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4th International Conference on Clinical & Experimental Ophthalmology

Equilibrium Binding Interactions Between Lotrafilcon A Soft Contact Lenses And The Two Prostaglandin Anti-glaucoma Drugs Bimatoprost And Tafluprost

Advantar Laboratories, Inc

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PRESENTATION OVERVIEW
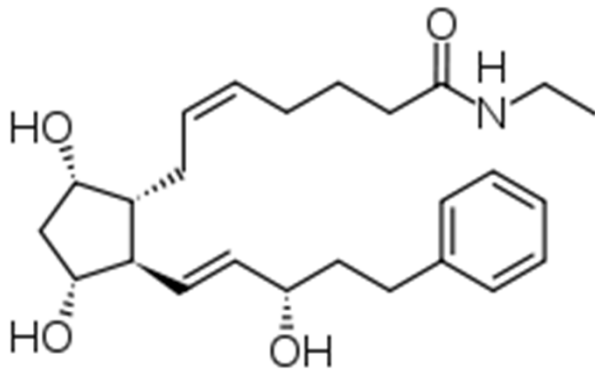
- Prostaglandin Drugs Description
- Lotrafilcon Lens Description
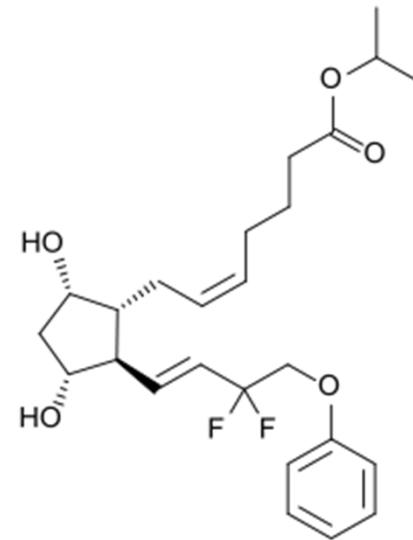- Equilibrium Binding Equations
- Methods
- Results
- Conclusions

Prostaglandin Drugs

- Bimatoprost
  - LogP = 3.2
  - 300 µg/mL plus sodium chloride, sodium phosphate, and citric acid in water

- Tafluprost
  - LogP =4.5
  - 15 µg/mL plus glycerol, sodium dihydrogen phosphate, disodium edetate, polysorbate 80, and water

Lotrafilcon Soft Contact Lens

- block copolymer of poly(dimethylsiloxane) and poly(perfluoroether)
- highly porous and highly permeable
- rapid absorption of various drugs from solution into Lotrafilcon A lens material

Equilibrium Binding

- $E_B = M_P * V_S / W_P * M_S$
  - E_B = Equilibrium Binding Constant
  - M_P = Solute Mass Bound to Polymer (lens)
  - V_S = Volume of Solution
  - W_P = Polymer (lens) Weight
  - M_S = Solute Mass in Solution Phase
- $1/F_{soln} = E_B * (W_P/V_S) + 1$
  - $F_{soln} = [Solute]_{obs} \div [Solute]_{init}$ = Fraction of Initially-added Solute in Solution Phase at equilibrium

Methods

- Incubate lens pieces with drug in solution (formulation)
- Vary Solution Volume with constant mass of lens pieces
- Assay for [Drug] by UPLC
- 25 or 37 C
- Marker Compounds With Known LogP Values
  - Dimethyl, Diethyl, and Dipropryl Phthalates (DMP, DEP, DPP)
  - Methyl, Ethyl, and Propyl Esters of p-Hydroxybenzoic Acid (MePB, EtPB, and PrPB)
  - Incubated in PBS with lens pieces and analyzed by UPLC

