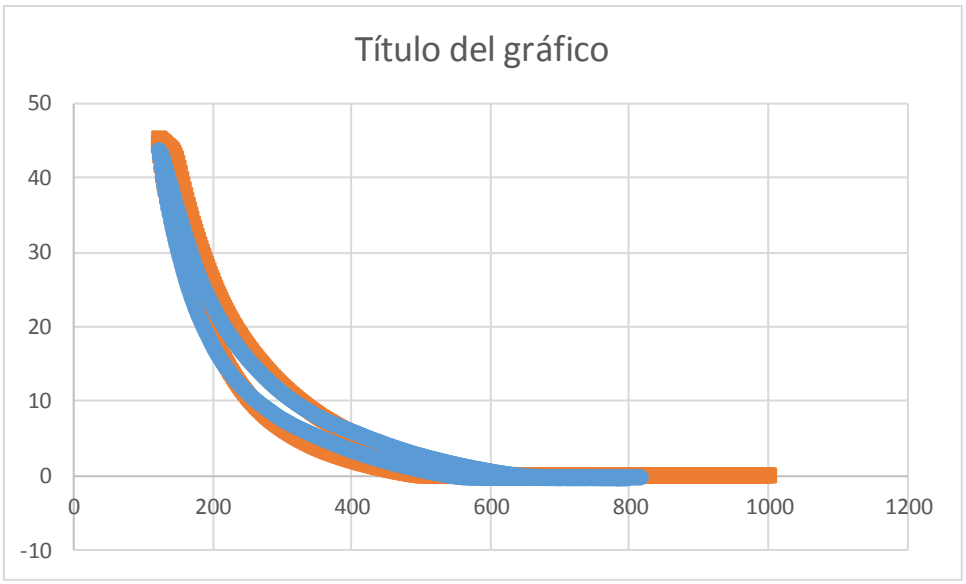
Optrex 1, Optrex 2, Optrex 3, Optrex 4, Optrex 5 and Optrex 6 (water subphase, t=22.5ºC, v=50 cm^2/min), Optrex 7, Optrex 8, Optrex 9 and Optrex 10 (NaCl 0.9% aqueous subphase, t=22-22.3ºC, v=50 cm^2/min).

When spraying, the initial pressure is more similar to Innoxa (near zero) than to Opticalm. The collapse pressure is around 45 mN/m and no inflexion is presented. Thus optrex seems more similar to innoxa than to optical. Hysteresis is important when isotherm gets the plateau, but little hysteresis appears when the isotherm return is bellow the collapse pressure.

In presence of saline subphase, the isotherm is similar than in absence of NaCl when comparing isotherms performed with lower PC amount. (No tenim isoterma en NaCl amb molta quantitat de PC)



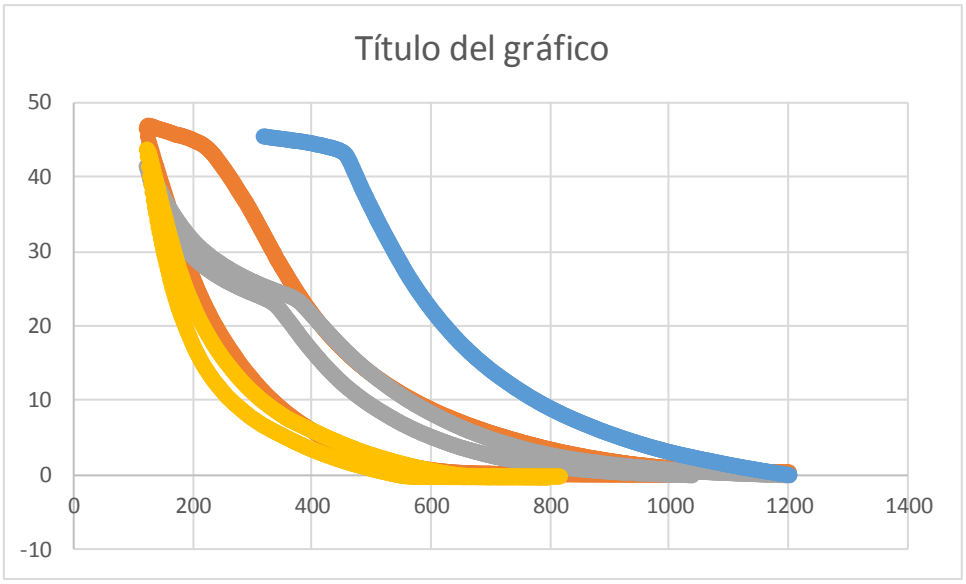
optrex4	marro
optrex5	gris
optrex6	blau



optrex10	marro	NaCl
optrex2	blau	water

Comparison

Till the inflexion point of the isotherm shown by opticalm, both opticalm and innoxa present the same shape, practically the same “arising”. The isotherm of innoxa2 shows a long inflexion at pressures of 5-10 mN/m, but this inflexion is not always shown by innoxa isotherms meanwhile it is always present in optical isotherms.



innoxab1	marro
opticalm2	gris
optrex1	taronja
optrex5	blau

b) Experiments with control of volume

The analyzed lipid tears are: innoxa, opticalm and optrex.

b.1) Innoxa

Innoxa stored at fridge but opened since several months.

Isotherms: ginnoxa1, ginnoxa2

Isotherm ginnoxa1: C=10 mg/mL, V= 20 microL, Considering POPC (M=760.1)

5 sprays were performed inside a recipient (day 26-5-15), isotherm 27-5-15

With 20 microL barriers have had to be opened since 1100 cm^2.

V=50 cm^2/min, P initial=0, t=23ºC

Isotherm gets to 45 mN/m, the area per molecule at collapse has no sense (10 A^2/molecule)

Cs-1 max of 47 (LE)

Isotherm ginnoxa2: C=10 mg/mL, V= 15 microL, Considering POPC (M=760.1)

5 sprays were performed inside a recipient (day 27-5-15), isotherm 27-5-15

With 15 microL barriers have been opened at 800 cm^2.

v=50 cm^2/min, P initial=0, t=23ºC

Isotherm with cycle, it arrives at 45 mN/m, the area per molecule at collapse have no sense, isotherm similar to the previous but gets up, arises, more quickly and the area collapse is a little bigger (15 A^2/molecule).

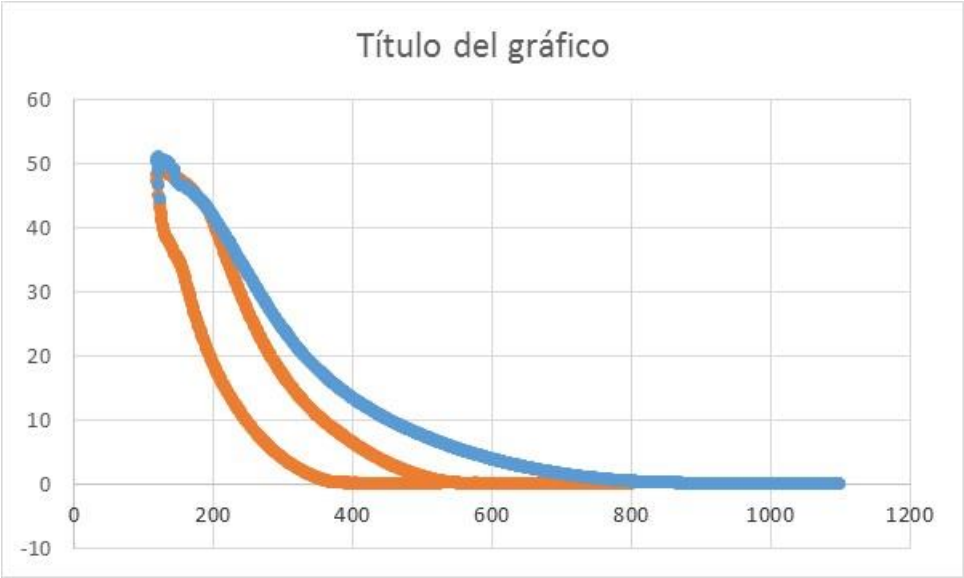
Cycle with hysteresis

Cs-1 max de 65 mN/m (LE or liquid)

Comparison: el fet que en agafar menys volum l'area per molecula sigui un xic mes gran pot deures a que no es forma tanta bicapa, els liposomes s'han estes millor. Pero com l'area de col·lapse continua sent petita hi ha formació de bicapa (o liposomes no estesos totalment). Tambe pot haver-hi un efecte de que la concentració real i la indicada no coincideixin. Potser la real es inferior a la indicada, i per això tenim la isoterma desplaçada a àrees menors. Tambe pot ser que la M sigui duiferent ja que hem suposat POPC però realment hi ha una barreja de fosfolípids PC i potser altres lípids. Ara be, el fet que les isotermes pugin diferent pot indicar també i reafirmar l'anterior argument. Si s'estenen mes la Cs-1 augmenta ja que la monocapa esta mes ben organitzada que la bicapa.

Perhaps the isotherms present a slight inflexion at low pressures, below 10 mN/m (see better Cs-1).

blau	ginnoxa1	20 micro
marro	ginnoxa2	15 micro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Opticalm

Opticalm stored at fridge but opened since several months.

Isotherms: goptical1, goptical2, goptical3

Isotherm goptical1: C=10 mg/mL, V= 15 microL, Considerem POPC (M=760.1)

5 sprays were performed inside a recipient (day 28-5-15), isotherm 28-5-15

With 15 microL barriers have had to be opened since 1200 cm^2 and even so pressure is positive. It seems that the concentration of phospholípid is very high.

v=50 cm^2/min, P initial=16, t=23ºC

Isotherm arrives to 44 mN/m, the area per molecule at collapse has no sense (25 A^2/molecule) but gets close to that of POPC.

Cs-1 max de 25, value very low (LE)

Isotherm goptical2: C=10 mg/mL, V= 8 microL, Considering POPC (M=760.1)

isotherm 28-5-15

With 8 microL pressure is still positive; barriers have been opened to the maximum at 1200 cm^2.

v=50 cm^2/min, P initial=12, t=23ºC

Isotherm arises a bit quicker, but a jump is present and then arrives at >45 mN/m (a value of 52 that is not good), the area per molecule of collapse seems to have sense, isotherm similar to the previous one but arises more quickly and the area collapse is a little bigger (55 A^2/molecule).

Cs-1 max of 35 mN/m (LE)

Isotherm goptical3: C=3.33 mg/mL, V= 8 microL, Considering POPC (M=760.1)

The concentration has been diluted to 1/3 with water.

isotherm 28-5-15

With 8 microL pressure is still positive, but less; barriers have been opened to the maximum at 1200 cm^2.

v=50 cm^2/min, P initial=7, t=23ºC

Isotherm arrives at 45 mN/m, the area per molecule of collapse seems no have sense, value perhaps to much high, isotherm different to the previous but arises much slowly and presents an inflexion at 28 mN/m (area 320 A^2/molecule) and area collapse bigger (110 A^2/molecule).

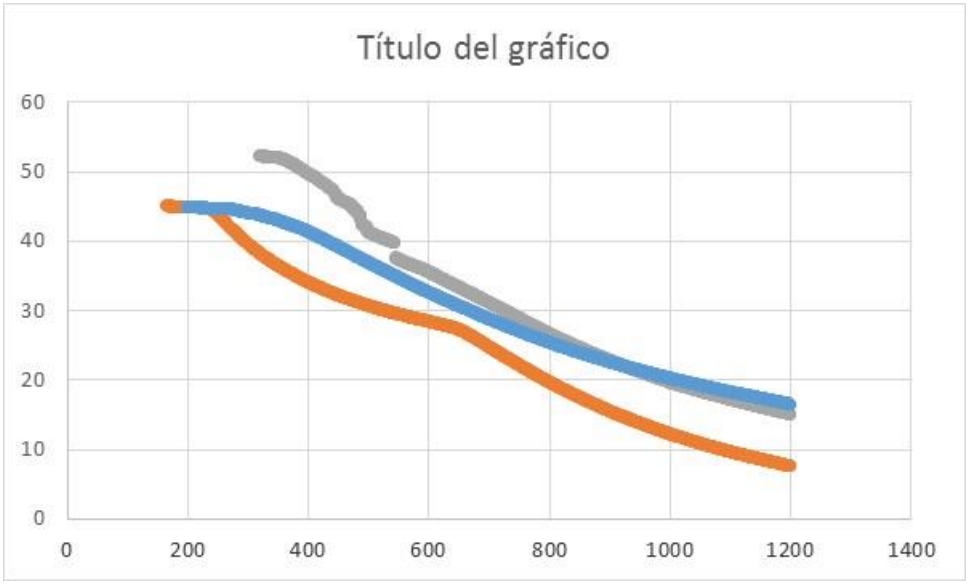
Cs-1 max of 40 at first tram (LE) and 24 mN/m at second tram (LE) (the later similar to that of case 1). Curiously, the first tram presents Cs-1 higher, perhaps because is more a monolayer and the inflexion corresponds to the formation of a bilayer (but the area of collapse is very big, and then it does seem feasible). Perhaps when diluting, the effective concentration changes since liposomes can disaggregate, and then the c becomes higher than 3.33 meanwhile for optical1 it gets lower than 10.

Discussion: The inflexión appears because a transition from monolayer to bilayer. (Es molt follon ja que la concentració real no esta controlada). El cas 2 esta entremig del cas 1 i del cas 3. Per tant cas 1 molta bicapa, cas 3 mes monocapa i pas a bicapa. Cas 2 poca monocapa i majoritàriament bicapa !!! Pero si es bicapa perquè surt area propera al POPC, monocapa.!!! (no acaba de quadrar)

I think this product is complex and has a high proportion of surfactants, including proteins, which provoke a non null value of surface tension at the beginning. This makes the interpretation very difficult.

Comparison:

blau	goptical1	c 10	V 15
gris	goptical2	c 10	V 8
marro	goptical3	c 3,33	V 8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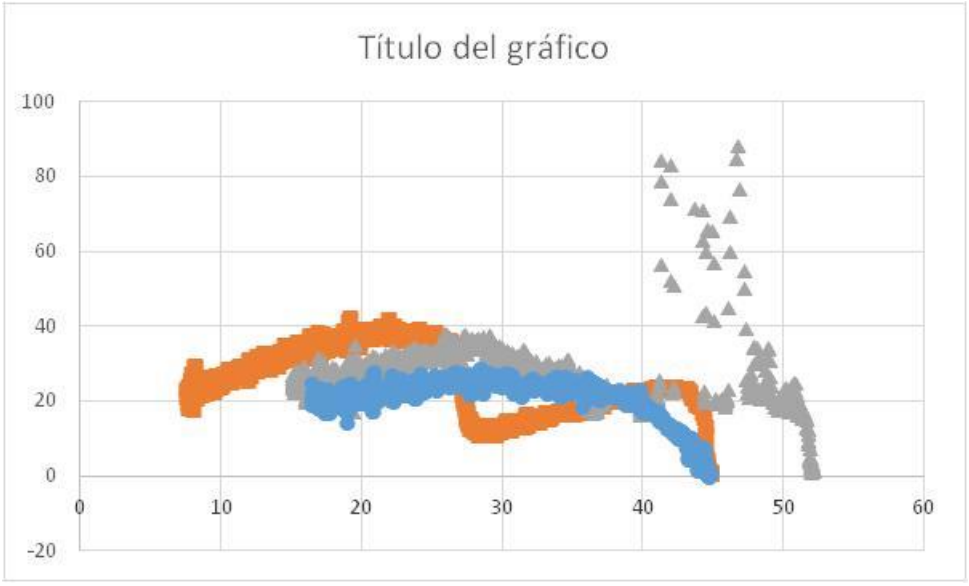
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50
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Optrex

Isotherm goptrex1: C=10 mg/mL, V= 15 microL, Considering POPC (M=760.1)

5 sprays were performed inside a recipient (day 29-5-15), isotherm 29-5-15

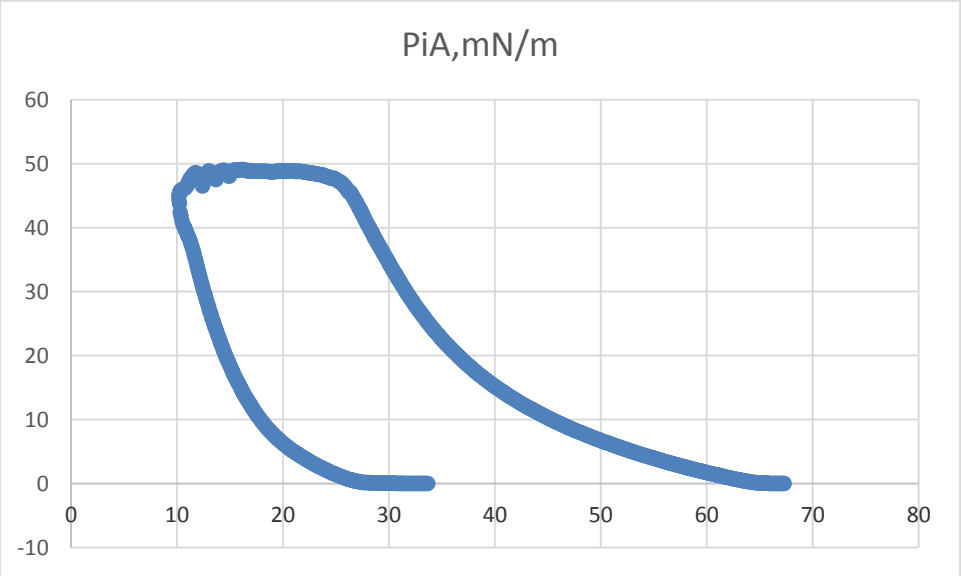
With 15 microL barriers have been opened at 800 cm^2.

