



UvA-DARE (Digital Academic Repository)

Performance of a light applicator for photodynamic therapy in the oral cavity: calculations and measurements

van Benthem, H.E.; Sterenborg, H.J.C.M.; van der Meulen, F.W.; van Gemert, M.J.C.

DOI

[10.1088/0031-9155/42/9/002](https://doi.org/10.1088/0031-9155/42/9/002)

Publication date

1997

Published in

Physics in Medicine and Biology

[Link to publication](#)

Citation for published version (APA):

van Benthem, H. E., Sterenborg, H. J. C. M., van der Meulen, F. W., & van Gemert, M. J. C. (1997). Performance of a light applicator for photodynamic therapy in the oral cavity: calculations and measurements. *Physics in Medicine and Biology*, 42, 1689-1700. <https://doi.org/10.1088/0031-9155/42/9/002>

General rights

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

Performance of a light applicator for photodynamic therapy in the oral cavity: calculations and measurements

H E van Benthem, H J C M Sterenborg, F W van der Meulen and
M J C van Gemert

Laser Centre, Academic Medical Centre, University of Amsterdam, Meibergdreef 9,
1105 AZ Amsterdam, The Netherlands

Received 27 November 1996, in final form 2 May 1997

Abstract. Photodynamic therapy (PDT) is an experimental therapy for the treatment of superficial cancer using laser light. In PDT a uniform light distribution is usually required for an optimal therapeutic effect. To irradiate part of the oral cavity uniformly for PDT, two prototype applicators were built, each for a different lower jaw. The applicators made use of the light transmitted through the wall of a cavity of diffusely reflecting material. The radiant exitance of the applicators was measured at 632.8 nm. For the radiant exitance M of the two applicators, a uniformity ratio, $UR = M_{\max}/M_{\min} < 2$ was found, which was considered reasonable for clinical applications. Calculations predict that the UR can be improved by decreasing the thickness of the cavity wall.

1. Introduction

Photodynamic therapy (PDT) is an experimental modality for treatment of superficial cancers (Henderson and Dougherty 1992). In PDT, a light sensitive drug (photosensitizer) is activated with light of a proper wavelength. This results in the production of singlet oxygen, which in turn can destroy cells and tissues. Because the drug preferentially accumulates in malignant tissue, activation of the photosensitizer mainly destroys the malignant tissue. In most cases, a laser is used as a light source.

To achieve the full potential of PDT, optimum light delivery is necessary. This would mean a uniform fluence rate Ψ in the treated area. However, due to tissue optics, Ψ will decrease with depth into the tissue and is in practice difficult to measure during a treatment. Therefore we chose to aim for the application of a uniform irradiance distribution on the tissue. As a measure for the uniformity, the uniformity ratio UR was introduced by Allardice *et al* (1993) as ratio of the maximum to minimum light flux ϕ over the target,

$$UR = \frac{\phi_{\max}}{\phi_{\min}}. \quad (1)$$

The light flux ϕ can either be the irradiance E (light incident on a surface), the radiant exitance M (light emitted from a surface) or the fluence rate $\Psi(0)$ at the surface. The uniformity of the light distribution is optimal if $UR = 1$ and an increase of UR indicates a less uniform light distribution.

Recently special light delivering devices (applicators) were developed to ensure a uniform light distribution. Nseyo *et al* (1990), Marijnissen *et al* (1993b) and Unsöld *et al* (1989) reported on applicators for the bladder, Marijnissen *et al* (1993a) described an

applicator for the bronchus and Overholt *et al* (1994) one for the oesophagus. Allardice *et al* (1993) developed several applicators for intraoperative PDT. However, all these applicators are not directly applicable for the oral cavity and in the studies of PDT in the oral cavity (Savary *et al* 1994, Grant *et al* 1993, Feyh and Kastenbauer 1992, Feyh *et al* 1993, Herzog *et al* 1992, Lippert *et al* 1993), the authors did not mention the use of special applicators. Herzog *et al* 1992 emphasized that special applicators were needed to improve PDT in the oral cavity.

Uniform irradiation of the rear part of the mouth by direct fibre illumination presents a technical problem for two main reasons. First the available space to position the fibre in the oral cavity is becoming increasingly limited, moving toward the back of the mouth. Furthermore, the oral cavity is far from flat close to the jaw bone. This can cause a variation from perpendicular to parallel incidence and even shadowing, resulting in a non-uniform irradiance distribution. In order to improve uniformity of illumination in the PDT treatment of malignancies in the oral cavity, Rem *et al* (1997) proposed the use of transmitted light through the wall of a hollow mould. This idea is worked out for the posterior lower jaw bone of edentate people in this paper (figure 1) and resulted in two prototype applicators. The production and performance is also presented in this paper. Applicators for other areas in the oral cavity can probably be produced using the same design principle.

