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To cite this version:
Matthias Ober, Daniel Dermody, Mathieu Maillard, Franck Amiot, Géraldine Malet, et al.. Development of Biphasic Formulations for Use in Electrowetting-Based Liquid Lenses with a High Refractive Index Difference. ACS Combinatorial Science, 2018, 20 (9), pp.554-566. 10.1021/acscombsci.8b00042. hal-02087636

HAL Id: hal-02087636
https://univ-lyon1.hal.science/hal-02087636
Submitted on 18 Jul 2022

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Development of Biphasic Formulations for Use in Electrowetting-Based Liquid Lenses with a High Refractive Index Difference

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§Supporting Information

ABSTRACT: Commercial electrowetting-based liquid lenses are optical devices containing two immiscible liquids as an optical medium. The first phase is a droplet of a high refractive index oil phase placed in a ring-shaped chassis. The second phase is electrically conductive and has a similar density over a wide temperature range. Droplet curvature and refractive index difference of two liquids determine the optical strength of the lens. Liquid lenses take advantage of the electrowetting effect, which induces a change of the interface’s curvature by applying a voltage, thereby providing a variable focal that is useful in autofocus applications. The first generation of lens modules were highly reliable, but the optical strength and application scope was limited by a low refractive index difference between the oil and conductive phase. Described herein is an effort to increase the refractive index difference between both phases, while maintaining other critical application characteristics of the liquids, including a low freezing point, viscosity, phase miscibility, and turbidity after thermal shock. An important challenge was the requirement that both phases have to have matching densities and hence had to be optimized simultaneously. Using high throughput experimentation in conjunction with statistical design of experiments (DOE), we have developed a series of empirical models to predict multiple physicochemical properties of both phases and derived ideal locations within the formulation space. This approach enabled the development of reliable liquid lenses with a previously unavailable refractive index difference of $\Delta n_D \geq 0.290$, which enabled true optical zooming capability.

KEYWORDS: liquid lenses, electrowetting effect, statistical design of experiments, simultaneous optimization

INTRODUCTION

Electrowetting-based liquid lenses, initially developed by the startup Varioptic S.A., now available under the brand name Corning Varioptic Lenses, are cover a wide range of applications in consumer and industrial optical systems. The liquid lenses provide access to high resolution optics with autofocus functionalities without the need for mechanical moving parts. They are used in many applications including barcode readers, medical imagery, or biometry. Liquid lenses are composed of two immiscible liquids encapsulated into a sealed cell. One of these liquids is a hydrophilic conductive phase and the other one is a hydrophobic oil. The interface between both liquids is spherical and forms a dioptr because of refractive index difference. When application of voltage to the system, the liquid/liquid meniscus’ curvature changes due to electrowetting and, with it, the focal distance of the lens. The liquid lens technology offers many advantages over traditional technologies: low power consumption, high speed, shock and vibration resistance, resistance to wear, and high optical quality.

Critical to the development of reliable and functional lenses is the formulation development of liquid/liquid pairs that are suitable to meet application requirements. One of the key parameters of the liquid pair is its refractive index difference, as it directly determines the optical power range. Whereas low refractive index differences ($0.080 < \Delta n_D < 0.120$) are sufficient for autofocus applications, high $\Delta n_D$ values are needed to implement zooming capabilities. Unfortunately, interface refractive index difference between two liquid phases can be modified over a much more limited range than the step between a solid and surrounding air. For instance, feasible lowest refractive index liquids are in the range $n = 1.3−1.4$ whereas the upper limit is in the range of $n = 1.7−1.8$, but these high refractive liquids have significant issues regarding chemical stability and formulation performance. Hence, pushing refractive index difference toward high values of above $\Delta n_D \geq 0.290$ drastically reduces the size of the formulation space (Figure 1) that also meets other application requirements.

A particularly important requirement is the need that both phases have a minimum density difference to prevent gravity from deforming the liquid–liquid interface. In addition, low...
First, the refractive indices $n_{D,pure}$ of the pure hydrophobic and corresponding hydrophilic phases were determined at the temperature of interest as described. Next, the phases were combined and equilibrated by agitating the mixture overnight at the prescribed temperature. The refractive indices $n_{D,eq}$ of the top and bottom phase were remeasured at an identical temperature. The volume fraction of phase 1 in phase 2 as a function of temperature was estimated by using the equation

$$\frac{V_{phase1inphase2(T)}}{V_{phase2,eq,total}} \approx \frac{n_{D,pure}(phase2, T) - n_{D,eq}(phase2, T)}{n_{D,pure}(phase2, T) - n_{D,pure}(phase2, T)}$$

assuming an additive behavior of the refractive indices (Arago-Biot approximation). Miscibility of multicomponent biphasic liquid systems was estimated by treating each phase as a single component (having the refractive index of the multicomponent phase).

### Density

Densities were measured with an Anton Paar DMA-500 density meter at 25 °C by injecting 1 mL of sample into the measurement cell.

### Melting Point

Melting points were determined by DSC measurements in a single measurement cycle. A 5 mg of sample, encapsulated into a hermetic aluminum DSC pan, was equilibrated for 1 min at 25 °C. Next, the sample was cooled to −90 °C with a temperature gradient of −10 K/min, equilibrated at −90 °C for 1 min and finally heated to 45 °C with a temperature gradient of 10 K/min. Generally, the maximum of melting peak endotherms, $m_p$ rather the onset of melting $m_m$ was used as a melting point. If several phase transitions or melting points were observed, the one with the highest temperature was used as the data point for model fitting.