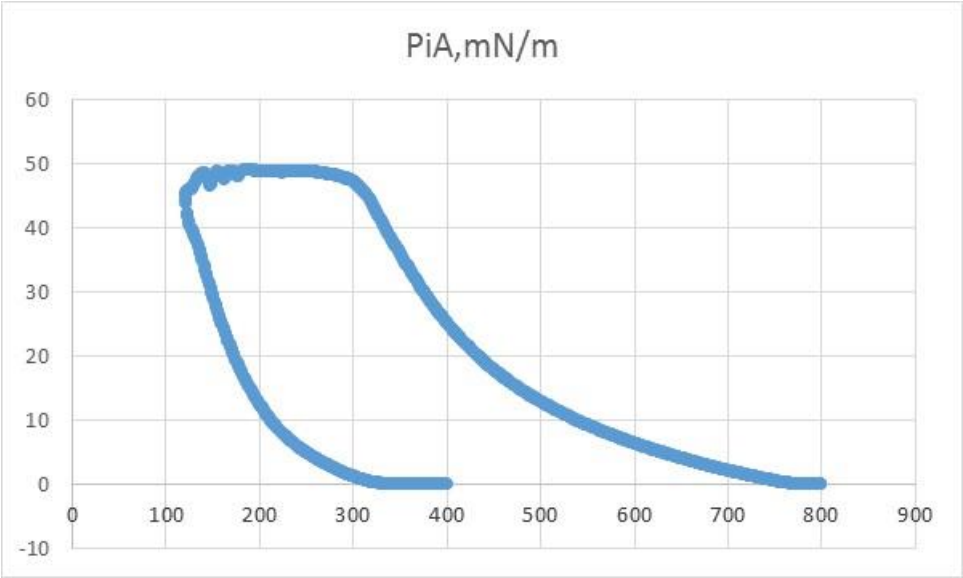
v=50 cm^2/min, P initial=0, t=23ºC

Isotherm with cycle, arrives at 48 mN/m, and pressure arises early, the area per molecule of collapse has little sense, isotherm similar to that of innoxa 2 but arises early and nearly parallel, and area collapse is a little bigger (27 A^2/molecule).

Isotherm with a slight inflexion at P below 10. Cycle with hysteresis.

Cs-1 max of 25 mN/m (LE) and of 85 (second tram) (LE or liquid).




PiA,mN/m
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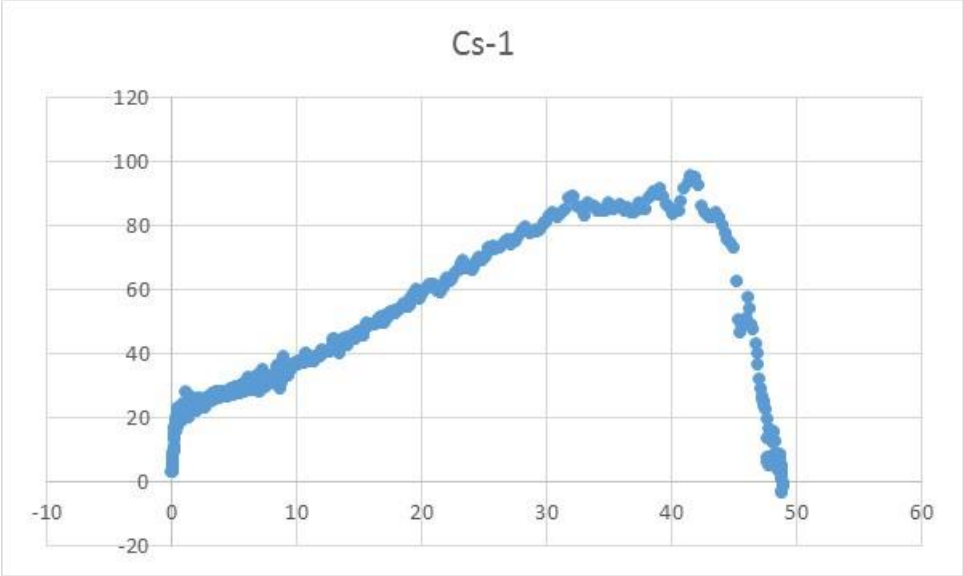
Cs-1
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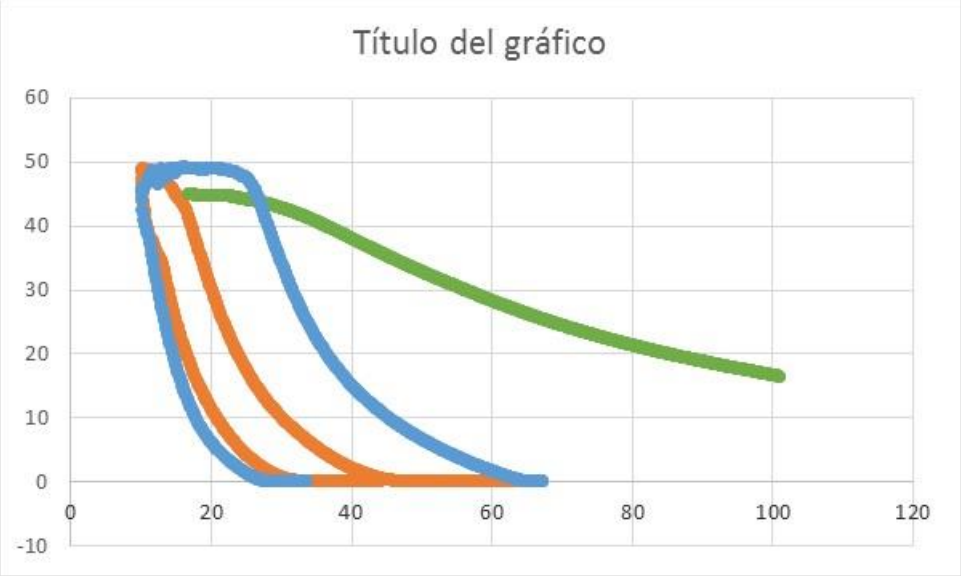
Discussion

(FINAL COMPARISON BETWEEN THREE SUBSTANCES)

Optrex is between Innoxa and Opticalm in respect to concentration, even closer to innoxa. In respect to compressibility, Optrex is closer to Innoxa than to Opticalm. Curves of C_s^{-1} indicated that fact more effectively, they are better, because in this case the area effect is practically negligible according to the equation.



innoxa2	marro	V 15 microL
opticalm1	gris/verd	c 10 mg/mL
optrex1	blau	POPC

In order to discuse more deeply the isotherms, the area in the X-axe has been transformed to area per molecule (Figure) assuming the concentration indicated in the product and that the phospholipid present in the lipid tears is POPC. This is an arbitrary selection but is in according with the composition reported previously for lecithins of soya, and the selection of another PC does not change significantly the discussion since the molecular weight is not much different.

Table 2

Tear	A left-off	A collapse	Π collapse	A inflexion	Π inflexion	C_s^{-1}max
Innoxa	45	15	50			65
Opticalm	>100	30	45			25
Optrex	65	25	50			90

Table 3 shows the values of several isotherm parameters found in literature for several PC, in order to compare these values with those of the isotherms reported here for the lipid tears.

Table 3

PC	A left-off	A collapse	Π collapse	A inflexion	Π inflexion	C_s^{-1}max	Reference
POPC	150	70	46				Domenech 2005
DPPC	90-95	45	55	75-80	7-8		Torrent 2011, 2012
DSPC	58	44	55			334	Dynarowicz 2004
SOPC	112	58	50			122	"
DOPC	108-110	55	49			121	"
DPPC	>100	45-50	58-72	90	5-6		Yan 2005
DOPC	>100	60	48				"
DOPC	130-135	65	44				Yuan 2002

The collapse area observed in all the tear isotherms is less than that of POPC [Torrent,] and other PC (see table 3) which could indicate that part of the lipid is still in a bilayer state, that is the liposomes present in the product are not completely extended as a monolayer when deposited on the water surface. Thus, the values of Πcollapse and C_s^{-1} are more deliable to discuss.

The values of C_s^{-1} and the isotherm shape suggest that the PC in Opticalm present more insaturations and it is in a more fluid state (possibly indicate the presence of linoleic acid in

C2). These values are lower than those reported in literature for some PC with and without insaturations (Table 3). As all values are lower than that of DOPC, it could also indicate that more insaturations are present in soy PC used for the tear products, and the presence of linoleic acid as is expected from natural soy PC.

It is seen that the collapse pressure of Opticalm (P=45) is closer to that of POPC and DOPC (table 3), according with the presence of more insaturations in Opticalm PC than in Innoxa or Optrex PC (collapse pressure of 50 mN/m), even the presence of larger chains in the later is also coherent with the observation. The collapse pressure of the laters is nevertheless lower than those of fully saturated PC, as DPPC or DSPC (table 3), which indicates that a certain grade of insaturations is present in the PC of Innoxa and Optrex.

Conclusions

The lecithins present in the tears studied contains lateral chains with insaturations, more pronounced for Opticalm than for Innoxa or Optrex, that is, the lecithins present in Opticalm contains more linoleic acid in the C2 position than those lecithins present in Innoxa or Optrex composition.

In the future it is planned to perform a clinical study using the lipid artificial tears presented here and to tray to correlate their clinical behaviour with the film properties reported in this study.

Lipid-containing artificial tears: ZERO, Optrex and Opticalm. Physicochemical study.

Temperatures of 23 and 32ºC. Water subphase.

Abstract

Lipid artificial tears are a sort of tear supplement formed by lipids and some other components that have the goal of restoring the physiological lipid layer of the tear film. The lipid layer function is to diminish the evaporation of the tear and to lubricate the eye during blinking. For this reason, lipid tears are especially indicated for dry-eye patients whose rate of tear film evaporation is excessive. One of the lipid components used in this type of artificial tears is soy lecithin. In the present study, the physical and chemical properties of three commercial artificial tears based on soy lecithin have been analyzed. These include Zero, Optrex and Opticalm in spray format. Surface pressure-area isotherms have been obtained and the effectiveness of these techniques has been tested in order to study the behaviour of the lipid components of the tears and work out conclusions on some of their properties.

Opticalm was the tear that showed the greatest fluidity of the three tears under study.

Materials and methods

Physicochemical part

2.1. Materials

The lipid-containing artificial tears under study are Zero (Manufacturer: Optima Medical Swiss AG, Distributor: DISOP), Optrex (Manufacturer: Optima Medical Swiss AG, Distributor: Reckitt Benckiser Healthcare) and Opticalm (Manufacturer: Medena AG, Distributor: Omega Pharma). Their compositions are detailed below (Table 1). As it can be seen, Zero and Optrex have exactly the same components and the only difference between them is that Zero does not specify their concentration. Opticalm, in

opposition to the other two brands, does not contain phenoxyethanol and has a lower concentration of sodium chloride than Optrex.

Table 1

Composition of the lipid-containing artificial tears of the study in 1 ml.

Composition in 1ml	Zero	Optrex	Opticalm
Soy lecithin	*	10 mg	10 mg
Sodium chloride	*	8 mg	2.8 mg
Ethanol	*	8 mg	8 mg
Phenoxyethanol	*	5 mg	-
Vitamin A	*	0.25 mg	0.25 mg
Vitamin E	*	0.02 mg	0.02 mg

*Contains the component but concentration is not specified

Surface pressure-area isotherms have also been taken and studied of the POPC (palmitoyloleoylphosphatidylcholine), DPPC (dipalmitoylphosphatidylcholine) and DDHA-PC (didocosahexenoylphosphatidylcholine), being all three type PC phospholipids.

2.2 Methods

To measure surface pressure-area isotherms a NIMA teflon trough, model 1232D1D2 (1200 cm^2) with two movable barriers was used and a Wilhelmy plate was been used to measure surface pressure. A linear velocity with barriers of 50 cm^2/min was used and the volume used in each isotherm was 30 µl. This procedure was carried out at 23ºC (room temperature of the laboratory). The trough and the teflon barriers were cleaned with chloroform and distilled water after each measure.

Since the instilled volume with this kind of spray diffuser cannot be controlled with precision, a micro-syringe was used in the experiments. The tear was instilled drop by drop distributed onto the trough and it was left to settle during 15 minutes (the necessary time considered to allow for the extension of the lipids). After this period,

compression was initiated by closing the barriers at the mentioned speed until the collapse point was reached.

Physicochemical part

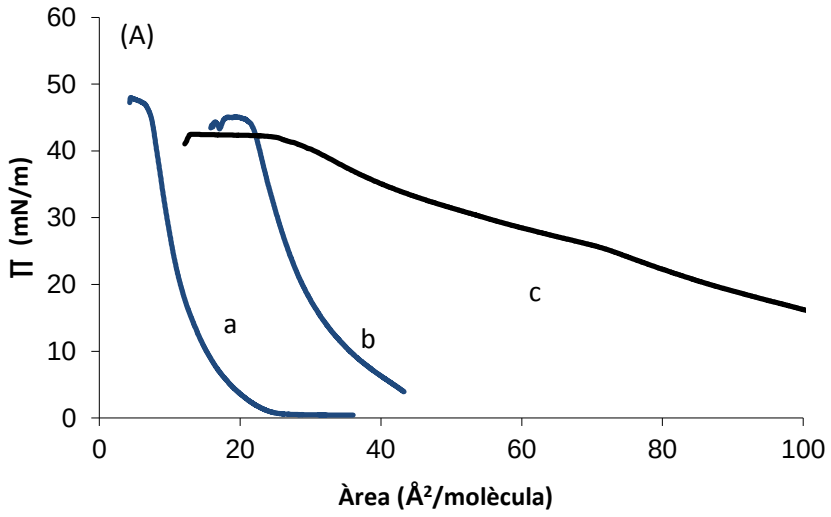
In Fig. 1A, the isotherms obtained with 30 µl of the tears Optrex (a), Zero (b) and Opticalm (c) over a sub-phase of water at 23ºC can be seen. In order to obtain a better comparison, in the X axis the area was transformed in area per molecule, taking the concentration prescribed by the manufacturer and considering that the lipid present in these tears is POPC, since PC (phosphatidylcholine) is one of the main lipids that is formed by soy lecithin, as explained in the introduction. There are other components with tensioactive characteristics in the composition of the tears but in a very low concentration that could not alter significantly the values of area per molecule.

The isotherms of Optrex and Zero tears are almost the same and are not very apart one of each other, therefore we can conclude that the concentrations of the latter (not specified by the manufacturer) are similar to those of Optrex. Fig. 1A shows that the initial surface pressure of Optrex is 0 and that of Zero is very close to 0, which but, on the contrary, Opticalm starts above 15 mN/m. It can also be seen that the isotherm that starts to go up first, although in a smoother way than the other ones is that of Opticalm, followed by Zero and finally Optrex. If the area value per molecule in the collapse point is observed in the isotherms of Optrex, Zero and Opticalm, it can be inferred that a perfect monolayer was not formed, since if it had been formed the collapse area should be ≈50 $Å^2$/molecule (the area of a POPC molecule). On the contrary, the areas found were ≈7 $Å^2$/molecule (Optrex), ≈20 $Å^2$/molecule (Zero) and ≈25 $Å^2$/molecule (Opticalm), indicating the existence of a bilayer or even more. Since lipids present in the artificial tear are in the form of liposomes (one bilayer or two or more), this seems to indicate that they remain in the form of extended bilayer or even as two bilayer in the case of Optrex (but a more accurate analysis of the areas can't be done since they strongly depend on the concentration and the volume spread, which always have an error range). As far as the concentration is concerned, it is specified in the commercial product and hence it can be approximate, not exact. In the case of Zero it is not specified and we have assumed a concentration equal to that of the other two tears. The value of area per molecule is also influenced by the lipid's molecular mass and we have

taken just one lipid, the POPC, as a reference but the exact composition of each tear is unknown.

The isotherms were obtained at a temperature of 32ºC and it was observed that the point of collapse takes place at a surface pressure slightly lower than when they are taken at room temperature (23ºC) but apart from this completely foreseeable fact, no significant differences were observed.

Fig. 1B shows the inverse of the compressibility module of the isotherms in Fig. 1A. Also, a very different behaviour in Opticalm (c) is observed, since it shows much lower C_s^{-1} values than those of the other two tears. This indicates that PCs present in the composition of Opticalm are more likely to have more unsaturations and hence a greater fluidity than the other two tears. This also fits the behaviour of the isotherms because if Opticalm has lipids with greater fluidity, they can spread better in a monolayer. In spite of this, the three tears show quite low C_s^{-1} values which means that all of them have certain fluidity.



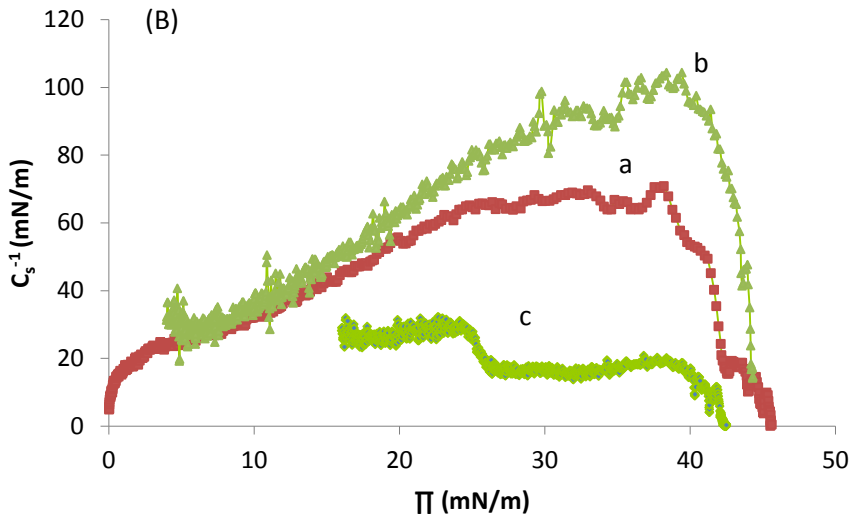


Fig. 1. (A) Surface pressure-area isotherms in the three lipid-containing artificial tears: (a) Optrex, (b) Zero, (c) Opticalm. (B) Inverse of the compressibility module isotherms of Fig. 1.A.

