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Miniaturized Osmotic Pump for Oromucosal Drug Delivery with External Readout Station

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***Abstract*—We report on a miniaturized, exchangeable drug delivery cartridge for Parkinson's Disease which is integrated in a partial removable prosthesis. An osmotic pumping principle uses saliva to release constantly a separately stored drug to the buccal mucosa, thus avoiding first pass metabolism and drug plasma level fluctuations. Therapeutic relevant information and fill level of the cartridge can be determined before and after usage with an external readout station. The selected material combinations of the cartridge fulfill both, functional and regulatory aspects as well as requirements for assembly and packaging, e.g. thermal fusion bonding, solvent bonding and capillary stop bonding. By using the cartridge, highly precise release rates over 97% of its storage capacity with a rate deviation of only 1.1% can be achieved.**

I. Introduction

MINITAURIZED drug delivery devices enable specific or chronotherapeutic medications [1] compared to the more convenient per os route of tablets where fluctuations in blood plasma and first-pass metabolism have often to be enfaced. Besides the different parenteral administration pathways, drug delivery devices can also be classified regarding their flexibility in transient delivery schemes [2]. Sorted according to increasing flexibility, the delivery schemes range from basic singular release, continuous delivery, over more complex and time controlled delivery of predefined amounts, to the ultimate closed-loop approach. However, system complexity, costs and particularly invasiveness are also increasing at the same time. Especially the treatment of Parkinson's disease (PD) reflects this trend. While in the early stages of PD singular release by tablets will remain the "gold" standard, the course of the disease is characterized by a narrowing therapeutic window in advanced stages. Treatment becomes more difficult and in general more invasive, e.g. by continuous dopaminergic subcutaneous infusion [3] or by bypassing the stomach with a duodenal catheter. If all pharmaceutical treatments fail, more radical interventions, such as deep brain stimulation have to be considered. The preferred goal to reach constant drug plasma levels sounds not too complex. However, up to date there is no transient delivery concept for PD that realizes this by a non-invasive treatment method.

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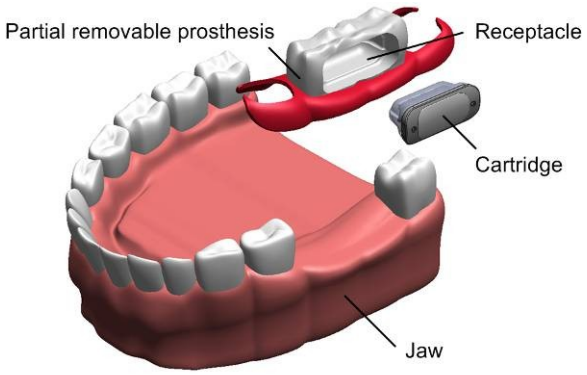

Fig. 1. Sketch of the intraoral device worn as cartridge on a partial removable prosthesis.

Osmotic actuation enables continuous flows without need of electric energy. The basic principle of osmosis in which either the drug is the osmotic driving agent itself [4] or an osmotic actuator can be used to eject a liquid drug solution [5] has been successfully applied in miniaturized drug delivery devices[6]–[10], microfluidic chips for LoaC applications [11]–[14], and propulsion for specific unit operations, i.e. crystallization of proteins[15].

Our approach uses an osmotic pump for dopaminergic stimulation worn as a cartridge on a partial removable prosthesis in the oral cavity (Fig. 1). Thereby, the buccal mucosa can be directly addressed as delivery pathway for increased bioavailability.

II. Materials and Methods

A. System Concept

The osmotic pumping principle uses water from saliva in the mouth to generate a volumetric flow rate J across a semi-permeable membrane of the cartridge by dissolving an osmotic pill (Fig. 2a). Thereby, a flexible barrier membrane is deflected and a separately stored liquid drug volume V_{drug} is ejected. J can be written as

$$J = K A (\sigma (\pi_{pill} - \pi_{saliva}) - P_{membrane} - P_{outlet}), \qquad (1)$$

where K is the permeability of the semi-permeable membrane with respect to water, A is its surface area and σ is