Phthalates Vs Time and W_p/V_s Ratio

Solute	[Solute]$_{Init}$, mg/mL	[Solute]$_{obs}$, mg/mL	W_P, mg	V_S, mL	Temp °C	Time, hr	100*F$_{soln}$
DMP	0.30	0.070	18.2	0.1	37	1	23
DMP	0.30	0.108	18.0	0.2	37	1	36
DMP	0.30	0.148	20.5	0.3	37	1	49
DMP	0.30	0.156	20.2	0.4	37	1	52
DMP	0.30	0.129	17.9	0.2	37	0.25	43
DMP	0.30	0.118	21.2	0.2	37	0.5	39
DMP	0.30	0.122	21.1	0.2	37	1	41
DMP	0.30	0.127	18.5	0.2	37	2	42
DEP	0.30	0.014	18.2	0.1	37	1	4.7
DEP	0.30	0.029	18.0	0.2	37	1	10
DEP	0.30	0.051	20.5	0.3	37	1	17
DEP	0.30	0.056	20.2	0.4	37	1	19
DEP	0.30	0.050	17.9	0.2	37	0.25	17
DEP	0.30	<LOD	21.2	0.2	37	0.5	*
DEP	0.30	0.034	21.1	0.2	37	1	11
DEP	0.30	0.036	18.5	0.2	37	2	12
DPP	0.30	<LOD	18.2	0.1	37	1	*
DPP	0.30	0.002	18.0	0.2	37	1	0.6
DPP	0.30	0.008	20.5	0.3	37	1	2.8
DPP	0.30	0.006	20.2	0.4	37	1	2.1

Results – E_B For Bimatoprost