In Table 2 the parameters that define the isotherms obtained at 23ºC can be seen for each of the artificial tears under study and for three different phospholipids. If we look at the Π collapse values, it can be seen that tear values are more similar to those of the unsaturated phospholipids, such as POPC and DDHA-PC, than those of the saturated phospholipid DPPC are.

Table 2

Characteristical parameters of the isotherms of the three lipid-containing artificial tears and other phospholipids of the PC family.

Tear of PC	A lift-off (A^2/molecule)	A collapse (A^2/molecule)	∏ collapse (mN/m)	C_s^{-1} max (mN/m)	Reference
ZERO	> 43	20	45	103	This work
OPTREX	25	7	47	65	This work
OPTICALM	> 100	25	42	31	This work
POPC	95	46	49	15	This work
DDHA PC	107	47	42	89	This work
DPPC	93	40	60	253	This work

Conclusions

The physicochemical part has demonstrated that Opticalm is the tear with greatest fluidity. Also, we have shown that Zero has a very similar behavior to that of Optrex and consequently we can infer that its concentrations (not given by the manufacturer) are also very similar.

Other isotherms from lipidic tears

ZERO from DISOP

Table : ZERO (LIPONIT)

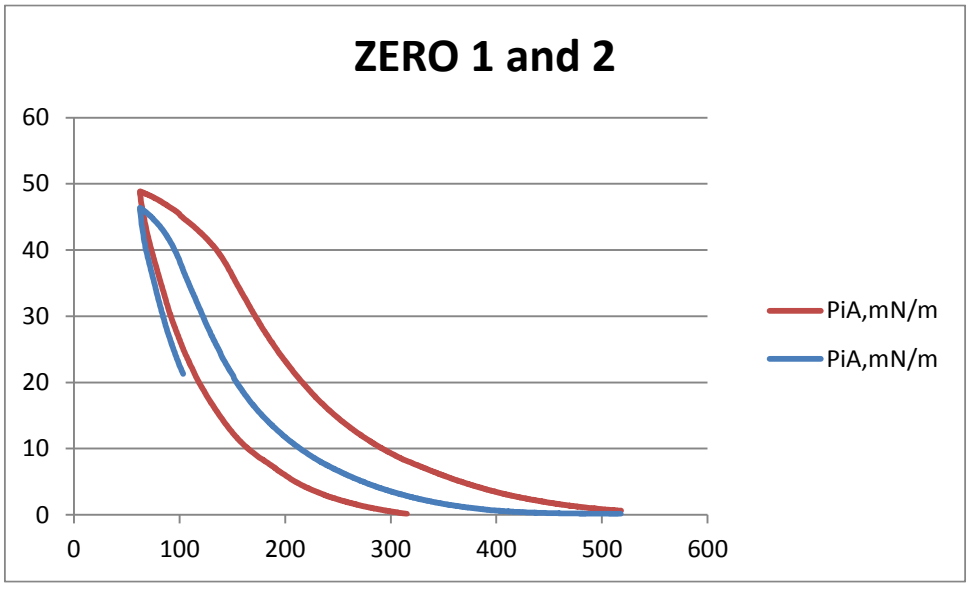
Composition in 1 mL:

- Lecithin of soya
- NaCl
- Ethanol
- Dexpantenol
- Vitamin A-palmitate
- Vitamin E
- Purified water

Manufacturer: Optima Medical Swiss AG

Distributor: Disop España

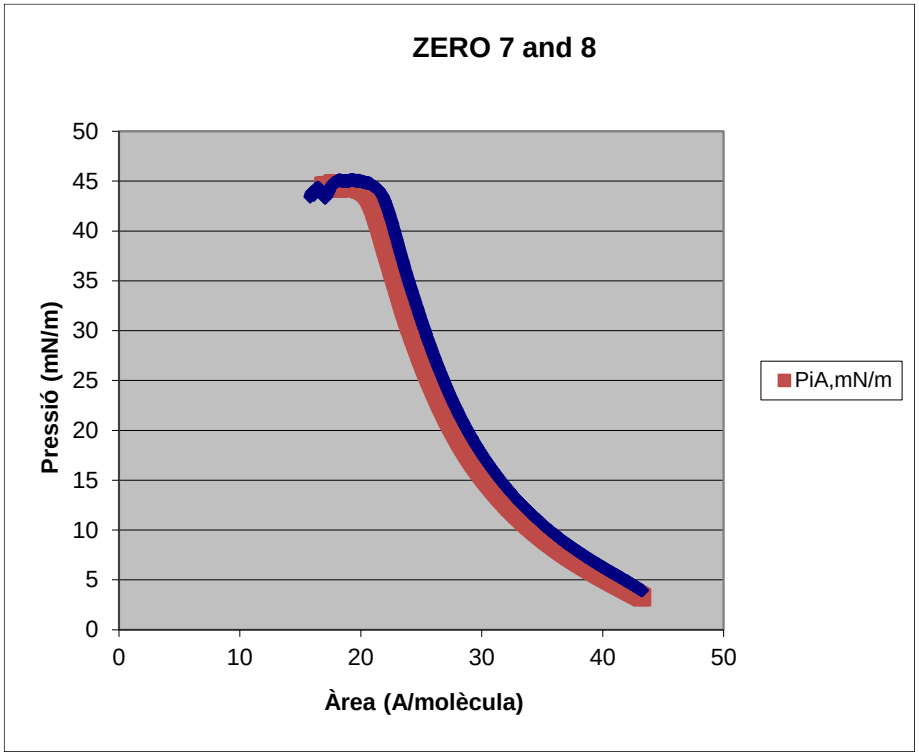
Isotherms without control of volume



Red: zero 1, blue: zero 2

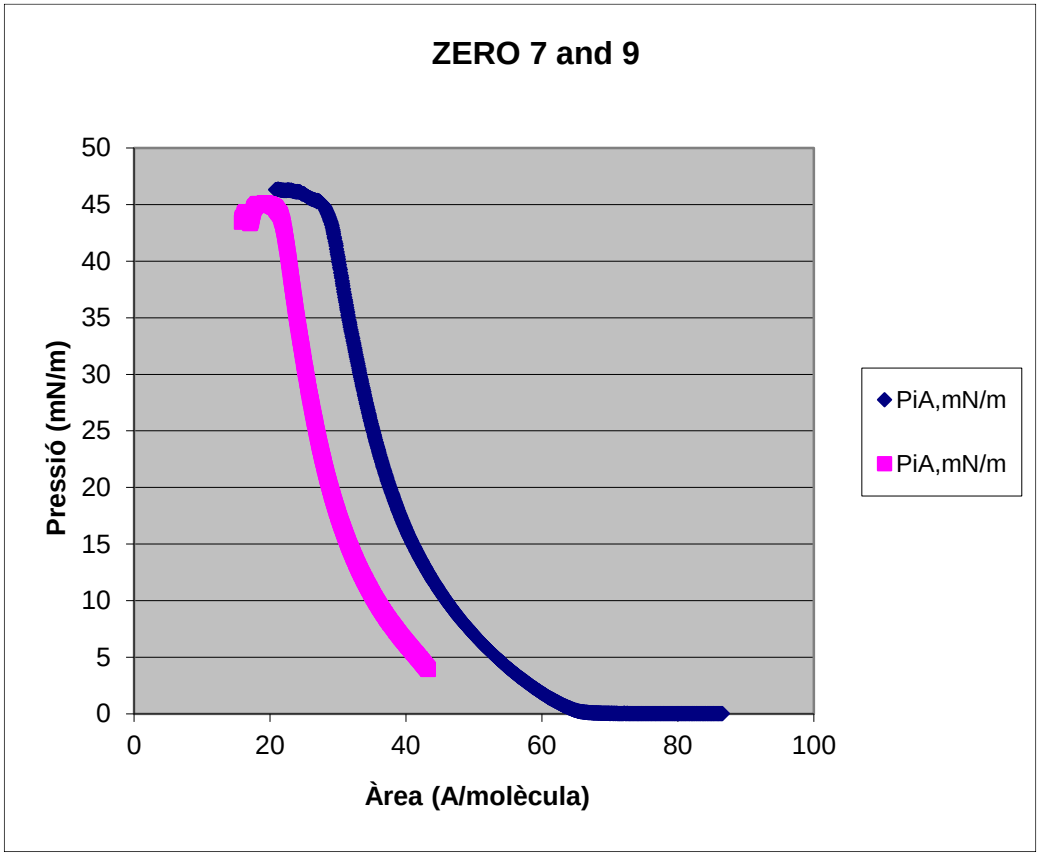
Figure. Isotherms without control of volume for the same lipid tear ZERO. 23ºC in water.

Isotherms with control of volume



Blue: zero 7, red: zero 8

Figure. Isotherms with control of volume for the same lipid tear ZERO. 23ºC in water.



Magenta: zero 7, blue: zero 9

Figure. Isotherms with dilution 1:1 (blue) versus non-diluted (magenta). 23ºC in water.

It is seen that the ZERO lipid tear behaves more similar to INNOXA and OPTREX than to OPTICALM. However, the volume necessary for obtaining the isotherm is higher for the ZERO tear, which means that the lipid concentration is lower for the ZERO tear (this concentration is not indicated in the product information).

Behaviour of the lipid artificial tear in spray at several temperatures and subphases

Lipid artificial tear ZERO of DISOP

(Fabricante: Optima Medical Swiss AG, Distribuidor: DISOP). Su composición esta especificada a continuación, aunque no se conoce la concentración de cada uno de sus componentes.

Tabla 1. Composición de la lagrima artificial lipídica Zero.

Composición Zero
Lecitina de Soja
Cloruro de sodio
Etanol
Fenoxietanol
Vitamina A
Vitamina E

The lipid tear in spray ZERO was studied at two temperatures, 23 and 32ºC, and two subphases, water and 0.9% NaCl aqueous solution.

The set of experiments was with control of the volume used. In this case, the desired volume was taken with a microsyringe and extended onto the subphase.

Para crear la monocapa se utiliza el spray de lágrima lipídica Zero. Se recoge haciendo spray en un vial una cierta cantidad de esta lágrima, seguidamente se extrae con una micro jeringa. Con la microjeringa se instila gota a gota un volumen de 30 µl en la cubeta de teflón de manera que quede repartida en toda el área de la cubeta, se deja 15 minutos reposar para que se extiendan los lípidos.

En el software donde obtenemos la isoterma se fija el límite de barreras i características del compuesto en referencia al POPC (palmitoiloleoilfosfatidilcolina) del cual si se conocen sus características, y también se toma como concentración 10 mg/ml por similitud con otras lágrimas lipídicas comerciales. (Área máxima: 1200 cm^2, área mínima: 120 cm^2, masa molecular: 760,10, concentración: 10 mg/ml, volumen: 30 µl y velocidad de compresión de las barreras: 50 cm^2/ min). A partir de este momento se procede a la obtención de la isoterma, iniciando la compresión de las barreras a la velocidad indicada anteriormente hasta llegar al punto de colapso, donde se rompe la monocapa.

A continuación se muestran las isotermas área-presión superficial obtenidas con diferentes subfases (agua y NaCl al 0,9%) y a diferentes temperaturas (23ºC y 32ºC)

En la figura 1 se pueden observar dos isotermas obtenidas a 23ºC de temperatura ambiente. La isoterma 1 se ha obtenido con 30 µl de lágrima lipídica Zero sobre una subfase de agua purificada, mientras que la isoterma 2 se ha realizado con 30 µl de lágrima lipídica sobre una subfase de cloruro de sodio (NaCl) al 0.9 %.

Las dos isotermas se encuentran muy desplazadas, en la isoterma 1 la presión superficial inicial es 0 mN/m, en 44 A^2/ molécula, a medida que se van cerrando las barreras y comprimiendo la monocapa, hasta 30 A^2/ molécula, momento en el cual la presión superficial empieza a subir de forma suave y se pasa a la fase de líquido expandido; a partir de 20 A^2/ molécula la presión superficial sube bruscamente hasta llegar al punto de colapso o rotura de la monocapa que se produce a 5 A^2/ molécula.

La presión superficial inicial de la isoterma 2 es de 6.9 mN/m, en 52 A^2/ molécula, esto nos indica que al añadir la monocapa de lípidos a la subfase de NaCl se ha producido un efecto de expansión en la monocapa. A medida que se cierran las barreras se produce una subida de la presión superficial llegando al colapso de la monocapa a 17 A^2/ molécula.

Esta diferencia en el comportamiento de la monocapa en las dos subfases se explica en que los iones de Na^+ y Cl^- de la subfase de NaCl separan los liposomas de la monocapa entre ellos de forma que el área inicial que ocupan es más grande y esto produce un mayor efecto en la tensión superficial. Cuando la subfase es agua la monocapa ocupa un área menor y no hay efecto de la tensión superficial hasta que la monocapa no se encuentra lo suficientemente comprimida.

En la figura 2 se representa la inversa del módulo de compresibilidad (Cs^{-1}) de las isotermas de la figura 1. Se puede observar que los valores de Cs^{-1} de la isoterma 2 son mayores que los de la isoterma 1, por lo que la isoterma 2 es menos compresible que la 1, esto es debido a que los iones de Na^+ Cl^- producen un efecto de fuerza en los liposomas que evita que se compriman, haciendo que la monocapa se comporte de una forma más rígida. En el caso de la isoterma 1, donde la subfase es agua, los liposomas se comprimen más al no actuar están fuerzas iónicas, por lo que la monocapa tiene un comportamiento más fluido.

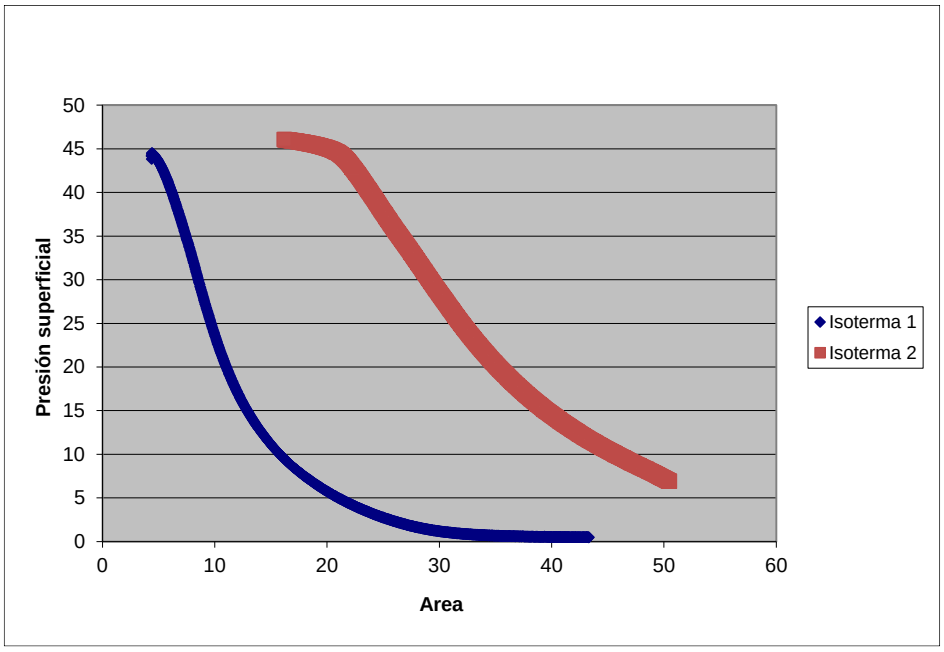


Figura 1. Isotermas presión superficial-area de la lágrima Zero con diferentes subfases: Isoterma 1: subfase agua e isoterma 2: NaCl al 0,9% a 23.

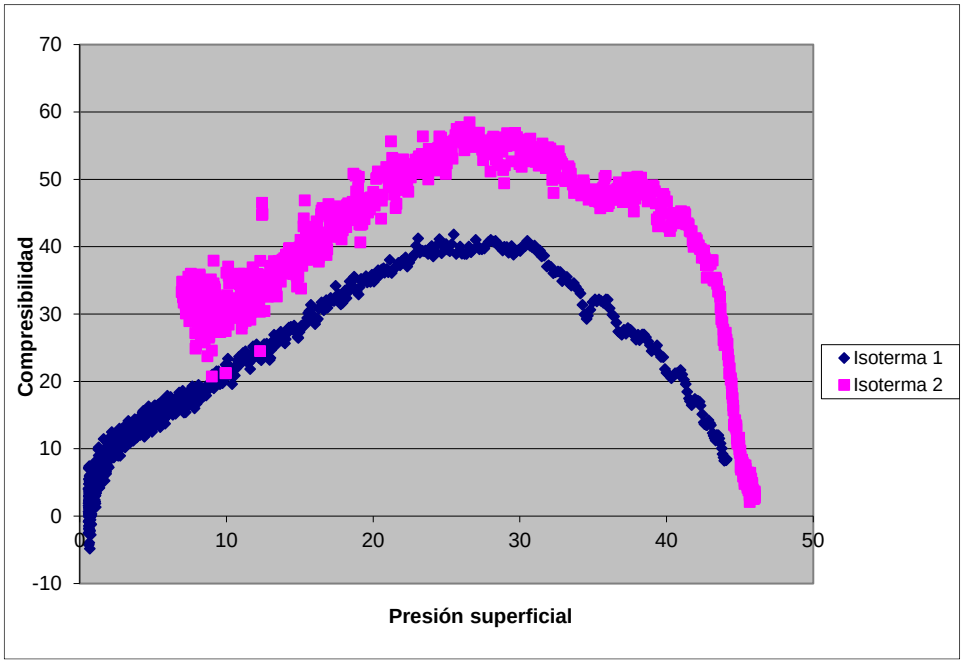


Figura 2. Inversa del módulo de compresibilidad de las isotermas de la figura 1.

