Published in final edited form as:

Chem Eng Sci. 2017 February 23; 159: 131–139. doi:10.1016/j.ces.2016.09.033.

Computer-aided Molecular Design of Water Compatible Visible Light Photosensitizers for Dental Adhesive

Farhana Abedin^{1,2}, Brock Roughton², Qiang Ye¹, Paulette Spencer^{1,3}, and Kyle Camarda⁴

¹The University of Kansas, Bioengineering Research Center, 1530 W 15th Street, Lawrence, KS 66045, USA

²The University of Kansas, Bioengineering Graduate Program, 1530 W 15th Street,, Lawrence, KS 66045, USA

³The University of Kansas, Department of Mechanical Engineering, 1530 W 15th Street, Lawrence, KS 66045, USA

⁴The University of Kansas, Department of Chemical and Petroleum Engineering, 1530 W 15th Street, Lawrence, KS 66045, USA

Abstract

Dental adhesive resin undergoes phase separation during its infiltration through the wet demineralized dentin and it has been observed previously that the hydrophilic-rich phase is a vulnerable region for failure due to the lack of photo-polymerization and crosslinking density. The lack of photo-polymerization is mostly due to the partitioning of photo-initiators in low concentrations within this phase. Here, a computational approach has been employed to design candidate water compatible visible light photosensitizers which could improve the photo-polymerization of the hydrophilic-rich phase. This study is an extension of our previous work. QSPRs were developed for properties related to the photo-polymerization reaction of the adhesive monomers and hydrophilicity of the photosensitizer using connectivity indices as descriptors. QSPRs and structural constraints were formulated into an optimization problem which was solved stochastically via Tabu Search. Four candidate photosensitizer molecules have been proposed here which have the iminium ion as a common feature.

Keywords

photosensitizer; dental adhesive; QSPRs; optimization; MINLP; connectivity indices; Tabu Search

Dr. Brock Roughton's current affiliation is with the U.S. Food and Drug Administration (FDA), 10903 New Hampshire Avenue, Silver Spring, MD 20993.

The opinions and information in this article are of the authors, and do not represent the views or policies of the FDA.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Introduction

Due to the aesthetic appeal and concern for mercury release, dentists are becoming more inclined towards using dental composite restoration than the conventional amalgam despite the shorter clinical lifetime of the former (Demarco *et al.*, 2012). This has drawn attention in the past to improve the mean clinical lifetime of the composite restoration. It was observed in the past that the weak link to failure of the composite restoration was the dentin/adhesive interface, the adhesive being applied prior to the composite restoration (Spencer *et al.*, 2010). Previous investigations indicated that incomplete infiltration of the dental adhesive resin through the demineralized dentin, poor polymerization, phase separation, enzymatic and hydrolytic degradation of the adhesive, degradation of the exposed collagen were some of the reasons for failure of the restoration (Cadenaro *et al.*, 2005; Hashimoto *et al.*, 2011; Pashley *et al.*, 2004; Santini and Miletic, 2008; Shokati *et al.*, 2010; Spencer and Wang, 2002). The major components of dental adhesives are dimethacrylate cross-linker, monomethacrylate monomer usually 2-hydroxyethyl methacrylate (HEMA) to facilitate infiltration, and a photo-initiator system. When exposed to the dental light curing unit (LCU), the photo-initiator system would trigger photo-polymerization reaction of the dental resin monomers. As the adhesive resin diffuses through the wet demineralized dentin, it undergoes phase separation into hydrophobic- and hydrophilic-rich phases (Spencer and Wang, 2002). It was found in a previous study that the cross-linker and the photo-initiator system being hydrophobic, were present in low concentrations within the hydrophilic-rich phase (Ye *et al.*, 2012). This meant that the hydrophilic-rich phase would become a vulnerable region for failure. This phase would undergo poor photo-polymerization and cross-linking density due to the lack of the photo-initiator system and cross-linker respectively. In this study, several candidate hydrophilic visible light photosensitizer molecules were designed specifically for dental adhesive application. Photosensitizer is a component of the photo-initiator system and when it is irradiated with the dental LCU, photosensitizer molecules are promoted to the excited state which in combination with the co-initiator form free radicals for triggering the polymerization reaction (Cook and Chen, 2011). The approach used here for the design was computer-aided molecular design (CAMD).

The overall goal of this study is to improve the lifetime of the dental adhesive layer and hence the composite restoration. A hydrophilic photosensitizer was designed because improved water compatibility will ensure partition of the photosensitizer in higher concentration within the hydrophilic-rich phase during phase separation, and hence this would enhance the photo-polymerization of this phase. The newly designed photosensitizer should have absorption wavelength in the visible range because the dental light curing units also possess emission wavelength in the visible range.

