Optical Fibers for Improved Light Delivery in Photodynamic Therapy and Diagnosis

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ABSTRACT

For most Photodynamic Therapy (PDT) applications a diffuse, broad and uniform source of irradiation is needed to obtain the most effective and consistent treatment. Since many treatments are within the patient’s body, an effective, compact fiber optic delivery system is needed for the activation of the photosensitizer drug at the site of the tissue to be treated. High Numerical Aperture (NA) optical fibers have benefits for PDT treatments but possibly even more so for PDT diagnostic applications. These are summarized and new optical fibers with high and ultra high NAs are described. Properties of these fibers are presented as well as advantages they have over other fibers for delivering light in various PDT applications. Silica fibers with enhanced, effective NAs approaching 0.6 are described.

1. INTRODUCTION

PhotoDynamic Therapy (PDT) is generally used to treat hyperproliferative tissue diseases, including dysplasia. Such diseases commonly affect extended volumes of tissue, although from a patient standpoint are relatively localized. In the normal application of PDT to these diseases the light, with appropriate wavelength for the photosensitizer being used, is transmitted to the treatment site through optical fibers which are terminated at their distal end with diffusers. Diffusers may be lenses, elongated sections used to scatter light sideways or special tips which deflect energy primarily around the fiber tip rather than forward.

In normal operation the diffusers used to distribute light from the optical fiber transmission medium to the diseased tissue take light from the higher order modes traveling in the fiber and disperse them into the surrounding tissue. The higher the Numerical Aperture (NA) of the optical fiber the greater the potential for having a majority of the light in higher order modes near the cladding core interface, where they can be more easily be harvested for treating the diseased tissue. Over-launching treatment light into the fibers helps to populate the higher order modes. The number of modes in the fibers grows much faster than linearly as the NA increases for a fixed core size and operating wavelength(s). Small gains NA thus can have great benefits.

Standard all silica fibers have in the past had a maximum NA value of about 0.22. Although these fibers have very good transmission properties for the range of wavelengths where established photosensitizers absorb, they have not been used extensively. Polymer clad fibers with NA values of 0.33 or 0.37 have been the primary types of fibers used in PDT when optical fibers are employed. Initially, the polymeric cladding was removed and a diffuser section/tip produced by applying a coating having scattering points within it. The index of refraction of the coating was higher than that of the fiber core and the scattering points were usually dispersed particles of inorganic oxides. More recently, diffusers have been separately formed and then attached to the distal end of the fiber. These have scattering points throughout the volume to scatter light traveling in 'core-modes' as well as in the higher order modes near the core/cladding interface. In both cases the availability of optical fibers with higher NAs can be seen to benefit the transfer of light into the diseased tissue under PDT treatment.

PhotoDynamic Diagnosis (PDP) is photochemically similar to PDT in that photosensitizers are used to locate the hyperproliferative tissue through the emissions of excited states of a photosensitizer upon irradiation of the suspected areas of the patient. Again relatively large areas of body tissue need to be exposed to the irradiation and secondly a means to collect the emission of the excited states throughout the potential treatment area. The latter function being a type of sensing function, where collection of data is important in directing the irradiation treatment. The energy to excite the photosensitizer is generally emitted from the fiber end. The luminescence of excited state spectra is captured by the fiber and transmitted to detectors and an analysis system. The NA of the fiber thus plays in both the excitation and the collection of the luminescence. The suspected area will usually be much larger than the optical fiber and thus a broad beam will cover the area/volume more efficiently than a narrower beam. Likewise for the collection of the luminescence a broader acceptance angle would allow more efficient collection of it. If the diagnosis is aimed at locating diseased tissue interstitially, then because of the narrowing of the emission beam and acceptance angle for collection are significantly reduced because the basically water medium has a refractive index of 1.33 versus the refractive index of air, 1.00.