En la figura 3 se pueden observar dos isotermas obtenidas a 32ºC de temperatura ambiente. La isoterma 1 se ha obtenido con 30 µl de lágrima lipídica Zero sobre una subfase de agua purificada, mientras que la isoterma 2 se ha realizado con 30 µl de lágrima lipídica sobre una subfase de cloruro de sodio (NaCl) al 0.9 %.

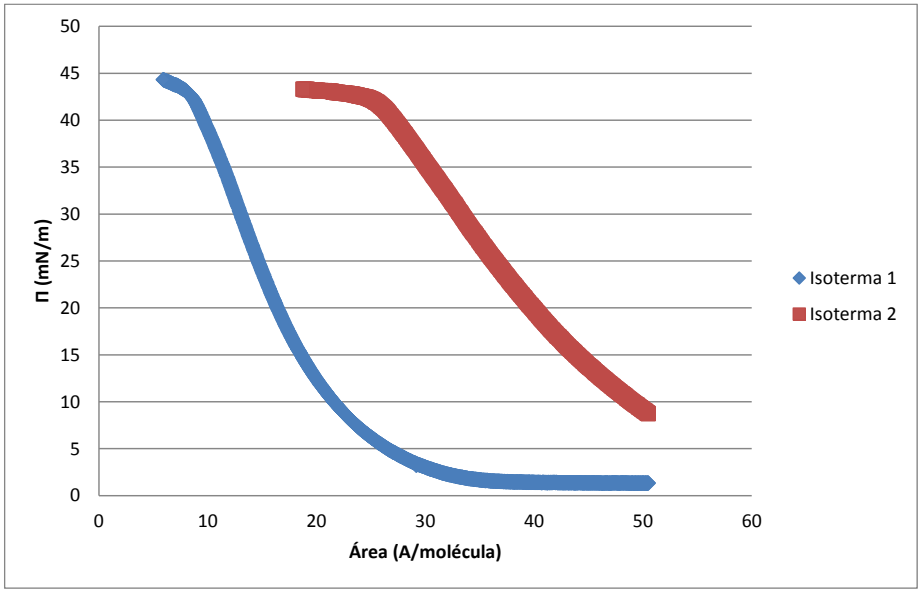


Figura 3. Isotermas área-presión superficial de la lágrima Zero con diferentes subfases: Isoterma 1: subfase agua e isoterma 2: NaCl al 0,9% a 32ºC.

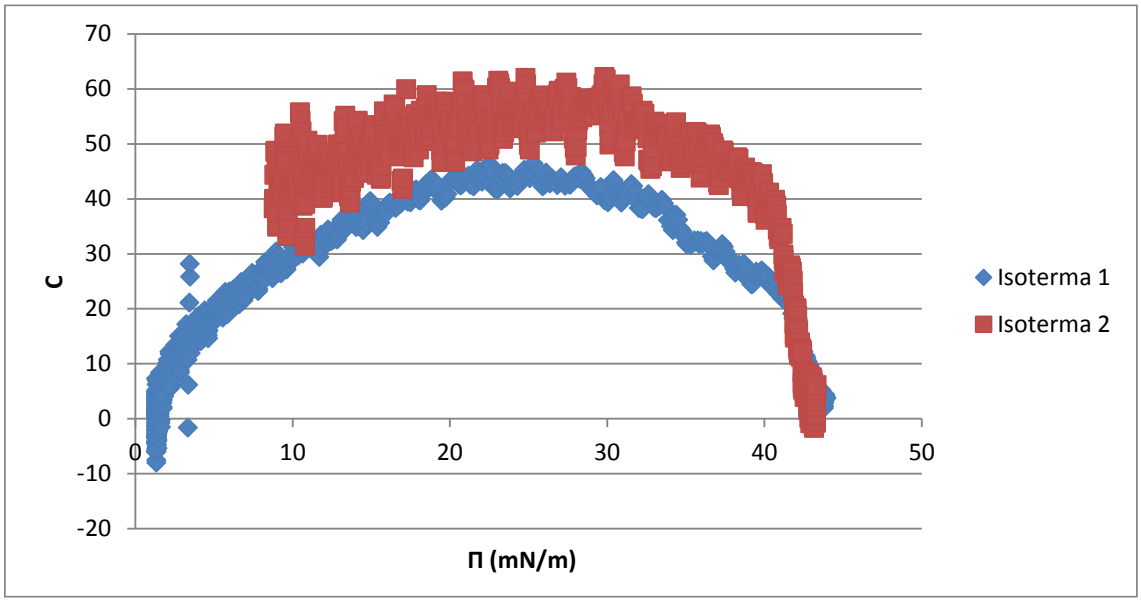


Figura 4. Inversa del módulo de compresibilidad de las isotermas de la figura 3 a 32ºC de temperatura.

En la figura 5 se representan las 4 isotermas mostradas anteriormente, a 23ºC y 32ºC, se puede observar que las isotermas a 32ºC se encuentran desplazadas respecto a las de 23ºC de temperatura, esto es debido a la agitación térmica de las moléculas como consecuencia del aumento de la temperatura, cuanto mayor es esta las moléculas se mueven más y ocupan un área más grande, por lo que se encuentran más expandidas. El colapso se produce antes que en las isotermas obtenidas a 23ºC.

En la figura 6 se representa la inversa del módulo de compresibilidad (Cs^{-1}) de las isotermas de la figura 5. Se puede observar que los valores de Cs^{-1} de la isotermas obtenidas a 32ºC son ligeramente mayores que los de las isotermas obtenidas a 23ºC, esto indica que los lípidos, de las isotermas que se han obtenido a mayor temperatura, son ligeramente menos compresibles que los que se han obtenido a menor temperatura que son ligeramente más compresibles. Como he explicado en la figura 5 este efecto se produce por la agitación térmica de las moléculas que producen una mayor expansión de los liposomas, como consecuencia estos ocupan un área mayor, son ligeramente más resistentes a la compresión.

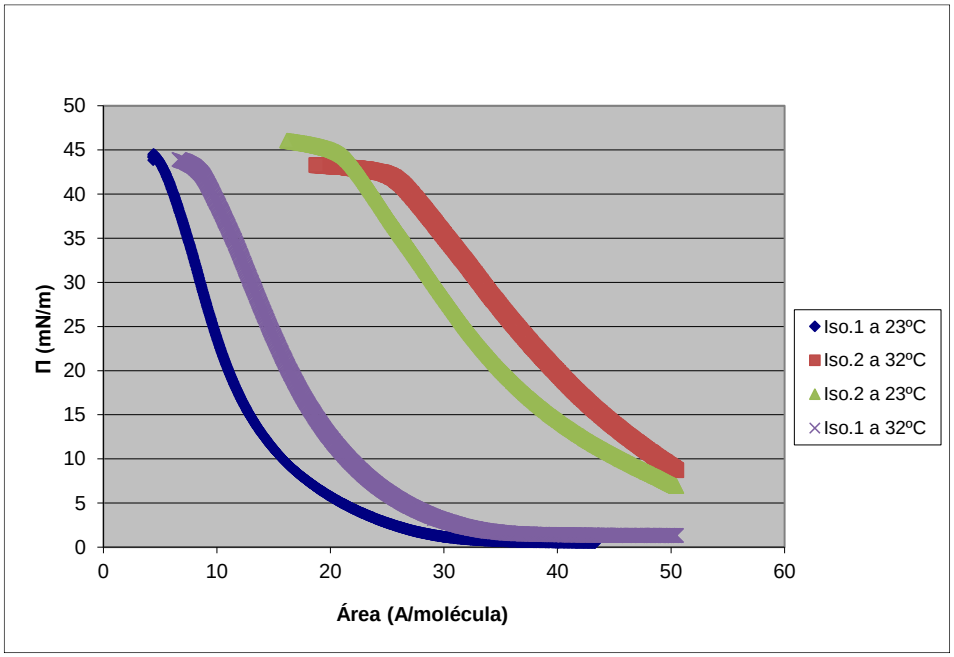


Figura 5. Isotermas área-presión superficial de la lágrima Zero con diferentes subfases: Isoterma 1: subfase agua e isoterma 2: NaCl al 0,9% a 23ºC y 32ºC.

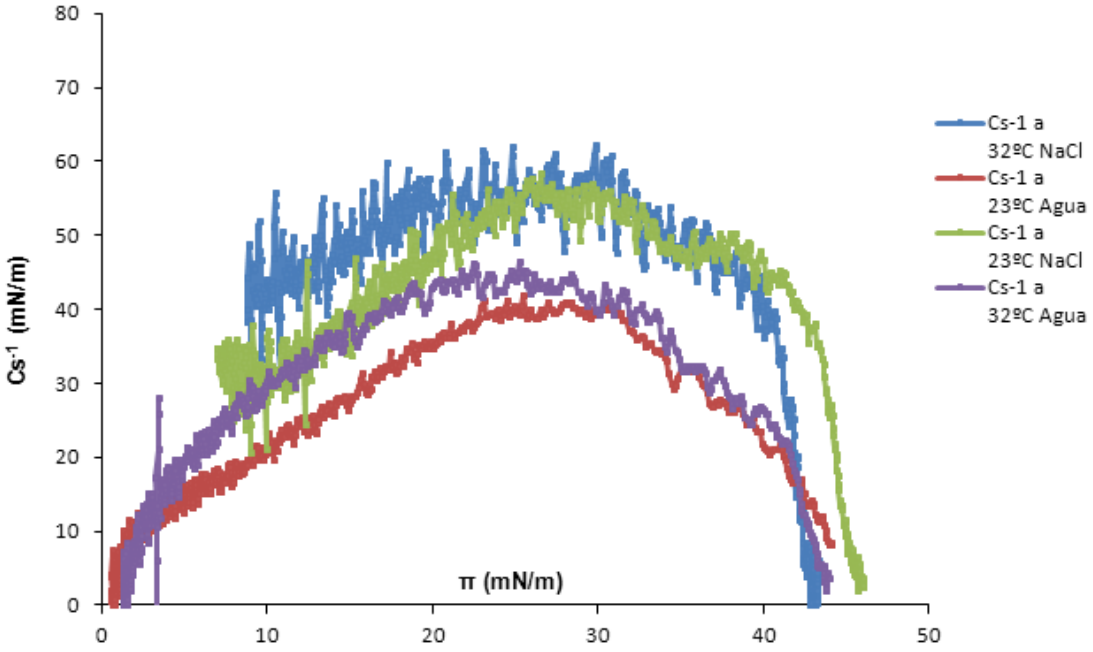


Figura 6. Inversa del módulo de compresibilidad de las isotermas de la figura 5 a 23 y 32ºC temperatura

Bibliography

Artificial tears potpourri: a literature review

[Moshirfar 2014] Majid Moshirfar[1] Kasey Pierson[2,*] Kamalani Hanamaikai[3,*] Luis Santiago-Caban[1] Valliammai Muthappan[1] Samuel F Passi[1]
Clinical Ophthalmology 2014:8 1419–1433

Abstract: Numerous brands and types of artificial tears are available on the market for the treatment of dysfunctional tear syndrome. Past literature has focused on comparing the components of these products on patient's clinical improvement. The wide array of products on the market presents challenges to both clinicians and patients when trying to choose between available tear replacement therapies. Different formulations affect patients based on etiology and severity of disease. In order to provide an unbiased comparison between available tear replacement therapies, we conducted a literature review of existing studies and National Institutes of Health clinical trials on commercially available, brand name artificial tears. Outcomes evaluated in each study, as well as the percent of patients showing clinical and symptomatic improvement, were analyzed. Fifty-one studies evaluating different brands of artificial tears, and their efficacy were identified. Out of the 51 studies, 18 were comparison studies testing brand name artificial tears directly against each other. Nearly all formulations of artificial tears provided significant benefit to patients with dysfunctional tear syndrome, but some proved superior to others. From the study data, a recommended treatment flowchart was derived.

[Benelli 2011] Systane® lubricant eye drops in the management of ocular dryness

Umberto Benelli

Clinical Ophthalmology 2011:5 783–790

Abstract: The understanding of dry eye disease has advanced recently through increasing recognition that the etiology of the condition involves both tear evaporation and insufficient tear production, and that tear film instability and inflammation play roles in the various stages of the disease. Of significance, it has been recognized that lipid layer thickness correlates with tear film stability. The management of dry eye involves various strategies and therapeutic approaches that address one or more etiopathological components of the disease. The purpose of this review is to outline the characteristics and clinical utility of the Systane® ocular lubricants that contain hydroxypropyl-guar and one or both of the demulcents, ie, polyethylene glycol 400 and propylene glycol. Clinically, these products are safe and are indicated for the temporary relief of burning and irritation due to dryness of the eye. In particular, this review describes the formulations, mechanisms of action, and clinical utility of the newest additions to this topical ocular lubricant family, Systane Ultra® and Systane Balance®. Both of these ocular products are formulated with an intelligent delivery system and both provide symptomatic relief to patients with dry eye. However, Systane Balance is a novel formulation that contains both polymer and lipid components designed to protect the ocular surface and replenish tear film lipids simultaneously, a factor that is of particular relevance to patients who have dry eye associated with meibomian gland dysfunction.

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Comparison of the Efficacy of Two Lipid Emulsion Eyedrops in Increasing Tear Film Lipid Layer Thickness

Robert C. Scaffidi, B.S., and Donald R. Korb, O.D.

Purpose. The lipid layer of the tear film is critical to maintaining the thickness of the multilayered tear film. This study was designed to determine whether a single drop of Refresh Dry Eye Therapy or Soothe, both lipid emulsion eyedrops, significantly increased the lipid layer thickness (LLT) of patients with selfreported dry eyes and thin lipid layers. **Methods.** Lipid layer interference patterns were used to quantify the LLT of both eyes of eligible patients before and after test drop instillation. Patients (*n* _ 41) reporting dry eye symptoms and having baseline LLT of no more than 75 nm received 40 _L of Refresh Dry Eye Therapy in one eye and 40 _L of Soothe in the contralateral eye. After instillation, LLT was quantified at 1, 5, and 15 minutes. LLT after drop instillation was averaged for the three time points. **Results.** The mean _ standard error baseline LLT was 59.6 _ 1.7 nm for eyes treated with Refresh Dry Eye Therapy and 61.5 _ 1.6 nm for eyes treated with Soothe. These means were not significantly different (*P*_0.05). The overall mean LLT after drop instillation was 83.2 _ 3.6 nm for Refresh Dry Eye Therapy (*P*_0.0001) and 121.5 _ 3.8 nm for Soothe (*P*_0.0001). The mean LLT increase from Soothe (60.0 nm) was significantly greater than that from Refresh Dry Eye Therapy (23.6 nm) (*P*_0.0001). **Conclusions.** The application of a lipid emulsion eyedrop will increase LLT and benefit patients with deficient lipid layers who experience dry eye symptoms. Although both products are lipid emulsions, one drop of Soothe essentially doubled LLT and provided a mean increase in LLT that was 2.5 times greater than that of Refresh Dry Eye Therapy.

[Korb 2005] The Effect of Two Novel Lubricant Eye Drops on Tear Film Lipid Layer Thickness in Subjects With Dry Eye Symptoms

DONALD R. KORB, OD, FAAO, ROBERT C. SCAFFIDI, BS, JACK V. GREINER, OD, DO, PhD, KENNETH R. KENYON, MD, JOHN P. HERMAN, OD, FAAO, CAROLINE A. BLACKIE, OD, PhD, THOMAS GLONEK, PhD, COURTNEY L. CASE, BA, VICTOR M. FINNEMORE, OD, FAAO, and TERESA DOUGLASS, BA

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OPTOMETRY AND VISION SCIENCE

ABSTRACT: *Purpose.* Because the lipid layer of the tear film is recognized as a critical component in dry eye disease, this study was designed to determine if a single eye drop of either Soothe or Systane produces a significant increase in lipid layer thickness (LLT) for subjects reporting symptoms indicative of dry eyes. *Methods.* A double-blind, internally paired study was performed. A custom-built lipid layer interferometer, enabling characterization of lipid layer interference patterns, was used to quantify baseline LLT (OU) of eligible subjects. Inclusion criteria included: 1) presence of dry eye symptoms and 2) baseline LLT <75 nm. Subjects (n _ 40) received a single eye drop of Soothe in one eye and a single eye drop of Systane in the contralateral eye. After the instillation of each test drop, LLT was reanalyzed for all subjects. *Results.* The mean _ standard error baseline LLT pre-eye drop instillation was 60.0 _ 1.8 nm for eyes treated with Soothe and 61.5 _ 1.8 nm for eyes treated with Systane. These means were not significantly different ($p > 0.5$). The mean LLT for eyes treated with Soothe increased to 124.4 _ 4.9 nm ($p < 0.0001$). The mean LLT for eyes treated with Systane increased to 71.3 _ 2.6 nm ($p < 0.0001$). The LLT increase from Soothe was significantly greater than that from Systane ($p < 0.0001$). *Conclusions.* In subjects with symptoms indicative of dry eye states and LLT <75 nm, one eye drop of Soothe more than doubled LLT, a 107% mean increase, whereas Systane increased LLT by 16%. (Optom Vis Sci 2005;82:594–601)

- [Kaercher 1993] Kaercher T, Hönig D, Möbius D. International Ophthalmology 17 (1993) 341-348.

- [Kaercher 1995] Kaercher T, Hönig D, Möbius D. Orbit 14 (1995) 17-24.

Meibomian lipid layers seen through BAM

*Orbit-1995, Vol. **14.** No. 1,*
***PP.** 17-24*

Thomas Kaercher' Dirk Honig' Dietmar Mobius'

Abstract Brewster Angle Microscopy (BAM) provides a direct observation of the spread Meibomian lipid layer under simultaneous registration of the surface pressure. It is based on the fact that He-Ne-laser light, which is incident at a water-surface under the Brewster angle, does not reflect visible light. After spreading of a lipid film, the angle of the incident light beam varies thus causing reflection of light.
The morphology of the Meibomian lipid layers was studied under continuous compression of the film. At 0.5 mN/m the film showed a loose, lagoonlike pattern. Compression up to **12.0** mN/m led to an immobile, soup-like, densely packed film.
Patients with meibomitis presented a simultaneous appearance of lagoonlike and densely packed parts of the film.
Differences in reflectivity at different areas of the film can be used for thickness measurements. Meibomian lipid layers, under the authors' *in vitro* conditions, proved not to be thicker than 100 **A.** These results coincide with

their results for Meibomian lipid layers on glass plates. BAM provides a new understanding of the function of the Meibomian lipid layers by visualizing the morphological alteration of the film under compression and decompression.