Computer-aided molecular design (CAMD) is an efficient and inexpensive technique capable of predicting molecular structures or mixture or system with desired optimal properties. The design approach consists of two phases which are forward and inverse problems. The forward problem involves selecting appropriate compounds or components in a mixture which form the model building set, and establishing correlations between the properties of interest and the model building set. This form the quantitative structure

property relationships (QSPRs). The inverse problem involves formulating an optimization problem using structural constraints and the correlations (QSPRs), and solving it to predict molecular structures or components with properties approaching the desired target values. CAMD has been used in the development of pharmaceutical products/biologics, catalysts, polymers, solvents or their mixtures, refrigerants etc. (Gani *et al.*, 1991). Group contribution in CAMD is a method in which the functional groups representing the compounds or mixture, and the number of times they occur are used to determine the properties (Gani *et al.*, 1991). Merrero *et al.* used group contribution method to predict properties such as critical pressure, critical volume, and normal boiling/melting temperatures of organic compounds (Marrero and Gani, 2001). In the study conducted by Merrero *et al.*, in addition to simple groups higher order groups were used to capture more information such as isomers and complex structures such as polyfunctional acyclic or heterocyclic compounds (Marrero and Gani, 2001). Folic *et al.* designed solvents for reactions by CAMD where the models for solvent properties were obtained using solvatochromic equations and group contribution method (Folic *et al.*, 2008). Solvents for enhanced reaction kinetics were also designed in the past using CAMD approach where the objective function was to maximize the reaction rate constant at 298 K (Struebing *et al.*, 2013).

Apart from group contribution, connectivity indices which are topological descriptors have been employed in the past to obtain QSPRs. Connectivity indices describe the molecular structure of an entity in terms of connectivity as well as electronic configurations (Bicerano, 2002). As a result connectivity indices are thought to contain more structural information than the group contribution method (Camarda and Maranas, 1999). Gani *et al.* used zero and first order connectivity indices to predict the contribution of missing groups and they described the approach as group contribution⁺ since group contribution was used in combination with the connectivity indices for property prediction (Gani *et al.*, 2005). Connectivity indices have been successfully used in the past to design pharmaceuticals, environmentally benign catalyst, cross-linked polymer etc. (Chavali *et al.*, 2004; Eslick *et al.*, 2009; Roughton *et al.*, 2012b; Siddhaye *et al.*, 2000). Roughton *et al.* employed connectivity indices to estimate properties such as glass transition temperature, Gordon-Taylor constant for carbohydrate excipient (Roughton *et al.*, 2012b).

The inverse problem of CAMD could be solved either deterministically or by a stochastic method. Roughton *et al.* designed ionic liquids by a deterministic method using CPLEX solver in GAMS optimization software package (Roughton *et al.*, 2012a). Genetic algorithm and Tabu Search are stochastic methods which have been employed in the past to solve the inverse problem in CAMD. Roughton *et al.* have used Tabu search to design carbohydrate excipient to minimize protein aggregation (Roughton *et al.*, 2012b). Camarda *et al.* and Eslick *et al.* have also used Tabu Search for polymer design (Camarda and Maranas, 1999; Eslick *et al.*, 2009). Venkatasubramanian *et al.* showed a CAMD framework using genetic algorithm for polymer design (Venkatasubramanian *et al.*, 1994).

Although in the past, quantitative structure property relationships (QSPRs) of dyes for properties specifically related to photovoltaic applications have been developed but in this study QSPRs using model building set of mostly dyes have been developed for dental application. Vankatraman *et al.* successfully developed quantitative structure property

relationships (QSPRs) of dyes representing coumarin derivatives for properties important to photovoltaic application using frequency based eigenvalue descriptors (Venkatraman *et al.*, 2014). A recent study by Venkatraman *et al.* exhibited the QSPRs for phenothiazine dyes for application in photovoltaic cell using the eigenvalue descriptors (Venkatraman and Alsberg, 2015).

In this study, a model building set consisting of mostly dyes was used to develop the QSPRs for properties such as octanol/water partition coefficient, molar extinction coefficient, photon absorption efficiency (PAE), degree of conversion and rate of polymerization of dental monomers within the hydrophilic-rich phase. Finally the QSPRs are used in the inverse problem to design water compatible visible light photosensitizers with properties that will result in improved durability of the hydrophilic-rich phase. This is an extension of our previous study where only octanol/water partition coefficient and molar extinction coefficient were used as properties to design the photosensitizer molecules for dental application (Abedin *et al.*, 2015a). This study represents a more complete step towards designing optimum photosensitizer for improved performance of the hydrophilic-rich phase.