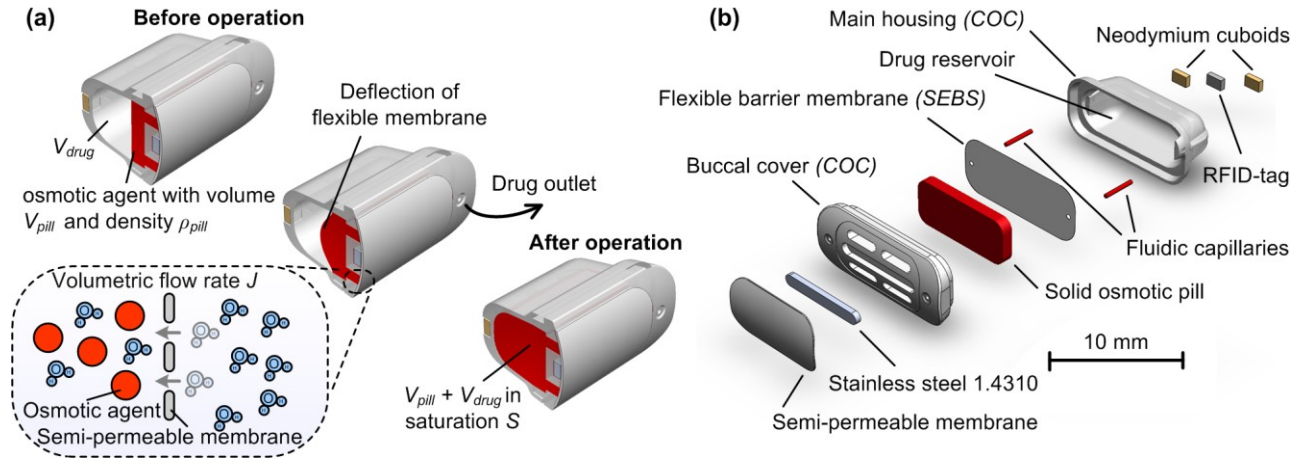

Fig. 2. (a) Functional principle of the osmotic drug delivery cartridge. (b) Exploded view of the cartridges components.

its osmotic reflection coefficient. The osmotic pressure difference across the semi-permeable membrane is $(\pi_{pill} - \pi_{saliva})$. $P_{membrane}$ and P_{outlet} are the hydrostatic pressures needed to deflect the flexible membrane and the rate dependent pressure drop through the outlet of the cartridge, respectively. The osmotic pressure of the solid pill π_{pill} is given by

$$\pi_{pill} = S\, i\, R\, T, \tag{2}$$

where S is the solubility of the osmotic agent in water, i is the number of ions per mole in the solution, R is the ideal gas constant and T is the absolute temperature in the oral cavity.

Since π_{saliva}, $P_{membrane}$ and P_{outlet} are negligibly small (< 1 bar) compared to π_{pill} which can be as high as hundreds of bars and σ is close to unity, (1) can be simplified to

$$J = K\, A\, \pi_{pill}. \tag{3}$$

Hence, the three parameters of (3) can be used to tailor a constant (zero-order) release rate which determines in turn the the operational time of the cartridge.

In order to achieve a constant release rate, the osmotic agent must remain in a saturated state during the entire operational time [5]. Consequently, the stored M_{pill} should not be completely dissolved before the end of operation is reached.

This can be expressed to the following before (4) and after (5) operation:

$$\text{Before operation: } M_{pill} = \rho_{pill}\, V_{pill}, \tag{4}$$

$$\text{After operation: } M_{pill} = S\,(V_{pill} + V_{drug}), \tag{5}$$

where ρ_{pill} is density of the osmotic driving agent and V_{pill} is its initial volume. For a constant release rate, the initial ratio of both reservoirs can be derived from (4) and (5) and is

$$V_{pill} / V_{drug} = S / (\rho_{pill} - S). \tag{6}$$

Consequently, the required amount of osmotic agent is given by

$$M_{pill} = V_{drug}\, S / (1 - S\, \rho_{pill}). \tag{7}$$

Since space for the cartridge is strictly limited, the osmotic agent should be selected to obtain (i) a small V_{pill}/V_{drug} ratio, i.e. a small S (6), and (ii) an adequate osmotic pressure, i.e. a high S (2). We are applying potassium nitrate (KNO_3) as osmotic agent which can be easily tapped to a pill. KNO_3 has a solubility in H_2O at body temperature of $S_{37°} = 565$ g/l and a calculated osmotic pressure π_{pill} of 28.8 MPa. Therefore, a chamber ratio V_{pill}/V_{drug} of 0.366 is obtained. The chamber ratio can be further lowered by taking smaller osmotic pressures into account (e.g. by using potassium sulfate K_2SO_4: $V_{pill}/V_{drug} = 0.056$ and $\pi_{pill} = 6.3$ MPa).