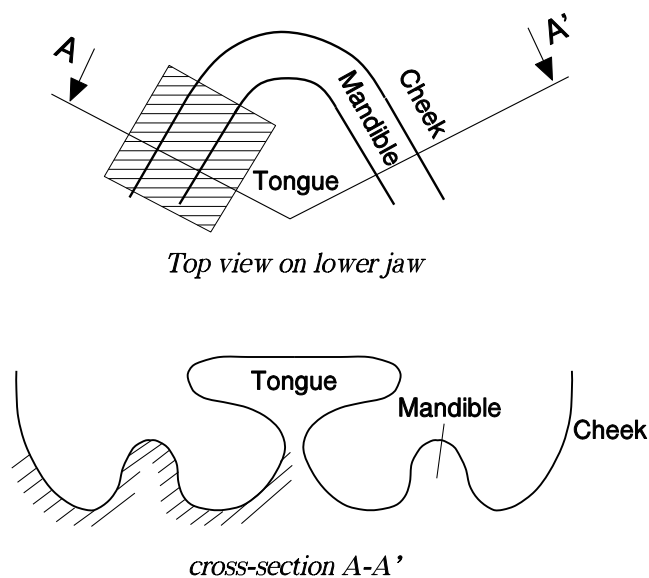


Figure 1. Top view and cross-sectional view of the lower part of the oral cavity. The shaded part is the target area.

The applicators deliver a constant uniformity of initial irradiation, independent of the optical properties. This is an advantage, because no dosimetric data concerning uniformity of irradiation of this anatomical area have been published so far. Measurements of the differences in light flux incident on various parts within the laser spot is hardly feasible in an actual patient. To get an indication of the difference between $UR_{\Psi(0)}$ and UR_M in this non-flat geometry, fluence rate measurements in a tissue phantom are performed and the results are presented in this paper.

To support the idea that an integrating cavity improves the UR on a mouth-shaped cavity surface, results of numerical simulations (based on the radiosity method (Rem *et al* 1997))

are also presented. The UR of the two produced applicators (each for a different mandible) was below two. The numerical simulations indicate that changes in the production process can improve the UR even further.

2. Methods and materials

2.1. The device

2.1.1. Principle. The applicator uses the light transmitted through the highly reflective wall of a closed cavity to irradiate the tissue (figure 2). On the cavity's inner surface an integrating effect will make the irradiance $E(\mathbf{r})$ more uniform. This irradiance $E(\mathbf{r})$ consists not only of a first irradiation $e^{(0)}(\mathbf{r})$, induced by the light source, but also of contributions $e^{(n)}(\mathbf{r})$ of photons that experienced n reflections on the wall. So,

$$E(\mathbf{r}) = \sum_{n=0}^{\infty} e^{(n)}(\mathbf{r}). \quad (2)$$

The vector \mathbf{r} denotes a place on the surface and is in some cases omitted for clarity. For a sphere with a diffuse reflecting wall, this irradiance-increasing effect is known as the integrating sphere effect (ISE) (Goebel 1967). Following the idea of Rem *et al* (1997), the term integrating cavity effect (ICE) is introduced here to indicate the multiple incidence of photons in arbitrarily shaped cavities.

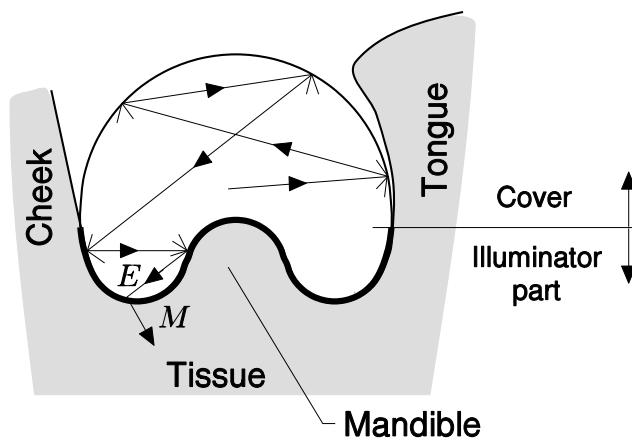


Figure 2. Basic idea of the applicator, illustrated in a frontal schematic section of the mouth. The irradiation E at the inner surface of the cavity is uniformized due to multiple diffuse reflections. The small fraction of light transmitted through the wall of the illuminator part will irradiate the tissue.

The ISE is known to improve the UR. Unsöld *et al* (1989) and Allardice *et al* (1993) also assumed the UR to improve in their cavities, which were non-spherical. Numerical simulations of Rem *et al* (1997) showed that the ICE indeed improved the UR for a cylinder, cube and bottleneck shape. With similar numerical simulations the ICE-induced UR improvement was calculated for a range of realistic cavity shapes.

The initial irradiance E_{tissue} on the tissue surface is equal to the initial radiant exitance M of the applicator. A simple approximation between irradiance E on the inside of the applicator cavity wall and M can be found if we assume

$$M = T_{\text{flat}}(d)\xi(d, R(\mathbf{r}))E \quad (3)$$

in which T_{flat} is the diffuse transmittance of a flat slab and ξ a geometry correction factor; both depend on the thickness d .

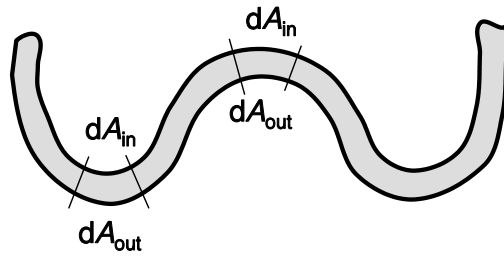


Figure 3. The geometry factor ξ : difference in the local inner surface dA_{in} and the local outer surface dA_{out} .