Table 1   **Equilibrium Binding Results and Computations for Bimatoprost (In Topical Ophthalmic Solution) Interactions with Lotrafilcon A Lens Material***

Sample	V_s, mL	W_p, mg	F_{soln}[†]	W_p/V_s	$1/F_{soln}$
1-1	0.10	15.38	0.239	154	4.19
1-2	0.10	17.07	0.244	171	4.10
1-3	0.10	17.24	0.202	172	4.94
2-1	0.20	16.71	0.504	83.6	1.99
2-2	0.20	16.70	0.348	83.5	2.88
2-3	0.20	16.99	0.345	85.0	2.90
3-1	0.30	15.62	0.473	52.1	2.11
3-2	0.30	15.80	0.513	52.7	1.95
3-3	0.30	16.20	0.470	54.0	2.13
4-1	0.40	15.23	0.466	38.1	2.14
4-2	0.40	16.03	0.492	40.1	2.03
4-3	0.40	15.77	0.482	39.4	2.07
	Mean =	16.23		Slope** =	0.0194
	%RSD =	4.27%		Intercept** =	1.13
				RSQ** =	0.907

* At 37 °C, incubation interval = 60 min. † See equation (2). ** Slope, intercept and RSQ per equation (5).
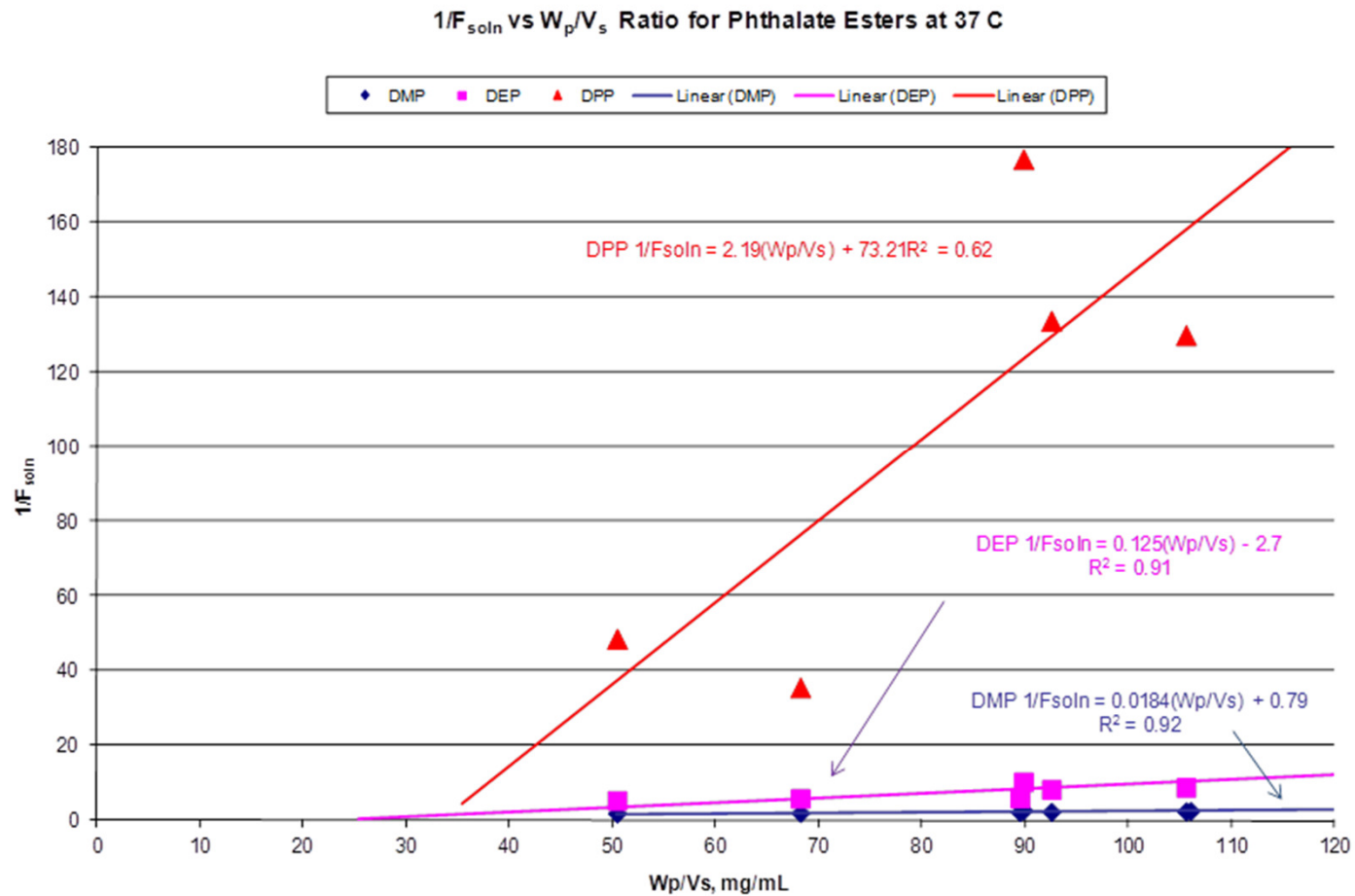
E$_B$ For Tafluprost