Materials and Methods

Forward Problem: Properties and Model Building Set

The model building set was chosen rationally so that all the compounds have photosensitizing capability, possess maximum absorption wavelength in the visible range and are hydrophilic in nature. The properties of interest for the design are octanol/water partition coefficient, molar extinction coefficient, photon absorption efficiency (PAE), degree of conversion and rate of polymerization of dental monomers within the hydrophilic-rich phase. Octanol/water partition coefficient was chosen as a measure of the hydrophilicity of the molecules and the logarithm of the octanol/water partition coefficient ($\log P$) for the molecules in the model building set were obtained from the literature (Pellosi *et al.*, 2012; Sheikh, 1976; Wagner *et al.*, 1998; Wainwright *et al.*, 1999). The molecules in the model building set for the property, $\log P$ were: Bromophenol blue, Eosin Y, Erythrosin B, Fluorescein, Methylene blue chloride, Rose bengal, Victoria blue B and Victoria blue R. Table 1 shows the $\log P$ values for the molecules in the model building set. These eight molecules formed the model building set to develop the QSPR for the $\log P$.

The molecules in the model building set for the rest of the properties were: New Fuchsin, Victoria blue B, Methylene blue chloride, Eosin Y disodium salt, Bromophenol blue sodium salt, Erythrosin B, Fluorescein sodium salt, [3-(3,4-dimethyl-9-oxo-9H-thioxanthen-2-yl oxy)-2-hydroxypropyl]trimethylammonium chloride (QTX) and Rose bengal sodium salt. There were nine candidate molecules in this model building set and most of them were dyes. Figure 1 shows the molecular structure of the compounds in this model building set.

Molar extinction coefficient (ξ) of a molecule at a given wavelength is a measure of the probability of a molecule to absorb energy when it is irradiated at that wavelength and be promoted to the excited state. This phenomenon would play an important role in the generation of reactive species for photo-polymerization reaction. Therefore, molar extinction coefficient (ξ) of a photosensitizer is an important property to determine the performance of

the photoinitiator system. The absorbance of the photosensitizer and hence the photoinitiating performance is also dependent on the overlap of the emission spectrum of the light curing unit (LCU) and the absorption spectrum of the photosensitizer. This overlap between the two spectra is the photon absorption efficiency (PAE). These properties were experimentally determined, and the details for the experimental procedure along with the data were discussed by Abedin *et al.* (Abedin, 2016). Aqueous solution of each compound in de-ionized water was prepared and the absorption intensity was measured at 480 nm using a UV-vis spectrophotometer, Cytation 3 multimode microplate reader (BioTek, Winooski, VT). The molar extinction coefficient (ξ) was determined using the following equation and it was determined at 480 nm which was close to the maximum emission wavelength of the halogen LCU (Eacute *et al.*, 2008).

$$\text{Absorbance} = \xi \times \left[C_{\frac{\text{mol}}{\text{L}}} \right] \times X_{\text{cm}} \quad (1)$$

where ξ is the molar extinction coefficient in L/(mol cm) and X is the path length and [C] is the molar concentration.

The UV-vis spectrum of the aqueous solution of each compound was determined experimentally using the UV-vis spectrophotometer, Cytation 3 multimode microplate reader (BioTek, Winooski, VT). The PAE was obtained by converting the energy densities of the LCU at each wavelength to the number of photons per square centimeter and seconds ($n_{ph\lambda}$) by using equation 2 and multiplying this quantity with the absorption of the photosensitizer at the corresponding wavelength (Abedin, 2016). The resultant quantity was then plotted against wavelength which was integrated to give PAE. The PAE was normalized for concentration and the relative values of the normalized PAE was used for determining the QSPR. PAE had been determined similarly in the past (Neumann *et al.*, 2005; Stahl *et al.*, 2000) and the emission spectrum of halogen Spectrum 800 LCU was used for the calculations here (Eacute *et al.*, 2008).

$$n_{ph\lambda} = \frac{W\lambda}{hc} \quad (2)$$

where W is the energy output of the LCU, λ is the wavelength, h is the Planck's constant and c is the speed of light.

Although the molar extinction coefficient and relative normalized PAE, representing the photochemistry of the photosensitizer play an important role in the generation of the reactive species but the effectiveness of these species in triggering the polymerization reaction is also an important parameter to consider for the efficiency of the reaction. Degree of conversion (DC) could indicate the effectiveness of the reactive species in driving the reaction and hence they had been considered as target properties. The rate of polymerization can be linked to the polymer shrinkage which is detrimental for the seal at the adhesive/dentin interface. The DC and rate of polymerization of only the hydrophilic-rich phase have been

considered here. The procedure to obtain these data have been discussed by Abedin *et al.* (Abedin, 2016). Briefly, the photoinitiator system (0.5 wt% Camphorquinone, 0.25 wt% Photosensitizer in the model building set, 0.25 wt% Ethyl 4-(dimethylamino)benzoate, 0.5 wt% 2-(dimethylamino)ethyl methacrylate, 0.5 wt% Diphenyliodonium hexafluorophosphate) within the dental adhesive resin (45 wt% HEMA and 55 wt% BisGMA) was partially replaced with each photosensitizer molecule in the model building set, and then 33 wt% deuterium oxide was added to separate the adhesive into hydrophobic and hydrophilic-rich phases. Ye *et al.* and Abedin *et al.* have discussed this phase separation process (Abedin, 2016; Abedin *et al.*, 2016; Ye *et al.*, 2012). The polymerization kinetic study was performed in ATR sampling mode using the time resolved spectrum collector with a resolution of 4 cm⁻¹. A PerkinElmer Spectrometer Frontier (PerkinElmer, Waltham, MA, USA) was employed to collect the data (Abedin, 2016; Abedin *et al.*, 2015b).