### Turbidity

The turbidity of the oil phase/conductive phase system after thermal shock was determined by high-throughput nephelometry measurements. Turbidity originates from partial miscibility from liquids at high temperature, after a thermal cycling, condensation occurs in oversaturated liquids, forming light scattering dispersion of immiscible liquids. Turbidity is characterized by two main parameters, the maximum turbidity related to the amount and size of liquid dispersion, and the recovery time necessary to retrieve liquids within transparency specifications.

First, 150 µL of the hydrophilic and 100 µL of the hydrophobic phase were pipetted into a 96-well optical glass plate that was sealed with a corresponding 96-well silicone lid. The plate was then heated to 85 °C (compound selection stage) or 70 °C (formulation DOE) for 20 min in a convection oven. After temperature equilibration, the plate was removed from the oven, the lid was removed and the hot plate was immediately placed into an Ascent Nephelosan nephelometer (Thermo Labsystems). The turbidity of the oil/conductive phase binary systems of the plate was measured at 5 min intervals with an integration time of 1000 ms/well. Proprietary formulations with a known behavior, as well as water blanks were used as internal standards. At least two, usually three independent measurements of each sample were performed and the turbidity/time curves were averaged among these measurements.

### Viscosity

Viscosities were measured at variable temperatures on a Brookfield CAP 2000+ instrument with the appropriate speed and short response times. Low wettability of the water phase on the substrate is necessary to reduce lens hysteresis. Cross miscibility, resistance to temperature shocks, and low melting points of the two phases have to be minimized over a wide temperature range to ensure functionality at different environmental conditions.

Many of these requirements are antagonistic. The main challenge is to find the best compromise between all these parameters while increasing the refractive index difference. We approached this problem in three stages. The goal of the first stage was to identify formulation candidate compounds and develop a high-resolution empirical model of the refractive index, melting point and density of the formulation space of the aqueous conductive phase. An important discovery here was the inclusion of salts of fluorinated acids, which allowed minimization of its refractive index. During the second stage, we evaluated new candidate compounds for the organic phase by evaluating their performance in binary biphasic systems in combination with common candidate compounds for the aqueous or hydrophobic phase. In the final stage, we developed comprehensive statistical models of properties of oil phases and oil phase formulations paired with a corresponding ideal water phase as derived from the water phase model obtained during the first stage. These final stage models enabled us to identify optimal ranges within the formulation space and guided further commercial development.

On a larger scenery, this example illustrates how high throughput experimentation in combination with statistical design of experiments can solve a complex multiparameter industrial challenge.

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**Materials.** Materials were purchased from Sigma-Aldrich (Sigma-Aldrich Corporation, St. Louis, Missouri, now owned by Merck KGaA) or Gelest (Gelest Inc., Morrisville, Pennsylvania) and used without further purification. Oligo(diphenylethers), including Santovac MCS-293 and Santolight SL-5267 were purchased from SantoVac Fluids (now SantoLubes LLC, Missouri, US).

**General Methods.** Refractive Index. The refractive index measurements were performed on an Atago refractometer RX-7000ct. The temperature of the sample was held at 20 °C and sample size was approximately 0.2 mL. For pure liquids, refractive indices were remeasured in-house and compared with supplier data for calibration purposes.

Miscibility. Miscibility of two-component biphasic liquid systems at variable temperatures was measured as follows.
spindle for the expected viscosity range. High-throughput measurements of viscosities were performed by using the Dow TADM Viscosity experiment,\(^a\) utilizing a Hamilton Microlab Star dispensing robot and measuring the pressure drop during aspiration. All high-throughput viscosity measurements were performed at room temperature.

**Solubility (Semi-quantitative).** Experiments were conducted combinatorially using a 96 well plate containing individual 1.5 mL vials. A small amount of any of the solid candidate compound series (~5 mg) was combined with a series of liquids of interest. The vials were sealed and the plate was shaken overnight at room temperature. The next day, the vials were visually inspected for solubility of the solid.

**High Throughput Powder Dispensing.** Solid components of high throughput experiments were dispensed using an Autodose Powdernium (Symyx) solids handler. The robotic handler was used in a Many to Many configuration with on-deck weighing. Twenty-five or fifty milliliter hoppers were used as sources and the powders were dispensed into 1 mL vials.

**Design of Experiments, Surface Modeling, and Data Visualization.** Constrained D-optimal mixture designs were calculated with JMP,\(^{15}\) which was also used to perform multi-variate regression and model development with the acquired data points. JMP was further utilized to search for optimal areas in the formulation space, sorting and clustering of data, generation of bivariate plots and phase diagrams.

**RESULTS AND DISCUSSION**

**Formulation Development.** Biphasic formulations consist of a low refractive index conductive hydrophilic phase and a high refractive index, nonconductive hydrophobic phase. The formulation of these phases for liquid lens applications have to meet a variety of physicochemical requirements. The most important constraints are (1) low cross miscibility (<0.2%) at the temperature range of 20 °C and +85 °C, (2) identical densities of both phases, (4) turbidity after thermal shock in contact with water phase as low as possible (ideally <20 NTU), (5) viscosity as low as possible (ideally <10 cP), (6) melting point below −25 °C, and (7) refractive difference as high as possible. High refractive indices are obtained by introducing formulants containing structural features positively correlated with a high refractive index in existing QSPR models,\(^{18,20,21}\) such as a saturation, aliphatic and/or aromatic ring structures, a high Balaban index\(^{19}\) (correlated with molecular compactness and branching), a high dipole moment,\(^{18,20,21}\) and high atomic number elements. Therefore, refractive index is often positively correlates with the density of the fluid. Because of its unique electronic properties, fluorine tends to lower the refractive index of a compound,\(^{22}\) while still increasing the material’s density. The highest refractive index optical fluids (n ≥ 1.6) are often brominated or chlorinated compounds, but their light-induced homolysis/radical formation, and sensitivity to hydrolysis usually limit their use in liquid lenses.