Recent development of new methods for preform production as well as new optical fiber structures have now made it possible to make more robust all silica core/clad fibers with numerical apertures for pure silica cores approaching 0.30 and with doped silica cores approaching 0.60. Properties of high NA optical fibers produced with doped silica cores are presented and their benefits for PhotoDynamic Therapy and Photodynamic Diagnosis are discussed below.

2. EXPERIMENTAL

The numerical apertures for the different fibers in this study were made using a set up which involved taking diameter measurements of the projections onto a black surface shielded from direct ambient light at five different distances from the fiber end. A white light source was over-launched and overfilled into the input end of the fiber. Meter long samples were used with about a 90 degree angle bend relative to the output end. The bend radius was on the order of a 40-50 cm. The ends were secured to metal blocks to guarantee stability of placement during testing and to improve reproducibility. NAs calculated at the five distances were averaged to yield the reported NA.

The NIR and VIS spectral losses of low-OH fibers were measured. The "cutback" method was employed using a Monolight Optical Spectrum Analyzer (OSA), manufactured by Macam Photometric Ltd of Livingston, Scotland. The system includes a scanning monochromator, a 3-channel controller, a power supply, two light sources (deuterium and tungsten), and input and output blocks to handle fiber from 70 µm to 1000 µm in diameter. A plastic tent was framed around the equipment table to prevent air disturbances from vibrating the fiber and affecting the measurements.

The "cutback" method consisted of using two pieces of same-type fiber with a length ratio of about 1:4. For this study, the two fiber lengths were in the range of 20-50 m and 60-200 m. The longer lengths were measured via a Tektronix OTDR, and the shorter lengths were manually calculated (i.e. the number of loops were counted and multiplied by Π times the diameter of the spool.) The "cutback" length (in meters) was calculated by subtracting the shorter length from the longer length of fiber.

The four fiber ends from the two spools of fiber were each prepared with a fresh cleave and inspected under a microscope for blemishes and re-cleaved if necessary. The ends were then dipped into acetone and air-dried for 15 seconds prior to insertion into the OSA.

The OSA input and output blocks have removable rubber and neoprene foam clamps for securing the fiber ends into a choice of six differently sized 90° V-Grooves. For this study, we opted to remove the clamps and used tape instead, as we found it easier to handle the smaller diameter fibers. It was critical to position the input and output fiber ends exactly the same for each test. We found a 10X-magnified eyepiece helped us to achieve this. Also, each test was repeated twice to ensure reproducibility.

The test involved first inserting the two ends of the short length fiber into the input and output blocks to measure the signal and to make any gain adjustments. The short length fiber ends were marked "in" and "out" with tape, and the fiber was then carefully removed from the system without touching the core/clad surface. Then the long length fiber was inserted into the same groove and position. Its signal was measured and had to be lower than the short length fiber for the test to proceed. (If it was not, the test was halted, and the long and short fibers were re-spooled, re-measured, and re-cleaved.) In order to ensure signal accuracy, the window of stability for the OSA was 15 minutes beginning with the capture of an acceptable signal from the long length fiber.

A tungsten light source was used for the VIS and NIR tests while a deuterium light source was used for the UV tests. (UV eye protection was worn). The light was launched into the fiber via the over-fill, over-launch method. There was a block of glass between the light source and the input core/clad surface. The channel for the desired spectrum (UV, VIS, NIR) was selected, and the spectral analysis of the long length fiber was taken. The OSA took 400 averages over 30-40 seconds.

At the computer prompt, the long length fiber was removed and the short length fiber was exactly positioned as used in the previous signal acquisition. At the computer prompt, the cutback length (in meters) was entered. The OSA again took 400 averages, and the resulting spectral loss graph was displayed over the selected spectral range. The spectral loss graph was saved to the ASCII format and imported into Excel.

3. RESULTS

Figure 1 shows the typical spectral loss of low-OH fiber with core/clad glass geometries of 200µm/220µm and a numerical aperture (NA) of 0.22 from the wavelengths 300 nm to 1800 nm. This fiber has pure undoped silica as the core material and Fluorine-doped silica as the cladding.

