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An automatic dose dispenser for microtablets—a new concept for individual dosage of drugs in tablet form

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Abstract

A new concept for individualising the dosage of drugs in solid form is presented. The principle is based on the use of standardised units (microtablets), each containing a subtherapeutic amount of the active ingredient. The required dose is fine-tuned by counting out a specific number of these units. The microtablets are counted electronically from the attached cassette by the automatic dispensing device. The individual dose is set and the dispenser counts and delivers the correct number of microtablets. The usefulness of the automatic dispenser concept and acceptability of the apparatus were evaluated in patients with Parkinson's disease (PD). After initial instruction on use of the dispenser, 20 patients operated it themselves. All patients were generally satisfied with their management of the automatic dispenser and most would be happy to use the device again. Further technical development is required before use in clinical practice, but the current prototype may be acceptable for some patients. It is concluded that the final version of the automatic dose dispenser concept will offer potential for improvement of drug administration for patients with PD or other diseases requiring individual dosage.

Keywords: Individual dosage; Drug dispensing device; Parkinson's disease; Levodopa; Microtablets

1. Introduction

1.1. Background

In the development of new drugs, the recommended dosages are selected in accordance with patient population averages. However, over the past few years, the importance of individualised dosage has been discussed in various medical publications. Individual dosages should reflect interpatient differences such as gender, age, weight, ethnicity and environment, as well as details such as genetically controlled drug-metabolising enzymes (Sjöqvist, 1999). Further, the administration of the right drug in the wrong dosage can result in adverse effects or decreased efficacy, especially for drugs with narrow therapeutic indices. Fredholm and Sjöqvist (2001) claim that these problems have increased rather than decreased over recent years and that it should be possible to avoid adverse effects by using individualised dosages. For example, Evans et al. (1998) demonstrated that individualising the dosages of methotrexate in children with B-lineage acute lymphoblastic leukaemia significantly improved outcomes without increasing

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toxicity. It is believed that, in future, molecular diagnostics will be used to identify genetic polymorphisms in drug-metabolising enzymes, transporters and receptors in order to individualise, and thereby optimise, drug therapy (Evans and Relling, 1999).

The oral tablet is still the most commonly used dosage form, with advantages such as cost effective manufacturing along with convenient handling and administration for the patient. Hitherto, although the tablet form has many advantages, it has not always been suitable for the fine-tuning of doses to individual patients. Normally, there are only a limited number of standard tablet strengths. Combining tablets containing different amounts of the active substance has been one method of achieving a more individualised dose. However, this approach is not very convenient for the patient, who has to handle several different tablet containers and take different numbers of tablets that may be confusingly similar in dimension and shape. Further, it is not cost effective for the manufacturer to produce a manifold of tablets containing differing doses. Dividing tablets is also a common and simple technique of obtaining smaller doses, but some patients, e.g. those suffering from movement disorders and elderly people, could have difficulties with this. Breaking tablets by hand can also decrease dose uniformity, which can cause problems for some patients, especially those using drugs with narrow therapeutic indices (Teng et al., 2002). In spite of the obvious drawbacks associated with combining tablets of different strengths or splitting tablets containing standard doses, these approaches are sometimes applied because of a lack of more effective alternatives. Levodopa for treatment of Parkinson's disease (PD) (Granérus, 1999), morphine for pain relief (Hasselström and Olsson, 1999), levothyroxin for hypothyroidism (Hallengren, 1999) and warfarin for anticoagulation (Bergqvist and Johnsson, 1999) all require individualised dosages, and administration of these drugs involves the dispensing of tablets with different doses or the use of divided tablets.

1.2. The new concept

1.2.1. The principle

In principle, despite their antiquity, divided powder dosage forms have the distinct advantage of permitting fine tuning of the dose. The disadvantage is of course that dispensing small amounts of powdered drugs "by weighing" requires the use of a balance with adequate precision. An alternative approach involves the technique of administration "by volume", as has traditionally been used in tableting and capsule filling. The patients dispense their own dose from the bulk powdered or granulated drug with a measuring spoon. This approach has been available for a long time for some of the less potent drugs, where the demand for an exact dose is less pronounced. It is, however, obviously much more difficult to achieve a precise volume or dose when using a spoon than when using the standardised filling of a die during automatic tableting procedures.

