Microfluidics for Drug Delivery

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Abstract— **Drug delivery, i.e. the way a pharmacologically active substance is delivered to the body, has a significant impact on the therapeutic value of medication. The paper gives an overview on different drug delivery schemes and describes the limitations of the oral route, which is the current gold standard in the market. Following these limitations, plenty of alternative (parenteral) drug delivery technologies are currently under development. Many of them require the precise handling of small liquid volumes using small sized and low energy consuming devices. So microfluidics is a key enabling technology for these upcoming drug delivery devices.**

Ease of use and autonomous operation are the most important aspects for high acceptance and compliance of the patients. So for short term therapy (e.g. antibiotics), the devices should be small and portable. For long term therapy (e.g. cardiac), implantable devices are favorable since they can operate autonomously and deliver precise doses exactly to the target site (local therapy). The paper describes two examples for microfluidic drug delivery devices in more detail, namely the intra-oral transmucosal *IntelliDrug system* and the transdermal *ChronopaDD* device.

Keywords— **microfluidics, drug delivery, microsystems**

I. Introduction

Due to the demographic change and the therewith related prevalence of chronic diseases, the health care market is facing increasing cost pressure within the upcoming years. Nevertheless, people demand high standard treatment to maintain or improve their health condition. Facing this situation and looking from a technology perspective, drug delivery is one of the most obvious and close to market domains where innovative products can make an important difference.

Looking at the drug delivery market in more detail, three main drivers for innovation can be identified:

1. **New types of drugs**: future biopharmaceutical drugs cannot be delivered via the oral route (first pass metabolism). Consequently, parenteral delivery routes will be increasingly addressed in the future.
2. **New types of therapy**: adopting the drug dosage to the patient (personalized medicine) and time of the day (chronotherapy) is required for the upcoming more sophisticated medication scenarios.
3. **Patent expiration**: many patents of current block buster drugs will expire within the upcoming years, leading to increased competition from generic manufacturers. One possible strategy for pharmaceutical companies is to add a new drug delivery technology to their existing drug.

Based on these considerations, we discuss the chances of different drug delivery technologies and pathways to meet these challenges with a clear focus on microfluidic approaches.

II. State of the art in Drug Delivery

An ideal drug delivery technology enables the optimum medication of every patient. Therefore, the plasma level, i.e.
concentration of drug in the circulatory system, hast to be permanently maintained within the therapeutic window (see 0).

The therapeutic window can alter from patient to patient (personalized therapy) and over the course of the day (chronotherapy). Many state of the art delivery systems are not able to maintain this optimum delivery scheme. Consequently, the different drug delivery technologies can first be classified regarding their flexibility in transient delivery schemes as described within the following section.

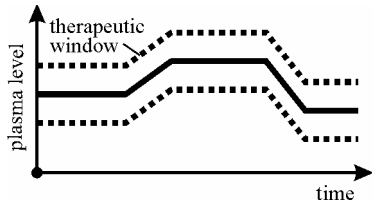

Fig. 1. Course of plasma level for an optimum drug delivery.

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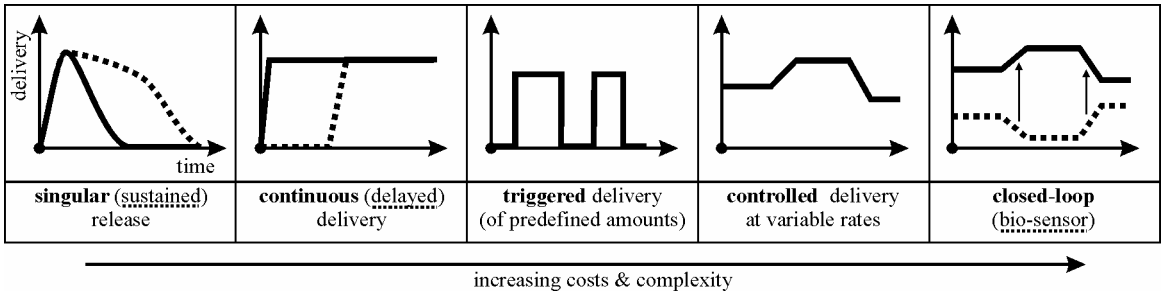

Fig. 2. Classification of different drug delivery schemes regarding delivery profiles.