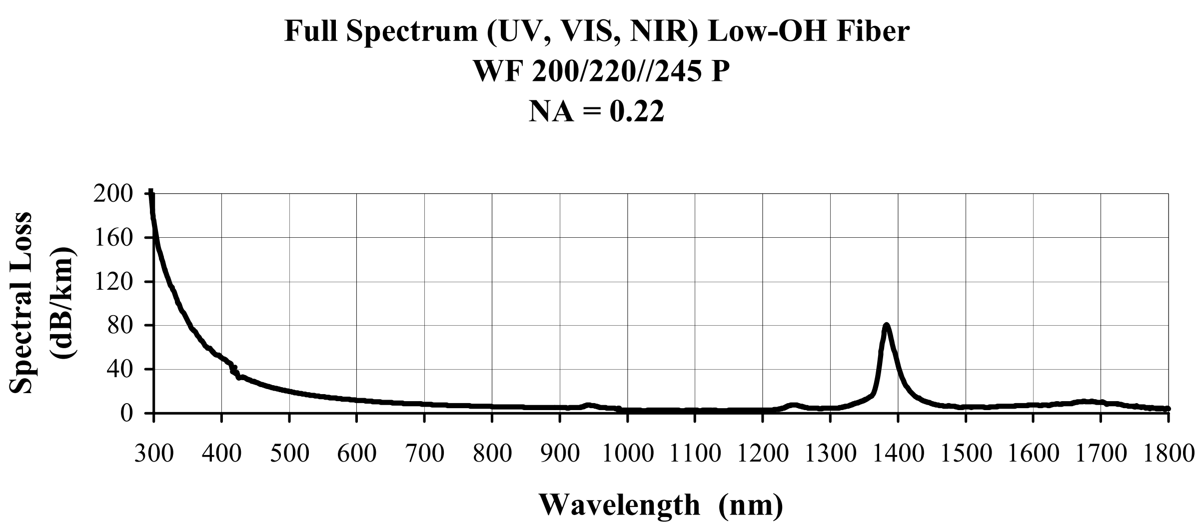


Figure 1: Full spectrum (UV, VIS, NIR) low-OH fiber

Figure 2 shows the typical spectral loss for a low-OH fiber where the core material is now a Germanium-doped silica and the clad material is Fluorine-doped silica. This is the Optran Ultra[1] fiber with an NA of 0.37. Note that the OH level for these fibers is about 1/5 that of the standard fiber represented n Figure 1.