Table 1   **Equilibrium Binding Results and Computations for Tafluprost (in Saflutan Drug Product) Interactions with Lotrafilcon A Lens Material***
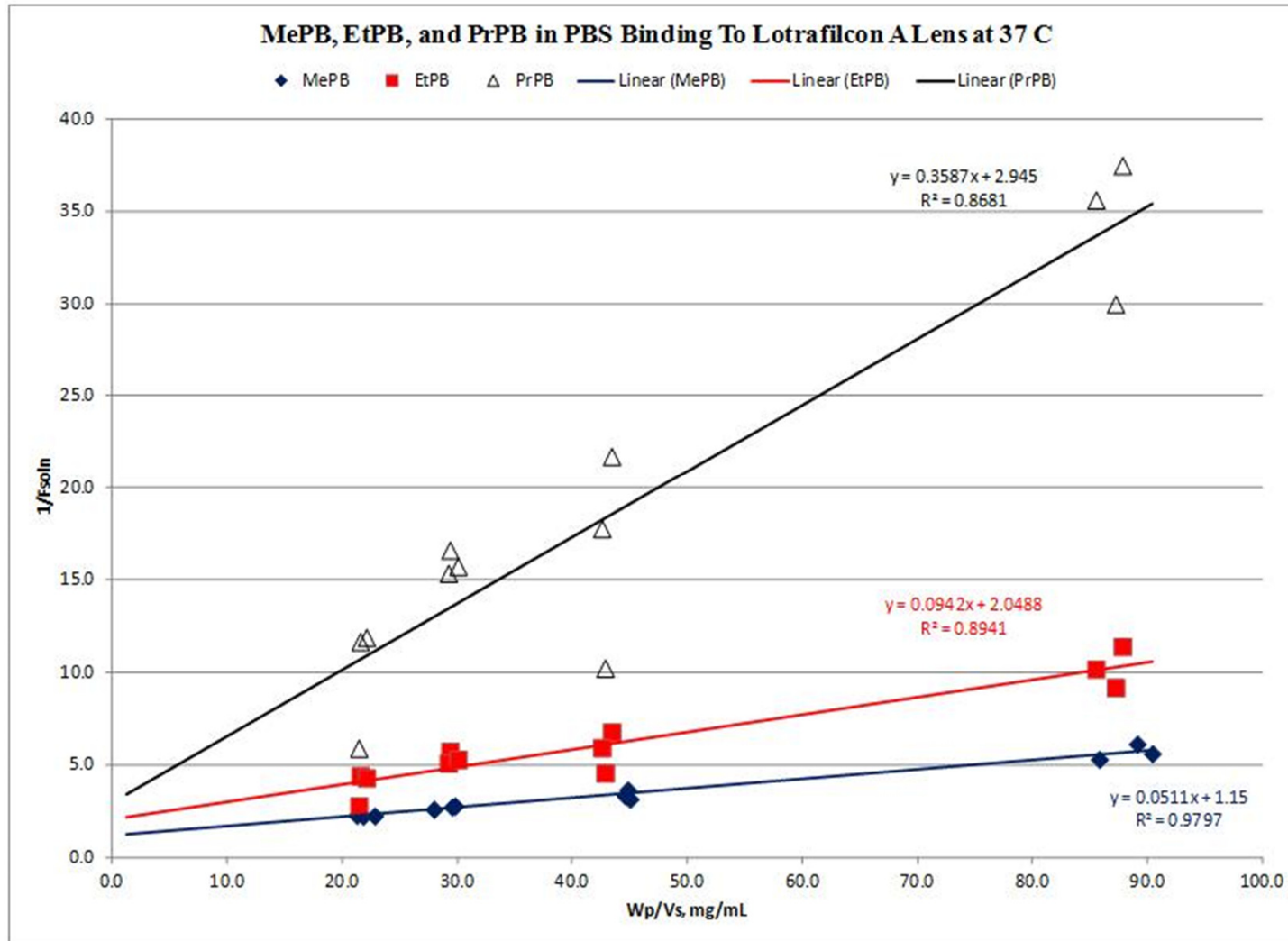
Sample	V_s, mL	W_p, mg	F_{soln}[†]	W_p/V_s	$1/F_{soln}$
1-1	0.20	18.96	0.198	94.8	5.04
1-2	0.20	19.88	0.111	99.4	9.03
1-3	0.20	19.09	0.199	95.5	5.03
2-1	0.40	19.35	0.245	48.4	4.09
2-2	0.40	18.34	0.227	45.9	4.40
2-3	0.40	17.97	0.316	44.9	3.16
3-1	0.60	17.6	0.327	29.3	3.05
3-2	0.60	18.51	0.340	30.9	2.94
3-3	0.60	19.83	0.342	33.1	2.93
4-1	0.80	17.77	0.416	22.2	2.41
4-2	0.80	19.13	0.509	23.9	1.96
4-3	0.80	17.33	0.659	21.7	1.52
	Mean =	18.6		Slope** =	0.0575
	%RSD =	4.6%		Intercept** =	-0.038
				RSQ** =	0.745