**Requirements 6 and 7 are counteractive because water antifreeze additives (salts, glycols) raise the refractive index of the hydrophilic phase considerably, thereby limiting the maximum possible ΔnD.**

**Matching the densities of both phases while maximizing the refractive index is not trivial. Each formulation adjustment in phase 1 to change its refractive index will affect its density and require an adjustment in phase 2. In turn the second phase’s refractive index, and thereby ΔnD changes in a nonobvious fashion. In order to address this problem, it is necessary to establish a method to predict ideal compositions of one of the phases (we selected the simpler conductive phase) and describe its expected refractive index as a function of density.** An “ideal” conductive phase was considered to have the lowest possible refractive index within the formulation space for a given density and does not freeze within the specification range. To guide formulation development of the oil phase, we were particularly interested in determining for which density range a refractive index below 1.37 could be achieved.

**Part I. Empirical Model and Optimization of the Conductive Phase.**

**Formulation Component Selection.** Water is a key component of the conductive phase, both because of its low refractive index and its conductivity after dissolution of salt components. Its key disadvantage for the application is its high freezing point, which needed to be lowered by antifreeze components. To achieve a high refractive index difference, an important goal was to find salts and additives that only minimally increase the reactive index of the water phase, while still reduce its freezing and melting point below the designed application range. As freezing point depression is, according to Blagden’s law,\(^3\) a function of the molality of a solute in a solvent, a high water miscibility or solubility and a low molecular weight is favored. Because of their miscibility and low volatility, common antifreeze agents like ethylene glycol (EG) and 1,3-propanediol (TMG) are suitable agents, but they significantly increase the refractive index of the water phase.

In our quest to identify suitable candidate compounds with a lower optical impact, we first investigated low nD fluorinated or 263 perfluorinated aliphatic amines, alcohols or acids, such as triflic 250 or trifluromethanesulfonic acid. Their high miscibility with 265 the nonconductive hydrophobic phase (resulting in turbid 266 systems) and/or corrosivity led us to quickly abandon this 267 class of compounds. On the other hand, we found that salts of 268 fluorinated acids, such as sodium triflate (NaOTf) and sodium 269 trifluoroacetate (NaTFA) showed promise because of their 270 high water solubility, compatibility with the construction 271 material of the encasing, better optical properties, and a more 272 moderate impact on the refractive index in comparison to 273 sodium bromide (NaBr) or potassium acetate (KOAc), 274 additives used in previous formulations. Candidate formulation 275 components of the hydrophilic phase that were ultimately 276 selected for further investigation were water, EG, TMG, NaBr, 277 KOAc, NaTFA and NaOTf.

**Refractive Index Model.** In first approximation, and assuming ideal density behavior, refractive indices nD,i of individual compounds i in a mixture contribute to the refractive index nD,mix in proportion to their respective volume fraction 282 φi according to the Arago-Biot model.\(^{12}\) As all of the liquid formulation candidates have densities close to 1, the refractive 284 index is also proportional to the respective weight fractions w,i. 285

\[
\Phi\text{D}_{\text{mix}} \approx \sum_i w_i n_{\text{D},i} / \sum_i \rho_i n_{\text{D},i} \approx \sum_i w_i n_{\text{D},i} \quad (1)
\]

For solid compounds apparent refractive index/density quotients υD,i = nD,i × ρ−1 were determined by measuring 288 the refractive index for different weight fractions of these 289 compounds in water up to the solubility limit (Tables S1–S4). 290
As expected, not all of the parameters were statistically significant within a range of 90 and 25 °C (Figure S3). Determined by regression and constrained for a maximal allowable density, the lowest achievable refractive index of a formulation component was only advantageous, if very low densities (between 1.03 and 1.15) are targeted. Notably, it is not possible to obtain a refractive index of less than 1.37 at a melting point of below −25 °C for conductive phases that do not utilize NaTFA as one of the antifreeze components. Formulations that contain any amount of NaBr are not ideal concerning the investigated properties, as they never have the lowest possible refractive index within the investigated space. Formulations containing a TMG component are only advantageous, if very low densities (between 1.03 and 1.15) are targeted. The density of NaBr is approximately 1.15 and 1.31 g/mol. For densities above 1.31, the least relevant in ideal formulations (additional slices through the hypersurface are shown in Figures S4–S7). Because the refractive index generally increases with the content of antifreeze agents and salts, ideal formulations with the lowest possible refractive index can be found at the isosolvent maximum of allowable melting point (i.e., −25 °C) for densities between 1.15 and 1.31 g/mol. For densities above 1.31, NaTFA and NaBr at TMG weight fractions at 0, as these two components are along the system, KOAc and NaOTf were excluded due to their similar refractive indices of the respective liquid components and their similar density/quotients of the respective solid components. Table 1 summarizes $n_D$ and $\rho_D$ values of key formulation candidates.

### Table 1. Refractive Indices of Candidate Liquids and Apparent Refractive Index/Density Quotients of Candidate Salts

<table>
<thead>
<tr>
<th>Liquid Candidate Components</th>
<th>$n_D$</th>
<th>Solid Candidate Components</th>
<th>$\rho_D$</th>
</tr>
</thead>
<tbody>
<tr>
<td>certified water$^a$</td>
<td>1.33273</td>
<td>sodium bromide$^b$</td>
<td>1.4660</td>
</tr>
<tr>
<td>ethylene glycol$^b$</td>
<td>1.4310</td>
<td>potassium acetate$^b$</td>
<td>1.4527</td>
</tr>
<tr>
<td>1,3-propanediol$^b$</td>
<td>1.4393</td>
<td>sodium trifluoroacetate$^b$</td>
<td>1.3721</td>
</tr>
</tbody>
</table>

$^a$Refractive index of distilled water available in-house against Cargille reference standard. $^b$Rereasured in-house. $^c$Determined by regression as described in text.