If the irradiance E and the curvature R of the surface do not vary significantly over an arc of length d , the geometry factor ξ can be estimated by the local difference between the inner (dA_{in}) and outer (dA_{out}) surface area (figure 3) resulting in

$$\xi = dA_{\text{in}}/dA_{\text{out}}. \quad (4)$$

and for a translation-invariant geometry resulting in

$$\xi = 1 - d/R \quad (5)$$

with R the local curvature of the outer surface in the cross-section (figure 4). In the case of the oral cavity, R will change sign and therefore cause variations in the radiant exitance M , even in the case of a uniform irradiance E . This variation in ξ can also be expressed as a uniformity ratio UR_{ξ} .

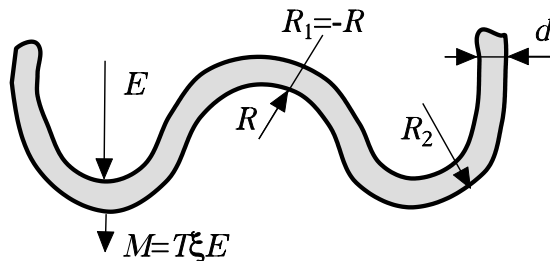


Figure 4. Definition of the local curvature R . In the middle of the picture an example of a negative curvature R_1 . In the right side of the picture one of a positive curvature R_2 .

2.1.2. Production. In the cavity, three parts can be distinguished: the illuminator part, the cover and the endplates (figure 5). The illuminator part of the applicator was formed on a plaster representation of a mandible and is in direct contact with the tissue. The illuminator part was made of a diffusely reflecting and diffusely transmitting material. It is produced by polymerization of a one-to-one polymethylmethacrylate (PMMA) dimer (clear Paladon, Kulzer, Wijk bij Duurstede, The Netherlands) and BaSO_4 powder mixture, with 20% more PMMA monomer added as necessary for the dimer polymerization. The polymerization was performed at 70°C for 4 hours followed by 1 hour at 100°C .

The wall thickness d of the illuminator part was (1.5 ± 0.3) mm. In an integrating sphere setup (IS-060, Labsphere, North Sutton, UK), a diffuse reflection coefficient $\rho = (80 \pm 5)\%$

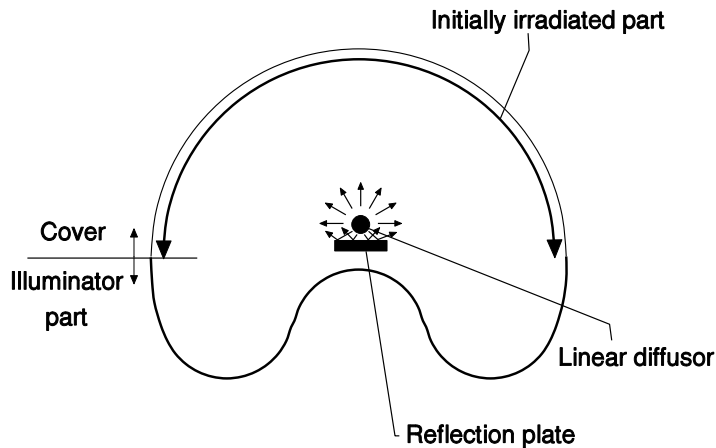


Figure 5. Schematic cross-section of an applicator, distinguishing between the illuminator part and cover. The endplates are perpendicular to the cross-section and close the cavity. They are about 25 mm apart. Due to the reflection plate, the light from the linear diffuser can for the first irradiation only irradiate the cover.

and a diffuse transmission coefficient $T = (10 \pm 1)\%$ were found for a 1.5 mm thick flat slab. The emission of this slab was measured and its deviation from a Lambertian emission profile was less than 10%. The endplates and the cover were made of plastic that was painted white on the inner surface resulting in $\rho = (80 \pm 5)\%$ and the transmission $T < 1\%$.

Two applicators with different dimensions were produced. The first applicator (A1) was produced on a rubber test mouth with realistic dimensions, the second applicator (A2) on a volunteer's lower jaw. The cover was a half a cylinder with a radius of 15 mm. In the centre of the cylinder a 25 mm long linear diffuser (400 μm lightstick, Rare Earth Medical, West Yarmouth, MA, USA) was placed, which in combination with a reflection plate created a more or less homogeneous first irradiation of the cover (figure 5). This 1.5 mm thick BaSO_4 -PMMA plate was 10 mm wide for A1 and 5 mm wide for A2 and covered with aluminum foil at the side of the linear diffuser which prevents transmission through the plate. This shielding of the mandible causes a lower irradiance E on the mandible and therefore compensates for the high ξ on the mandible.

2.2. Numerical simulations

To calculate the UR improvements due to the ICE inside a mouth-shaped cavity, a numerical simulation was set up for translation invariant cavities with an arbitrary cross-section. The simulations were based on the radiosity method as described by Rem *et al* (1997).