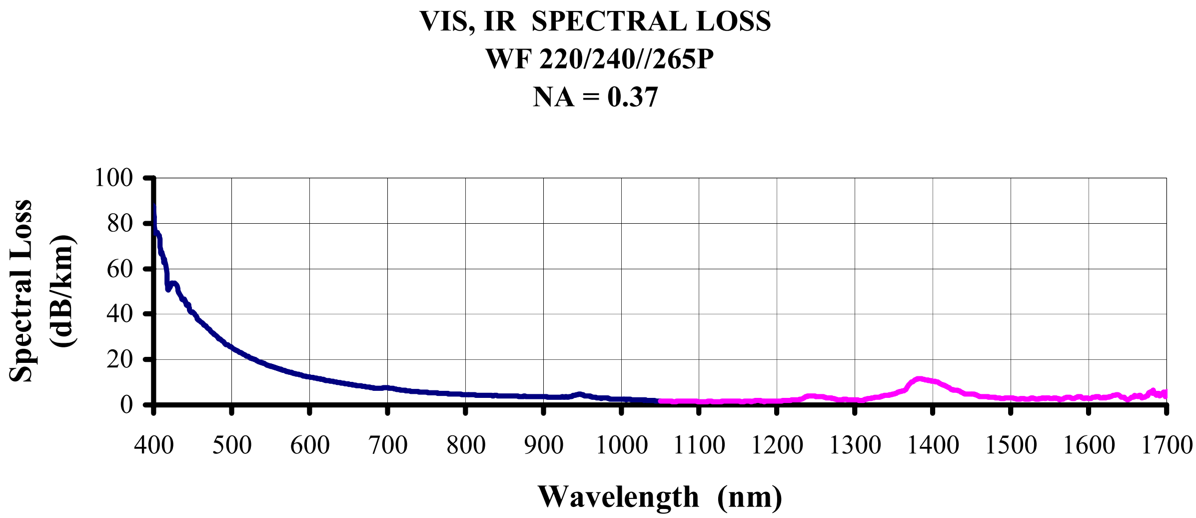


Figure 2: Visible, near infrared spectral loss for 0.37 NA low-OH fiber

Figures 3 and 4 show the visible and near infrared spectral loss for fibers with NA values of 0.47 and 0.56. The spectral loss behavior is essentially similar to the fiber measured in Figure 2. All have Ge-doped silica cores and F-doped silica claddings.