In this paper, the concept of individual drug dispensing "by counting" is presented, as a potential solution to the above-mentioned shortcomings. This new concept is based on the use of standardised dosage units, each containing a subtherapeutic amount of the active ingredient. Subsequently, by counting out a specific number of these units, a therapeutically effective dose can be achieved. Tablets, containing, for example, 2–20% of the required dose, would be an effective dosage form for this method. Each unit should contain as close as possible to identical amounts of the active ingredient. It would thus be possible, by counting these tablet units, to adjust the dose for each specific patient. The required precision could in principle be obtained by utilising monosized pellets or granules instead of tablets. However, current techniques such as extrusion/spheronization, wet granulation, spraying onto excipient beads, etc. do not allow the production of close-to-identical granular units. This can only be achieved by traditional tableting compression methodology. Thus, in this paper, tableting was used to obtain units of relatively small dimension, each containing a precise, subtherapeutic amount of the active ingredient. Because of the relatively small dimensions (diameter: 3 mm, thickness: 1.3 mm) of these tablets, they are hereafter referred to as microtablets.

1.2.2. The counting device

Because of the limited dimensions of the tablets, some kind of counting device is required for patient assistance. In this paper, an automatic dose dispenser is described and evaluated (Fig. 1). This is an improved and upgraded version of a prototype presented previously (Aquilonius et al., 1998). The dispenser

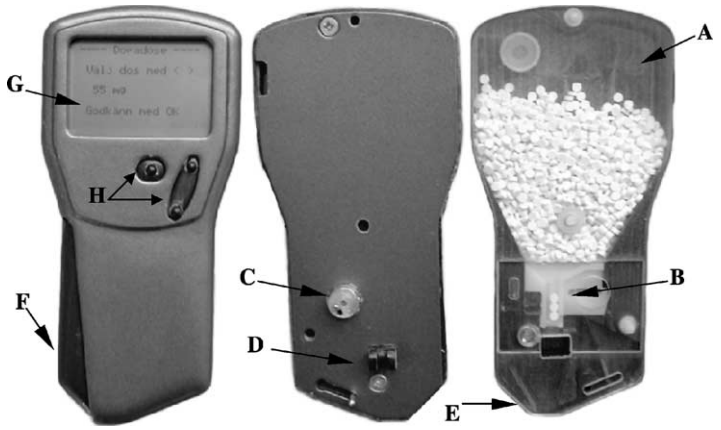

Fig. 1. The dose dispensing device, consisting of a cassette filled with microtablets (A), plastic components (B), electronic motor (C), and a photocell (D) which monitors the number of microtablets transported from the cassette to the receiving compartment (E). An actuator (F) releases the microtablets into a collecting vessel or a glass of water. The digital display (G) and buttons (H) are used to adjust the dose.

comprises a cassette filled with microtablets, buttons operated by the patient (with an associated digital display) for dose adjustment, a battery-driven electronic motor, a photocell monitoring the number of microtablets dispensed from the cassette to a receiving compartment, and an actuator, by which the microtablets are emptied from the receiving compartment into a collector or a glass of water (Fig. 1). The usefulness of the automatic dose dispenser and patient acceptance of the device were evaluated in patients with PD.