[Miano 2005] Insertion of tear proteins into a meibomian lipids film

F. Miano[a,*], M. Calcara [a], T.J. Millar [b], V. Enea [a]

Colloids and Surfaces B: Biointerfaces 44 (2005) 49–55

Abstract

The eyelid meibomian gland secretions form the outer layer of the tear film. That layer functions as a lubricant during a blink, and as a barrier against intrusion of foreign bodies. The lipid film is also exposed to proteins present in the aqueous phase that may adsorb there, and thus form an integral part of the surface of the tear film, or possibly, cause disruption to the outermost layer. Therefore, the adsorption of tear proteins to the meibomian lipid layer was object of the present investigation.

A model tear was set up coating a pendant drop of saline with a film of meibomian lipids and measuring variations of the interfacial pressure after the injection of tear proteins into the aqueous subphase at their physiological concentration. All tear proteins adsorbed at the interface causing the initial surface pressure to increase. For each protein, a limiting surface pressure at which a given protein was no longer able to insert into the lipid layer was found. Among the proteins tested, lipocalin was the most surface active one and inserted into the lipid layer in the whole range of surface pressure exerted by the meibomian lipid mixture. Lactoferrin, lysozyme and IgA also interacted with the lipids whereas albumin interacted more weakly. The timescale of the protein insertion into the lipid layer was of the order of 102 s. It was hypothesized that protein adsorption at the interface could be associated with structural changes. Indeed, the enzymatic activity of lysozyme was maintained in the presence of an outermost meibomian lipid layer that prevented its denaturation while exposure at the air/aqueous interface induced significant lysozime degradation. meibomian lipid composition is therefore functional to maintain tear proteins activity.

[Mudgil 2006] Adsorption of lysozyme to phospholipid and meibomian lipid monolayer films

Poonam Mudgil, Margaux Torres, Thomas J. Millar *

Colloids and Surfaces B: Biointerfaces 48 (2006) 128–137

It is believed that a lipid layer forms the outer layer of the pre-ocular tear film and this layer helps maintain tear film stability by lowering its surface tension. Proteins of the aqueous layer of the tear film (beneath the lipid layer) may also contribute to reducing surface tension by adsorbing to, or penetrating the lipid layer. The purpose of this study was to compare the penetration of lysozyme, a tear protein, into films of meibomian lipids and phospholipids held at different surface pressures to determine if lysozyme were part of the surface layer of the tear film. Films of meibomian lipids or phospholipids were spread onto the surface of a buffered aqueous subphase. Films were compressed to particular pressures and lysozyme was injected into the subphase. Changes in surface pressure were monitored to determine adsorption or penetration of lysozyme into the surface film. Lysozyme penetrated a meibomian lipid film at all pressures tested (max = 20 mN/m). It also penetrated phosphatidylglycerol, phosphatidylserine or phosphatidylethanolamine lipid films up to a pressure of 20 mN/m. It was not able to penetrate a phosphatidylcholine film at pressures ≥10 mN/m irrespective of the temperature being at 20 or 37 ◦C. However, it was able to penetrate it at very low pressures (<10 mN/m).

Epifluorescence microscopy showed that the protein either adsorbs to or penetrates the lipid layer and the pattern of mixing depended upon the lipid at the surface. These results indicate that lysozyme is present at the surface of the tear film where it contributes to decreasing the surface tension by adsorbing and penetrating the meibomian lipids. Thus it helps to stabilize the tear film.

[Millar 2009] Adsorption of Human Tear Lipocalin to Human Meibomian Lipid Films

Thomas J. Millar,[1] *Poonam Mudgil,*[1] *Igor A. Butovich,*[2] *and Chendur K. Palaniappan*[1]

(*Invest Ophthalmol Vis Sci.* 2009;50:140–151) DOI:10.1167/iovs.08-2097

PURPOSE. Tear lipocalin (Tlc) is a major lipid binding protein in tears and is thought to have an important role in stabilizing the Meibomian lipid layer by transferring lipids to it from the aqueous layer or ocular surface, or by adsorbing to it directly. These possible roles have been investigated in vitro using human Tlc.
METHODS. Tlc was purified from human tears by size exclusion chromatography followed by ion exchange chromatography. Three additional samples of the Tlc were prepared by lipidation, delipidation, and relipidation. The lipids extracted from the purified Tlc were analyzed by HPLC-MS followed by fragmentation. Adsorption of these different forms of Tlc to a human Meibomian lipid film spread on the surface of an artificial tear buffer in a Langmuir trough were observed by recording changes in the pressure with time (_-T profile) and monitoring the appearance of the film microscopically. These results were compared with similar experiments using a bovine Meibomian lipid film.
RESULTS. The results indicated that Tlc binds slowly to a human Meibomian lipid film compared with lysozyme or lactoferrin, even at 37°C. The adsorption of Tlc to a human Meibomian lipid film was very different from its adsorption to a bovine Meibomian lipid film, indicating the nature of the lipids in the film is critical to the adsorption process. Similarly, the different forms of Tlc had quite distinct adsorption patterns, as indicated both by changes in _-T profiles and the microscopic appearance of the films.
CONCLUSIONS. It was concluded that human Tlc was capable of adsorbing to and penetrating into a Meibomian lipid layer, but this process is very complex and depends on both the types of lipids bound to Tlc and the lipid complement comprising the Meibomian lipid film.

[Mudgil 2008] Adsorption of apo- and holo-tear lipocalin to a bovine Meibomian lipid film

Poonam Mudgil, Thomas J. Millar*

Experimental Eye Research 86 (2008) 622-628

Adsorption of apo- and holo-tear lipocalin (Tlc) to bovine Meibomian lipid film was studied. A Langmuir trough was used for these studies and the adsorption of protein was observed by recording changes in the pressure with time (peT profile). The films were photographed at different stages of adsorption by doping Meibomian lipids with a fluorescently tagged lipid. The results indicated that apo-Tlc adsorbed much more quickly than holo-Tlc to the Meibomian lipid film. Contrary to the expectation that holo-Tlc would release lipids to the surface and surface pressure would be higher, it was found that the surface pressure was higher with the adsorption of apo-Tlc to the surface. Photography of the films showed that apo- and holo-Tlc interacted differently with the Meibomian lipid layer. Adsorption of holo-Tlc resulted in big bright patches and adsorption of apo-Tlc resulted in many small patches along with the big patches. Both forms of Tlc produced a more stable film as indicated by decreased movement of the protein adsorbed films, and a higher maximum surface pressure upon compression of these films compared with Meibomian lipid films alone. Isocyles of apo-Tlc adsorbed films gave a higher surface pressure than that of holo-Tlc. From these results, it is concluded that both apo- and holo-Tlc adsorbed to the Meibomian lipid layer and the delivery of the lipids from Tlc to the outer lipid layer could not be detected by our techniques. Its scavenging role to remove lipids from the corneal surface and bind with them might be beneficial for increasing tear viscosity but whether those lipids are delivered to the outermost lipid layer still remains unclear.

[Peters 2002] The role of different phospholipids on tear break-up time using a model eye

Karl Peters and Thomas J. Millar

Current Eye Research 0271-3683/02/2501-055$16.00
2002, Vol. 25, No. 1, pp. 55–60

Abstract
Purpose. The effect of different phospholipids in stabilizing the tear film was investigated to determine if particular polar head groups gave greater stability than others.
Methods. Purified phosphatidylcholine (PC), lysophosphatidylcholine (LPC), phosphatidylethanolamine (PE), phosphatidylglycerol (PG), phosphatidylserine (PS) and cardiolipin (CL) were used. These were applied to a model eye loaded with an artificial tear fluid and the tear breakup time (TBUT) was measured. Three variants of the artificial tear fluid were utilised: buffered saline alone; one with proteins and mucins; and one containing proteins, mucins and lipids.
Results. TBUT was improved by the presence of phospholipids. In particular, the best performance was with PI applied to artificial tear fluid containing proteins mucins and lipids. Use of buffered saline as the artificial tear fluid gave very short break-up times.
Conclusion. Increase in tear film stability by phospholipids is probably not due to the charge carried by the polar head group, but more likely due to the charge distribution, and the presence of hydroxyl groups in the head group also tends to increase stability, possibly through specific interactions with proteins and mucins in the subphase.

[Petrov 2007] Two-dimensional order in mammalian pre-ocular tear film

P.G. Petrov [a,*], J.M. Thompson [a], I.B. Abdul Rahman [a], R.E. Ellis [a], E.M. Green [a], F. Miano [b], C.P. Winlove

Experimental Eye Research 84 (2007) 1140-1146

We report a grazing incidence x-ray diffraction (GIXD) investigation of the surface lipid layer of the pre-ocular tear film. For the first time we demonstrate the existence of 2D order over a wide range of surface pressures in this system, with typical spicing of 3.75 A°and 4.16 A° independent of the monolayer surface pressure. Analogous lipid ordering is also found in an artificial lipid mixture of the major lipid components of the tear film, suggesting that the 2D ordering is set by generic lipidelipid interactions. Fluorescence microscopy of the natural and artificial tear film mixture reveals the co-existence of a dilute and a much more condensed phase in the amphiphilic lipid matrix over the pressure range of 15e45 mN/m investigated by GIXD, plus an additional structure due to the much more hydrophobic part of the mixture. This evidence supports the previous hypothesis that tear film has a layered structure.

[Hagerdon-Jones 2015] Atomic force microscopy and Langmuir---Blodgett monolayer technique to assess contact lens deposits and human meibum extracts

Sarah Hagedorn[a,1], Elizabeth Drolle[b,c,1], Holly Lorentz[a,e], Sruthi Srinivasan[a,*], Zoya Leonenko[b,c,d], Lyndon Jones[a,b,d]

Journal of Optometry (2015) **8,** 187-199

Abstract *Purpose:* The purpose of this exploratory study was to investigate the differences in meibo-mian gland secretions, contact lens (CL) lipid extracts, and CL surface topography between participants with and without meibomian gland dysfunction (MGD). *Methods: Meibum study:* Meibum was collected from all participants and studied via Langmuir---Blodgett (LB) deposition with subsequent Atomic Force Microscopy (AFM) visualiza-tion and surface roughness analysis. *CL Study:* Participants with and without MGD wore both etafilcon A and balafilcon A CLs in two different phases. CL lipid deposits were extracted and analyzed using pressure-area isotherms with the LB trough and CL surface topographies and roughness values were visualized using AFM. *Results: Meibum study:* Non-MGD participant meibum samples showed larger, circular aggre-gates with lower surface roughness, whereas meibum samples from participants with MGD showed more lipid aggregates, greater size variability and higher surface roughness. *CL Study*: Worn CLs from participants with MGD had a few large tear film deposits with lower surface roughness, whereas non-MGD participant-worn lenses had many small lens deposits with higher surface roughness. Balafilcon A pore depths were shallower in MGD participant worn lenses when compared to non-MGD participant lenses. Isotherms of CL lipid extracts from MGD and non-MGD participants showed a seamless rise in

surface pressure as area decreased; however, extracts from the two different lens materials produced different isotherms.

[Domenech 2005] Surface thermodynamics study of monolayers formed with heteroacid phospholipids of biological interest

O` scar Dome`nech a, c, Juan Torrent-Burgue´s c, 1, Sandra Merino b, c, Fausto Sanz a, c, M. Teresa Montero b, c, Jordi Hern´andez-Borrell b, c, *

Colloids and Surfaces B: Biointerfaces 41 (2005) 233–238

The interaction of 1-palmitoy-2-oleoyl-*sn*-glycero-3-phosphocoline (POPC) and 1-palmitoy-2-oleoyl-*sn*-glycero-3-phosphoethanolamine (POPE), two of the major components in biological membranes, were investigated using the monolayer technique at the air–water interface.
The pressure–area isotherms indicate that both phospholipids are miscible through all range of compositions. POPE–POPC form stable mixtures, with a minimum for the Gibbs energy of mixing at *X*POPC = 0.4. A virial equation of state was fitted to the experimental values. Positive values found for the second virial coefficient indicate repulsion between POPC and POPE. The interaction parameter was evaluated which indicated that a corresponding decrease in the repulsion occurs when POPC molar fraction is low. This effect suggests the existence of hydrogen bonds between POPE and the water beneath the interface.

[Torrent 2011a] Oleamide and Oleamide–Lipid Mixed Monolayers

Juan Torrent-Burgués

BioNanoSci. (2011) 1:202–209
DOI 10.1007/s12668-011-0023-4

Abstract Oleamide (OA) and its mixtures with other lipids are of interest in some biological systems, such as the tear film or the cerebrospinal fluid. In this work, the behavior of OA, OA–dipalmitoylphospatidylcholine (DPPC), and OA–cholesterol films is studied using surface pressure–area isotherms and atomic force microscopy, and analyzing the collapse pressure vs. composition, the compressibility, and the mean area vs. composition for several surface pressures.
It is observed that OA forms homogeneous monolayers in a liquid-expanded state until the collapse surface pressure and the mixing with DPPC and cholesterol. The collapse surface pressure changes with the mixture composition, and in the case of DPPC, a noticeable influence of OA in the liquid-expanded/liquid-condensed phase change of DPPC is observed. The excess area is positive for the OA/DPPC films, butmostly negative for the OA–cholesterol films. These results are of interest for the target of formulation of artificial tears containing lipids.

[Torrent 2012b] Biomimetic monolayer films of monogalactosyldiacylglycerol incorporating ubiquinone

Javier Hoyo a, Juan Torrent-Burgues a,b,⇑, Ester Guaus a

Journal of Colloid and Interface Science 384 (2012) 189-197

Ubiquinone and plastoquinone are two of the main electron and proton shuttle molecules in biological systems, and monogalactosyldiacylglycerol (MGDG) is the most abundant lipid in the thylakoid membrane of chloroplasts. Saturated MGDG, ubiquinone-10 (UQ) and MGDG:UQ mixed monolayers at the air/water interface have been studied using surface pressure-area isotherms and Brewster Angle Microscopy.
Moreover, the transferred Langmuir-Blodgett films have been observed by Atomic Force Microscopy.
The results show that MGDG:UQ mixtures present more fluid phase than pure MGDG, indicating a higher order degree for the later. It is also observed an important influence of UQ on the MGDG matrix before UQ collapse pressure and a low influence

after this event, due to UQ expulsion from the MGDG matrix. This expulsion leads to a similar remaining UQ content for all the tested mixtures, indicating a limiting content of this molecule in the MGDG matrix at high surface pressures. The thermodynamic studies confirm the stability of the MGDG:UQ mixtures at low surface pressures, although presenting a nonideal behaviour. Results point to consider UQ as a good candidate for studies of artificial photosynthesis.

Review Article

[Doughty 2009] Efficacy of different dry eye treatments with artificial tears or ocular lubricants: a systematic review

Michael J. Doughty and Sara Glavin

Ophthal. Physiol. Opt. 2009 29: 573–583

Abstract
Purpose: To objectively review the outcome of clinical studies where rose bengal stain (RB) has been used as an outcome measure to assess the efficacy of artificial tears (AT) in patients with dry eye.
Methods: From peer-reviewed articles published between 1947 and 2008, information was sought on dry eye status, as reported using a grading scheme, after use of RB as a diagnostic test, before and after use of a specific regimen of artificial tears or ocular lubricants for approximately 30 days. Mean baseline scores and post-treatment scores were calculated, along with the net change and the percentage change in the RB scores.
Results: From a total of 33 suitable data sets, published between 1985 and 2006, the group mean pre-treatment RB score was 4.25 ± 1.55 (±S.D.), which decreased to 2.84 ± 1.24 after 30 days of treatment. This represented a net change of)1.43 (95% CI of)1.04 to)1.45). For use of traditional AT (saline, hypromellose, etc), the net change was)0.95, it was)1.33 for use of carbomer (polyacrylic acid) gels and)2.10 for hyaluronic acid (HA) products. These changes represented net improvements of 25.9 ± 18.4%, 38.0 ± 20.7% and 41.8 ± 16.3% respectively. The greater change with HA was not associated with a lower final outcome score, but with higher pretreatment scores.
Conclusions: Based on RB grading schemes used by numerous different clinicians over many years, treatment of dry eye with artificial tears or ocular lubricants can be expected to improve the condition of the exposed ocular surface. Assuming no improvement without treatment, a 30 days treatment period can be projected to produce an overall improvement of around 25%, but with no unambiguous statistical differences between product types.