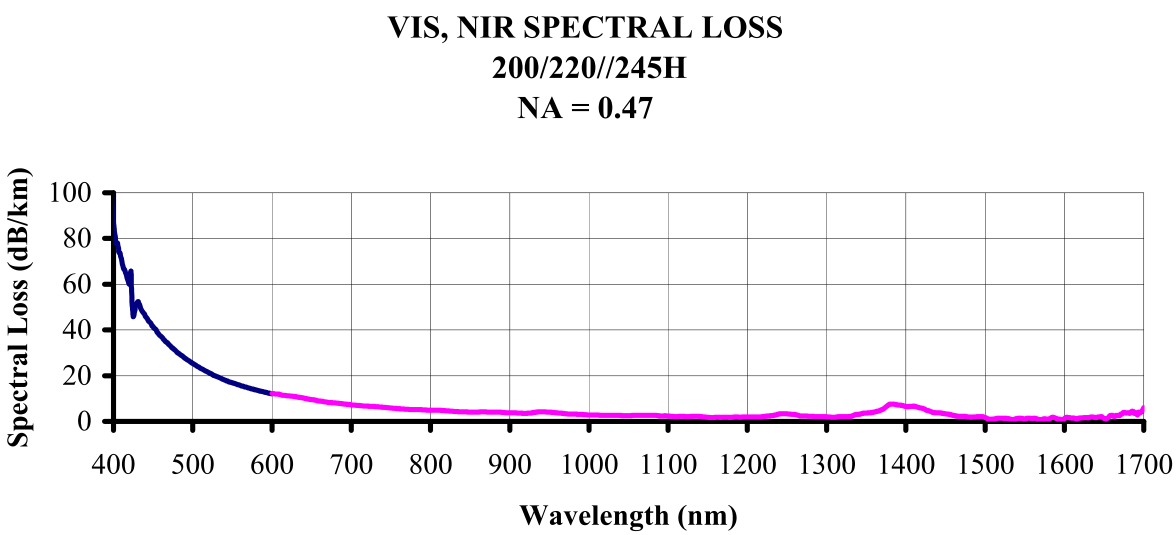


Figure 3: Visible, near infrared spectral loss for 0.47 NA low-OH fiber

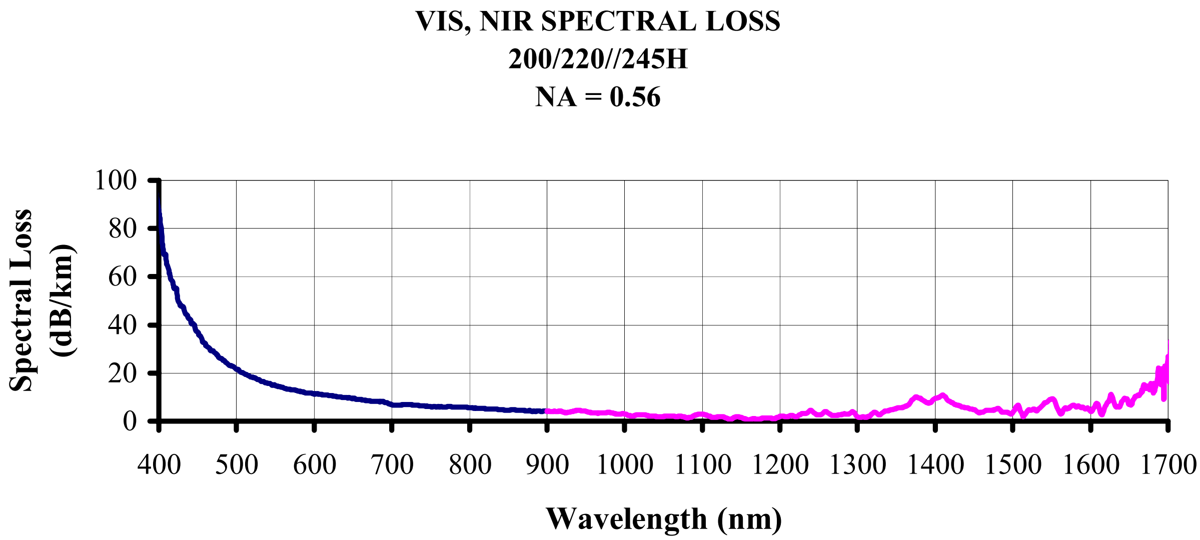
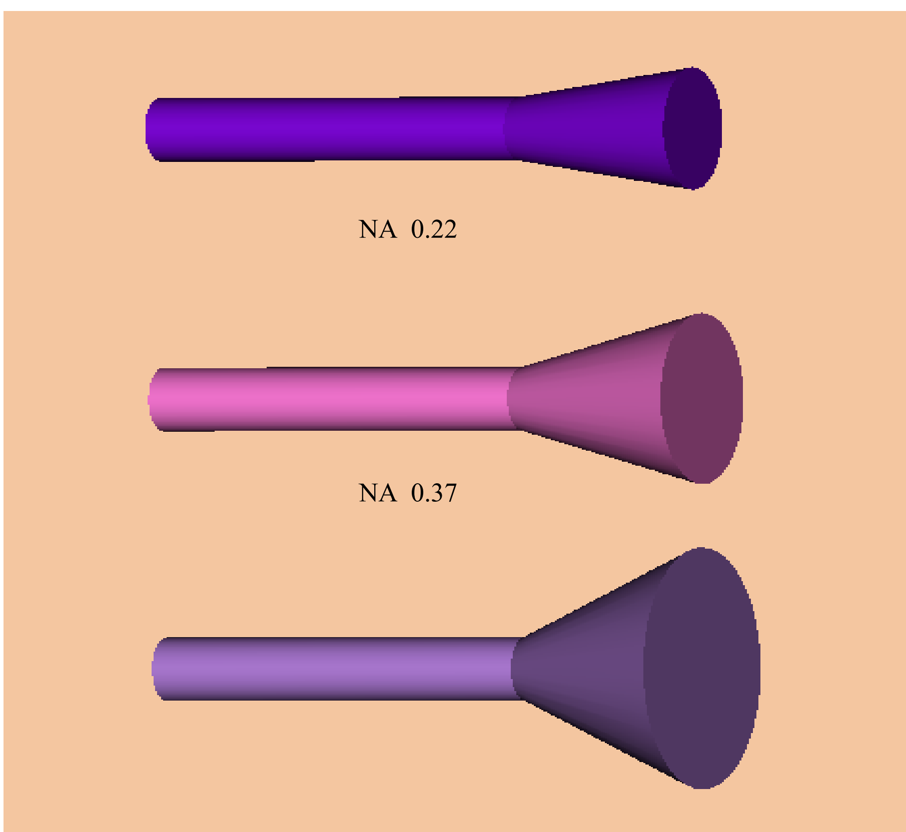