* At 37 °C for 60 min. † See equation (2). ** Slope, intercept and RSQ per equation (5).

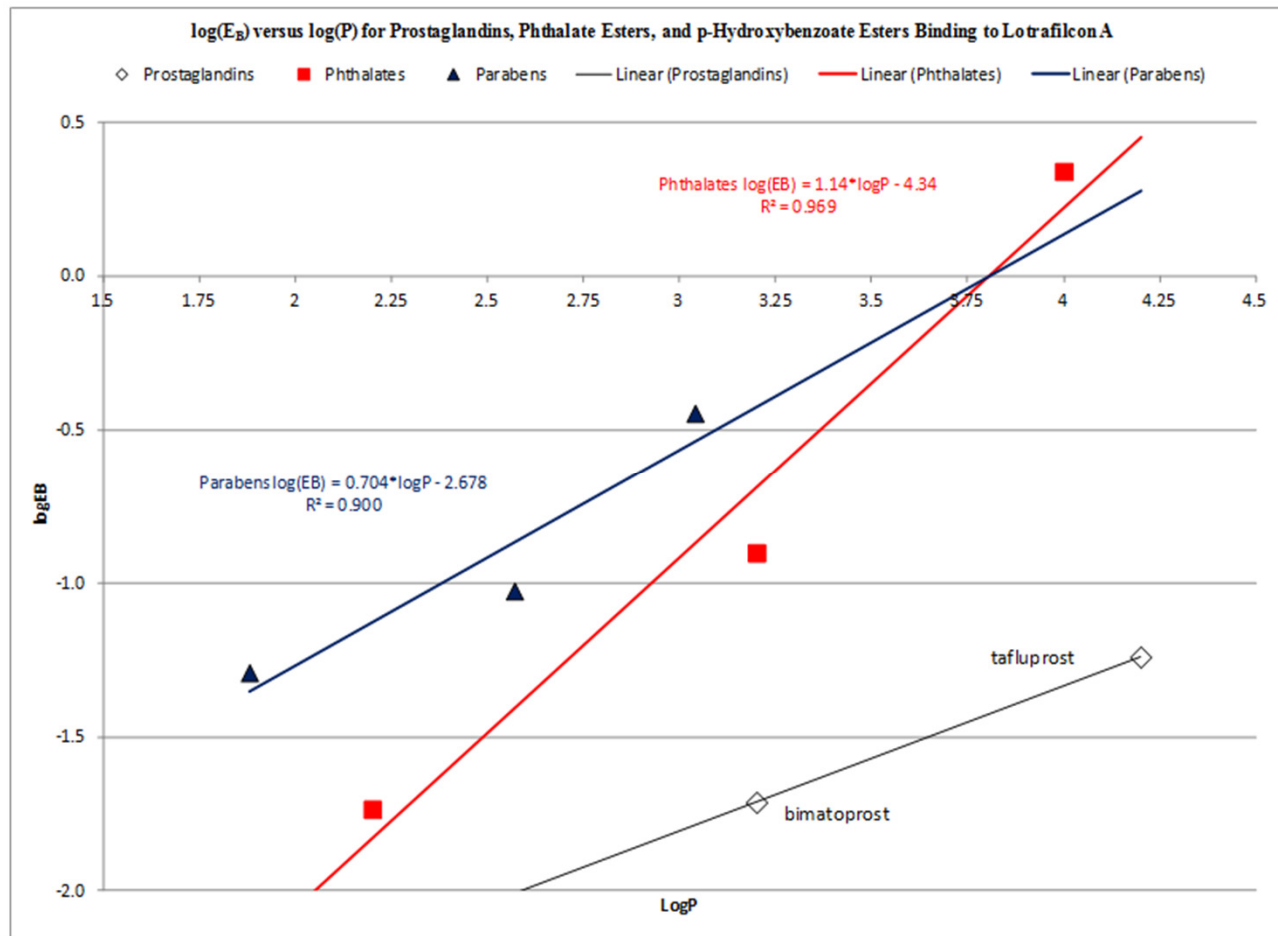# 1/F$_{soln}$ vs. W$_p$/V$_s$ Ratio for Phthalates

1/F$_{soln}$ vs W$_p$/V$_s$ Ratio for Phthalate Esters at 37 C

DPP 1/Fsoln = 2.19(Wp/Vs) + 73.21R^2 = 0.62

DEP 1/Fsoln = 0.125(Wp/Vs) - 2.7
R^2 = 0.91

DMP 1/Fsoln = 0.0184(Wp/Vs) + 0.79
R^2 = 0.92

$1/F_{soln}\ W_p/V_s$ Ratio for Parabens

MePB, EtPB, and PrPB in PBS Binding To Lotrafilcon A Lens at 37 C

♦ MePB   ■ EtPB   △ PrPB   — Linear (MePB)   — Linear (EtPB)   — Linear (PrPB)