1.3. Evaluation of the dispenser in patients with Parkinson's disease

PD is a progressive, disabling neurological disorder, which is mainly caused by loss of dopamine-producing neurons in the substantia nigra pars compacta and results in a lack of dopamine in the brain (Agid, 1991, for review). Since the late 1960s, levodopa has been the most effective pharmacological treatment of the disease (Lees, 2002, for review). While initial treatment with levodopa is often successful, after 3–5 years patients begin to experience motor complications. Fluctuations in motor response appear, firstly in a so-called "wearing off" of efficacy (motor fluctuations appearing at the end of each dose as drug concentrations fall) and later in an "on-off" phenomenon (Marsden and Parkes, 1977; Wooten, 1988). The "on-off" phenomenon involves unpredictable fluctuations from effective mobility (the "on" period) to disability (the "off" period) and can include dyskinesias during the "on" period and akinesia with or without rigidity and tremor during the "off" period (Marsden and Parkes, 1976). Dyskinesias, the most common adverse effect of levodopa, are abnormal, involuntary movements associated with each dose in patients with advanced disease. The development of dyskinesias and the "on-off" phenomenon have been attributed to the duration of levodopa treatment but may also be attributable to high doses of levodopa (Marsden and Parkes, 1976; Rinne, 1983). It is possible to obtain more stable plasma levodopa concentrations (thus potentially minimising motor fluctuations) by using an intraduodenal infusion of levodopa (e.g. Bredberg et al., 1993; Nilsson et al., 2001) or controlled-release levodopa tablets (e.g. Grahnén et al., 1992) rather than conventional oral tablets. However, for patients in the early stages of PD, the adverse effects of levodopa can often be managed by minimising or titrating the dose on an individual basis (Durif, 1999).

At present levodopa tablets containing 50, 100, 200 and 250 mg of the drug are available. Dividing the 50 mg tablets allows dosage adjustments in 25 mg steps. More refined dosage adjustment would offer potential for further reduction of adverse effects, as discussed above. The time spent by a patient waiting for the previous dose to take effect can occupy as much as 70% of the "off" periods (periods of no drug effect) experienced by the patient (Merims et al., 2002), implying that levodopa doses should be taken

more frequently. However, if the dosage interval is reduced, the dose itself must be lowered and more finely tuned. Dissolving the drug in water and adding ascorbic acid to make a levodopa/carbidopa/ascorbic acid solution (LCAS) may have some advantages over standard tablets (Kurth et al., 1993; Kurth, 1997, for review). Firstly, LCAS offers the opportunity for dose adjustment and, secondly, the solution is less dependent on gastric emptying which, if irregular, can cause marked fluctuations in plasma levodopa levels after administration of tablets (Nyholm et al., 2002). However, a study by Verhagen Metman et al. (1994) did not find any significant difference between tablets and LCAS regarding plasma levodopa oscillations and motor response fluctuations, although absorption and peak plasma levodopa concentrations occurred more quickly with LCAS. A single-dose crossover study of a dispersible levodopa formulation versus the standard form confirmed the shorter time to peak plasma levodopa concentrations (Contin et al., 1999). Further, in a double-blind crossover comparison of LCAS and standard tablets, patients responded to LCAS with significantly improved "on" time, without an increase in the severity of dyskinesia (Pappert et al., 1996). A follow-up of the patients in that study revealed that LCAS therapy was successfully continued for up to 9 years (Janko et al., 2002). However, using LCAS for individual dosage adjustment still involves division of tablets or swallowing an accurate volume of liquid to achieve the right dose.

For a levodopa dose range of 5–200 mg, individual oral doses with a sensitivity of 5 mg would be desirable. This could theoretically be accomplished by the patient manipulating a large number of 5 mg tablets. The small size of these tablets coupled with the motor dysfunction experienced by patients with PD suggest that the patients could require help in handling the tablets and taking the correct dose. This could be achieved by using the automatic dose dispenser described above. For the application of PD, the dispenser would then contain microtablets, each containing 5 mg levodopa and 1.25 mg carbidopa. The automatic dispenser delivers the correct dose for each patient who then is able to swallow them either undissolved or dissolved in liquid.

The aim of this study was thus to present and evaluate a new drug administration concept, which includes an electronic automatic dose dispenser for adjustable individualised delivery of a specific number of microtablets. Further, patients with PD tested the usability of this dispensing device and offered their opinion of the concept.