A. *Classification of Drug Delivery Devices*

Different drug delivery schemes are depicted in 0. They range from basic singular release, over continuous delivery, to more complex and time controlled delivery of predefined amounts. The ultimate closed-loop approach (right), where the drug release is directly triggered by a biosensor measuring relevant physiological parameters (e.g. glucose level in diabetes care) could not be realized so far due to missing long-term stable *in vivo* biosensors. Thus, the controlled delivery at variable rates is the most complex delivery scheme today.

Based on these considerations, we can categorize the capabilities of the different pathways to deliver the drug to the body (see 0). Basically, the drug can either be administered directly (injectable, implantable) or indirectly (oral, inhalable, transmucosal, transdermal). The different pathways are assessed concerning their potential to meet the future challenges in drug delivery:

- **Delivery scheme**: complex profiles possible?
- **Bioavailability**: efficiency of absorption to body
- **Macromolecules**: suitable for biopharmaceuticals?
- **Autonomous** operation possible?

Type	Oral	Inhalable	Injectable[1]	Transmucosal	Transdermal	Implantable
delivery scheme[2]						
bioavail-ability	low	good	high	good	middle / good [3]	high
macro-molecules	O	+	++	+	+[4]	++
auto-nomous	no	no	yes[3]	yes[4]	yes[4]	yes

[1]including intravenously (IV); [2]most complex; [3]portable infusion pumps; [4]see examples in this paper

Fig. 3. Different pathways for drug delivery.

B. *Oral Drug Delivery – Limitations of the Gold Standard*

The oral route (taking pills) is the gold standard in drug delivery with a market share of approximately 40 % [1]. It is based on the absorption of the active agent within the stomach, the small intestine or the colon. However, the transit time through the gastrointestinal tract depends on multiple factors, like activity or food consumption, and therefore it is hardly reproducible even in a single individual, and thus the bioavailability is quite low. Due to the first pass metabolism, also future macromolecular biopharmaceuticals can hardly be administered via this route. So-called "intelligent pills" could be a possible solution to overcome this drawback [2, 3]. However, they are technically complex and thus seem to be applicable in high-price niche applications only.

Consequently, alternative approaches to the oral route are required to meet the future challenges described before. These novel devices should be small and low energy consuming for portable use on the one hand, and allow the precise and controllable dosage of small amounts of liquids

on the other hand. Both challenges can be met by microfluidics as described by some examples within the following section.

III. Microfluidic Drug Delivery Approaches

Several microfluidic drug delivery devices have already been proposed within the last years. Straight forward approaches are based on the integration of micropumps [4, 5] or other means of liquid propulsion (like osmosis [6] or electrolysis [7]) into delivery systems. For further miniaturization, also new materials like hydrogels for direct stimuli response [8-11] or electroactive polymers ("micro muscles") [12-15] are intensively investigated. Another very promising and already commercialized [16] technology is the release of drug from microcavities by thermal disruption [17-20] or resorption [21] of a thin membrane.

A comprehensive overview of microfluidic and MEMS-based drug delivery devices can be found in recent review papers [22-27]. In the following, two concrete examples of microfluidic drug delivery devices are presented, that are currently under development at HSG-IMIT. Namely, the miniaturized intra-oral transmucosal delivery device *IntelliDrug* and the transdermal delivery device *ChronopaDD.*

A. IntelliDrug: Intra-Oral Transmucosal Delivery Device

The different mucous membranes (buccal, anal, nasal, and vaginal) are promising interfaces to deliver drugs to the vascular system. They are available anytime for drug delivery and therefore allow automated drug delivery in principle. Especially the buccal mucosa features additional advantages as the easy accessibility of the quasi-implant for refilling, and the available high absorptive surface area.

To take advantage of these opportunities, a highly miniaturized and self-contained delivery device for the oral cavity has been developed by a multinational EU-consortium (FP6-IST project "IntelliDrug" FP6-IST-002243). The *IntelliDrug* device is an integrated, controlled drug delivery system to be implanted into the human denture and delivers the drug through the buccal mucosa. The challenges for such a system are the minimal space requirements (volume of few mm^3) and the harsh environment in the oral cavity regarding chemical stability and mechanical loads up to 250 N. The main target application is the treatment of chronic diseases.