B. Design and Materials of the Cartridge

The cartridge is composed of the following components (Fig 2b): (i) A micro injection molded housing of a cyclic olefin copolymer (COC, TOPAS® 8007) with good barrier properties against water and high stiffness, (ii) a semi-permeable Polyimide composite membrane (PA-TFC, Toray® UTC 70 HB), (iii) a hyperelastic styrenic copolymer barrier membrane (SEBS, Kraton® G1645 M) and (iv) fluidic capillaries. For attachment of the cartridge to the partial removable prosthesis, two neodymium cuboids (1.6 × 1.0 × 0.5 mm³) are fixed on top of the main housing in addition to the a similarly sized RFID-tag for identification purposes (e.g. sort of drug, adjusted release rate and operational time, expiration date, etc). A laser-cut magnetizable stainless steel plate is used for insertion and removal of the cartridge with a magnetic assistive tool.

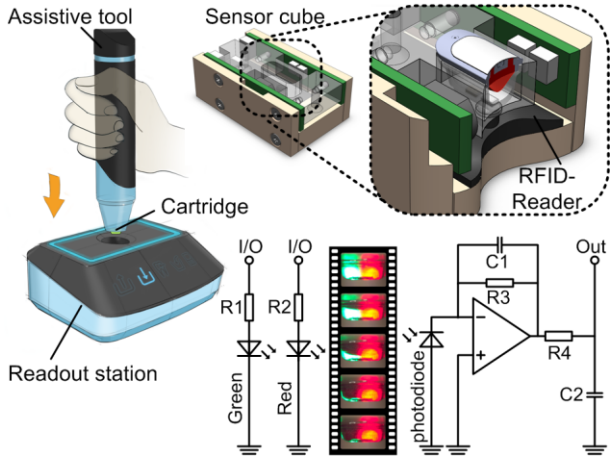

Fig. 3. Readout station with optical fill level sensor and RFID reader inside.

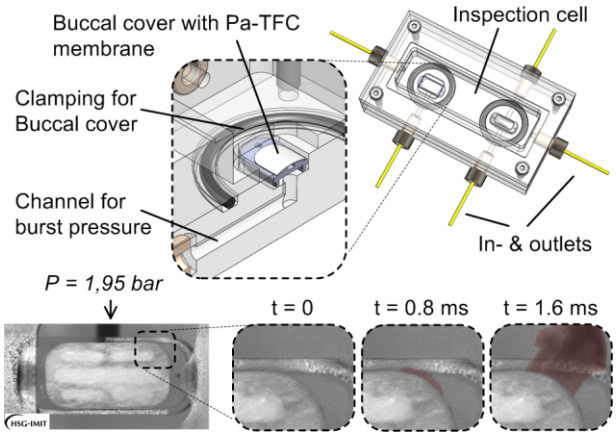

Fig. 5. Inspection cell for characterization of bond qualities. The Pa-TFC membrane is stable up to a burst pressure of 1.95 bar.

C. Readout Station

The Readout station (Fig. 3) includes an optical fill level sensor applied to determine the delivered amount of the cartridge. Therefore, Allura Red AC is added to the solid osmotic pill as a dye. The sensor uses two light emitting diodes (LEDs) with different wavelengths. One wavelength is absorbed by the dye depending on the membrane deflection and the second one passes through the cartridge as a reference. A photodiode on the opposite side is used to measure the difference signal of the LEDs. An additional RFID readout at the bottom of the sensor cube is used to access the data stored in the RFID tag.

III. Experimental

A. Assembly and Packaging

The PA-TFC semi-permeable membrane is bonded to the COC buccal cover with a custom built thermal bonder. A pressure of 5 bar is applied with a stamp to increase the contact forces between the two parts. The stamp is then heated to 135 °C above the glass transition temperatures T_g of COC (T_g =78 °C) and Polyamide (T_g about 60-75 °C) for 30 s. To limit the bond temperature only to the contact surface, the COC is protected by an aluminum heat sink.