2. Materials and methods

2.1. Materials

Drugs: levodopa (Apoteksbolaget, Sweden) and carbidopa (Apoteksbolaget, Sweden). *Filler*: microcrystalline cellulose (MCC; Avicel PH 101, FMC, USA), crystalline lactose (α-lactose monohydrate; DMV, The Netherlands). *Granulation liquid*: ethanol (95%, w/w, Solveco Chemicals AB, Sweden) containing 10% (w/w) polyvinylpyrrolidone (PVP; Kollidon 25, BASF, Germany) as a binder. *Lubricant*: magnesium stearate (Kebo Lab, Sweden).

2.2. Characterisation of materials

The apparent particle density (B.S. 2955, 1958) of the materials was assessed using a helium pycnometer (AccuPyc 1330 Pycnometer, Micromeritics, USA) ($n = 3$). Blaine permeametry (Kaye, 1967) was used to determine the external specific surface area of all powders (except magnesium stearate) and the surface areas were corrected for slip flow because of the small particle size (Alderborn et al., 1985).

2.3. Compaction of microtablets

Levodopa (25.0 g), carbidopa (6.25 g) and MCC (28.75 g) were mixed in a glass jar in a tumbling mixer (2L Turbula mixer, W.A. Bachofen AG, Basel, Switzerland) at 120 rpm for 5 min. Ethanol containing 10% (w/w) PVP (30 ml) was added during stirring and the granulation mass was pressed through a 500 μm sieve (Retsch, Germany). The granulate was dried at room temperature for 48 h. The dry granulate was then sieved (300 μm), magnesium stearate powder (0.5%, w/w) was added and the combination was mixed in glass jars in the tumbling mixer for 2 min. Tablets were made in a single punch press (Diaf, Denmark) using 3 mm flat-faced punches and a hopper shoe. The tablet weight was held constant at 12 mg and

the height at 1.3 mm. For the handling study, placebo tablets were prepared in the same way but containing lactose (12.0 g) and MCC (48.0 g) instead of levodopa and carbidopa.

2.4. Characterisation of tablets

All tablets were stored at 40% relative humidity (RH) for at least 48 h before characterisation.

2.4.1. Tablet weight, thickness and diameter

Twenty tablets were weighed on an analytical balance and the dimensions (height and diameter) were measured using a manual micrometer.

2.4.2. Porosity

The tablet porosity was calculated from the dimensions and weight of the tablet and apparent particle density of the mixture, calculated according to Jerwanska et al. (1995).

2.4.3. Friability

The friability of the tablets was measured using the Roche friability apparatus (Erweka Apparatebau GmbH, Germany). Forty-one tablets corresponding to a weight of approximately 0.5 g were weighed before and after rotating for 4 min at a speed of 25 rpm and the weight loss was calculated ($n = 3$).

2.4.4. Tensile strength

A diametral compression test (Holland C50, UK) was performed and the radial tensile strength of the tablets was calculated according to Fell and Newton (1970) ($n = 20$).

2.4.5. Assay of levodopa and carbidopa

The content of levodopa and carbidopa in 20 microtablets was analysed using reversed-phase high-performance liquid chromatography (HPLC) with electrochemical detection (ESA 5100A). The method is a modification of one previously reported (Bredberg et al., 1993). The mobile phase consisted of 0.05 M phosphate buffer (pH 2.8) with 10% methanol. The HPLC system was equipped with a 5A5 Hypersil C18 reversed-phase column (150 mm × 4.6 mm, 5 μm). The oxidation potential for detector one was 0 V and for detector two +0.4 V; the flow rate was 1 ml/min.

2.5. The automatic dose dispensing device

The cassette portion of the device, which can be manually refilled but is also planned to be available as a new prefilled cassette for convenience, contains >2000 microtablets (Fig. 1). The microtablets are transported within the dispenser by the plastic components which are moved by a battery driven electronic motor. A photocell monitors the number of microtablets transported from the cassette to the receiving compartment and the electronic motor stops when the preset number of microtablets has passed the photocell. The actuator then causes the microtablets to be emptied from the receiving compartment in the device into an external collector or a glass of water. A digital display guides the patient through the process, i.e. using the buttons, the patient starts the dispenser device and sets the correct dose; instructions then appear to empty the microtablets from the device into the collector. The weight of the device, without microtablets, is 232 g and the dimensions are 132 mm (height), 63 mm (width) and 32 mm (thickness).