Molecular Descriptors

In this study, connectivity indices have been used to predict the properties. Connectivity indices are topological descriptors (Randic, 1975) and to calculate the connectivity indices of various order it is first necessary to understand the simple connectivity index, δ and the valence connectivity index, δ^v . For a hydrogen suppressed graph of a molecule, δ for a non-hydrogen atom is the number of edges emanating from the atom that is the number of non-hydrogen atoms to which it is connected (Bicerano, 2002). δ^v of a non-hydrogen atom can be obtained from equation 3 and it stores information regarding the electronic configuration of the atom (Bicerano, 2002).

$$\delta^v = \frac{Z^v - N_H}{Z - Z^v - 1} \quad (3)$$

where Z^v is the number of valence electrons of a non-hydrogen atom, Z is the sum of Z^v and the number of inner shell electrons and N_H is the number of hydrogen atoms bonded to the non-hydrogen atom of concern.

Zeroth order connectivity index of a molecule is the summation of δ over the all non-hydrogen atoms (vertices) which form the nodes of the hydrogen suppressed graph (Bicerano, 2002). Zeroth order valence connectivity index of a molecule is obtained similarly using δ^v . The zeroth order connectivity indices stores atomic information of the molecule. The first order connectivity indices were obtained by summing the product of simple connectivity indices of two connected atoms that is the summation is made over the bonds within the molecule (Bicerano, 2002). Higher order connectivity indices such as 5th order can be obtained by summing over a path length of 5. The extent to which structural and electronic information of a molecule is stored increases as the order of the connectivity becomes higher. In this study, connectivity indices of up to 5th order were used and for compounds which were salts in the model building set, the connectivity indices of the organic anion or cation had been calculated. Generalized equations that were used for the calculation of connectivity indices of molecules in the model building set and also during building novel molecules in the inverse problem had been discussed by Roughton *et al.*

(Roughton *et al.*, 2012b). Table 2 shows the connectivity indices for one of the dye molecule, Erythrosin B in the model building set.

Quantitative Structure Property Relationships (QSPRs)

The mathematical correlations between molecular structures and target properties which represent QSPRs were obtained by linear regression using the statistical software package R (R-Development-Core-Team, 2010). The linear regression was carried out by the ordinary least squares (OLS) method. Based on the coefficient of correlation (R^2), the number of descriptors were reduced from 10 to 5 in case of the rate of reaction, 6 for log P, and 7 for $\ln(\xi)$, normalized PAE, DC. Leaps package was used to select the descriptors (Lumely, 2009). The reduced number of descriptors were then used to develop linear models. The model with high R^2 and lowest Mallow's C_p was selected. Mallow's C_p statistics is a measure of precision and bias in the model (Roughton *et al.*, 2012b). As descriptors are added to the model, the C_p statistic is penalized and it increases after a certain number of descriptors (Roughton *et al.*, 2012b). Figure 2 shows that the model with 6 descriptors for the relative normalized PAE exhibited minimum C_p , and hence this model was selected. A small C_p statistic means that the regression coefficients of the model are true. The predictive capability of the correlations were evaluated by the cross-validation method "Leave-one-out" (LOOCV). The DAAG package in R was used for carrying out the cross-validation. In LOOCV, each molecule in the model building set was left out and the correlation was carried out again using the selected descriptors. This correlation was then used to predict the property for the molecule left out. The predictive squared correlation, Q^2 was then determined which gave a measure of the predictive capability of the model. Q^2 close to R^2 indicates a good predictive capability of the model.