$y = 0.3587x + 2.945$
$R^2 = 0.8681$

$y = 0.0942x + 2.0488$
$R^2 = 0.8941$

$y = 0.0511x + 1.15$
$R^2 = 0.9797$

y-axis: 1/fsoln

x-axis: Wp/Vs, mg/mL

F_{soln} vs V_s/W_p Ratio for Tafluprost at 25 and 37 C

FSoln vs Vs/Wp Ratio Tafluprost Initial = 0.015 mg/mL

Log(E_B) vs LogP

log(E_B) versus log(P) for Prostaglandins, Phthalate Esters, and p-Hydroxybenzoate Esters Binding to Lotrafilcon A
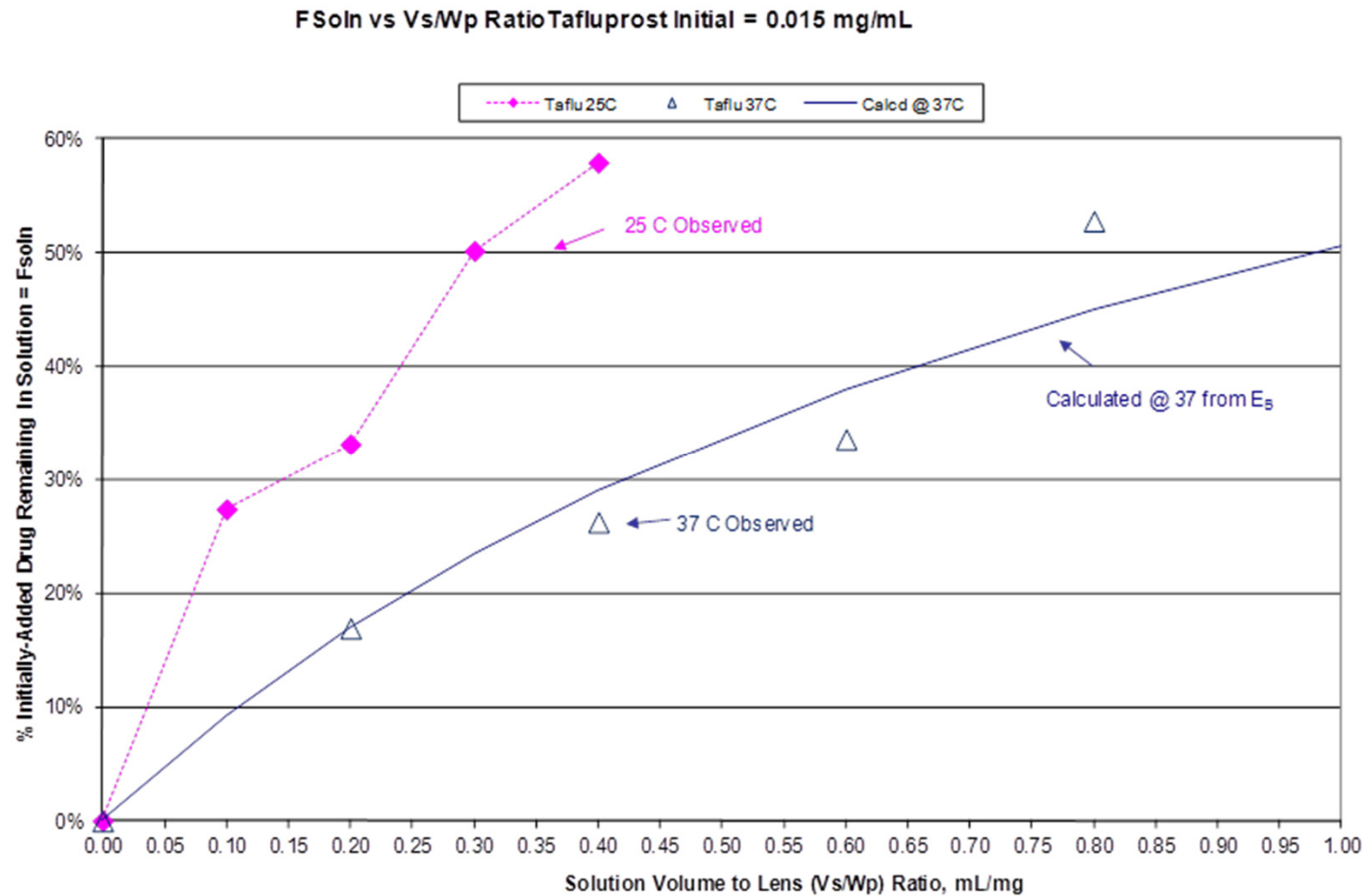
Conclusions

- The fraction of either bimatoprost or tafluprost that binds to Lotrafilcon A increases with increasing lens:solution (w/v) ratio.

- Both drugs partition very rapidly (< 15 min) and extensively into Lotrafilcon A lens

- Calculate that a 60-μL dose volume applied to a single contact lens yields 16% of initially bimatoprost remaining in solution, but only 6% of tafluprost remains in solution

- Advise contact lens wearers to remove the lenses before administering either prostaglandin drug

- Hydrophobic interactions are important but not the only significant factor controlling drug binding to Lotrafilcon A

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