### Density Model

An empirical density model for the multi-component conductive phase had been previously developed by Varioptic SA and was expanded for the components used in this study. The development and characteristics of this model is beyond the scope of this report.$^{24}$

### Freezing Point Model

We used statistical design of experiments (DOE) to develop an empirical model of the phase transition behavior of the conductive phase as a function of formulation. In order to obtain a high-resolution model with a manageable number of required experiments, it was necessary to limit the number of formulation ingredients. To simplify the system, KOAc and NaOTf were excluded due to their similar formulation behavior of NaBr and NaTFA, respectively. Permitted formulation components were water, EG, TMG, NaBr and NaTFA. We designed 96 experiments to explore the freezing points of formulations containing these five candidate compounds at any weight fraction within the approximate solubility boundaries outlined in Table 2. These 96 experiments provide sufficient resolution to explore main interactions plus second and third degree interactions and allow room for a number of standards, center points and repeats (Figure S3 and Table S7).

All samples were measured by DSC, melting points were determined within a range of −90 and 25 °C (Figure S3). As expected, not all of the parameters were statistically significant in the model, and we removed parameters with the highest $P$-values until $R^2_{adj}$ did not increase any further and was within proximity of $R^2$. Data was fitted the following model equation optimized to exclude statistically insignificant coefficients:

$$\nu_{D,i} = n_{D,\text{water}} + m$$

wherein $m$ is the slope of the regression line. We have experimentally determined apparent refractive index/density quotients for sodium bromide, potassium acetate, sodium triflate and sodium trifluoroacetate (Figure S1). With this, the refractive index of the conductive phase can be predicted by the equation

$$n_{D,\text{conductivephase}} \approx \sum_i w_{iD}n_{D,i} + \sum_j w_{jD}n_{D,j}$$

wherein $w_i$ and $w_j$ are the weight fractions of the respective liquid or solid formulation components, $n_{D,i}$ are the refractive indices of the respective liquid components and $\nu_{D,j}$ are the refractive index/density quotients of the respective solid components. Table 1 summarizes $n_D$ and $\rho_D$ values of key formulation candidates.

### Table 2. DOE Boundaries of the Water Phase (Mixture Design)$^{a}$

<table>
<thead>
<tr>
<th>Component</th>
<th>Low Boundary</th>
<th>High Boundary</th>
</tr>
</thead>
<tbody>
<tr>
<td>water</td>
<td>0.3</td>
<td>0.8</td>
</tr>
<tr>
<td>ethylene glycol</td>
<td>0</td>
<td>0.8</td>
</tr>
<tr>
<td>1,3-propanediol</td>
<td>0</td>
<td>0.4</td>
</tr>
<tr>
<td>sodium bromide</td>
<td>0</td>
<td>0.333</td>
</tr>
<tr>
<td>sodium trifluoroacetate</td>
<td>0</td>
<td>0.5</td>
</tr>
</tbody>
</table>

$^a$Additional constraints: $w_{\text{water}} + w_{\text{NaTFA}} = w_{\text{water}} + 3w_{\text{NaBr}}$ and $w_{\text{EG}} + w_{\text{TMG}} + w_{\text{NaBr}} + w_{\text{NaTFA}} = 1$

Coefficients $a_i$, $b_i$, and $c_i$ and a regression summary are listed in the Table S8.

**Combined Model.** By combining the density, refractive index, and melting point models of the conductive phase, constraining the combined model for a maximal allowable freezing point (e.g., −25 °C) and iteratively solving for minimal achievable refractive index, it is possible to predict an ideal conductive phase formulation and its associated refractive index over a wide density range (Figure 2).

Figure 3 shows a slice through the response hypersurface along the $\nu_{\text{EG}}$ and $\nu_{\text{NaTFA}}$ coordinates (water weight fraction is 0.5, and $\nu_{\text{water}} = 1.38$). This model was experimentally determined apparent refractive index/density quotients for sodium bromide, potassium acetate, sodium triflate and sodium trifluoroacetate (Figure S1). With this, the refractive index of the conductive phase can be predicted by the equation

$$n_{D,\text{conductivephase}} \approx a_{\text{EG}}w_{\text{EG}} + a_{\text{water}}w_{\text{water}} + a_{\text{NaBr}}w_{\text{NaBr}}$$

$$+ b_{\text{NaTFA}}w_{\text{NaTFA}} + b_{\text{TMG}}w_{\text{TMG}} + b_{\text{EG,NaTFA}}w_{\text{EG,NaTFA}}$$

$$+ b_{\text{EG,water}}w_{\text{EG,water}} + b_{\text{water,NaTFA}}w_{\text{water,NaTFA}}$$

$$+ b_{\text{NaBr,NaTFA}}w_{\text{NaBr,NaTFA}}$$

$$+ b_{\text{TMG,NaTFA}}w_{\text{TMG,NaTFA}}$$

$$+ c_{\text{EG,water}}(w_{\text{EG}}^2 - w_{\text{EG}}^2) + c_{\text{NaTFA,water}}$$

$$+ (w_{\text{NaTFA}}^2 - w_{\text{NaTFA}}^2)$$

By combining the density, refractive index, and melting point models of the conductive phase, it is possible to predict an ideal conductive phase formulation and its associated refractive index over a wide density range (Figure 2).

Part II. Candidate Compound Selection of the Hydrophobic Phase. Formulation Component Preselection. To find suitable formulation components for the hydrophobic phase, we have tested 32 high-refractive index 375 candidates.
compounds that had been preselected for characteristics including high refractive index, low toxicity, and low volatility. Compounds featuring a high refractive index typically contain fluorine, chlorine, or oxygen atoms or aromatic esters (Figure 4). Twenty-two compounds in our selection were liquids, and 11 were solids.