2.6. Handling study

2.6.1. Patients

Twenty patients with PD (7 women and 13 men) gave their written informed consent to participate in the usability study. Patients were recruited consecutively at the Uppsala University Hospital neurology clinic and the only exclusion criterion was dementia.

2.6.2. Testing procedure

Patients were characterised according to medication, concomitant diseases and severity of PD. The unified PD rating scale (UPDRS), parts I (mentation, behaviour and mood), II (activities of daily living) and IV (complications of therapy) were applied along with the Modified Hoehn and Yahr scale for staging of disease severity scored from 1 to 5 (Fahn and Elton, 1987).

All patients were instructed once on how to use the dispensing device. After the demonstration, the patients were asked to operate the dispenser themselves. Any additional instructions were recorded. Patients were asked to start the dispenser, to set the dose to 65 mg (from a default dose of 20 mg), to confirm the dose and to release the 13 microtablets into a glass. The patients were also asked to pick up five

microtablets from the table. These tests were observed by two investigators, who recorded the outcomes. The first five patients were observed by both investigators who reached a consensus on how to assess the performance of the tasks. Then the tests were observed by one investigator per patient. Any difficulties in assessing the outcome were discussed to reach concordance. After the tests, all patients answered 15 questions on their impressions of the method. Only placebo microtablets were used for the tests and patients did not ingest any microtablets. The study was approved by the ethics committee of Uppsala University.

3. Results and discussion

3.1. The microtablets

3.1.1. Characteristics of the microtablets

The composition of the microtablets and the densities and specific surface areas of the materials are presented in Table 1. Since the microtablets contained a relatively large amount of drug (approximately 50%, w/w), a granulate was prepared in order to increase the compactability of the materials while retaining uniformity of drug content. The mean weight of the tablets, the average content and the uniformity of levodopa and carbidopa content were all within the limits specified by the European Pharmacopeia (2002) (Table 2). This implies that only minor segregation had occurred during processing (i.e. mixing, granulation, and tableting).

As described in Section 2, the tablets are stored in the cassette and transported within the dispensing device by mechanical movement of the plastic components. Therefore, it is important that the microtablets are sufficiently strong to withstand this treatment, i.e. both storage within the cassette and transportation through the device. The results showed that the microtablets containing levodopa and carbidopa were relatively dense (porosity 11.2%) with both high radial tensile strength and low friability (Table 2). A common industrial specification limit for friability is a maximum weight loss of 1.0%. The obtained value (0.44%) is well within this limit and should be sufficient in this context. During the handling study,

Table 1
Primary characteristics of test materials and composition of the microtablets

Material	Apparent particle density (g/cm^3)[a]	External specific surface area (m^2/g)[b]	Composition (mg)
Levodopa	1.503 (±0.000)	1.3 (±0.05)	5.00
Carbidopa	1.466 (±0.002)	8.5 (±0.31)	1.25
MCC	1.564 (±0.002)	0.33 (±0.06)	5.69
Magnesium stearate	1.071 (±0.004)	–[c]	0.06
Total	1.52[d]		12.00

[a] Measured with a helium pycnometer (AccuPyc 1330 Pycnometer, Micromeritics, USA). Mean ± S.D., $n = 3$.
[b] Measured with a Blaine permeameter (Kaye, 1967; Alderborn et al., 1985). Mean ± S.D., $n = 3$.
[c] Not determined.
[d] Particle density for the mixture, calculated according to Jerwanska et al. (1995).