The radiosity method requires a subdivision of the total reflecting surface into N surface elements called *patches*. The variables for patch i are represented by E_i , $e_i^{(n)}$, ρ_i , and the length l_i . A compact notation is obtained by a vector representation. For example the irradiance \mathbf{E} , stands for the vector (E_1, E_2, \dots, E_N) . Because of the translation invariancy, only the cross-section is considered, and therefore E_i is expressed in $[\text{W m}^{-2}]$.

Because of multiple diffuse reflections in the cavity, all patches exchange power. A patch-to-patch power transfer factor is defined, the configuration factor C_{ij} , which denotes

the fraction of radiant power originating from patch i that is received by patch j ,

$$C_{ij} = C_{i \rightarrow j} = \frac{\text{transferred radiant power from patch } i \text{ to } j}{\text{total radiant power from patch } i}. \quad (6)$$

In vector representation, all elements C_{ij} are arranged in a matrix \mathbf{C} . From the radiosity theory follows that the irradiance $e^{(n+1)}$ after $n + 1$ reflections can be written as a function of $e^{(n)}$

$$e^{(n+1)} = f(\mathbf{C}, e^{(n)}, \rho, l). \quad (7)$$

For a cavity with given ρ and l , every contribution $e^{(n)}$ can be calculated by calculating \mathbf{C} and using $e^{(0)}$ as an input parameter. Combined with the vector representation of equation (2),

$$\mathbf{E} = \sum_{n=0}^{\infty} e^{(n)} \quad (8)$$

the total irradiance \mathbf{E} can be calculated.

In the numerical calculations, the summation was stopped after term W , which was determined by

$$\sum_{n=0}^W \sum_{i=0}^N e_i^{(n)} > 0.999 \sum_{n=0}^{\infty} W \sum_{i=0}^N e_i^{(n)}. \quad (9)$$

The term on the left side is estimated by the loss of light ($= 1 - \rho$) per iteration step. The configuration factors C_{ij} were calculated with a 3D Monte Carlo method, launching the photons from a random position on patch i with a Lambertian angular distribution and calculating the patch j where the photon landed. For each patch, 10^4 photons were launched, from which an absolute error in C_{ij} of 0.005 can be estimated.

2.3. Measurements

2.3.1. Radiant exitance. The radiant exitance M was measured in air with the bare tip of a 600 μm fibre (PCS600A, Quartz & Silice, Uithoorn, The Netherlands), not in contact with the surface. To prevent light emitted elsewhere from the applicator influencing the signal, a black piece of cotton was fabricated around the fibre tip to shield the measuring area. A HeNe laser (105-2, Uniphase, San Jose, USA) which was chopped at 40 Hz was coupled into the fibre with the linear diffusor. A photomultiplier (R928, Hamamatsu, Toyooka-village, Japan) in combination with a lock-in amplifier (5209, EG&G, Princeton, NJ, USA) was used for detection. If the applicator's angle distribution is assumed constant over its illuminator part, the measured signal is a good measure for the radiant exitance M . For quantitative interpretations a CCD image was taken and processed on a computer (Indy, Silicon Graphics, Mountain View, USA). For a perfect Lambertian emitting surface, the pixel values would represent a measure for the radiant exitance M .

2.3.2. Fluence rate. The fluence rate $\Psi(0)$ at the surface of the applicators was measured in a tissue phantom that consisted of 39.84 ml l^{-1} Intralipid-10% and 20.2 ml l^{-1} 5.15 mg l^{-1} Evans Blue in a buffered NaCl solution with pH = 7.4. According to the work of van Staveren *et al* (1991), this resulted in $\mu_a = 1.7 \text{ cm}^{-1}$ and $\mu'_s = (1 - g)\mu_s = 4.4 \text{ cm}^{-1}$. These values are comparable to the optical parameters of the muscle of a cow as reported by Karagiannes *et al* (1989). The same setup as in case of the radiant exitance measurements was used to feed the applicator and detect the light. The difference is that in this case a fibre optic isotropic probe was used (van Staveren *et al* 1991) instead of a bare fibre tip.

3. Results

3.1. Applicator comfort

A CCD image of applicator A2 is shown in figure 6. This applicator was tested for wearing comfort in the volunteer's mouth for 10 minutes. The applicator's discomfort was comparable with that of a prosthesis, i.e. no problems with breathing and swallowing.