**Turbidity in Binary Systems.** One important requirement of the application is that the system needs to remain clear both upon contact of the two phases and after thermal shock. We have screened the 21 liquid compounds 1–21 combinatorially in biphasic systems with eight model conductive phases in a full factorial library after mixing and simulated temperature shock (Figure S8). Model conductive phases were water, a 5% (w/w) aqueous NaBr solution, a 20% aqueous NaBr solution, pure ethylene glycol, pure 1,3-propanediol, a 20% aqueous NaTFA solution, a 60% aqueous NaTFA solution, and a 40% aqueous NaOTf solution (all percentages are w/w). This setup not only allowed identification of organic compounds that are robust under a variety of conditions but gave initial information about the effect of different salts on turbidity formation.

The plates were heated to 85 °C as described in the Experimental Techniques. Typically, the turbidity initially increased upon cool-down (likely caused by phase demixing and microdroplet formation), followed by gradual clear up. For most systems, the maximum turbidity was reached after 30–40 min. Whereas some system (especially most of the silanes) cleared up quickly or overnight, other systems did not improve or became even more turbid (most notably, 1-bromonaphthalene). The compounds that performed best in the test were 17, 18, and 19, the germane Me₃PhGe, and the silanes/siloxanes Me₃Ph₂Si, 1, 1,3-diphenyl-1,1,3,3-tetramethyldisiloxane 9, and especially, 11, SIP6827.0 11 and DMS-T15 12.

Among the compounds with a particularly high refractive index were 1-chloronaphthalene 6, 1-phenynaphthalene 8, 4-bromodiphenylether 16, and Santolight SL-5267 18. It is evident that systems that contain salt in the water phase performed better than systems with pure water, which can be explained with a lower phase miscibility due to salting-out effects. The highly concentrated and polar 20% NaBr solution performed better than the 5% NaBr solution or pure water, and a 20% NaTFA behaved, with exceptions, similar to 20% NaBr solutions. The NaOTf solution gave higher turbidities than any other aqueous phase, possibly due to slight emulsifying characteristics of the large organic anion. Biphasic systems with pure EG and TMG as the simulated conductive phase were among the most turbid upon cooling, with EG being slightly better than TMG in general. This observation corresponds with the highly temperature-dependent miscibility of the glycols with many of the candidate compounds. Figures 5 and S9 summarize the results of this screening study. Experimental values are shown in Table S9.

**Miscibility with Water and Glycols.** We have determined the miscibility of the candidate compounds with water, EG, and TMG by refractive index measurements as described in the Experimental Techniques, assuming additive behavior. Again, the silanes/siloxanes and germanes performed very well in this test. In addition, 1-chloronaphthalene 6, 1-phenynaphthalene 8, 4-bromodiphenylether 16 and Santolight SL-5267 18 gave promising results. The measurements were conducted at −20 °C and 70 °C. Figure 6 shows the results, raw data and miscibility calculations are presented in Tables S10 and S11.

**Additional Selection Criteria.** To achieve short response times of the liquid lens, lower viscosity candidate compounds were given preference. As discussed above, the lowest refractive indices for an optimal water phase can be found at a density range of 1.25–1.40. To achieve the highest possible refractive
index difference, this density range is ideally matched by the high refractive index oil phase. As most of the candidate compounds had lower densities, both a high density and a high refractive index were important selection criteria. In addition to these parameters, emphasis was placed on compounds with a low toxicity. To this end published MSDS toxicity data was used as a selection criterion. Table S12 summarizes the assessment of all selection criteria of the evaluated compounds.

**Solubility of Solid Compounds and Influence on Refractive Index.** The goal of this study was to identify solid candidates that are soluble in the oil phase while simultaneously raising its refractive index. Each solid (Figure 4b) was combinatorially prescreened for solubility in a selection of major oil phase components. In addition, we tested for undesirable solubility in EG, TMG and water. Among the solid candidates, only naphthalene, 31, thianaphthene, 31, vinyltriphenylsilane, 1,3-dimethyl-1,3,3-tetramethyldisiloxane, 9, dibenzothenephene, 29 and diphenyl phthalate 29 warranted further investigation. The results of this prescreening study is shown in Table S13.

We next tested the remaining candidates for their capacity to increase the refractive index of the oil phase formulation. To this end, each of these compounds was dissolved combinatorially in a series of oil-phase candidates to saturation at 20 °C. The refractive index offset of the saturated solutions in comparison to the pure liquid compounds was then measured. Table 3 summarizes the result of these experiments. Unfortunately, in solution, none of the compounds had a higher refractive index than the Santovac/Santolight oils and consequently lowered the refractive index in a mixture with SL-5267. Thianaphthene 31 has the best solubility in all silanes/germanes and a positive effect on their respective refractive indices.

**Viscosity of Santovac MCS-293/Thianaphthene Mixtures.** During these studies, we have serendipitously discovered that thianaphthene reduces the viscosity of Santovac MCS-293/ Santolight SL-5267, without a significant reduction of its high refractive index. To investigate this effect further, we measured the viscosity of thianaphthene/MSC-293 mixtures at different weight concentrations and at various shear rates and temperatures. We have found that an addition of just 10% (w/w) of thianaphthene to Santovac MCS-293 or Santolight SL-5267 lowered the viscosity in all cases by a factor of approximately two (Figure 7).