Table 2
Primary characteristics of microtablets

Tablet weight[a] (mg)	Tablet height[a] (mm)	Tablet porosity[a] (%)	Friability[b] (%)	Radial tensile strength[a] (MPa)	Mean content of levodopa and carbidopa[a] (mg)	Uniformity of content of levodopa and carbidopa[c] (min–max) (%)
12.3 (±0.29)	1.32 (±0.02)	11.2 (±2.3)	0.44 (±0.01)	3.89 (±0.37)	5.12 (±0.097)[d] 1.22 (±0.022)[e]	96.3–102.5[d] 96.6–104.0[e]

[a] Mean ± S.D., $n = 20$.
[b] Mean ± S.D., $n = 3$.
[c] $n = 20$.
[d] Levodopa.
[e] Carbidopa.

placebo tablets were run through the dispensing device several times with only small amounts of weight loss estimated. However, it will be important to study tablet strength and friability in detail in the development of the final version of the device, to ascertain that the tablets can withstand this handling.

3.2. The patient study

3.2.1. Patient characteristics and medication

The patients were on average 65 years of age (range 49–79 years), with a mean duration of PD of 8.5 (range 0–26) years and exposure to levodopa of 7.2 (range 0–24) years. Nineteen of the patients took levodopa a mean of 5.3 (range 3–9) times per day and one used a continuous enteral levodopa infusion (Bredberg et al., 1993; Nilsson et al., 2001). Two of the patients used a continuous apomorphine infusion (Pietz et al., 1998) concomitantly with oral levodopa. The mean total daily dose of levodopa was 692 mg (range 200–2160). Nine patients divided their tablets for dose optimisation, five had no difficulties with the process but two reported difficulties and two always required help. A few patients were using a tool, obtained from the pharmacy, for dividing tablets. One patient divided her tablets into pieces smaller than half a tablet with a pair of scissors. Nine patients reported that they used extra levodopa when needed. Eleven patients used other antiparkinsonian medications concomitantly with levodopa; all 11 took dopamine agonists, 3 also took a catechol-*O*-methyl transferase-inhibitor, 4 took a monoamine oxidase-B inhibitor and 1 took amantadine. Five patients reported no difficulties in remembering dose intakes, whereas the other patients had some or major problems. The patient on continuous levodopa infusion did not take any other drugs and therefore did not have to remember any dose intakes. Patients were at all various stages of PD using the Modified Hoehn and Yahr scale "at worst" score (3 patients at stage 1, 2 at 1.5, 3 at 2, 4 at 2.5, 2 at 3, 3 at 4 and 3 at 5). The mean UPDRS score (parts I, II and IV) was 23 (range 6–38). All patients were able to handle the dispensing device independently. One patient had rheumatoid arthritis but this did not affect her ability to handle the device. One left-handed patient used his right hand for operating the device without difficulty. This is an important finding, suggesting that the device can be used by hemiparkinsonian patients whose dominant hand is affected.

3.2.2. Test results from the handling study

The results from the handling test are shown in Table 3. All patients were generally satisfied with their own management of the automat, suggesting that, from a management point of view, the present prototype could be used for daily treatment with little instruction required.

Seven patients were able to start the device properly, while 13 either pressed the button too long or more than once, due to tremor. It was apparent that the buttons were too sensitive. Entering the dose was also difficult for some patients because of this high sensitivity. All patients could release the microtablets into the glass. Since the microtablets were very small, it was anticipated that patients with tremor and/or dyskinesia might find it troublesome to handle them. However, since all patients managed to pick up five

Table 3
Patient test ($n = 20$)

Patient tasks	Investigators' assessments of the patients' performance				Patients' answers[a]	
	Without problems	Some difficulties	After repeated instructions	Cannot perform the task	Yes	No
Starting the dose dispensing device	7	1	12	0	20	0
Entering dose	14	5	1	0	20	0
Confirming dose	19	1	0	0	20	0
Releasing tablets	19	1	0	0	20	0
Pouring tablets into a glass	20	0	–	0	20	0
Picking up five tablets from table	20	0	–	0	20	0

[a] To questions on ability to perform each task, such as "Do you think that you were able to start the dose automat?", etc.