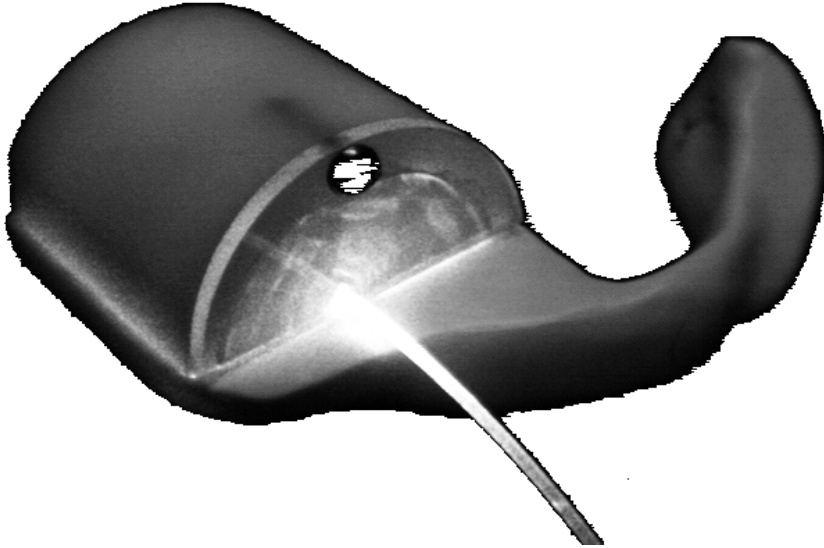


Figure 6. CCD image of applicator A2. On the left side the outside of the cavity is visible. The part on the right side is only present for fixation of the cavity.

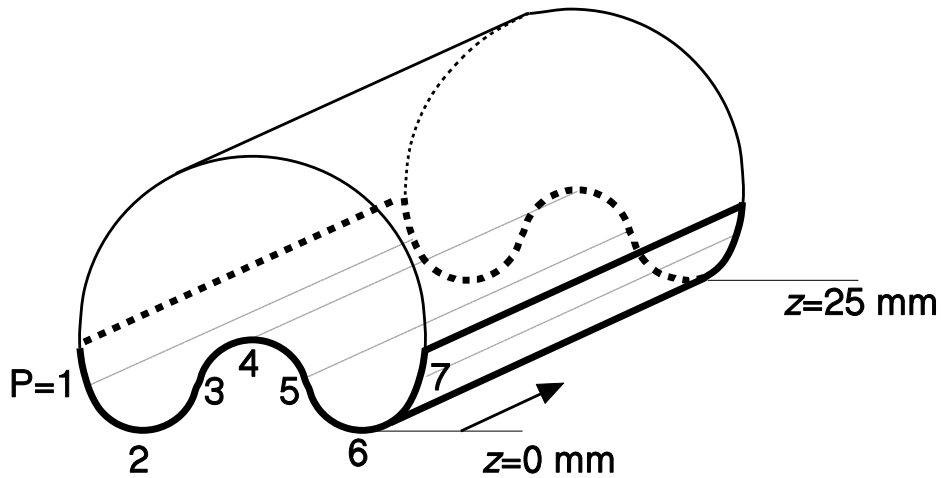


Figure 7. Schematic 3D representation of an applicator with the definition of the z -axis and seven measurement lines P .

3.2. Applicator performance

The UR_M of both applicators A1 and A2 was 2.0 ± 0.1 and 1.9 ± 0.1 respectively over an area of $25 \times 25 \text{ mm}^2$. To indicate the place at the outer surface, parameters P and z are introduced (figure 7). For the middle cross-section ($z = 12.5 \text{ mm}$) the radiant exitance M and the fluence rate $\Psi(0)$ at the surface are plotted for both applicators in figures 8 and 9.

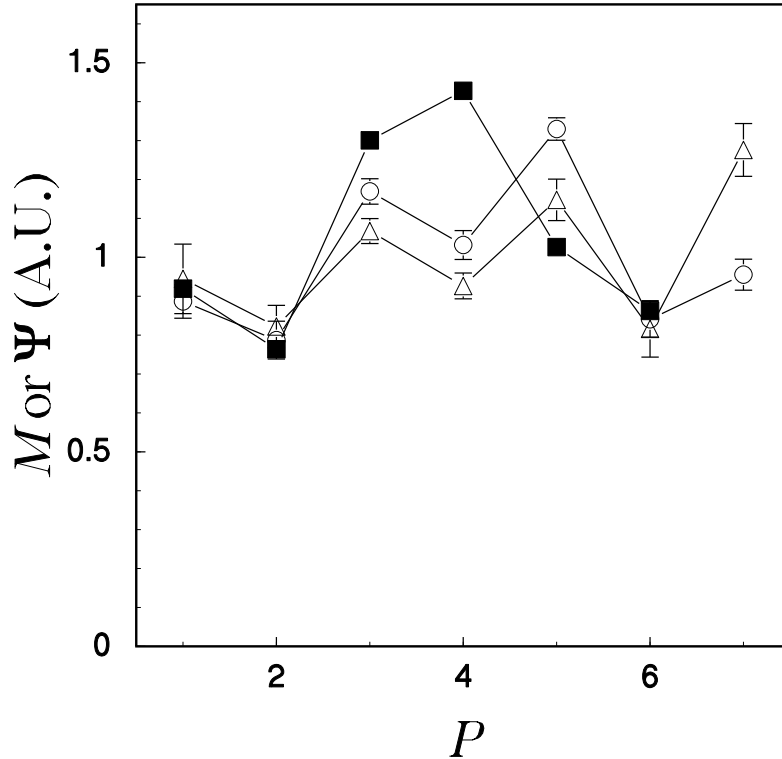


Figure 8. Radiant exitance M measured with bare fibre tip (Δ) and from CCD image (\circ) and fluence rate $\Psi(0)$ (\blacksquare) at the surface as a function of the position P for the applicator A1. The measurements were performed at $z = 12.5 \text{ cm}$.