**Selection of Compounds for Use in Liquid Lens Formulations.** On the basis of these screening results, we have selected eight candidate compounds for potential use in improved oil phase formulations. Dimethyldiphenylsilane was included, as it performed excellently in turbidity/miscibility tests but has a relatively low refractive index. Diphenyl sulfide was selected because of its low viscosity despite its average performance in other screening tests. Santolight SL-5267 stood out because of its high reactive index. It performed decently in the turbidity test, especially in combination with high-salt water phases. 4-Bromodiphenylether showed good results in all tests and has a high density, which is important to gain sufficient freedom in formulating oil phases in the desirable density range of 1.25–1.40. Ethylthiobenzothiazole was retained because of its high refractive index and low viscosity despite its less favorable miscibility/turbidity test results. 1-Chloronaphthalene showed...
good performance in the biphasic tests and has a low viscosity, but its refractive index does not stand out. 1-phenylnaphthalene, again, had very good test results and has a high refractive index, but its viscosity is also very high. The only solid compound...
Part III. Optimization of the Biphasic System by Empirical Modeling. Design of Experiments. A D-optimal mixture design was created as follows: Key input variables were the weight fractions of the nine previously identified candidate compounds (hereafter, the variables \( w_{Me2PhSi} \), \( w_{Ph2S} \), \( w_{SL5267} \), \( w_{Ph2S,MePhSi2} \), \( w_{Ph2S,MePhSi2-SL5267} \), \( w_{1-chloronaphthalene} \), \( w_{1-phenylnaphthalene} \), \( w_{2,5-dibromotoluene} \), and \( w_{thianaphthene} \) designate the weight fractions of dimethylphenylsilane, diphenyl sulfide, Santolight SL-5267, 4-bromodiphenyl ether, ethylthiobenzothiazole, 1-chloronaphthalene, 1-phenylnaphthalene, 2,5-dibromotoluene, and thianaphthene, respectively). The design space was further limited by additional constraints summarized in Table 4. At least 45 experiments were necessary to resolve first and second degree interactions. We augmented that design with proprietary formulations and pure materials as standards. For the purpose of this experiment, mixture densities were assumed to follow an ideal, linear behavior (i.e., \( d_{oil} = \sum w_i d_i \) with \( d_i \) being the estimated mixture density and \( w_i \) and \( d_i \) being the weight fractions and densities of the formulation components, respectively).

For each designed formulation of the oil phase library, we calculated an ideal composition for the corresponding conductive phase by constraining the water phase model developed above to a density of \( d_{oil} \), a melting point of \(-25 \, ^{\circ}C\) and iteratively resolve the model for the minimum achievable refractive index. Figure 8 shows a graphical representation of the designed oil- and conductive-phase libraries. Numeric tables with the experimental formulation compositions are listed in Tables S14 and S15.

Table 3. Change of Refractive Index of Several Liquids (Rows) after Saturation with Various Solid Refractive Index Modifiers (Columns)

<table>
<thead>
<tr>
<th>liquid</th>
<th>( n_\text{r} ) (pure)</th>
<th>refractive index modifier (solid)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5644</td>
<td>0.01(^a)</td>
</tr>
<tr>
<td>4</td>
<td>1.5735</td>
<td>n.d.(^b)</td>
</tr>
<tr>
<td>5</td>
<td>1.5071</td>
<td>0.04 n.d.</td>
</tr>
<tr>
<td>9</td>
<td>1.5170</td>
<td>n.d. 0.02 n.d.</td>
</tr>
<tr>
<td>11</td>
<td>1.4376</td>
<td>0.02 n.d.</td>
</tr>
<tr>
<td>12</td>
<td>1.4041</td>
<td>n.d. 0.02 n.d.</td>
</tr>
<tr>
<td>18</td>
<td>1.6739</td>
<td>0.00 n.d.</td>
</tr>
<tr>
<td>water</td>
<td>1.3327</td>
<td>0.00 0.00 0.00 0.00 0.00 0.00</td>
</tr>
</tbody>
</table>

\(^a\)Numbers printed in italics indicate a solubility of >50% (w/w) of the modifier in the respective liquid. \(^b\)Offset of refractive index in comparison to pure liquid after saturation with refractive index modifier. n.d.: Not determined because of low solubility.
Because, as shown above, the composition of an ideal low refractive index water phase (consisting of water, EG, TMG, NaTFA, and NaBr as the only permitted components) can be unambiguously derived for a given density, the only input variables needed to characterize each complete biphasic system are the weight fractions of each oil phase components.

This fact greatly simplifies the optimization of parameters that depend on the composition of both phases, such as refractive index difference, turbidity formation or phase cross miscibility. Refractive Index Difference Model and Mutual Miscibility.

An important goal of this study was to optimize the refractive index difference between oil and conductive phase and thereby the optical strength of Varioptic lenses. At the same time, miscibility and extraction of components into the opposite phase should be kept to a minimum. Miscibility changes induced by temperature changes are problematic as demixing upon cooling may cause temporary or permanent turbidity in the liquid lens. To generate data to develop empirical models for these two parameters, refractive indices of both phases of each library sample were measured in the initial state and after equilibration at 20 and 70 °C with the opposite phase.

For the refractive index model, the refractive index difference as a function of the weight fractions of all permitted oil phase formulation components (Table S18).

The viscosity of each sample at 20 °C (Table S16) was fitted against a model parametrized for linear and two-way cross terms of the weight fractions of potential formulation components of the oil phase. We performed multivariate regression and model simplification (i.e., elimination of insignificant cross terms) until $R^2_{adj}$ did not increase any further. The resulting empirical model fits the data tightly ($R^2 = 0.9996$, $R^2_{adj} = 0.9992$) and predicts the refractive index difference as a function of the weight fractions of all permitted oil phase formulation components (Table S18).

Because of the initial constraints placed on the experimental design, a substantial amount of samples (~30%) had a desirable refractive index difference ($\Delta n_{oi}$) greater than 0.29.