For material selection of the flexible barrier membrane, the Hansen Solubility Parameter model was applied [16] to select SEBS as compatible material to COC. Spin coated membranes of SEBS can be solvent bonded to the COC Buccal cover by cyclohexane or by a less harmful solvent blend from anisole and heptane. The two-part COC housing is finally bonded by solvent bonding using a capillary stop.

The partial removable prosthesis with integrated receptacle is made from prosthetic acryl according to the patients individual CAD/CAM-model. A rapid prototyping method was used for a first prototype (Fig. 4).

Fig. 4. Prototype of the Cartidge and the partial removable prosthesis.

B. Characterization of Assembly and Packaging

The bond between buccal cover and Pa-TFC membrane was characterized with an inspection cell (Fig 5). The bond proved to be stable up to a burst pressure of 1.95 bar. The solvent bonded SEBS membrane was characterized with a contact angle measurement instrument. The membrane is fully deflected by applying a pressure $P_{membrane}$ of 300 mbar being the highest pressure during intended operation (Fig. 6). No separation from the buccal cover substrate was detected.

C. Characterization of the Cartridge

The drug release was determined by immersing cartridges with air-filled drug reservoirs in a temperature-controlled water bath of 37 °C. In this case, the osmotic agent volume increases and the stored air is expelled during actuation. Consequently, the weight increase of the cartridges

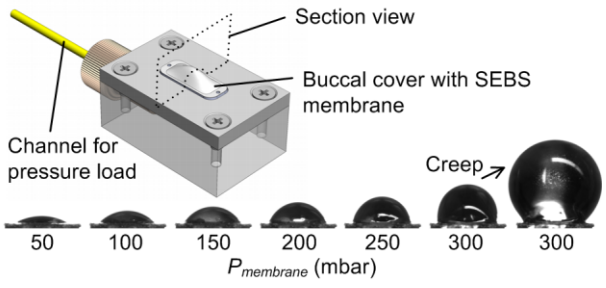

Fig. 6. Deflection of flexible SEBS membrane on Buccal Cover with respect to $P_{membrane}$. No shear is detected.

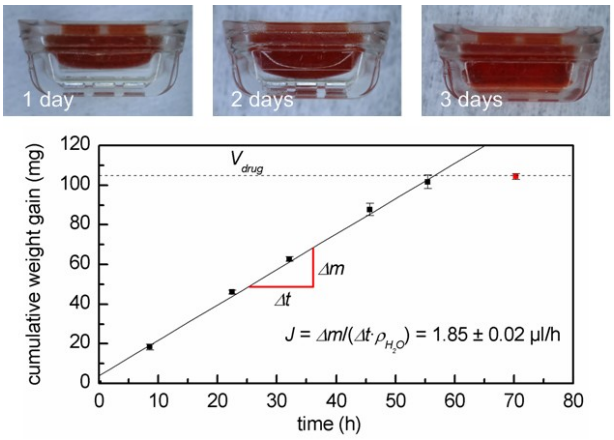

Fig. 7. Exemplary delivery scheme of the cartridge.

corresponds to the amount of drug liquid which can be delivered.

The cartridges were removed several times a day for weighting. For a semi-permeable membrane of type Toray® UTC 70 HB, the volumetric flow rate J of 1.85 ± 0.02 µl/h was determined for more than 97% of V_{drug}(Fig. 7). Hence, the release rate can be considered to be very precise and reproducible.

D. Characterization of the fill level sensor

During operation of the cartridge, the amount of dye in the osmotic chamber dilutes in comparison to the KNO_3 which stays saturated. The optimal initial (highest) concentration of the dye required in the work range was determined by measuring different dye concentrations (Fig. 8, top). The measured differential signal of the cartridge is reproducible and particularly sensitive within the middle third of V_{drug} (Fig. 8,bottom).

