Beyond the Pill Personalisation by Integrating Oral Medication and Digitalisation

Pharmaceutical innovation has accelerated, but the way of dosing oral medicines to patients has broadly stayed the same. Prescription medicine delivered as tablets in a bottle often does not provide a good fit for patients or treatment goals. However, better personalisation and improved treatment outcomes could be achieved if oral medicines could be integrated into a handheld digital device. Oral medicine formulated as granules coupled with digital technology could provide the flexibility that patients and physicians are looking for, thus helping with the goal of moving beyond the pill.

Treatment of ADHD

Treatment goals, depending on the therapeutic area and patient group, can be significantly impacted in the simplest way. The formulation may be appropriate, but the patient can be the source of the challenge, whilst at other times, the patient is willing, but the formulation can be the issue. The challenges that can be experienced for different patient groups using oral medicine for treatment of different conditions can be summarised:

- Accurate dose titration
- Difficulties swallowing
- Ease of use
- Confusion which medicines to take at what time for what disease
- Avoidance of misuse and or abuse
- Diversion and use by others than the intended patient
- Compliance and monitoring
- Integration with other sources of health data and information.

Several efforts looking for improvement of these challenges have been developed or are in development. For example, compliance-supporting measures such as a pill incorporating a mini-transmitter, digital-calendarised pill boxes, extended release formulations, a capsule which once swallowed can dispense medication for a week; help with swallowing difficulties such as oral disintegrating tablets, powder formulations; enabling dose titration using mini-tablets in a syringe for paediatrics or a self-fill digital container. However, most of these ideas focus on one or two of the challenges and not the whole solution.

One product in development integrates oral prescription medicine with intelligent dosing in a handheld digital device. It is a prescribed regimen consisting of two parts: a re-usable control unit and a disposable prefilled cartridge with active medicine. One development treatment area is ADHD. For these medications the control unit would last for 12 months or more whilst the cartridge would last for one month's prescription. New cartridges are attached by the patient each month.

Attention-deficit hyperactivity disorder (ADHD) is a common, neuro-behavioural disorder, with onset in childhood, that can result in inappropriate inattentiveness, increased impulsivity and hyperactivity, affecting multiple areas of life. Prevalence of ADHD has been estimated to be 11% in children and 4% in adults[1]. Stimulants (methylphenidates and amphetamines) are the best-known and most widely-used ADHD medications, despite concerns about their adverse effects and potential for abuse. These drugs are highly effective in reducing core ADHD symptoms, and help patients to concentrate better, be less impulsive, feel calmer, and learn and practise new skills.

In clinical practice, however, stimulants require substantial efforts in fine-tuning and titration of doses for the maximum patient benefit without adverse effects. This is especially true during treatment beginnings but can also remain an issue as patient grows [2]. Moreover, there is a growing concern over misuse, abuse and diversion of stimulant drugs. ADHD medicines are controlled substances, yet one in eight teenagers has misused or abused them, which increases to one in five among college students[3]. An investigation which tracked calls to the American Association of Poison Control Centres from 1998 to 2005 observed a 76% increase in calls related to teenaged victims of prescription ADHD drug abuse over that eight-year span[4].

A further challenge for treatment of ADHD and many other diseases is the difficulty in swallowing pills which can subsequently impact compliance. This is observed frequently in children but also in 10 to 40% of the adult population [5,6]. Eventually treatment success depends on compliance and adherence to medication. This has been found to be a key challenge for children, even when treated by caregivers, adolescents and adults with ADHD[7,8].

Personalisation Through Formulation

The company formulates the oral medication as small granules or micro-units (less than 1000 µm). This supports patients who do not like to swallow pills or find difficulty swallowing pills. The granules can be administered directly orally or taken together with liquid or soft food. Depending on medication, the company can utilise taste-masking (if needed) to solve palatability. The use of small granules or mini-units also helps with more accurate and individualised dose titration. Often titration of medication is needed due to a drug narrow therapeutic range, dosing based on the weight of the patient, and dose adjustment to optimise effect and minimise side-effects[7].

However, the use of small pellets or granules can present a technological challenge for product development. The ability to dose titrate accurately within regulatory guidelines can vary depending on the API used, loading of the API in each granule and physical characteristics of the formulated granule (such as surface properties, shape, size and hardness). In addition, the optimal approach is to use a mechanical dispensing technology rather than dispensing being dependent on gravity. The company has developed a proprietary technology to achieve these goals. Therefore, setting the dose and adjusting the dose and dispensing the dose on the ADHD prototype is achieved through a simple D-pad on the control unit showing the chosen dose on an LED display.