[Ridder 2005] Effect of Artificial Tears on Visual Performance in Subjects With Dry Eye

WILLIAM H. RIDDER III, OD, PhD, FAAO,
ALAN TOMLINSON, PhD, DSc MCOptom, FAAO, and JERRY PAUGH, OD, PhD, FAAO

1040-5488/05/8209-0835/0 VOL. 82, NO. 9, PP. 835–842
OPTOMETRY AND VISION SCIENCE, 2005

ABSTRACT: *Purpose.* Disruption of the anterior refracting surface of the eye (i.e., the tear layer) reduces visual performance. Tear layer breakup occurs soon after a blink in contact lens wearers and patients with dry eye. This study determined whether artificial tears stabilize the tear film and improve visual performance in contact lens wearers who also exhibit a dry eye. *Methods.* Five subjects with mild to moderate dry eye (probably as a result of an evaporative dry eye) during spectacle and contact lens wear were fitted with a Focus Night & Day hydrogel lens for this study. A temporal, two-alternative, forced-choice paradigm was used to measure contrast sensitivity. The stimuli were vertically oriented sine wave gratings (between 0.5 and 14 cpd) presented for 16.67 msec. The stimuli were presented at two different times after blink detection: 2 sec after blink

detection (i.e., before tear layer breakup) or 4 sec after tear film breakup. Four conditions were investigated at 4 sec after tear layer breakup: 1) without artificial tears added, 2) with Clerz2 (Alcon, Fort Worth, TX) instilled, 3) with Sensitive Eyes (Bausch & Lomb, Rochester, NY), and 4) with GenTeal (Novartis, Basel, Switzerland) applied. The artificial tears were instilled at 10-min intervals during the data collection.
The short-term visual effects of drop instillation were also investigated by continually monitoring contrast sensitivity for a 14-cpd grating after a single-drop administration. ***Results.*** **High spatial frequency contrast sensitivity and visual acuity were found to be reduced after tear film breakup in the absence of supplementation with artificial tears. For the group data (and four of five subjects), the instillation of Sensitive Eyes improved the contrast sensitivity and visual acuity to the level attained before tear breakup, thus prolonging visual performance. Clerz2 and GenTeal did not produce any enhancement in visual performance. A short-term decrease in contrast sensitivity was also observed with a single administration of Clerz2 and GenTeal.** ***Conclusions.*** **This study indicates that there was a benefit of Bausch & Lomb Sensitive Eyes tear supplementation on visual performance in subjects with an evaporative dry eye. This may be the result of 1) aqueous supplementation in these subjects and/or 2) the minimal tear layer disruption found with Sensitive Eyes drop administration. The results suggest that practitioners need to identify those patients who can benefit from the use of appropriate artificial tear supplements. (Optom Vis Sci 2005;82:835–842)**

[Grene 1992] Unpreserved Carboxymethylcellulose Artificial Tears Evaluated in Patients with Keratoconjunctivitis Sicca.

Grene, R Bruce M.D.; Lankston, Penny B.A.; Mordaunt, Julie M.S.; Harrold, Marsha B.S.; Gwon, Arlene M.D.; Jones, Robert M.D.

Cornea:
July 1992, vol 11 nº 4, pg 277-368

Abstract

In order to evaluate the therapeutic value of an unpreserved carboxymethylcellulose-based artificial tear in treatment of keratoconjunctivitis sicca (KCS), 56 patients with severe keratoconjunctivitis sicca were enrolled, at a single study center, in a randomized, double-masked, 8-week comparison with a preserved hydroxypropylmethylcellulose (HMC)-based artificial tear. Patients treated with the carboxymethylcellulose (CMC)-based tear showed significant improvement in fluorescein staining, symptoms, and impression cytology grades. Patients treated with HMC-based tears showed minimal improvement in a few variables. Impression cytology specimens were analyzed by a modified technique that maps the distribution of the various grades present on the specimen. With this technique, improvement in the cytology grades was noted in the group of patients using CMCbased tears. The improvement correlated with observed decreases in symptoms of discomfort and with scores for superficial punctate staining. This study supports the observed therapeutic value of unpreserved CMC-based artificial tears and suggests the possible reversal of squamous metaplasia in patients with KCS. Further studies are required to separate the benefit of the CMC formulation from the benefits of preservative elimination.

[Nilforoushan 2005] Effect of Artificial Tears on Visual Acuity

MOHAMMAD-REZA NILFOROUSHAN, MD, ROBERT A. LATKANY, MD, AND MARK G. SPEAKER, MD, PHD

(Am J Ophthalmol 2005;140:830–835.

● **PURPOSE: To study the effect of commonly used preservative free artificial tear, carboxymethylcellulose (CMC) 0.5% (Refresh Plus, Allergan, Irvine, California) on visual acuity in symptomatic dry eye (SDE) and asymptomatic dry eye (ADE) patients.**

● **DESIGN: Nonrandomized prospective clinical trial.**

● **METHODS: Prospective study involving 20 patients (40 eyes) with SDE and 20 patients (40 eyes) with ADE, all 40 years and older, were recruited from a clinic setting over a 1-month period. Distance visual acuity was measured by the Early Treatment of Diabetic Retinopathy Study (ETDRS) vision chart and near visual acuity was measured by the Lighthouse Near Vision chart before and 30 seconds after instillation of one drop of CMC.**
Distance and near visual acuity was measured both with and without correction. The duration of action of CMC was measured at 1-minute intervals until the patient's visual acuity returned to pretear level.

● **RESULTS: In both SDE and ADE groups, uncorrected and corrected near and distance vision showed a statistically significant improvement after the use of CMC (*P* <.05). There was no statistically significant difference in improvement between the SDE and ADE groups in all categories (*P* values > .05). The mean duration of improvement of vision was 2.93 minutes in the SDE group and 3.70 minutes in the ADE group (*P* _ .036).**

● **CONCLUSIONS: CMC 0.5% provides a temporary yet significant improvement in the visual acuity of SDE and ADE patients. The effect of artificial tears on visual acuity may be of diagnostic value in detecting ocular surface abnormality in symptomatic and asymptomatic patients.**

[Urzua 2012] Randomized Double-Blind Clinical Trial of Autologous Serum Versus Artificial Tears in Dry Eye Syndrome

Cristhian A. Urzua MD, Dario H. Vasquez MD, Andres Huidobro MD, MSc, Helio Hernandez MD & Jorge Alfaro MD

Current Eye Research, 2012, 37:8, 684-688

Purpose: To determine symptoms improvement in dry eye patients with short-term autologous serum (AS) eyedrops treatment using the standardized Ocular Surface Disease Index (OSDI) survey.
Materials and methods: A double-blind randomized crossover clinical trial was conducted, comparing short-term (2 weeks) topical treatment with AS eyedrops diluted at 20% versus conventional artificial tears treatment in adult severe dry eye syndrome (DES) patients. The main outcome measure was assessment of symptoms with OSDI survey. Secondary outcomes were corneal and conjunctival fluorescein staining score of OXFORD and tear break up time (TBUT). The protocol was registered in www.clinicaltrials.gov, ID number: NCT00779987.
Results: Twelve severe DES patients were included. Autologous serum treatment showed a statistically significant ($p = 0.002$) higher OSDI decrease (50%) versus conventional treatment (22%). There were no significant changes in objectives parameters (OXFORD and TBUT).
Conclusions: Severe DES patients treated with AS achieve better symptoms improvement compared to artificial tears in a short-term treatment.

[Nepp 2001] The clinical use of viscoelastic artificial tears and sodium chloride in dry-eye syndrome

Johannes Nepp*, Joerg Schauersberger, Gebtraud Schild, Kerstin Jandrasits, Jinus Haslinger-Akramian, Agnes Derbolav, Andreas Wedrich

Biomaterials 22 (2001) 3305–3310

This study was performed to test viscoelastic artificial tears (VAT) based on both subjective and clinical parameters in patients with keratoconjunctivitis sicca (KCS). Twenty-eight patients were evaluated in a randomized double-blind study. Sodium hyaluronate was used in two different concentrations (0.4%,

0.25%) and in combination with chondroitin sulfate. Each preparation was used for one week preceded by another weekly cycle using a sodium chloride solution. Before and after each cycle, clinical examinations were performed: tear film break-up time, Schirmer's test, lipid-layer thickness and fluorescein staining. Patients kept a record of the drop-frequency, subjective response and side effects. After the study, they were asked to give a rating of the various preparations. The severity of KCS was expressed based on a sicca score and correlated with response to viscoelastic treatment. Both
the subjective and the clinical parameters revealed no statistically significant differences between the various viscoelastic agents or between the viscoelastics and the sodium chloride solutions. Severe side effects did not occur. There was a positive correlation of response to viscoelastic treatment with severe KCS (+0.36) but not with mild KCS (_0.07). The VAT seems to be indicated in severe cases of dry-eye syndrome. Sodium chloride solutions may be a useful short-term alternative to other tear formulations.

[Wang 2010] Comparison of the Clinical Effects of Carbomer-Based Lipid-Containing Gel and Hydroxypropyl-Guar Gel Artificial Tear Formulations in Patients With Dry Eye Syndrome: A 4-Week, Prospective, Open-Label, Randomized, Parallel-Group, Noninferiority Study

Tsung-Jen Wang, MD[1,2,3]; I-Jong Wang, MD, PhD[3]; Jau-Der Ho, MD, PhD[1,2]; Hsiu-Chu Chou, PhD[4]; Szu-Yuan Lin, MD[5]; and Man-Ching Huang, MD, PhD[1,2]
Clinical Therapeutics/Volume 32, Number 1, 2010, pg 44-52

ABSTRACT

Background: Most marketed artificial tears are substitutes for the aqueous layers of the tear film; therefore, frequent instillation of artificial tears is necessary.
Newer gel-, cellulose-, and mineral oil-based formulations have been designed to overcome the disadvantages of current aqueous tear substitutes by offering prolonged retention times.

Objectives: The aim of this study was to compare the efficacy, safety, and local tolerance of artificial tears containing carbomer-based lipids or hydroxypropyl (HP)-guar gel in patients with dry eye syndrome.

Methods: A 4-week, prospective, randomized, parallel-group, comparative, noninferiority study was conducted at the Taipei Medical University Hospital(Taipei, Taiwan) in patients with dry eye syndrome who were randomly assigned to 1 of 2 treatment groups: the carbomer-based lipid-containing (CBLC) gel group and the HP-guar gel group. The primary end point was global assessment of study treatment by the patients at weeks 2 and 4. All patients met the diagnòstic criteria of impaired tear function and ocular surface abnormalities. Outcomes measured at baseline and 2 and 4 weeks included Schirmer' s test values, tear breakup time (TBUT), and a patient subjective assessment of symptoms. Safety and tolerability were assessed by clinically significant changes in terms of incidence of adverse events and conducted by unmasked investigators.

Results: A total of 30 Taiwanese patients with dry eye syndrome were included and randomly assigned to the 2 treatment groups: the mean (SD) age was 40.37 (14.96) years in the CBLC gel group and 49.49 (12.20) years in the HP-guar gel group. At baseline, the mean (SD) Schirmer' s test value was 4.53 (2.28) mm in the right eye and 5.13 (2.42) mm in the left eye in the CBLC gel group; 4.40 (2.16) mm in the right eye and 4.20 (1.78) mm in the left eye for the HP-guar gel group. The mean (SD) for both eyes was 4.83 (2.36) mm in the CBLC gel group and 4.30 (2.08) mm in the HP-guar gel group. There was no statistically significant difference between Schirmer' s scores at baseline. Patients in both treatment groups experienced an improvement from baseline in symptoms and signs, Schirmer' s test value, and TBUT at 2 and 4 weeks after treatment. The Schirmer' s test score increased to a mean of 8.20 (4.49) mm in the right eye and 9.33 (4.94) mm in the left eye in the CBLC gel group after 2 weeks, and increased to 10.07 (5.56) mm in the right eye and 10.86 (5.58) mm in the left eye after 4 weeks. The increases in Schirmer' s test score and TBUT were also observed in the HP-guar gel group. The Schirmer' s test score increased to 5.13 (2.18) mm in the right eye and 5.60 (2.74) mm in the left eye after 2 weeks, and increased to 6.93 (3.37) mm in the right eye and 6.53 (3.16) mm in the left eye after 4 weeks. The increase in Schirmer' s test values in both eyes was significantly greater at 2 and 4 weeks in the CBLC gel group than that in the HPguar gel artificial tear group (all, $P < 0.05$). Subjective patient assessment was better with the CBLC group

(excellent and good reported by 26.6% and 73.4%, respectively, of the CBLC gel group vs 13.4% and 33.4% of the HP-guar gel group at 4 weeks; both, $P = 0.004$).
Conclusions: Both artificial tear formulations were effective in relieving dry eye syndrome in these patients. The tolerance of CBLC gel artificial tears was comparable to that of HP-guar gel artificial tears.
(*Clin Ther.* 2010;32:44-52)

[McCann 2012]Effectiveness of Artificial Tears in the Management of Evaporative Dry Eye

McCann, Louise C PhD*; Tomlinson, Alan PhD, DSc*; Pearce, Edward I PhD*; Papa, Vincenzo MD, PhD†

Cornea:
January 2012 - Volume 31 - Issue 1 - pp 1-5
doi: 10.1097/ICO.0b013e31821b71e6

Abstract

Purpose: To compare the efficacies of sodium hyaluronate, hydroxypropyl methylcellulose (HPMC), and a new oil-in-water emulsion (Emustil unidose; SIFI) in the management of lipid-deficient dry eye.

Methods: Seventy-five subjects with dry eye were randomly divided into 3 groups. Each was allocated sodium hyaluronate, HPMC, or emulsion eyedrops to be used four times daily for 90 days. Parameters were measured at baseline, 30 days, and 90 days. A compliance visit was performed at days 7 and 60.

Results: Significant reduction ($P < 0.05$) in evaporation and improvement in symptoms in all groups were found. No statistically significant increase in tear turnover rate (TTR) was found with any solution. A significant difference in tear stability and noninvasive tear break-up time (NITBUT) was found in the emulsion and sodium hyaluronate groups but not in the HPMC group ($P > 0.05$). There was a significant decrease in osmolarity and corneal staining in the emulsion group ($P < 0.001$) but not in the sodium hyaluronate or HPMC group ($P > 0.05$).

Conclusions: A significant reduction in evaporation and improvement in symptoms in all therapy groups were found from baseline to 90 days. However, no significant effect was seen on TTR for any group. The emulsion drops were shown to perform best, improving tear stability, and decreasing osmolarity and corneal staining. These results are consistent with improvements in the lipid layer of the tear film as a result of prolonged use of emulsion drops.

[Mudgil 2011] Surfactant Properties of Human Meibomian Lipids

Poonam Mudgil and Thomas J. Millar

(*Invest Ophthalmol Vis Sci.* 2011;52:1661–1670) DOI:10.1167/iovs.10-5445

PURPOSE. Human meibomian lipids are the major part of the lipid layer of the tear film. Their surfactant properties enable their spread across the aqueous layer and help maintain a stable tear film. The purpose of this study was to investigate surfactant properties of human meibomian lipids in vitro and to determine effects of different physical conditions such as temperature and increased osmolarity, such as occur in dry eye, on these properties.
METHODS. Human meibomian lipids were spread on an artificial tear solution in a Langmuir trough. The lipid films were compressed and expanded to record the surface pressure–area (_-A) isocycles. The isocycles were recorded under different physical conditions such as high pressure, increasing concentration and size of divalent cations, increasing osmolarity, and varying temperature.
RESULTS. _-A isocycles of meibomian lipids showed that they form liquid films that are compressible and multilayered. The isocycles were unaffected by increasing concentration or size of divalent cations and increasing osmolarity in the subphase. Temperature had a marked effect on the lipids. Increase in temperature caused lipid films to become fluid, an expected feature, but decrease in temperature unexpectedly caused expansion of lipids and an increase in pressure suggesting enhanced surfactant properties.
CONCLUSIONS. Human meibomian lipids form highly compressible, non-collapsible, multilayered liquid films. These lipids have surfactants that allow them to spread across an aqueous subphase. Their surfactant properties are unaffected by increasing divalent cations or hyperosmolarity but are sensitive to temperature. Cooling of meibomian lipids enhances their surfactant properties.

[Phillips 1968] **Monolayer characteristics of saturated 1,2-diacyl phosphatidylcholines (lecithins) and phosphatidylethanolamines at the air-water interface**

- M.C. Phillips, D. Chapman

Biochimica et Biophysica Acta (BBA) - Biomembranes
Volume 163, Issue 3, Pages 285-428 (1968) ***Pages 301-313***

Abstract

Surface pressure—area data have been obtained for the homologous series of saturated 1,2-diacyl phosphatidylcholines and phosphatidylethanolamines at the air—water interface. The results are compared with data already in the literature and the various physical states of the monolayers are described. The lecithins formed more expanded films than the phosphatidylethanolamines and this is interpreted in terms of differences in the size and orientation of the polar groups. The heats and entropies associated with the transition from condensed to liquid-expanded film were calculated for dipalmitoyl lecithin. The values of these themodynamic parameters were similar to those observed for the transition from gel to smectic mesophase for this lecithin. This transition occuring in the bimolecular lamellae in water corresponds to the transition from condensed to expanded monolayer.

[Haç-Wydro 2009] Cholesterol and phytosterols effect on sphingomyelin/phosphatidylcholine model membranes-Thermodynamic analysis of the interactions in ternary monolayers

Katarzyna Ha¸c-Wydro *, Paweł Wydro, Patrycja Dynarowicz-Ła¸tka, Maria Paluch
Journal of Colloid and Interface Science 329 (2009) 265-272

In this work thermodynamic analysis of the interactions between lipids in ternary sphingomyelin/DPPC/sterol Langmuir films were performed to compare the effect of cholesterol, β-sitosterol and stigmasterolon a model membrane. The condensing effect of the respective sterols and the interactions between molecules in ternary mixtures were analyzed on the basis of the excess area per molecule and the excess free energy of mixing values. The stability of the mixed monolayers was verified with the free energy of mixing values. The conclusions on the ordering effect of sterols were drawn from the analysis ofthe compression modulus values. It was found that the stoichiometry of the mixed films of the highest thermodynamic stability and of the strongest interactions is the same for all the sterols investigated.
The results obtained prove that the mammalian sterol induces the strongest contraction of the area and reveals the strongest stabilizing and ordering effect among the investigated sterol. Stigmasterol was found to condense a model membrane in a weaker extent as compared to β-sitosterol, however, the differences in ordering properties of both phytosterols are less pronounced. The magnitude of the influence of the investigated sterols on a model membrane was thoroughly discussed from the point of view of the structure of their side chain, which determines the geometry of a sterol molecule.