3.3. Simulations

The uniformity of the irradiance E on the inner wall of a translation invariant cavity was calculated for six different cross-sections. To characterize a cross-section, the variables h_0 , w_{ch} , w_t , r_m , h , and r_c were introduced as illustrated in figure 10. The cross-section was built up of elliptical sections. The number of patches in the different cross-sections was between 47 and 58, dependent on the dimensions of the cross-section.

In the simulations, a uniformly irradiated half circle was assumed, which is an approximation for the currently used cavity illumination. In table 1 the calculated uniformity ratio UR for the illuminator part is shown for six different cavity cross-sections. In table 1 also the characteristic dimensions of the two applicators are included. The influence of the reflection plate was not included in the simulations. Inclusion of the reflection plate in the simulations showed a 20 to 40% decrease of the irradiance on the mandible, which effect was needed to compensate the larger ξ on the mandible.

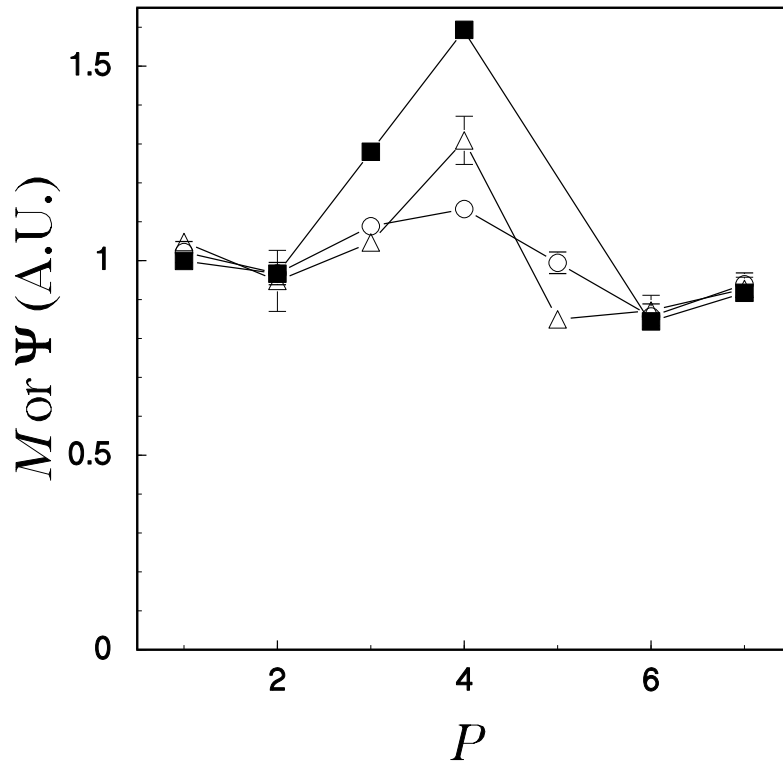


Figure 9. Radiant exitance M measured with bare fibre tip (Δ) and from CCD image (\circ) and fluence rate $\Psi(0)$ (\blacksquare) at the surface as a function of the position P for the applicator A2. The measurements were performed at $z = 12.5$ cm.

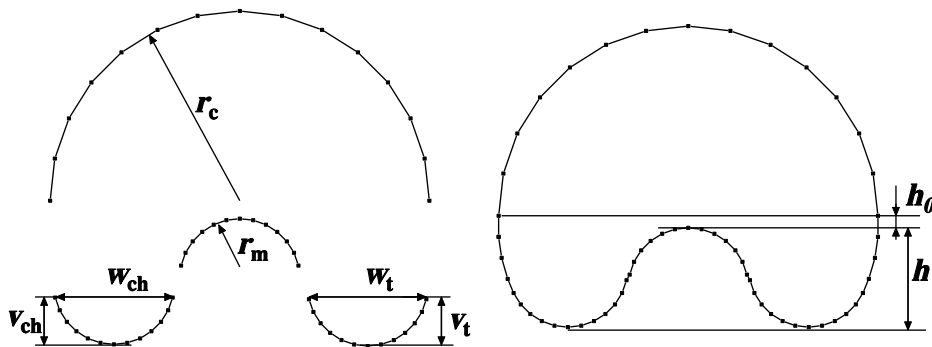


Figure 10. Eight variables (v_{ch} , w_{ch} , v_t , w_t , r_m , r_c , h , h_0) characterizing the shape of a cross-section. Because in the simulations $v_{ch} = v_t = v$ is assumed therefore $h = r_m + v$, only six of these variables are needed to fully describe the shape.

4. Discussion

The presented applicators showed a reasonable uniformity ratio for clinical application; however, the ICE-induced UR improvements (predicted by the numerical simulations) were partially cancelled out because of a position-dependent geometry factor ξ of the

Table 1. Numerically calculated uniformity ratio UR for at the inner wall of the illuminator part of translation invariant integrating cavities with various cross-sections. $UR(e^{(1)})$ is the uniformity ratio of the first irradiance on the illuminator part and $UR(E)$ is the uniformity ratio of the total irradiance E . In the simulations a diffuse reflectance coefficient $\rho = 80\%$ is used. For comparison the characteristic dimensions (in mm) of the two actual applicators A1 and A2 are given. For all cross-sections UR_{ξ} is estimated using equation (5).