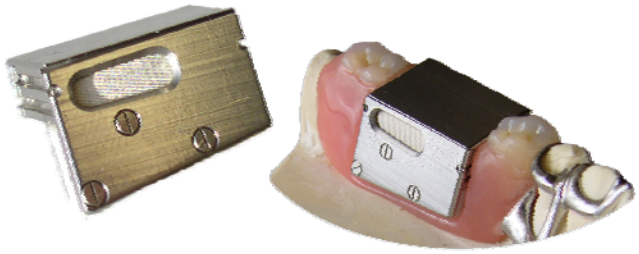

Fig. 4. Intra-oral transmucosal drug delivery device (*IntelliDrug*).

Due to the limited space, the *IntelliDrug* system is designed to deliver a maximum amount of drug solution with a minimum amount of energy. Thus, the system concept comprises an osmotic pump [28] for liquid propulsion (i.e. no energy consumption) and a normally closed 2/2 microvalve. Additionally, a flow and filling level sensor are integrated to monitor the delivered amounts. 0 shows the final prototype of the system developed in the *IntelliDrug* project (integrated in a partial denture on the right).

B. ChronopaDD: Transdermal Device for Chronotherapy

Another promising pathway for drug delivery is the human skin. It allows the administration from an extracorporeal device without using intravenous pathways. Based on mechanical penetration of the stratum corneum by micro needles, a universal pathway for drugs into the vascular system can be established. This pathway offers possibilities for self administrated drug delivery and opens up a large range of applications, e.g. pain therapy, hypertension treatment, rheumatism.

Currently we develop the *ChronopaDD* called transdermal drug delivery device where all components, like the pump, drug reservoir and interface are located within a patch like system. Using this device, a well defined volume of liquid drug will be delivered at a pre-defined time to the vascular system. For example a patch for hypertension or rheumatism treatment can be attached in the evening and delivers the drug at two o'clock in the morning, where the therapeutic effect is best. A drug containing bag and a one-time actuator are integrated in a disposable plastic housing (0, top). The drug is delivered through the stratum corneum by polymer micro needles (0, bottom).

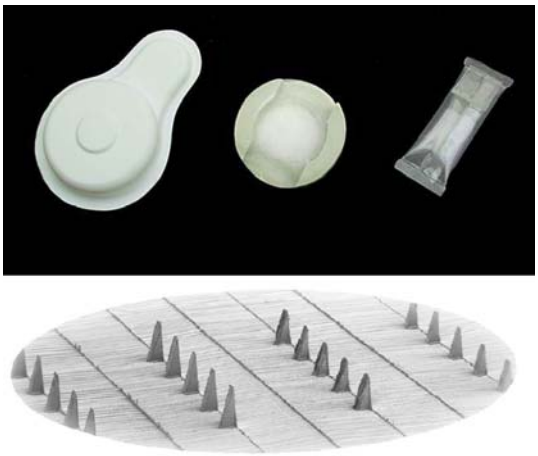

Fig. 5. Transdermal delivery device (*ChronopaDD*)

IV. Conclusion

Due to the current drivers in the drug delivery market (new types of drugs & therapies, patent expiration), we think that future drug delivery devices will be more sophisticated in terms of delivery schemes and medication scenarios. Thus, microfluidics certainly is one of the enabling technologies for these new technologies, since it meets the challenges in size, energy and precision.

Based on these considerations, we assessed the different possible pathways for drug delivery and presented two new microfluidic approaches, namely the *IntelliDrug* device for oral transmucosal, and the *ChronopaDD* device for transdermal delivery. Both approaches enable automated and thus patient independent operation which is important for e.g. elderly patients who often forget to take their medication. Additionally, both allow complex transient delivery schemes.

Overall, we see two possible directions in "microfluidics for drug delivery". Firstly, adding additional functionality and precision to conventional extracorporeal drug delivery devices for short term therapy; and secondly, innovative and highly miniaturized systems for implantable scenarios in long term therapy.

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