Inverse Problem: CAMD Formulation and Solution Technique

The molecules in the model building set were broken down into fragments which form the sub-groups for building new molecules. Figure 3 shows some example sub groups used in designing the new candidate molecules. A total of 42 sub-groups were created and 6 sub-groups at maximum were allowed to build the molecule. This meant that there were approximately 5489 million possibilities since the order in which the sub-groups were connected was important and repeated sub-groups were allowed. The inverse problem was formulated as a mixed integer non-linear problem (MINLP). The non-linearity arises due to the presence of higher order connectivity indices. The MINLP was solved via an optimization technique and the objective was to minimize the difference between the property value and the corresponding set target value. The problem formulation is given below (Abedin *et al.*, 2015a; Roughton *et al.*, 2012b):

$$\begin{aligned} \text{Minimize } s &= \sum_M \frac{1}{P_m^{\text{scale}}} |P_m - P_m^{\text{Target}}| \\ P_m &= f_m(\chi) \\ \chi &= g(a_{i,j}, w_i) \\ h_c(a_{i,j}, w_i) &\geq 0 \end{aligned} \quad (4)$$

where P_m is the property m obtained from the QSPR designated as $f_m(X)$, X are the connectivity indices which are obtained from the function g , a_{ij} and w_i are adjacency matrix and identity vector respectively, h_c represents structural molecular constraints, P_m^{Target} is the target value for the property m , P_m^{scale} is the scaling factor.

In this study, the CAMD framework used previously by Roughton *et al.* to design carbohydrate excipient for preventing protein aggregation was employed (Roughton *et al.*, 2012b). The difference between the property value and target value for each property was normalized. Here, the scaling factor for DC was 0.4 and for log P it was 0.3. The rest of the properties were given equal scaling factor of 0.1.

The optimization problem was then solved stochastically by “Tabu Search” which yields locally near optimal solutions. Tabu Search stores a set of previous solutions in the Tabu list to which it can compare the current solution, and if it is similar to those in the list, the solution is rejected. This allows new search space to be explored and prevents the solution from oscillating around a local optimum.

Results and Discussions

Quantitative Structure Property Relationships (QSPRs)

QSPRs link the molecular structures in the training set (model building set) with the target properties. The correlations with the combination of descriptors (connectivity indices) yielding lowest C_p and relatively high R^2 were chosen to form the QSPRs for the properties. Cross-validation was also carried out to ensure that the models were able to accurately predict the properties of the newly built molecules. In case of the octanol/water partition coefficient, correlation between log P and descriptors was obtained and for the molar extinction coefficient (ξ), the correlation was between $\ln(\xi)$ and the descriptors. The QSPRs for these properties had been discussed in a previous study and hence would not be discussed here (Abedin *et al.*, 2015a). The QSPRs for the other three properties which were PAE, degree of conversion and rate of polymerization of the hydrophilic-rich phase are discussed below. In case of all the properties R^2 is close to Q^2 , indicating good predictive capability of the QSPRs. Table 3 summarizes the characteristics of the QSPR for each property.

Photon Absorption Efficiency (PAE)

As mentioned earlier PAE is a measure of the performance for photosensitizer/LCU combination. Maximizing PAE would enhance the absorption of the photosensitizer and hence could in turn improve the photo-polymerization reaction. Figure 4 is the parity plot for the relative normalized PAE. The QSPR for relative normalized PAE is given below:

$$\text{Relative Normalized PAE} = 34.3226 - (1.7485 \times \chi^0) - (8.0407 \times \chi^2) + (6.1803 \times \chi^3) + (5.108 \times \chi^5) + (9.9007 \times \chi^v) - (26.9838 \times \chi^v)$$

(5)

$$\text{Adjusted } R^2 = 0.9996, Q^2 = 0.9861$$

Degree of Conversion (DC) for the Hydrophilic-rich Phase

The degree of conversion (DC) is a means to understand the effectiveness of the reactive species in driving the photo-polymerization reaction. For the design purpose, it is desired that the degree of conversion is high to enhance the durability of the dentin/adhesive bond within the hydrophilic-rich region. Figure 5 shows that the predicted and experimental DC are close. The QSPR for DC is given below:

$$\text{DC} = -5.1037 - (1.3282 \times \chi^1) + (2.1164 \times \chi^2) - (3.0557 \times \chi^4) + (2.9822 \times \chi^5) + (0.7338 \times \chi^v) - (1.1734 \times \chi^v)$$

(6)

$$\text{Adjusted } R^2 = 0.9896, Q^2 = 0.8633$$

Rate of Polymerization for the Hydrophilic-rich Phase

High rate of polymerization indicates that the reactive species are effective in the polymerization reaction but for dental application very high rate will lead to high shrinkage which will be detrimental for the dentin/adhesive bond (Braga and Ferracane, 2002; Lim *et al.*, 2002). On the contrary, if the rate is too slow it will take a long time for the reaction to complete. Figure 6 exhibits the parity plot for the rate of polymerization. The QSPR for the rate of polymerization (RT) is given below:

$$\text{RT} = -0.0393 + (0.0176 \times \chi^0) - (0.0559 \times \chi^1) + (0.0383 \times \chi^2) - (0.0286 \times \chi^3) + (0.0299 \times \chi^v)$$

(7)

$$\text{Adjusted } R^2 = 0.9742, Q^2 = 0.9169$$

Complex properties such as the degree of conversion and rate of polymerization are difficult to predict, and factors such as steric hindrance and impact of experimental conditions/errors are not taken into account by the descriptors used here. Hence, the R^2 and Q^2 for these two properties were found to be inferior compared to the other three properties.