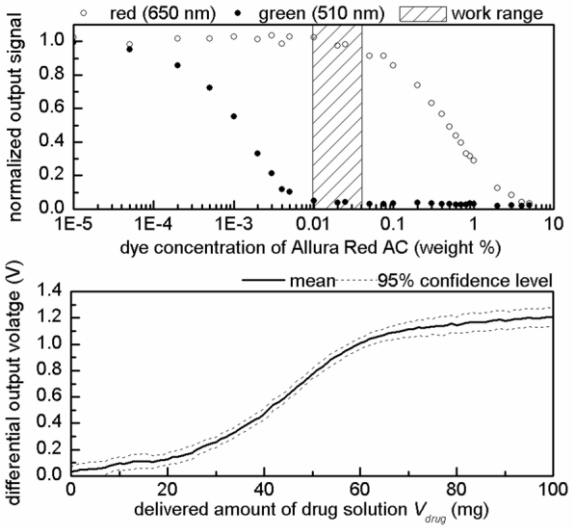

Fig. 8. (top) Determination of the ideal dye concentration. (bottom) Differential output signal of the fill level sensor.

IV. Conclusion and Outlook

The osmotically powered drug delivery cartridge proved to provide constant delivery rates over the entire operational time. Together with the optical fill level measurement and RFID readout, precise PD therapy monitoring is possible. Further investigations deal with dependence of the cartridge to changing environmental conditions in the oral cavity like temperature, pH level, saliva quantity and consistency. Afterwards the cartridge will be tested in clinical trials with PD patients.

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References

[1] D. A. LaVan, T. McGuire, and R. Langer, "Small-scale systems for in-vivo drug delivery," *Nat. Biotechnol.*, vol. 21, pp. 1184–1191, 2003.

[2] S. Haeberle et al., "Microfluidics for Drug Delivery," in *WC 2009, IFMBE Proc. 25/VIII*, pp. 359–362.

[3] S. Herrlich et al., "Ambulatory Treatment and Telemonitoring of patients with Parkinson's Disease," in *Ambient Assisted Living*, 1st ed., Springer Verlag, Berlin, 2011

[4] F. Theeuwes, "Elementary osmotic pump," *J. Pharm. Sci.*, vol. 64, 1975.

[5] F. Theeuwes and S. I. Yum, "Principles of design and operation of generic osmotic pumps for delivery of semisolid or liquid drug formulations," *Ann. Biomed. Eng.*, vol. 4, pp. 343–353, 1976.

[6] Y. C. Su, L. W. Lin, and A. P. Pisano, "A water-powered osmotic microactuator," *J. Microelectromech. S.*, vol. 11, pp. 736–742, 2002.

[7] Y. C. Su and L. W. Lin, "A Water-Powered Micro Drug Delivery System," *J. Microelectromech. S.*, vol. 13, pp. 75–82, 2004.

[8] W.H. Ryu et al., "Biodegradable micro-osmotic pump for long-term and controlled release of basic fibroblast growth factor," *J. Control. Release*, vol. 124, pp. 98–105, 2007.

[9] Y. H. Li and Y. C. Su, "Miniature osmotic actuators for controlled maxillofacial distraction osteogenesis," *J. Micromech. Microeng.*, vol. 20, 065013 (8pp), 2010.

[10] T. Nagakura et al., "The study of micro liter Insulin injection system by Osmotic pressure for Diabetes therapy," in *WC 2009, IFMBE Proc. 25/VIII*, pp. 382–383.

[11] M. Ehwald, H. Adleff, P. Geggier, and R. Ehwald, "A Long-Term Stable and Adjustable Osmotic Pump for Small Volume Flow Based on Principles of Phloem Loading," *Biotechnol. Bioeng.*, vol. 94, pp. 37–42, 2006.

[12] B. T. Good, C. N. Bowman, R. H. Davis, "A water-activated pump for portable microfluidic applications," *J. Colloid Interf. Sci.*, vol. 305, pp. 239–249, 2007

[13] K. H. Jensen, J. Lee, T. Bohr, and H. Bruus, "Osmotically driven flows in microchannels separated by a semipermeable membrane", *Lab Chip*, vol. 9, pp. 2093–2099, 2009.

[14] Z. R. Xu, C. G. Yang, C. H. Liu, Z. Zhou, J. Fang, J. H. Wang, "An osmotic micro-pump integrated on a microfluidic chip for perfusion cell culture", *Talanta*, vol. 80, pp. 1088–1093, 2010.

[15] P. H. Chan and Y. C. Su, "Rapid protein crystallization by a micro osmotic screening system," *J. Micromech. Microeng.*, vol. 17, pp. 642–650, 2007.

[16] S.Herrlich et al., "Solvent bonding of polymer combinations for micromedical applications," in *Proc. of MMB 2011*, pp. 265–266.