Miscibility estimates at 20 and 70 °C were calculated from the change of refractive index of the pure oil phase before and after equilibration (overnight) with the water phase at the respective temperatures as described in the Experimental Techniques. The results of these measurements are presented in Table S18. We fitted these data points to the underlying DOE model and removed significant terms until $R^2_{adj}$ did not improve any further. The final models had acceptable $R$-values and satisfactory statistical validity tests (Tables S19 and S20).

They predict miscibilities between the oil phase and its corresponding ideal water phase at 20 and 70 °C as a function of the weight fractions of all included oil phase formulation components.

Empirical Model of Viscosity.

The viscosity of each sample of the oil phase library was determined by averaging the results of three independent runs of the Dow TADM high throughput viscosity screening experiment, performed on a Hamilton MicroLab Star robot (Figure S12). The accuracy of this measurement was confirmed to be within ±5% by amending the library with a series of Brookfield viscosity standards ranging from 0.9 to 81 cP. None of the library samples had a viscosity below the desired 10 cP, but the best formulations came with approximately 14 cP close to this threshold.

Empirical Model of Turbidity Formation of Equilibrated Biphasic Systems after Temperature Shock. Formation and clearance of turbidity upon cooling was measured by high throughput nephelometry after equilibration of both phases at 70 °C as over the course of 5 h (Figure S10). Most formulations exhibit a strong increase in turbidity as the system cools down and phase separation/droplet nucleation occurs. After 600 min, the samples reached a maximum turbidity at approximately 603 min, the systems subsequently clear up until a plateau is reached, which often remains above the initial turbidity. This plateau was typically reached after approximately 4 h and persisted over prolonged times (>3 days per control measurement). A photograph of the formulations after temperature treatment is shown in Figure S11. This general trend is clearly related to a migration/droplet nucleation phenomenon.

Turbidity is caused by nucleation of droplets, inducing Mie scattering of light.26 Scattering efficiency $\Sigma$ is proportional to $n_{oi}^2$droplet radius. As droplets coalesce, the number of droplets decreases and droplets radius increases consequently. Considering as a first approximation a constant total volume of liquid inclusion $v = 4N_{oi}/3\pi a^3$, leading to the relation $a = (3v/4\pi N_{oi})^{1/3}$, scattering efficiency is expected to vary as $\Sigma \propto N_{oi}^{-1/2}$ that is, decreases as droplets grow in size.

The overall recovery trend is now a balance between migration kinetic and droplet coalescence: it is critical that droplets coalesce to decrease the number of them, but at the same time, droplet diffusion coefficient due to Brownian motion is inversely proportional to diameter. Thus, if the droplet coalescence process is too fast, droplet migration speed becomes too slow to migrate back to their original phase, leading to a diffusing plateau because of nonmobile droplets. The optimum here is to thus a compromise between nucleation, coalescence and migration speed and the complexity of the solution emphasizes the need of a high-throughput approach.

Individual data from this experiment for every library sample (average of all individual measurements taken between 240 and 300 min) are presented in Table S17. To improve the quality of the fit, turbidity data in NTU was logarithmized before regression. The final model, consisting of main terms 636 and statistically significant second degree cross terms can be found in Table S21.

Empirical Model of Viscosity. The viscosity of each sample of the oil phase library was determined by averaging the results of three independent runs of the Dow TADM high throughput viscosity screening experiment, performed on a Hamilton 642 MicroLab Star robot (Figure S12). The accuracy of this measurement was confirmed to be within ±5% by amending the library with a series of Brookfield viscosity standards ranging from 0.9 to 81 cP. None of the library samples had a viscosity below the desired 10 cP, but the best formulations came with approximately 14 cP close to this threshold.

DOI: 10.1021/acscombchem.8b00042
ACS Comb. Sci. XXX, XXX, XXX–XXX

Figure 8. Oil and conductive phase library designed to explore the formulation space of liquid lenses’ systems with nine candidate compounds for the oil phase and three candidate compounds for the water phase.
Individual data is presented in Table S17. The final model obtained after multivariate regression is presented in Table S22. Empirical Melting Point Model. We measured the melting temperature of each oil phase in the library by DSC. The results of these targets are presented in Table S17. Most of the melting points were below −40 °C. As before, we performed regression and model simplification until \( R^2 \) did not increase any further. The final model has a good fit to the experimental data (Table S23).

Optimization of the Biphasic System. To find areas in the formulation space that simultaneously meet the optimization targets, a Monte Carlo simulation was performed by calculating predicted properties of \( 2 \times 10^3 \) random biphasic formulations within the original definition range (Table 4). All formulations that did not meet the desired requirements were discarded.

Selection criteria were as follows: turbidity after temperature shock after 4 h cool down, \( T < e^{1.75} \approx 5.75 \) NTU; refractive index difference of oil phase and corresponding ideal water phase \( \Delta n_p > 0.295 \); phase miscibility at room temperature, \( \Phi_{\text{oil-water phase}} (20 \, ^\circ\text{C}) < 0.15\% \); miscibility at 70 °C, \( \Phi_{\text{oil-water phase}} (70 \, ^\circ\text{C}) < 0.3\% \); melting point of oil phase, \( m_p < -35 \, ^\circ\text{C} \). As no simulated formulation had a viscosity of \( \nu < 10 \) cP, the requirement was relaxed to \( \nu < 16 \) cP. Duplicate hits were removed and the remaining data set consisted of 124 simulated formulations. The data points were sorted and grouped into seven clusters by using Ward’s minimum variance method (Figure 9).