[Dynarowicz 2004] Interactions between phosphatidylcholines and cholesterol in monolayers at the air/water interface

Patrycja Dynarowicz-Ł˛atka*, Katarzyna H˛ac-Wydro

Colloids and Surfaces B: Biointerfaces 37 (2004) 21–25

Mixtures of cholesterol and synthetic phospholipids, differing in saturation of phosphatidylcholine (PC) acyl chains, such as distearoylphosphatidylcholine (DSPC), stearoyl–oleoyl phosphatidylcholine (SOPC) and dioleoyl phosphatidylcholine (DOPC) have been studied as floating Langmuir monolayers at the air/water interface. In order to examine the influence of a polar group, distearoyl phosphatidylethanolamine (DSPE) was chosen. The films were spread at room temperature on aqueous subphases and characterized by the surface pressure–area (π–A) isotherms and compression modulus (C_{-1s}) values. The interactions were examined by analyzing the mean molecular areas and quantified by the excess free energy of mixing values. The obtained results indicate that the affinity of cholesterol to saturated/unsaturated phosphatidylcholines does not differ significantly, and revealed strong influence of the kind of a polar group on the cholesterol–phospholipid interactions. On the other hand, the apolar group structure was found to modify the stoichiometry of sterol–PC complexes.

[Stottrup 2005] Miscibility of Ternary Mixtures of Phospholipids and Cholesterol in Monolayers, and Application to Bilayer Systems

Biophysical Journal Volume 88 January 2005 269-276

Benjamin L. Stottrup, Daniel S. Stevens, and Sarah L. Keller

ABSTRACT We investigate miscibility transitions of two different ternary lipid mixtures, DOPC/DPPC/Chol and POPC/PSM/ Chol. In vesicles, both of these mixtures of an unsaturated lipid, a saturated lipid, and cholesterol form micron-scale domains of immiscible liquid phases for only a limited range of composítíons. In contras!, in monolayers, both of these mixtures produce two dístínct regions of immiscible liquid phases that span all compositions studied, the a-region at low cholesterol and the (3-region at high cholesterol. In other words, we find only limited overlap in miscibility phase behavior of monolayers and bilayers for the lipids studied. For vesicles al 25ºC, the miscibility phase boundary spans portions of both the monolayer a-region and (3-region. Within the monolayer (3-region, domains persist to high pressures, yet within the a-region, miscibility phase transition pressures always fall below 15 mN/m, far below the bilayer equivalent pressure of 32 mN/m. Approximately equivalen! phase behavior is observed for monolayers of DOPC/DPPC/Chol and for monolayers of POPC/PSM/Chol. As expected, pressure-area isotherms of our ternary lípid mixtures yield smaller molecular area and compressibility for monolayers containing more saturated acyl chains and cholesterol. All monolayer experiments were conducted under argon. We show

that exposure of unsaturated lipids to air causes monolayer surface pressures to decrease rapidly and miscibility transition pressures to increase rapidly.

[Wiegart 2005] Nanocrystal Induced Organization of a Langmuir Phospholipid Monolayer

Lutz Wiegart, Sea´n M. O'Flaherty, and Bernd Struth*
Langmuir **2005,** *21,* 1695-1698

The influence of crystal surface charge on the thermodynamic and structural behavior of phospholipid monolayers has been investigated. We present how charged nanocrystals in the vicinity of an inherently nonordered lipid membrane provoke strong effects on the molecular arrangment within the monolayer. Apart from the induction of phase shifts and nucleation processes, the molecules were forced to adopt an ordered phase. A very recently developed X-ray scattering method is used for the first time to replace time-consuming specular reflectivity measurements.Weconclude on the potential effects of crystal surface charge on cellular membranes.

[Wydro 2012] Sphingomyelin/phosphatidylcholine/cholesterol monolayers – analysis of the interactions in model membranes and Brewster Angle Microscopy experiments

Paweł Wydro*

Colloids and Surfaces B: Biointerfaces 93 (2012) 174– 179

In this work the properties of two ternary sphingomyelin/phosphatidylcholine/cholesterol monolayers imitating erythrocyte membrane were studied at various content of sterol. Phosphatidylcholines chosen for experiments differ in the length of sn-1 saturated chain in the molecule (1-stearoyl-2-oleoyl-sn-glycero-3-phosphocholine–SOPC vs. 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine – POPC). Langmuir monolayer experiments combined with Brewster Angle Microscopy prove that for both investigated systems the most favorable effect of cholesterol appears at 30% of sterol in the film. However, the interactions between molecules at 50% of sterol are only slightly weaker as compared to those for 1:1:1 films. It was also found that only at higher sterol concentration appear differences in the ordering effect of cholesterol on the systems containing PC molecules of various length of sn-1 saturated chain. Although the differences in the properties of POPC versus SOPC-containing monolayers were found, similarities in the morphology of the respective systems and stoichiometry of thermodynamically the most favorable mixture allow one to conclude that both SM/POPC/Chol as well as SM/SOPC/Chol monolayer can be used to mimic raft systems.

[Vranceanu 2007] Surface rheology of monolayers of phospholipids and colesterol measured with axisymmetric drop shape analysis

Marcel Vrˆanceanu a,b, Karin Winkler a, Hermann Nirschl b, Gero Leneweit a,*
Colloids and Surfaces A: Physicochem. Eng. Aspects 311 (2007) 140–153

Surface rheology of monolayers of a saturated phospholipid (dipalmitoylphosphatidylcholine, DPPC), an unsaturated phospholipid (dioleoylphosphatidylcholine, DOPC) and cholesterol is studied with axisymmetric drop shape analysis at the argon/water interface. Measurement techniques for lipids are described in detail. Profile analysis tensiometry (PAT) is used to determine the film pressure Π, surface elasticity and surface dilational viscosity of monolayers upon sinusoidal oscillations of the drop surface for various amplitudes a and frequencies f to assess their dependence on these dynamic parameters. It is shown that surface dilational viscosity strongly depends on the frequency and decreases by a factor

2–5 with increasing *f* in the considered range. Dilational viscosity is higher the more the monolayer approaches a relaxed state. Thus, the molecular interactions are stronger in the relaxed than in the stressed state. Surface elasticity is much less dependent on dynamic conditions. For DPPC a minimum of the dynamic surface elasticity is found for $f = 12.5$ mHz (at $\Pi = 17.5\text{mNm}^{-1}$) which coincides well with the relaxation freqüències measured in stress relaxation experiments. The dynamic surface elasticity of DPPC exhibits a plateau in the range $13.5\text{mNm}^{-1} \leq \Pi \leq 27\text{mNm}^{-1}$ in good coincidence with the phase boundaries of the coexistence region of micron-sized liquid crystalline domains surrounded by a fluid monolayer phase. In equilibrium measurements (Π/A-isotherms) a plateau of the film pressure is seen at the lower bound and a break at the upper bound of the coexistence region. Film pressure/area isotherms produced by PAT and a Langmuir film balance closely coincide as is shown in a comparison to literature values. However, the surface elasticities measured dynamically with oscillating surfaces widely deviate from those derived from isotherms in the case of DPPC and cholesterol, whereas for DOPC very good agreement can be found.

[Yan 2005] The Collapse of Monolayers Containing Pulmonary Surfactant Phospholipids Is Kinetically Determined

Wenfei Yan, Barbara Piknova, and Stephen B. Hall

Biophysical Journal Volume 89 July 2005 306-314

ABSTRACT Prior studies have shown that during and after slow compressions of monomolecular films containing the complete set of purified phospholipids (PPL) from calf surfactant at an air/water interface, surface pressures (7T) reach and sustain values that are remarkably high relative to expectations from simple systems with model lipids. Microscopy shows that the liquid-expanded, tilted-condensed, and collapsed phases are present together in the PPL films between 45 and 65 mN/m. The Gibbs phase rule restricts equilibrium coexistence of three phases to a single 7T for films with two components but not for more constituents. We therefore determined if the surprising stability of PPL reflects release from the thermodynamic restrictions of simple model systems by the presence of multiple components. Experiments with binary films containing dioleoyl phosphatidylcholine and dipalmitoyl phosphatidylcholine first tested the predictions of the phase rule. The onset of three-phase coexistence, determined by fluorescence microscopy, and its termination, established by relaxation of collapsing films on a captive bubble, occurred al similar 7T. Experiments for PPL using the same methods suggested that the three phases might coexist over a range of 7T, but limited to 2 mN/m, and extending below rather than above the coexistence 7T for the binary films. Our results show that the PPL films at high 7T must deviate from equilibrium and that they must then be metastable.

[Wydro 2011] The magnitude of condensation induced by cholesterol on the mixtures of sphingomyelin with phosphatidylcholines—Study on ternary and quaternary systems

Paweł Wydro*

Colloids and Surfaces B: Biointerfaces 82 (2011) 594–601

The studies on the condensing and ordering effect of cholesterol by application of the Langmuir monolayer technique are usually performed on binary lipid/cholesterol systems. The results concerning a quantitative analysis of these effects in multicomponent monolayers are very limited. In this work the condensing and ordering effect of cholesterol in ternary (SM/DSPC/Chol and SM/DOPC/Chol) and quaternary (SM/DSPC/DOPC/Chol) films was investigated. It was evidenced that the systems containing saturated PC (both SM/DSPC and SM/DSPC/Chol) are always more condensed and chain-ordered than the systems containing unsaturated PC (SM/DOPC and SM/DSPC/DOPC and their mixtures with cholesterol). However, the magnitude of condensation provoked by cholesterol at higher surface pressures is stronger on the monolayers containing unsaturated PC. The addition of cholesterol into SM/PC films induces the increase of chain-ordering however, the effectiveness of cholesterol as an ordering agent is determined

by the presence/absence of unsaturated phospholipid. The magnitude of the effect of cholesterol on the investigated mixed monolayer was analyzed in the context of the influence of sterol on lipid chains (ordering, straightening and reorientation of chains) as well as the reorientation of polar heads.

[Yuan 2002] The Size of Lipid Rafts: An Atomic Force Microscopy Study of Ganglioside GM1 Domains in Sphingomyelin/DOPC/Cholesterol Membranes

Chunbo Yuan, Jennifer Furlong, Pierre Burgos, and Linda J. Johnston
Biophysical Journal Volume 82 May 2002 2526-2535

ABSTRACT Atomic force microscopy has been used to study the distribution of ganglioside GM1 in model membranes composed of ternary lipid mixtures that mimic the composition of lipid rafts. The results demonstrate that addition of 1% GM1 to 1:1:1 sphingomyelin/dioleoylphosphatidylcholine/cholesterol monolayers leads to the formation of small ganglioside-rich microdomains (40-100 nm in size) that are localized preferentially in the more ordered sphingomyelin/cholesterol-rich phase. With 5% GM1 sorne GM1 microdomains are also detected in the dioleoylphosphatidylcholine-rich phase. A similar prefer- ential localization of GM1 in the ordered phase is observed far bilayers with the same ternary lipid mixture in the upper leaflet. The small GM1-rich domains observed in these experiments are similar to the sizes for lipid rafts in natural membranes but considerably smaller than the ordered bilayer domains that have been shown to be enriched in GM1 in recent fluorescence microscopy studies of lipid bilayers. The combined data from a number of studies of model membranes indicate that lateral organization occurs on a variety of length scales and mimics many of the properties of natural membranes.

Effect of a liposomal spray on the pre-ocular tear film

Jennifer P. Craig, Christine Purslow, Paul J. Murphy, James S.W. Wolffsohn
Contact Lens & Anterior Eye 33 (2010) 83–87

Purpose: With the potential to address evaporative dry eye, a novel spray has been developed in which phospholipid liposomes are delivered to the tear film via the surface of the closed eyelid. This study evaluated the short-term effects of liposomal spray application on the lipid and stability characteristics of the pre-ocular tear film in normal eyes.
Methods: Twenty-two subjects (12M, 10F) aged 35.1 _ 7.1 years participated in this prospective, randomised, double-masked investigation in which the liposomal spray was applied to one eye, and an equal volume of saline spray (control) applied to the contralateral eye. Lipid layer grade (LLG), non-invasive tear film stability (NIBUT) and tear meniscus height (TMH) were evaluated at baseline, and at 30, 60, 90 and 135 min post-application. Subjective reports of comfort were also compared.
Results: Treated and control eyes were not significantly different at baseline ($p > 0.05$). Post-application, LLG increased significantly, at 30 and 60 min, only in the treated eyes ($p = 0.005$). NIBUT also increased significantly in the treated eyes only ($p < 0.001$), at 30, 60 and 90 min. TMH did not alter significantly ($p > 0.05$). Comfort improved relative to baseline in 46% of treated and 18% of control eyes, at 30 min post-application. Of those expressing a preference in comfort between the eyes, 68% preferred the liposomal spray.
Conclusions: Consistent with subjective reports of improved comfort, statistically and clinically significant improvements in lipid layer thickness and tear film stability are observed in normal eyes for _1 h after a single application of a phospholipid liposomal spray.

Effect of three different liposomal eye sprays on ocular comfort and tear film

Heiko Pult, Felicity Gill, Britta H. Riede-Pult
Contact Lens & Anterior Eye 35 (2012) 203– 207

Purpose: To evaluate the effect of three different liposomal eye sprays on ocular comfort and tear film stability.

Methods: OptrexActiMist (AM, Optima-Pharma, Germany) was applied onto one, randomly selected eye of 80 subjects (female = 49; mean age = 49 years±18.6 SD) in a multi-centred, double-masked study. DryEyesMist (DEM, Boots) or TearMist (TM, Tesco) was applied onto the contralateral eye in randomized order. Over-all symptoms were investigated using the Ocular Surface Disease Index (OSDI). Ocular comfort (visual-analogue scale 0–100 [100 = perfect]) and non-invasive tear film stability (NIBUT) of each eye was evaluated before application (randomized order) and were again measured 10 min after application.

Effects of products on ocular comfort and NIBUT were calculated as "factor" (=after-treatment/beforetreatment).

Differences between measurements were analysed by ANOVA repeated measurements and differences between groups by the dependent t-test (or the non-parametric equivalent).

Results: OSDI-scores (mean = 8.1±9.0 SD), comfort (65±24) and NIBUT (12 s±12.3) were statistically similar between centres ($p > 0.400$). Comfort and NIBUT were not different ($p > 0.14$) between product groups before application. Comfort and NIBUT improved significantly after application of AM ($p < 0.001$) but worsened with the comparing products ($p < 0.058$). Comfort improved by a mean factor of 1.5 (±0.82 SD) after application of AM but decreased after application of the comparing products (DEM: 0.9±0.33; TM: 0.9±0.34). Both factors were significantly better in AM ($p < 0.027$).

Conclusion: The original liposomal eye-spray 'OptrexActiMist' significantly improved ocular comfort and tear film stability while 'TearMist' or 'DryEyesMist' worsened both criteria. The latter two products may not be clinically effective in the treatment of dry eye.

Compatibility of phospholipid liposomal spray with silicone hydrogel contact lens wear

Michael T.M. Wang[a], Kalaivarny Ganesalingam[b], Chee Seang Loh[b], Trisha Alberquerque[b], Suhaila Al-Kanani[b], Stuti L. Misra[a], Jennifer P. Craig

Contact Lens and Anterior Eye 40 (2017) 53–58

Purpose: To assess the effects of two weeks of regular phospholipid liposomal spray application on lipid layer grade, tear film stability, subjective comfort, visual acuity, and lipid deposition in silicone hydrogel contact lens wearers. Methods: Thirty-one existing contact lens wearers were enrolled and fitted with two week planned replacement silicone hydrogel contact lenses (Acuvue1 Oasys1) in a prospective, randomized, paired-eye, investigator-masked trial. A phospholipid liposomal spray (Tears Again1) was applied to one eye (randomized) four times daily for two weeks. LogMAR high contrast visual acuity (VA), low contrast glare acuity (LCGA), non-invasive tear film break-up time (NIBUT), and lipid layer grade (LLG) were measured at baseline and day 14, in both treated and control eyes. Subjective comfort relative to baseline, and spectrofluorophotometric assessment of contact lens surface lipid deposition were also assessed on day 14. Results: All measurements did not differ at baseline between treated and control eyes. Lipid layer thickness and tear film stability were increased on day 14 in treated eyes (all $p < 0.05$), but not in control eyes (all $p > 0.05$). A greater proportion of participants reported improved comfort in the treated eye relative to the control eye ($p = 0.002$). There were no significant differences in visual acuity or in contact lens surface lipid deposition, between treated and control eyes, on day 14 (all $p > 0.05$). Conclusion: The phospholipid liposomal spray increased tear film stability, lipid layer thickness and subjective comfort in silicone hydrogel contact lens wearers, without adversely affecting visual acuity or contact lens surface lipid deposition.

H Pult, R Khaireddin, BH Riede-Pult, The effect of three diferent phospholipid-containing eye sprays on tear film and symptoms. 7th International Conference on the Tear Film & Ocular Surface. September 18-21, 2013, Taormini, Sicily, Italy.

Effects of Lipid Supplements on Tear Biochemistry in Contact Lens Wearers

Athira Rohit*, Mark D. P. Willcox*, and Fiona Stapleton*

OPTOMETRY AND VISION SCIENCE, VOL. 93, NO. 10, PP. 1203-1209

Purpose. To establish the effect of lipid supplements on tear lipid biochemistry and their influence on lens wear comfort in habitual lens wearers.

Methods. Forty habitual soft contact lens wearers were recruited to a double-masked, randomized crossover trial. An emulsion drop containing phosphatidylglycerol (Systane Balance; Alcon) and a liposomal spray containing phosphatidylcholine (Tears again; BioRevive) along with saline placebos were used three times a day for 14 days with 48 hours of washout between each intervention. The Contact Lens Dry Eye Questionnaire categorized participants into symptomatic and asymptomatic wearers. Ocular comfort was measured using the Ocular Comfort Index. Basal tears (15 Kl from each eye) were collected with lenses in situ and assayed for the concentration and activity of phospholipase ($sPLA_2$) and the concentration of a malondialdehyde (MDA). Electrospray ionization mass spectrometry characterized the tear lipidome.