CAMD of Novel Hydrophilic Visible Light Photosensitizers for Dental Adhesive

The novel molecule was built by connecting the sub-groups with each other. A maximum of 6 subgroups could be connected to form a molecule. Solutions were then generated by making local moves such as swapping, inserting, deleting or replacing the sub-groups. The end groups that would be connected to the terminal connectors of the first and last sub-groups of the molecule were hydroxyl groups.

The target value for log P was -0.55 (Abedin *et al.*, 2015a) and the basis for this was that this represents the log P value for HEMA which was found to partition at relatively higher concentration in the hydrophilic-rich phase compared to the other components (Fujisawa and Masuhara, 1981). The target values for the relative normalized PAE and $\ln(\xi)$ were chosen such that they were approximately close to the maximum values obtained using the known candidates. The reason for keeping these target values close to the maximum is because maximizing these properties may increase the formation of reactive species and hence result in improved photo-polymerization reaction of the monomers. In our previous studies, it was observed that DC of the hydrophilic-rich phase mimics was in the range of 63% to 97% given that the photo-initiator concentration was sufficient (Abedin *et al.*, 2014; Abedin *et al.*, 2015c). In another study, it was observed that the DC of the hydrophilic-rich phase for physically separated model dental adhesive system was approximately 20% to 32% in presence of a reaction accelerator, iodonium salt (Abedin *et al.*, 2016). The low DC for this case was most likely due to the lack of either or both photosensitizer/co-initiator or low efficiency of the co-initiator within the hydrophilic-rich phase (Abedin *et al.*, 2016). Based on our earlier studies on the mimics, the target value for the DC was chosen to be 80% (Abedin *et al.*, 2014; Abedin *et al.*, 2015c). The hydrophilic-rich phase mimics exhibited initial and secondary rates and the formation of microgels was associated with the secondary rate (Abedin *et al.*, 2014; Abedin *et al.*, 2015c). For the target value of the rate of polymerization, only the initial rate of the mimics were considered which ranged from $14.3 \times 10^{-4} \text{ s}^{-1}$ to $47 \times 10^{-4} \text{ s}^{-1}$ (Abedin *et al.*, 2014; Abedin *et al.*, 2015c). The secondary rates were significantly slower than the initial rates, and hence the shrinkage would most likely to be dominated by the initial rate. The target value for the rate of polymerization was chosen to be close to the average of the lowest and highest initial rates observed for the mimics in presence of sufficient photo-initiators ($14.3 \times 10^{-4} \text{ s}^{-1}$ and $47 \times 10^{-4} \text{ s}^{-1}$). DC carried the highest scaling factor followed by log P and the rest of the properties carried equal but lowest scaling factor. The reasons for giving highest scaling factor to DC and then to log P are that a high DC is essential to ensure durable dentin/adhesive bond integrity within this phase, and it is critical that a hydrophilic photosensitizer is designed to ensure that it partitions at a higher concentration within the hydrophilic-rich phase. Four candidate photosensitizer molecules with low objective value out of 100 trials are shown in Figure 7 and Table 4 summarizes their properties along with the target values.

As mentioned earlier with the conventional photosensitizer camphorquinone (CQ), almost no polymerization of the hydrophilic-rich phase was observed, and in the presence of an iodonium salt it could reach 20% to 32% depending on the co-initiator (Abedin *et al.*, 2016). The proposed candidate molecules have a significantly higher DC which is an improvement over the camphorquinone for the hydrophilic-rich phase. The log P value of the candidates

suggest that their hydrophilicity is also high. All the candidate molecules have iminium ions ($C=NH_2^+$ bond) in their structures, indicating that structures consisting this feature may be beneficial for achieving high DC. The C=N bond, C=C bond and benzyl groups within the candidate molecules are structural features which impart them the photosensitizing capability.

Conclusion

In this study, a framework to design water compatible visible light photosensitizer for application in dental adhesive were demonstrated. The target properties were molar extinction coefficient, octanol/water partition coefficient, relative normalized photon absorption efficiency (PAE), degree of conversion (DC) of the hydrophilic-rich phase and rate of polymerization (RT). The target properties are all linked to the photo-polymerization reaction of the adhesive monomers except for the property log P which gives a measure of the hydrophilicity of the photosensitizer. QSPRs developed using connectivity indices by linear regression exhibited high predictive capability. Four candidate photosensitizers have been proposed here and it was observed that they all possess iminium ion in their structures. The predicted DC of the hydrophilic-rich phase were higher for the candidate molecules than in the case with conventional photosensitizer CQ.

