

# Clinical Evaluation of a Telemedically Linked Intraoral Drug Delivery System

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The miniaturized intraoral drug delivery system *BuccalDose* is composed of a replaceable cartridge which is worn in a removable prosthesis and an external base station for telemedical therapy monitoring. The system has now been tested for the first time with Parkinson's disease (PD) patients. The study evaluated the usability of the entire system, the functionality of the telemedical transmission path and the functionality of the cartridge, which uses an osmotic pumping principle to release a liquid drug formulation to the buccal mucosa. The *BuccalDose* system was generally considered to be easy to handle, even with movement disorders, up to a mild-moderate disease stage. In addition, the obtained in vivo release rates of the cartridges confirmed the previously achieved in vitro release behavior.

## The *BuccalDose* system

The drug delivery system *BuccalDose* is worn as a replaceable cartridge in a removable intraoral appliance (Fig. 1). During the manufacturing process, special attention is given to the installation procedures of a cartridge carrier into the appliance body, as its original functional capabilities (i.e. stability, durability, and occlusion) must be maintained [1]. The replaceable cartridge is fabricated from biocompatible materials with customized assembly & packaging technologies [2]. During operation, water from saliva in the mouth generates a volumetric flow rate across the semi-permeable membrane of the cartridge by dissolving salt. Thereby, a flexible barrier membrane is deflected and the separately stored drug is ejected (Fig. 2).



**Fig.1:** Intraoral *BuccalDose* cartridge integrated in a removable partial prosthesis.

For the phase I clinical evaluation, no drug has been used and air was instead ejected. In early stages of the disease, *BuccalDose* could administer dopamine agonists such as pramipexole or ropinirole [4], while in the later stages levodopa derivatives [5] are promising drug candidates.

The current design of the cartridge is in principle further miniaturizable as osmotic pumps in general [6]. On the other hand, the storable amount of active ingredients is then also reduced. The entire *BuccalDose* system is completed by a telemedically linked base station, a mobile gateway, and an assistive tool (Fig. 3). With the assistive tool, PD patients with limited motor skills are able to insert and remove the magnetically attachable cartridge into the prosthesis and into the base station, respectively. In addition, the assistive tool serves as a storage container for the cartridges. The base station measures automatically the fill level and reads out a RFID minitag when the cartridge is inserted [6]. This data is then transmitted together with a time stamp via ZigBee to a mobile gateway (smartphone) and from there via mobile internet

to a medical service center. The released amount of drug as well as additional information, such as compliance to the therapy plan, can be used for therapy adjustment.

## Clinical trials

The phase I study without drug was performed in two steps with 4 and 5 patients of Hoehn & Yahr stages 1-2 in Tel Aviv (IL) and in Palermo (I),

respectively. In the first step, the patients were observed over 1 day in a clinical environment, while during the second step they evaluated the system over 3 subsequent days in their home environment. The serial data transfer from the cartridge to the medical service center was successful in 71 of 72 performed measurements. Thereby, the non-redundant transmission path is able to cache and resend data at different times, if the connection is interrupted.

The usability of the *BuccalDose* system in daily life was evaluated in relation to the disease stage using a patient questionnaire. The usability of the base station and the assistive tool was mainly perceived as easy, while operation tends to be more difficult in higher disease stages. The wearing comfort was independent from the disease stage and consistently considered to be comfortable. However, the removal of the cartridge from the prosthesis with the assistive tool was difficult for patients with more limited motor skills in moderate or advanced disease stages. The osmotic pumping principle was charac-

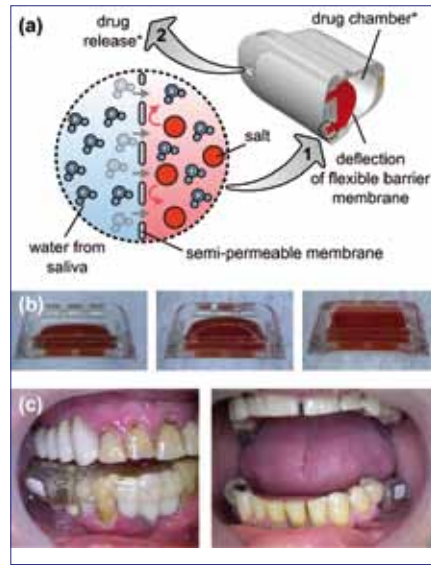
terized by the cumulative weight gain of each cartridge, which would be similar to its cumulative release rate. On average, the measured cumulative weight gain was  $1.65 \pm 0.3$  mg/h in vivo, which is comparable to previously obtained in vitro results ( $1.85 \pm 0.02$  mg/h). From the application and hygienic point of view, the cartridges should not be reused after removal, e.g. during night periods. Therefore, the release rates are ideally adapted to last for a period of one daytime as the cartridge should be completely depleted.

### Conclusion & Outlook

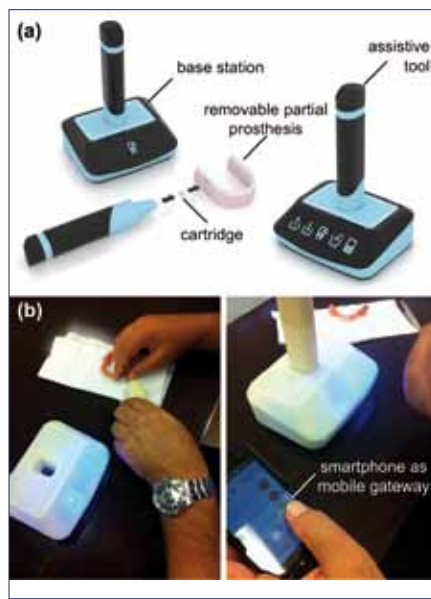
The idea of the entire system was thereby considered by the patients as "very good". The clinical evaluation provided important information on the necessary functional design features that are required for a miniaturized drug delivery device operated by patients with movement disorders. The present version of the system seems to be usable up to a mild-moderate disease stage in patients with medium to high education level. However, in advanced PD, intensive training for correct usage may be necessary and for PD patients with limited cognitive functions it appears to be not suitable.

The next step is the implementation of a new and improved version of the *BuccalDose* system which can be handled more intuitively with less operation steps, i.e. by integration of the mobile gateway into the base station.

In the framework of the EUREKA project OPTIMED, a new and miniaturized version of the cartridge is being developed that can be also worn on the teeth.



**Fig.2:** (a) Functional principle of the osmotic drug delivery cartridge; \*drug chamber was empty for clinical evaluation. (b) Exemplary membrane deflection during operation. (c) Integration of the cartridge into a splint or into a removable partial prosthesis during clinical evaluation.



**Fig.3:** (a) Telemedically linked base station and assistive tool for use with BuccalDose cartridge. (b) Clinical evaluation of the entire BuccalDose system by PD patient.

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