Simulated ideal formulations in cluster 1 contain about 40% 1-chloronaphthalene 6 and 60% Santolight SL-5267 18. Formulations in cluster 2 include the same compounds at weight fractions of ~30% and ~40%, respectively. Additionally, ~20% ethylthiobenzothiazole 21 and ~10% of other compounds, that is, 4-bromodiphenylether 16 are included. Formulations in clusters 3 and 4 do not contain 1-chloronaphthalene 6, but instead, 1-phenylnaphthalene 8 with a weight fraction of ~30–40%, supplemented by ~20–30% Santolight SL-5267 18. The remaining compounds are ~10% 2,5-dibromotoluene 33, ~15% diphenyl sulfide 17, and thianaphthene 31. Interestingly, diphenyl sulfide 17, which performed poorly in our turbidity screen, is in most simulated formulations accompanied by 2,5-dibromotoluene 22. 2,5-Dibromotoluene 22 increases the density of the oil phase, thereby permitting a larger salt fraction and density of the water phase. The higher salt fraction increases the polarity of the conductive phase and this effect may help counteracting a predicted turbidity associated with diphenyl sulfide. Cluster 5 contains five compounds at similar concentrations: 1-phenylnaphthalene 8, SL-5267 18, ethylthiobenzothiazole 21, 2,5-dibromotoluene 33, and diphenyl sulfide 17. Cluster 6 relies on high diphenyl sulfide 17 concentrations, accompanied by SL-5267 18 and 2,5-dibromotoluene 33. Cluster 7 is the only solution that does not require SL-5267 18 to achieve the high refractive index. Instead, high concentrations (~55%) of 1-phenylnaphthalene 8 are utilized, together with 2,5-dibromotoluene 33 and diphenyl sulfide 17 to increase the density and lower the viscosity, which goes along with lower reactive indices of the corresponding ideal water phase. Table 5 summarizes the weight fraction boundaries, which served as guideline for future improvements of Varioptic Liquid lenses.

On the basis of these results, prototype highly refracting liquid lenses (\( \Delta n_p = 0.290 \)) were built by Varioptic SA, which showed outstanding performance properties meeting critical requirements such as optical transmittance after temperature shock, short response time, and minimal optical drift/hysteresis. Although neither specifics about the formulation ultimately used in these prototypes nor detailed application testing data can be disclosed herein, the resulting prototype devices had sufficient optical power to focus at very close distance (<1 cm). At this distance, fine features can be imaged, here demonstrated with a leaf with a 130–140 μm venation pattern (Figure 10).

These prototype lenses spearheaded the development of a new generation of commercial Varioptic Lenses with high-power zooming capabilities.

**CONCLUSION AND SUMMARY**

Using statistically designed experiments in conjunction with high throughput/automated measurements, we have developed several statistical models to predict a variety of physicochemical properties of the both phases of formulations that can be used in Varioptic Lenses. These parameters include refractive index, melting point and density of the water phase, the viscosity and melting point of the oil phase, the cross miscibility at 20 °C and 70 °C, and the refractive index difference of the biphasic system. Additionally, we have demonstrated that fluorinated salts in the conductive phase, such as sodium trifluoroacetate, lower the achievable refractive index while improving transmittance after temperature shock. We developed a method to calculate ideal low reactive index conductive phases to match the density of any given high refractive oil phase. Next, nine oil phase candidate compounds were identified. With these candidate...
738 compounds, 59 oil experimental oil phases were formulated in a D-optimal experimental design and matched with ideal water phases of equal density. A number of physicochemical properties of these systems were determined experimentally and used to generate predictive models via multivariate regression. We used these models to predict ideal biphasic systems within the investigated formulation space by Monte Carlo simulation. The result was used as a basis to guide prototype development of a new generation of Varioptic Lenses, leading to devices with an optical strength that was previously not achievable.

ASSOCIATED CONTENT

* Supporting Information
  The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombosci.8b00042.
  Raw data, experimental details, and models (PDF)
  Predictive melting point model of the conductive phase (HTM)
  All DOE-derived predictive models for the biphasic systems (HTM)

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All authors have given approval to the final version of the manuscript.

Funding
This work was supported by The Dow Chemical Company (M.O., D.D., C.W.-G.) and Varioptic then Invenios France SAS (M.M., F.A., G.M., B.B., and B.B.). Invenios France SAS is 100% owned by Corning and operates under the commercial name of “Technology Center—Lyon”, selling products under the Corning Varioptic Lenses brand.

Notes
The authors declare no competing financial interest.
Corning Technology Center—Lyon was formerly called Varioptic S.A., Bâtiment Tony Garnier.

ACKNOWLEDGMENTS
The authors would like to thank Bruce Bell, Thomas Boomgaard, Suraj Deshmukh, Keith Harris, Paul Foley, Timothy Frank, Bill Heeschen, Christopher Jones, Terry McCabe, Andrew Pasztor, Dale Schmidt, Amy Tesolin-Gee, Deborah Rotte, and Chengu Zhi (The Dow Chemical Company). The authors would also like to thank Julien Legrand, Nelly Garcia Jaldon, Jean-Christophe Robert and Liana Voina (Varioptic Company).

ABBREVIATIONS
1-chloronaphthalene
phenylphthalein
2,5-dibromotoluene
4-BrPhOPh, 4-bromodiphenyl ether
2,5-Dibromotoluene
NaOTf, sodium trifluoracetate
TAD, total aspiration dispense monitoring
TMG, 1,3-propanediol
v, viscosity
V, volume
w, weight fraction of compound i
ΔnD, refractive index difference between water and oil phase
νD, apparent refractive index/density quotient of compound i
ρD, density of compound i
Σ, scattering efficiency
φ, phase miscibility
Φ, volume fraction of compound i

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Varioptic/Corning proprietary information. The authors expect that an ideal density model (i.e., \( d_{\text{water \ phase}} = \sum w_i d_i \)) with \( d_{\text{water}} \) being the estimated mixture density and \( w_i \) and \( d_i \) being the weight fractions and densities of the formulation components, respectively) in place of the actual Varioptic density model will be adequate to approximate the results and reproduce the key learnings disclosed herein.

