Computer-aided molecular design of water compatible visible light photosensitizers for dental adhesive

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A B S T R A C T

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.

1. 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

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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). Marrero and Gani (2001) used group contribution method to predict properties such as critical pressure, critical volume, and normal boiling/melting temperatures of organic compounds. In the study conducted by Marrero and Gani (2001), 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. Folić et al. (2008) designed solvents for reactions by CAMD where the models for solvent properties were obtained using solvatochromic equations and group contribution method. 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. (2005) 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. 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. (2012b) employed connectivity indices to estimate properties such as glass transition temperature, Gordon-Taylor constant for carbohydrate excipient.

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

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

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.

2. Materials and methods

2.1. 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-yloxy)−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. Fig. 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

Table 1
logP values used to develop the QSPR.

Name of the molecule	log P	Reference
Eosin Y	0.18	Venkatraman and Alsberg (2015)
Fluorescein	−0.32	Venkatraman and Alsberg (2015)
Rose bengal	0.59	Venkatraman and Alsberg (2015)
Erythrosin B	0.46	Venkatraman and Alsberg (2015)
Methylene blue	−0.96	Wagner et al. (1998)
Bromophenol blue	−2.35	Venkatraman and Åstrand (2014)
Victoria blue R	1.59	Wainwright et al. (1999)
Victoria blue B	2.8	Wainwright et al. (1999)