Table 4
Patients' opinions of features of the device

	Acceptable	Too light	Too heavy	No opinion
Weight of device?	13	0	7	0
		Too small	Too large	
Size of device?	6	0	14	0
Size of buttons?	13	7	0	0
Size of text on display?	9	11	0	0
		Too long		
Time for delivery?	18	1		1

tablets from a flat surface (a table), the size seems adequate for manual handling if needed. One patient also claimed that she would like to use the microtablets for her medication, but felt no absolute need for using the dispensing device. The assessment of the patient's ability to handle the device was mostly made by one investigator. Some of the assessments were subjectively rated, which might result in bias. However, all patients reported that they were able to perform all tasks, which is the ultimate aim of the concept, regardless of any initial difficulties or need for repeated instructions.

The patients were also asked their opinion of the concept and most patients were positive about future use, but many mentioned modifications of the current prototype (Table 4). Most patients found the device too large and some thought it too heavy. Many patients suggested changing the size to more closely resemble that of cellular telephones. The buttons were too small for seven patients and the text of the display was considered too small by 11 patients; however, all patients were able to read the text. All patients but one felt comfortable with the automatic counting of the correct dose, but some claimed they would check the number of tablets for the first few times of use (Table 5). All but one were positive about the concept of dose administration in general and 17 patients were interested in using the device for their own medication, thus replacing the conventional levodopa tablets. The patient on the levodopa infusion said that he would not exchange his infusion for microtablets, but would prefer microtablets before standard tablets if he had to choose. One patient was newly diagnosed with PD and preferred ordinary tablets, but he stated he would possibly change his mind in the future. One patient claimed that conventional tablets were easier and another did not want to use the device since he already took a great number of other medications. All patients were open to the idea of using an alarm to remind them of dose timing; however, one patient who already used an alarm watch did not need this option in the dispensing device. Another patient stated a preference for a discreet alarm, e.g. a vibration only, again with reference to cellular phones. The outcome of the tests was not clearly correlated with age or PD severity. These results are consistent with the results from the study of a previous prototype of the device in 14 patients with PD (Aquilonius et al., 1998). The mean Modified Hoehn and Yahr score was slightly lower in that group, 2.2 (range 1–4) versus 2.75 in our group. All patients but one in the previous study emphasised a need for the dose dispensing device concept.

Table 5
Patients' opinions on possible future use of the dose dispensing device

	Yes	No	No opinion
Would you rely on the correct dose being dispensed by the device?	19	1	0
Is this concept a good idea for dose optimisation of levodopa?	19	1	0
Would you like to use this device instead of regular levodopa tablets?	17	2	1
Would you like an alarm in the device as a dose intake reminder?	19	1	0

4. Conclusions

This study presents a new drug administration concept comprising a convenient electronic dose dispensing device containing microtablets for individualising dosages. This new concept allows fine-tuning of the dose, which may therefore result in more optimal therapy for patients with diseases requiring individualised dosage.

The microtablets were prepared by wet granulation and compaction, weighed only 12 mg and were small in dimension (diameter 3 mm, thickness 1.3 mm) with good tableting characteristics, such as adequate strength and low friability. Further, the average content of the drugs, levodopa and carbidopa, showed that high homogeneity of drug content was obtained.

A total of 34 patients with PD have tested prototypes of the dispenser. All were able to manage the device and 88% of patients (30 of 34) were interested in using the system in the future. The more recent version of the dispensing device was better accepted in terms of size and weight. 100% of patients who tested the previous prototype and 70% of patients who tested the present prototype found it too large, 64% found the previous prototype too heavy and this figure decreased to 35% for the present prototype.

While some technical changes are required for future versions of the device, the current prototype appeared to be acceptable for some patients. It is concluded that the dispensing device concept, once these technological adjustments have been made, offers potential for improvement of drug therapy and administration for patients with PD and also for other patients with diseases requiring individual dosage.

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