Cavity	h_0	w_{ch}	w_t	r_m	h	r_c	$UR(e^{(1)})$	$UR(E)$	UR_{ξ}
1	0	9.5	9.5	4.8	7.9	15.0	2.07	1.17	2.0
2	0	12.5	12.5	1.6	10.3	15.0	2.30	1.20	2.7
3	2.0	8.7	8.7	4.4	4.9	15.0	1.67	1.12	2.2
4	-1.5	9.3	9.3	5.4	8.3	15.0	1.99	1.15	2.0
5	0	7.6	11.5	4.6	7.6	15.0	2.28	1.21	2.3
6	0.6	9.1	9.1	4.6	7.1	15.0	1.60	1.10	2.1
A1	0	7	7	5	7	15			2.3
A2	0	13	11	2	5	15			2.4

manufactured illuminator part wall. This variation of ξ was due to the finite wall thickness d in combination with the variable wall curvature R (see equations (3) and (5)). Experience and development in manufacturing will yield thinner walls and therefore lower URs, assuming the same reflection and transmission coefficients can be obtained by switching to another material.

Because a finite d will result in a variable ξ over the illuminator part, one could argue that using the same applicator with elimination of the illuminator part could have a comparable UR. For the ICE, instead of ρ of the illuminator part, the remittance ρ_{tissue} of the tissue is experienced ($\rho > \rho_{\text{tissue}}$). Such an applicator would look similar to a device described by Allardice *et al* (1993). In principle a comparable UR is possible; however, there are three advantages in having an illuminator part in the applicator.

A main advantage of having a mouth-shaped illuminator part is that the UR of a certain geometry is independent of variations in the tissue reflection coefficient ρ_{tissue} . This makes it possible to measure and improve the uniformity outside the mouth before the treatment. The applicator will not affect the in-depth behaviour in the tissue, because, from a tissue optics point of view, only the boundary condition is altered. Without the applicator, the index of refraction difference of the tissue and the air will cause a reflection on the boundary $\rho_{21} = 0.5$ (Welch and Van Gemert 1995). With an applicator in contact with the tissue, the diffuse reflection coefficient of the surface ($\rho_{21} = 0.8$) is experienced.

The second advantage is that the ICE is stronger if ρ is larger, ρ is constant over the total cavity wall and the reflections are totally diffuse, which conditions are better satisfied if an illuminator part is present. Therefore, in that case the UR improvement is largest. Besides an eventually better UR, a strong ICE also leads to a more a predictable UR, because also the influence of the imperfectness of a linear diffusor (Murrer *et al* 1996) and of the translation invariancy will be suppressed.

A third advantage of having an illuminator part is that it is produced for the dimensions of a specific mouth. This results in a good fit and a fixed position in the mouth. Furthermore the applicator is rigid and easy to use. Once the applicator is fixed in place, no further optimization of light source(s) is needed.

The need to produce one applicator for each single patient could be a disadvantage because of the amount of work. On the other hand labour and time are saved during the treatment due to a simpler procedure. From the viewpoint of minimization of labour, one

'universal' applicator fitting all mouths would be ideal; however, in that case probably one or more of the three listed advantages are lost, dependent on how a universal applicator is produced.

Another disadvantage of the device is the relatively high loss of light power. For the presented applicators, the loss of light is estimated to be 80%, caused by absorption in the walls. Whether this amount of power loss is acceptable depends on the available power, the necessary dose, and the acceptable irradiation time. For the photosensitizer *m*-THPC and a laser power of 1 W entering the cavity, an irradiation time in the order of 10 minutes would be required to reach a dose of 10 J cm^{-2} on a treated area of 10 cm^2 . Because of the slight discomfort of the applicator even longer treatment times seem to be possible, so less laser power is required.

The numerical simulations showed excellent URs for the inner-surface irradiance ($\text{UR} < 1.3$) of translation invariant cavities within a range of realistic applicator cross-sections. In real applicator cavities however, one will not find constant cross-sections and in most cases experience a small longitudinal curvature. Simulations in 3D are needed to verify the validity of the 2D simulations in these real applicator shapes and predict the uniformity of realistic shapes that could be used for the human body. In this stage of development the accuracy of the 2D simulations will probably be sufficient, because the large variations in ξ currently dominate the uniformity in radiant exitance M .

The principle of applicator design was only tested on one volunteer. More applicators need to be produced for more volunteers (and/or patients) to improve the production process and see how successful the applicators will be in a real PDT treatment. Production of applicators for a number of mouths could also supply enough information to produce an applicator which fits for a group of patients.

Using a uniform irradiation E of the applicator will not necessarily result in a uniform fluence rate $\Psi(0)$ at the surface, as can be seen from comparing M and $\Psi(0)$ in the same cross-section (figures 8 and 9). This difference is caused by the penetration of light into tissue in combination with a non-flat geometry. The difference is almost independent of the way the uniform irradiation is obtained, because it is mainly dependent on the optical properties. Better insight into optical properties of the tissues in the oral cavity and the exact shape of the illumination area are needed to be able to predict the irradiation profile which is needed to obtain a uniform $\Psi(0)$.