Acknowledgments

This investigation was supported by the research grant R01 DE022054, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD 20892

References

- Abedin, F. Characterization of hydrophilic-rich phase mimic in dentin adhesive and computer-aided molecular design of water compatible visible light initiators. The University of Kansas; 2016.
- Abedin F, Roughton B, Spencer P, Ye Q, Camarda K. Computational Molecular Design of Water Compatible Dentin Adhesive System. PSE2015 ESCAPE25. 2015a:233.
- Abedin F, Ye Q, Camarda K, Spencer P. Impact of light intensity on the polymerization kinetics and network structure of model hydrophobic and hydrophilic methacrylate based dental adhesive resin. Journal of Biomedical Materials Research Part B: Applied Biomaterials. 2015b:n/a–n/a.
- Abedin F, Ye Q, Good HJ, Parthasarathy R, Spencer P. Polymerization- and solvent-induced phase separation in hydrophilic-rich dentin adhesive mimic. Acta Biomaterialia. 2014; 10:3038–3047. [PubMed: 24631658]
- Abedin F, Ye Q, Parthasarathy R, Misra A, Spencer P. Polymerization Behavior of Hydrophilic-Rich Phase of Dentin Adhesive. Journal of Dental Research. 2015c; 94:500–507. [PubMed: 25576471]
- Abedin F, Ye Q, Song L, Ge X, Camarda K, Spencer P. Effect of Partition of Photo-initiator Components and Addition of Iodonium Salt on the Photopolymerization of Phase-Separated Dental Adhesive. The Journal of the Minerals, Metals and Materials Society. 2016:68.
- Bicerano, J. Prediction of polymer properties. CRC Press; 2002.
- Braga RR, Ferracane JL. Contraction Stress Related to Degree of Conversion and Reaction Kinetics. Journal of Dental Research. 2002; 81:114–118. [PubMed: 11827255]
- Cadenaro M, Antonioli F, Sauro S, Tay FR, Di Lenarda R, Prati C, Biasotto M, Contardo L, Breschi L. Degree of conversion and permeability of dental adhesives. European Journal of Oral Sciences. 2005; 113:525–530. [PubMed: 16324144]
- Camarda KV, Maranas CD. Optimization in Polymer Design Using Connectivity Indices. Industrial & Engineering Chemistry Research. 1999; 38:1884–1892.

- Chavali S, Lin B, Miller DC, Camarda KV. Environmentally-benign transition metal catalyst design using optimization techniques. *Computers & Chemical Engineering*. 2004; 28:605–611.
- Cook WD, Chen F. Enhanced photopolymerization of dimethacrylates with ketones, amines, and iodonium salts: the CQ system. *Journal of Polymer Science Part A: Polymer Chemistry*. 2011; 49:5030–5041.
- Demarco FF, Corrêa MB, Cenci MS, Moraes RR, Opdam NJ. Longevity of posterior composite restorations: not only a matter of materials. *Dental Materials*. 2012; 28:87–101. [PubMed: 22192253]
- Pérez Mdel M, Pérez-Ocón F, Lucena-Martín C, Pulgar R. Stability and Reproducibility of Radiometric Properties of Light Curing Units (LCUs). Part I: QTH LCUs. *Dental Materials Journal*. 2008; 27:284–291. [PubMed: 18540405]
- Eslick JC, Ye Q, Park J, Topp EM, Spencer P, Camarda KV. A computational molecular design framework for crosslinked polymer networks. *Computers & Chemical Engineering*. 2009; 33:954–963. [PubMed: 23904665]
- Foli M, Adjiman CS, Pistikopoulos EN. Computer-Aided Solvent Design for Reactions: Maximizing Product Formation. *Industrial & Engineering Chemistry Research*. 2008; 47:5190–5202.
- Fujisawa S, Masuhara E. Determination of partition coefficients of acrylates, methacrylates, and vinyl monomers using high performance liquid chromatography (HPLC). *Journal of Biomedical Materials Research*. 1981; 15:787–793. [PubMed: 7309762]
- Gani R, Harper PM, Hostrup M. Automatic Creation of Missing Groups through Connectivity Index for Pure-Component Property Prediction. *Industrial & Engineering Chemistry Research*. 2005; 44:7262–7269.
- Gani R, Nielsen B, Fredenslund A. A group contribution approach to computer-aided molecular design. *AIChE Journal*. 1991; 37:1318–1332.
- Hashimoto M, Nagano F, Endo K, Ohno H. A review: Biodegradation of resin–dentin bonds. *Japanese Dental Science Review*. 2011; 47:5–12.
- Lim BS, Ferracane JL, Sakaguchi RL, Condon JR. Reduction of polymerization contraction stress for dental composites by two-step light-activation. *Dental Materials*. 2002; 18:436–444. [PubMed: 12098572]
- Lumely T. Package ‘Leaps’. 2009
- Marrero J, Gani R. Group-contribution based estimation of pure component properties. *Fluid Phase Equilibria*. 2001; 183–184. 183–208.
- Neumann MG, Miranda WG Jr, Schmitt CC, Rueggeberg FA, Correa IC. Molar extinction coefficients and the photon absorption efficiency of dental photoinitiators and light curing units. *Journal of Dentistry*. 2005; 33:525–532. [PubMed: 15935273]
- Pashley DH, Tay FR, Yiu C, Hashimoto M, Breschi L, Carvalho RM, Ito S. Collagen Degradation by Host-derived Enzymes during Aging. *Journal of Dental Research*. 2004; 83:216–221. [PubMed: 14981122]
- Pellosi DS, Estevão BM, Semensato J, Severino D, Baptista MS, Politi MJ, Hioka N, Caetano W. Photophysical properties and interactions of xanthene dyes in aqueous micelles. *Journal of Photochemistry and Photobiology A: Chemistry*. 2012; 247:8–15.
- R-Development-Core-Team. R: A language and environment for for statistical computing. 2010
- Randic M. Characterization of molecular branching. *Journal of the American Chemical Society*. 1975; 97:6609–6615.
- Roughton BC, Christian B, White J, Camarda KV, Gani R. Simultaneous design of ionic liquid entrainers and energy efficient azeotropic separation processes. *Computers & Chemical Engineering*. 2012a; 42:248–262.
- Roughton BC, Topp EM, Camarda KV. Use of glass transitions in carbohydrate excipient design for lyophilized protein formulations. *Computers & Chemical Engineering*. 2012b; 36:208–216.
- Santini A, Miletic V. Quantitative micro-Raman assessment of dentine demineralization, adhesive penetration, and degree of conversion of three dentine bonding systems. *European Journal of Oral Sciences*. 2008; 116:177–183. [PubMed: 18353013]