The Potential of Digitalisation

Product design to develop an improved approach to dosing oral medicines relies on designing the mechanical, software and hardware systems as well as the user interface. Digitalisation provides several advantages compared to conventional pills in a bottle. The pre-filled cartridge (for ADHD, a one-month prescription) has an integrated circuit board chip which communicates relevant information to the control unit. The cartridge enables the control unit to set the dose, prevent from taking more than the maximum dose, allow titration, ensure notification of tampering, and record drug dispensing. The information available immediately provides opportunities to support compliance. Such information in an anonymised form could also be used in the future provide useful information on treatment.

The control unit of the device itself can provide dose reminders and a log of the previous dose taken. Further personalisation through connectivity, using Bluetooth and a companion application on a smartphone, opens the possibility to provide an accurate log of drug dispensing over time. Opportunities exist for self (caregiver)-reporting of symptoms. With ADHD these could include level of concentration, hyperactivity, behaviour, schoolwork etcetera, which can further support treatment outcomes[9,10].

For caregivers, access to information in a companion application will help provide reassurance regarding compliance and treatment effect[10]. Whilst many separate smartphone applications exist, the possibility to directly link to the device dispensing medication, showing both dose and time the dose was taken, adds an additional dimension to the data collected, especially when aligned with self-reported symptom monitoring. The product could be linked to existing applications or a dedicated application. Connectivity also opens opportunities enabling the device and companion application to be developed to link to other units, relevant to a disease area, such as wearables monitoring activity.

Personalisation Through User ID

With controlled substances the risk of misuse and abuse are key concerns and has more recently been the target of policy-makers. The company has an interest in the pain area with the aim to provide reassurance of correct medication use. Similar user identification can be important with ADHD medications which are controlled substances. This was observed as a positive product attribute by physicians, patients, caregivers and payers in market research focused on ADHD treatment which the company conducted in the US. The advantage of integrating medicine and digitisation allows for personalisation and user identification. The control unit would enable this through use of a pin code or biometric identification.

More Focus on Paediatric Formulations

There is an increasing focus toward paediatric medicines which presents a key challenge for regulatory authorities. Approximately 50–75%[11,12] of drugs used in paediatric medicine, lack FDA-approved paediatric formulations, leaving approximately 40% of children worldwide at increased risk of adverse events such as suboptimal dosing, lack of adherence to medication regimens, and reduced access to novel treatments[13]. This gap has resulted in a global effort towards an improvement of paediatric formulations and their delivery[13,14,15]. Different groups and consortiums such as the European Paediatric Formulation Initiative (EuPFI) are focused on this important area. Areas of interest are age-appropriate formulations, taste-masking, and use of excipients, as well as devices to dose accurately to support paediatric patients. Product development by the company recognises that this is an area where their granule-dispensing technology could be useful.

A qualitative investigation on how children received their medication highlighted that adult tablets are broken into smaller pieces, then crushed and added to food or liquid and often, parents resort to hiding or forcing administration, or discontinue treatment completely after unsuccessful attempts[16]. Liquid or syrup formulations can offer a suitable alternative but not all drugs can be formulated as such: the volume/dose ratio of liquid medicines can be impacted by solubility of the medicine, which may require additional excipients[17]. Product stability may require addition of other compounds such as antioxidants and preservatives, whereas taste-masking may require sweeteners and flavours.

Other challenges associated with liquid delivery form include the need to shake the suspension, transport and storage of liquid medicines (often requiring refrigeration), and an accurate measuring device (spoons, cups and others are not always accurate and/or are hard to read). The WHO specifically recommends a 'flexible solid oral dosage' design as the optimal formulation for oral paediatric medicines[18].

Product development using small granules will facilitate concerns of children and caregivers regarding swallowing conventional pills. Such formulation technology can be designed with taste-masking if needed to support palatability. Dose titration using the

same technology to accurately dispense pellets can be used. Depending on the course of treatment or treatment regimen, however, digitisation may be less critical and as such, compliance monitoring could be achieved mechanically on the device.

Individualisation and Personalisation with Oral Medicine

Oral medication for ADHD, pain management and paediatrics can be improved to support the needs of patients, caregivers and healthcare professionals. Different conditions and patient groups present many challenges which conventional oral medications do not currently meet. Treatment outcomes in other treatment areas can also benefit from improvements of integrating oral formulations with digital technology. Titration and compliance are critical for post-organ-transplant patients treated with immunosuppression drugs. Geriatric patient groups present issues with swallowing difficulties, compliance monitoring and dexterity issues with current tamper-proof packaging.

Several product development initiatives to improve aspects for oral medication address one or two of the issues being experienced. Through integrating medicine, intelligent dosing in a handheld digital device, the company hope to address the challenges experienced and therefore support improvements in treatment outcomes.

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