Results. Neither of the lipid supplements improved lens wear comfort compared to baseline. The spray treatment did not affect the concentration of the majority of lipid classes either at day 1 or at day 14. Both the lipid and placebo drops resulted in increased concentration of several lipid classes after day 1 of use, but by day 14, the concentration of most of the lípid classes had returned to baseline levels.With the lipid spray, $sPLA_2$ activity (0.38 T 0.2 vs. 0.73 T 0.6 mmol/min/ml, p = 0.03) and lysophosphatidylethanolamine (LPE) (1.3 T 0.5 vs. 2.7 T 0.07 pmol/Kl, p = 0.02) were higher in the symptomatic group compared to asymptomatic group at day 1 but not at day 14. The lipid drop resulted in increased LPE concentration in symptomatic wearers at day 1 (1.7 T 0.3 vs. 2.4 T 0.3 pmol/Kl, p = 0.01) and at day 14 (1.7 T 0.4 vs. 2.5 T 0.5 pmol/Kl, p =0.04). Ocular comfort was inversely proportional to the level (r = -0.21, p = 0.007) and activity of $sPLA_2$ (r = -0.20, p = 0.01).

There was an association between $sPLA_2$ and LPC (r = 0.41, p G 0.001) and LPE (r = 0.40, p = 0.001), and a negative association with (O-acyl)-U-hydroxy fatty acids (OAHFAs) (r = -0.30, p = 0.03) in tears.

Conclusions. Contact lens wear comfort was associated with $sPLA_2$ concentration and activity in tears. Lipid biochemistry was transiently influenced by exogenous supplements. Although the specific supplement formulations tested did not differ from placebo in this study, the results do suggest a potential role for lysophospholipids and OAHFAs in modulating symptoms during contact lens wear.

Annex I

Lágrimas artificiales

La problemática asociada a la sintomatología de ojo seco es ya importante en nuestros días, con un elevado número de personas afectadas clínicamente. No es el objetivo de este trabajo revisar y analizar las posibles causas de este problema, sino presentar las soluciones que se aplican a nivel de lágrima artificial para reducir sus efectos/mejorar la salud visual de las personas que lo padecen.

Tipos o estrategias

1. Suero fisiológico (solución salina)
    i. Composición: Agua con NaCl (0.9%)
    ii. Función: Aumentar el volumen de lágrima
2. Con componentes viscosantes
    i. Composición: Varios tipos (Carbómero o carbopol, derivados celulósicos, PVA, PAA, HA, hialuronato sódico, hidroxipropilguar, …)
    ii. Función: Aumentar el volumen de lágrima, evitar evaporación, dar confort
3. Con lípidos (“oil” en inglés) (Lágrimas biomiméticas)
    i. Función: Reforzar la capa lipídica, evitar evaporación, lubricar

Otros componentes de las lágrimas artificiales:

- Demulcentes: protegen las membranas mucosas, lubrican y pueden aportar viscosidad
    - Derivados celulósicos (HPMC, CMC), Dextrano 70, Gelatina, Polioles (PG, PEG), PVA, Povidona
- Conservantes
    - Polyquad (cloruro de polidronio)

Referencias

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Mastereyeasociates.com

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The eye digest

Tipo3:

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- SY Wishimura et al, Langmuir 24 (2008) 11728-33. Effect of lysozyme adsorption on the interfacial rheology of DPPC and cholesteryl myristate films.
- Soothe XP (Bausch & Lomb)

Lágrimas comerciales (orden alfabético)

Acuaiss gotas humectantes, de DISOP

Acuolens, de Alcon

Aquify, de CIBA Vision

Blink contacts soothing eye drops, de AMO

Colircusi humectante

Dexafree*, de Thea (colirio)

DISOP gotas

DISOP bany ocular

Hidrathea, de Thea (colirio)

Lacryvisc

Oculotect, de Alcon

Sensitive eyes** lubricante de lentes, de Bausch & Lomb

Tears humectante solución, de Alcon

Thera Tears de Conoptica, lubricante (0.25%), gel líquido (1%)

Timogel*, de Thea (farmacología)

Viscofresh, de Allergan

Lágrimas comerciales

- Aquify, de CIBA Vision
    - Hialuronato sódico

- *Acuaiss Drops:* (gotas humectantes)
    - Àcid hialuronic, hidroxietilcel·lulosa, clorur sòdic, tetraborat sòdic, àcid bòric, EDTA (àcid etilendiamintetraacètic) disòdic 0,02% i polihexanida 0,0001%.

- Acuaiss Bany ocular*:
    - Àcid hialurònic i polihexametilè biguanida al 0.0002%, clorur sòdic, fosfat disòdic, fosfat monosòdic en aigua purificada.

- Acuolens
    - Colirio, alivia sequedad ocular
    - Hipromelosa 3 mg/mL (hidroxipropilmetilcelulosa: polímero semisintético, polisacárido, viscoelástico, inerte), NaCl 5.5 mg/mL, KCl, $MgCl_2 \cdot 6H_2O$, $CaCl_2 \cdot 2H_2O$, $ZnCl_2$, hidrogenofosfato de disodio dodecahidrato, dihidrogenofosfato de sodio monohidrato, hidrogenocarbonato de sodio.

- Blink (TM) de AMO Ireland: sin conservantes
    - Colirio formulado para usuarios de lentes de contacto, calma y alivia los ojos secos y cansados. Adecuado para todas las lentes de contacto sin necesidad de quitarselas primero.
    - Hialuronato sódico 0.15% (polisacárido pertenecientea los glicosaminoglicanos), cloruro sódico, fosfato sódico, fosfato sódico dibásico, agua destilada

- *Blink® contacts:*
    - Hialuronat sòdic al 0,15%, OcuPure® conservant al 0,005%, clorur de calci (di hidratat), clorur potàssic, clorur sòdic, tampó de borat, clorur de magnesi i aigua destil·lada.

- Blink Intensive Tears
    - Hialuronat sòdic, OcuPure® conservant, polietilenglicol 400 (PEG 400) 0.25%, clorur de calci (di hidratat), clorur potàssic, clorur sòdic, tampó d'àcid bòric i borat de sodi (decahidratat), clorur de magnesi i aigua destil·lada.

- Colircusi humectante
  - Colirio en solución, de baja viscosidad que alivia los estados de sequedad ocular
  - Hipromelosa 3 mg/mL, NaCl 5.5 mg/mL, BAK, edetato disodico, fosfato disodico, fosfato monosodico.
- DISOP gotas
  - 0.1% povidona, 0.1% hidroxietilcelulosa, edetato disódico 0.1%, 0.0001% polihexametilenbiguanida, NaCl, ácido bórico, tetraborato sódico.
- DISOP baño ocular
  - Ácido hialurónico, 0.0002% polihexametilenbiguanida
- Hidrathea, colirio en solución
  - 9 mg NaCl/mL solución, hidrógeno fosfato de sodio dodecahidrato, dihidrógeno fosfato de sodio
  - Solución que humedece, lubrifica e hidrata la superficie ocular, alivia los síntomas de sequedad ocular.
- INNOXA
  - Contiene liposomas (formados por lípidos)
  - Composición: lecitina de soja, NaCl, etanol, otros
- Lacryvisc
  - Carbómero 3mg/g, BAK 0.005%, sorbitol, NaOH.
- Lipolac gel oftálmico
  - Lipolac gel oftálmico es un sustituto del flujo lagrimal que se utiliza en casos de producción inadecuada de lágrimas y en el tratamiento sintomático del ojo seco.
  - carbómero (ác. poliacrílico) 0.2% p/p (conc. carbomero 940 o carbopol 940), cetrimida, sorbitol, triglicéridos de cadena media, hidróxido sódico (para ajuste de pH) y agua purificada
- Sensitive eyes** lubricante de lentes, de Bausch & Lomb
  - Hipromelosa 2.5 mg/mL

- Systane Ultra
    - Polietilenglicol (PEG) 400, propilenglicol (PG), hidroxipropilguar, sorbitol, aminometilpropanol, NaCl, polyquad 0.001% (como conservante) y otros (ácido bórico, KCl)
- Systane UD de Alcon
    - Polietilenglicol (PEG) 400, propilenglicol (PG), hidroxipropilguar, NaCl, y otros (ácido bórico, CaCl2, MgCl2, KCl, ZnCl2)
    - Systane monodosis sin conservante no lleva polyquad.
- *Theratears®:*
    - Cada dosis unitària conté 0,6 ml de carboximetilcel·lulosa de sodi a al 0,25%, clorur de sodi, clorur de potassi, bicarbonat de sodi, clorur de calci, clorur de magnesi, fosfat de sodi, solució tampó de borat i aigua purificada.
- Tears humectante
    - Colirio en solución, lágrima artificial, alivio de sequedad ocular.
    - Dextran 70 1 mg/mL (polisacárido de glucosa ramificado, M=70000), hipromelosa 3 mg/mL, cloruro de benzalconio 0.1 mg/mL, edetato disódico, NaCl, KCl, NaOH y/o HCl (¡!)
- Viscofresh 0.5%
    - Solución oftálmica esteril. Alivia los síntomas de ojo seco.
    - Carmelosa sódica 2 mg/0.4 mL (carboximetilcelulosa sódica: polímero de alto peso molecular), NaCl,lactato sódico, KCl, CaCl2, MgCl2.

Farmacos

- Eloisin
    - Eledoisina trifluoroacetato 0.4 mg/mL, glucosa 50 mg/mL, BAK, manitol.
- Timogel 0.1%
    - Gel oftálmico, beta bloqueante que reduce la presión intraocular
    - Timolol (como maleato) 1 mg/g, BAK 0.05 mg/g, sorbitol, PVA, carbómero, acetato de sodio trihidratado, monohidrato de lisina.
- Dexafree 1mg/mL*
    - Colirio en solución
    - Fosfato de dexametasona y sodio (grupo de corticosteroides, inhiben los síntomas inflamatorios), edetato disodio, hidrogenofosfato de disodio dodecahidrato, NaCl.

Lágrimas comerciales de ALCON

- Acuolens
    - Hipromelosa (≈0.3%): hidroxipropilmetilcelulosa
- Systane UD
    - Hidroxipropilguar (polisacárido entrecruzado), polietilenglicol 400, propilenglicol
- Systane Ultra
    - Polietilenglicol 400, propilenglicol, hidroxipropilguar, polyquad (0.001%): cloruro de polidronio (derivado del BAK)
- Colircusi humectante
    - Hipromelosa (≈0.3%)
- Lacryvisc
    - Carbomero (≈0.3%): polímero sintético del ácido acrílico (ácido poliacrílico)
- Tears humectante
    - Dextrano 70 (≈0.1%, 1.0 mg/mL): polisacárido, hipromelosa (≈0.3%, 3.0 mg/mL). También contiene cloruro de benzalconio
- Oculotect
    - Povidona (50 mg/mL), BAK, NaCl
- Eloisin*
    - Eledoisina (farmacología)

Lágrimas artificiales comerciales de HIDRATHEA

- Hidrathea, colirio
- Dexafree, colirio

CLASIFICACION TIPOS DE LÁGRIMAS ARTIFICIALES:

PRINCIPIOS ACTIVOS

Ácido hialurónico: Acción más duradera que carmelosa y la hipromelosa.

GENTEAL HA 0.1% Colirio 10mL

HYALDROP advanced 0.24% colirio 10 mL

HYLO-COMOD CROMA 0.1% colirio 10 mL

LACRIMAX GERMED 0.2% colirio 10 mL

NOSA LENTS EYES RELAX 6 Ml

OPTICOL 0.3% solución oftalmica viscose 8 mL

OXYAL 0.15% colirio 10mL

VITADROP 0.15% COLIRIO 10 mL

Hipromelosa (Hidroxipropilmetil celulosa): Menos eficaz que la carmelosa, requiere instilaciones frecuentes sobre todo al principio del tratamiento. Acción más duradera con las concentraciones más altas.

TEARS HUMECTANTE® 0.3 % colirio 15mL (ALCON): Hipromelosa 3 mg, dextran 70 1 mg, conservantes.

ARTIFIC® 0.32% COLIRIO 10 mL

DACROLUX® 0.3% COLIRIO 10Ml

HIDROCIL FILAC® 0.25% 10mL

HIDROCIL PENSOLAC® 0.5% COLIRIO 10Ml

SUPRAFRESH® GOTAS 10Ml

COLIRCUSI HUMECTANTE 15Ml

Cloruro sódico: Acción de corta duración. Colirios utilizados para el confort ocular después de quitar las lentes de contacto. No contiene conservantes.

HIDRATHEA® 0.9% Colirio 10mL

Acetilcisteina: es un mucolitico. En combinación con hipromelosa es muy útil en ojo seco con deficiencia mucinica.

ILUBE®

Acetylcysteine 5.0% w/v
Otros componentes**:** Disodium edentate, Hypromellose, Benzalkonium chloride, Sodium hydroxide, Purified water

Acetylcysteine has marked mucolytic properties which reduce the viscosity and tenacity of mucus in the eyes. This combined with the emollient properties of hypromellose, ensures lubrication and soothing relief for dry eye syndromes.

Alcohol polivinilico: Su acción es más duradera que la hipromelosa, pero más corta que las lágrimas que contienen carbomero. Alta concentración de fosfatos con riesgo de depósito. Útil

si la presencia de mucina en la superficie ocular está disminuida. Se puede tolerar peor que la carmelosa o hipromelosa.

LIQUIFILM® (ALLERGAN)

Polivinílico alcohol 14.0 mg/1 ml
otros: Benzalconio cloruro

SON TEARS®

VISTYL COLIRIO® 1.4% 10 ML

Carbomeros: se adhieren a la superficie ocular y prolongan la duración de la lágrima. Se debe aplicar 4 veces al día. Acción más duradera y menos frecuencia de instilaciones que la carmelosa y la hipromelosa (máximo 4 veces al día). Efectos toxicos in Vitro en células corneales. Se puede tolerar peor que la carmelosa y la hipromelosa.

GELTEARS®

LIPOSIC®

LIQUIVISC®

VISCOTEARS® 2% gel

REFRESH LIQUIGEL® (ALLERGAN): Lubricante: Polímeros de Carboximetilcelulosa sódica 1%.

REFRESH TEARS® (ALLERGAN) idem Refresh Liquigel® 0,5%.

LIPOLAC® 0.2% gel

OFARSIN® 0.2% gel

SICCAFLUID® 0.25% gel

Carmelosa: Carboximetil celulosa. Lágrima de acción duradera. Es la alternativa a las lágrimas que contienen carbomero. Tiene efecto mucoprotector. Si se usa con lentes de contacto, escoger preparación de 0,5% en vez de 1%, para evitar dejar depósitos en estas. Se usa para rehidratar el ojo. Se suele usar en combinación con lágrimas de corta duración.

CELLUVISC®

CELLUFRESH®

INNOCLEAR® 0.5% COLIRIO 10 mL

THERATEARS® lubricante 0.25%-1% colirio

Povidona: Lagrima de larga duración. Apta para uso comitante con LC.

OCULOTECT® 5% colirio 10 mL

Gel: Forma un gel protector. Se puede usar con pacientes usuarios de LC

SYSTANE® (ALCON): Lubricantes: Polietilenglicol 400(0,4%) y polipropilenglicol (0,3%) con gel hidroxypropil como agente viscosante.

Lipidicas: lagrima de larga duración que contiene lípidos para estabilizar la capa lipidica de la lágrima.

REFRESH ENDURA®

Pomadas con parafina: Causa visión borrosa temporal. Se debe aplicar antes de dormir. No se debe usar en combinación con LC. No contienen conservantes.

LACRILUBE®

LACRITEARS®

TEARS GEL®: (ALCON) Parafina liquida 0,03 mg/g, lanolina líquida anhidra 0,03 mg/g

LUBRIFILM ®(PETROLATO, ACEITE MINERAL Y LANOLINA)

Hidroxipropil celulosa: inserto. Cilindro que se coloca en el fórnix inferior y se funden y se disuelven paulatinamente en la cuenca lagrimal durante 8-12 horas. Salvo problemas de extrusión o visión borrosa han dado resultados satisfactorios a algunos pacientes. Compatibles con uso LC

LACRISERT® (ATON PHARMA)

LAGRIMAS ARTIFICIALES VADEMECUM

- ACUOLENS Colirio en solución 3 mg/ml
- ARTIFIC Colirio en solución 3,2 mg/1 ml
- ARTIFIC Colirio en solución unidosis 3,2 mg/1 ml
- B.S.S. Sol.
- CELLUFRESH Sol. oft. 2 mg/unidosis
- COLIRCUSI HUMECTANTE Colirio en solución 3 mg/ml
- DACROLUX Colirio
- HIDRATHEA Colirio en solución 9 mg/ml
- LACRILUBE Pom. oft.
- LACRYVISC Gel oftálmico 3 mg/g
- LIPOLAC Gel oftálmico 0,2%
- LIQUIFILM LAGRIMAS Sol. oft. 14 mg/ml
- LIQUIFRESH Sol. oftálmica
- LUBRIFILM Pom. oft.
- OCULOTECT Sol. oft. 50 mg/ml
- OCULOTECT MONODOSIS Sol. oft. 50 mg/ml
- OFARSIN Gel oftálmico 2 mg/g
- OFARSIN Gel oftálmico unidosis 2 mg/g
- OPTAVA Colirio en solución 5 mg/ml
- OPTAVA Colirio en solución 5 mg/ml (unidosis)
- OPTREX Colirio natural 13 g/100 ml
- REVIC Gel oftálmico 0,3%
- REVIC MONODOSIS Gel oftálmico 0,3%
- SICCAFLUID Gel oftálmico 0,25%
- SICCAFLUID Gel oftálmico 0,25% monodosis
- TEARS HUMECTANTE SOLUCION Colirio en solución 3 mg/ml + 1 mg/ml
- VISCOFRESH Sol. oft. unidosis 0,5%
- VISCOFRESH Sol. oft. unidosis 1%
- VISCOTEARS Gel líq. oftálmico 0,2%