Highlights

- Framework to design water compatible photosensitizers for dental adhesives.
- Insight into photosensitizer structure linked to improved dental adhesive lifetime.
- Proposed four example candidate molecules showing high degree of conversion.
- Iminium ions were identified to have positive impact on the degree of conversion.

Figure 1. Molecules in the model building set which were used to the collect experimental data

Figure 2.

The model with 6 descriptors had the lowest C_p value. Addition of descriptor in excess of 6 led to an increase in the C_p value in case of the property, relative normalized PAE.

Figure 3.
Example of some molecular sub-groups used in building novel photosensitizer molecule.

Figure 4. Parity plot showing that the predicted relative normalized PAE by QSPR is close to the experimental values.

Figure 5. Parity plot for the property, degree of conversion (DC). The degree of conversion for the hydrophilic-rich phase was measured experimentally.

Figure 6.

Parity plot showing comparison between predicted rate of polymerization of the hydrophilic-rich phase to the experimental values.

Figure 7. Molecular structure of the candidate photosensitizers

Table 1
logP values used to develop the QSPR

Name of the molecule	log P	Reference
Eosin Y	0.18	[26]
Fluorescein	-0.32	[26]
Rose bengal	0.59	[26]
Erythrosin B	0.46	[26]
Methylene blue	-0.96	[28]
Bromophenol blue	-2.35	[27]
Victoria blue R	1.59	[29]
Victoria blue B	2.8	[29]

Table 2
Connectivity indices for Erythrosin B

Connectivity indices	Valence connectivity indices
${}^0\chi$: 20.6624	${}^0\chi^v$: 22.7251
${}^1\chi$: 13.7686	${}^1\chi^v$: 12.5208
${}^2\chi$: 13.4874	${}^2\chi^v$: 10.9956
${}^3\chi$: 12.9308	${}^3\chi^v$: 8.6793
${}^4\chi$: 10.9332	${}^4\chi^v$: 7.3461
${}^5\chi$: 9.8168	${}^5\chi^v$: 4.6871

Table 3
Summary of the models selected to represent QSPR for each property

Property	No. of descriptors used to develop QSPR	Adjusted R ²	Mallow's C _p statistic	Q ²
ln(ξ)	6	0.99999	6.0	0.99272
log P	5	0.99996	5.1	0.99813
Relative Normalized PAE	6	0.9996	6.0	0.9861
Degree of Conversion (DC)	6	0.9896	7.3	0.8633
Rate of Polymerization (RT)	5	0.9742	6.0	0.9169

Table 4
Summary of the properties of candidate photosensitizer molecules and the target values

Photosensitizer	ln(ξ)	log P	Relative Normalized PAE	DC	Rate (s ⁻¹)	Objective
Target	9.00	-0.55	7.00	0.80	0.0030	0.00
Candidate 1	15.28	-0.47	13.10	0.76	0.0061	0.32
Candidate 2	14.24	-0.70	12.93	0.48	0.0019	0.33
Candidate 3	16.25	-0.37	13.83	0.79	0.0006	0.36
Candidate 4	11.66	-0.29	9.63	0.67	0.0076	0.42