Figure 4: Visible, near infrared spectral loss for 0.56 NA low-OH fiber

Figure 5 presents a comparison of the acceptance volume/surface for optical fibers having the same core dimension and varying numerical apertures (NA) as indicated for each shape; standard silica/fluorosilica fibers at 0.22, germanium-doped silica/fluorosilica fibers at 0.37 and a new variation of the latter which has an NA of 0.56.

Note that the surface area of the acceptance circle, at a fixed distance from the fiber end grows very dramatically as one goes from the fiber with the lowest NA to one with the highest NA. Setting the NA = 0.22 fiber arbitrarily at 1, the NA = 0.37 fiber has an acceptance circular surface, which is 183% larger, and the NA= 0.56 fiber has an acceptance circular surface, which is 550% larger. This dramatic increase demonstrates the improvement in coupling possible under the proper circumstances.



NA 0.56

Figure 5: Schematic representation of the Numerical Aperture of selected optical fibers

4. DISCUSSION

Generally the photosensitizers used in PhotoDynamic Therapy operate in the visible to near infrared [NIR] ranges of the spectrum. As a result, germanium doped silica cores can be used for most applications. In medical applications that are the focus of this paper, where the power transmitted is sometimes low, it is critical to have very low loss optical fibers in order to capture and transmit the incoming signal with sufficient power to activate the photosensitizers to initiate PhotoDynamic therapy and diagnosis. Since the transparent region of the body generally also lies primarily in the NIR or visible ranges, the photosensitizers used for PDT or PD diagnosis (PDP) have also been chosen to have significant absorption in this region. An all silica, germanium doped core, optical fiber is an excellent choice. High NA, low loss optical fibers are a benefit in each of these cases. The problem, however, has been that thermal mismatches between doped and undoped silicas have placed serious restrictions on fiber sizes that can be used for even the moderate power required in non-surgical applications and on the numerical apertures [acceptance angles], for which stable fibers could be produced, for all applications.

The optical fibers, described herein, have been made with new methods of preform production and fiber production and include a new structure. As seen in the results above, the basic spectral properties are essentially similar to earlier fibers having the same chemical materials. These fibers, which are thermally stable over a broader temperature range than are their protective coatings, have much larger NAs allowing for improved distribution of light from a diffuser for PDT. Having silica core and cladding with their low transmission low, can be especially helpful for gathering low intensity luminescence for PDP. This also makes these fibers a preferred choice for transmission systems where more than one area may need to be irradiated, more or less simultaneously, to gain the greatest benefit, whether in PDT applications or for excitation of photosensitizers for PDP. The signal/light at a proximal end can be split into several smaller fibers in a bundle which then split off at the distal end into a pattern of fibers extended into the tissue to be tested or treated. In these latter cases, less fibers can cover/treat a larger volume of diseased tissue and thus the fiber bundle can be kept smaller and insertion is less invasive. Alternatively the large area requiring treatment can be treated with less number of insertions.

For PDP especially, the excitation beam exits from each fiber end and irradiates an area/volume of tissue to excite photosensitizer and then a fiber is used to collect the luminescence and bring it back to a detector for qualitative as well as quantitative analysis. If the dysplasia is in a mucous membrane, it might be possible for the exciting light to raster over a preselected area with maybe a second fiber to collect the luminescence. With either one fiber to excite and collect or a bundle used to excite and collect, larger NA fibers with low loss transmission improve the real time operation of the system by giving broader areas of excitation and the ability to collect any luminescence originating from the irradiated area. The low loss possibility of silica fibers is very important, and is enhanced by the increased NA of these new fibers.

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NOTES

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1. Optran Ultra is a trademark of CeramOptec Industries/Biolitec.