5. Conclusions

A rigid well fitting mandible applicator using light transmitted through the wall of an integrating cavity showed a reasonable uniformity ratio, $\text{UR} < 2$. Calculations indicate that even better URs can be reached if thinner cavity walls can be produced with the same reflection behaviour. Research performed on producing thinner cavity walls is therefore needed. To decrease the power loss in the applicator also reflecting materials with lower absorption are needed. Full 3D simulations will have to show how the ICE could be used more efficiently and how it should be used in other areas of the oral cavity.

Acknowledgments

We would like to thank H Ferwerda (ACTA, Amsterdam Centre for Dentistry) and A Steenbeek (Academical Medical Centre) for the production of the different parts of the applicators.

References

- Allardice J T, Abulafi A M, Dean R, Rowland C and Williams N 1993 Light delivery systems for adjunctive intraoperative photodynamic therapy *Lasers Med. Sci.* **8** 8–14
- Feyh J, Gutman R and Lennig A 1993 Die photodynamischen Lasertherapie im Bereich der hals, Nasen-ohrenheilkunde *Laryngo-Rhino-Otologie* **72** 273–8
- Feyh J and Kastenbauer E 1992 Die Behandlung der Larynxpapillomatose mit Hilfe der photodynamischen Lasertherapie *Laryngo-Rhino-Otologie* **71** 190–2
- Goebel D 1967 Generalized integrating-sphere theory *Appl. Opt.* **6** 125–8
- Grant W E, Hopper C, MacRobert A J, Speight P M and Bown S G 1993 Photodynamic therapy of oral cancer: photosensitization with systemic aminolaevulinic acid *Lancet* **342** 147–8
- Henderson B W and Dougherty T J H (eds) 1992 *Photodynamic Therapy: Basic Principles and Clinical Application* (New York: Dekker)
- Herzog M, Fellbaum C and Horch H H 1992 Erste klinische Erfahrungen mit der photodynamischen Therapit (pdt) des Mundholtenkarzinoms *Deutsche Zahn-, Mund-Kieferheilkunde* **80** 141–3
- Karagiannes J L, Zhang Z, Grossweiner B and Grossweiner L 1989 Applications of the 1d diffusion approximation to the optics of tissues and tissue phantoms *Appl. Opt.* **28** 2311–7
- Lippert B M, Werner J A, Gorogh T, Schade W and Rudert H 1993 Anthracyclinderivate als Photosensibilisatoren in der photodynamischen Lasertherapie: ein *in-vitro*-untersuchung an Plattenepithelkarzinomzellen der Mundhöhle *Laryngo-Rhino-Otologie* **72** 63–6
- Marijnissen J P A, Baas P, Beek J F, van Moll J H, van Zandwijk N and Star W M 1993a Pilot study on light dosimetry for endobronchial photodynamic therapy *Photochem. Photobiol.* **58** 92–8
- Marijnissen J P A, Star W M, In't Zand H J A, D'Hallewin M A and Baert L 1993b In situ light dosimetry during whole bladder wall photodynamic therapy: clinical results and experimental verification *Phys. Med. Biol.* **38** 567–82
- Murrer L H P, Marijnissen J P A and Star W M 1996 Light distribution by linear diffusing sources for photodynamic therapy *Phys. Med. Biol.* **41** 951–61
- Nseyo U O, Lundahl S L and Merril D C 1990 Whole bladder photodynamic therapy: critical review of present-day technology and rationale for development of intravesical laser catheter and monitoring system *Urology* **36** 398–402
- Overholt B F, Panjehpour M, DeNovo R C and Petersen M G 1994 Photodynamic therapy for esophageal cancer using a 180° windowed esophagael balloon *Lasers Surg. Med.* **14** 27–33
- Rem A I, van Gemert M J C, van der Meulen F W, Gijsbers G H M and Beek H F 1997 Uniform irradiation of irregularly shaped cavities for photodynamic therapy *Phys. Med. Biol.* **42** 583–93
- Savary J F, Fontollet C, Braichotte D, Monnier P and van den Bergh H 1994 First clinical results after photodynamic treatment of early squamous cell carcinomas of the oesophagus bronchi and mouth with *meso*-tetrahydroxyphenyl-chlorin (*m-thpc*) *Abstract 5th Int. Photodynam. Assoc. Bienn. Meeting (Florida, 1994)*
- Unsöld E, Beyer W, Heinze A and Sroka R 1989 Irradiation modalities for photodynamic therapy *Lasers Med. Sci.* (Suppl. 1) 159–64
- van Staveren H, Moes C J M, van Marle J, Prahl S and van Gemert M 1991 Light scattering in intralipid-10% in the wavelength range of 400–1100 nm *Appl. Opt.* **30** 4507–14
- Welch A J and van Gemert M J (eds) 1995 *Optical-Thermal Response of Laser Irradiated Tissue* (New York: Plenum)