

Adherence logger for a dry powder inhaler: A new device for medical adherence research

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Background: Adherence to inhaled steroid regimens is frequently poor. Finding ways to improve adherence depends on the ability to measure time and date of inhaler use reliably and to detect deliberate dose dumping. There is no such monitor for the popular new dry powder inhalers.

Objective: To develop and test an electronic monitor for a dry powder inhaler that will provide information on the time and date of use.

Methods: An electronic adherence monitor for the Advair Diskus dry powder inhaler was developed and tested. In this device, inhaler use is determined by detecting and recording the motion of the drug delivery lever in the inhaler with a magnetic sensor. An additional electronic interface and software were also developed to allow the adherence data to be uploaded to a computer for display and analysis.

Results: System and reliability tests involving multiple-day and repeated-use tests of the adherence monitor demonstrate the overall performance and reliability of the device, and specifically its ability to record the time and date of dose delivery. In the repeated-use test, 300 successive actuations of the dose delivery lever were correctly sensed and recorded without error.

Conclusion: The simple-to-use, low-cost, reusable adherence monitor accurately records time and date of inhaler use and thus allows clinical monitoring and adherence studies in patients using the Advair Diskus dry powder inhaler. The same technology should be adaptable to other dry powder inhalers, including the Pulmicort Tubuhaler and the Symbicort Tubuhaler. (J Allergy Clin Immunol 2004;114:863-8.)

Key words: Asthma, adherence, inhaled corticosteroids, clinical research

Poor adherence to inhaled corticosteroids (ICSs), the medication recommended for all but the mildest asthma, is

Abbreviations used

DAL: Diskus Adherence Logger

DPI: Dry powder inhaler

ICS: Inhaled corticosteroid

widely recognized¹⁻⁵ and contributes to asthma morbidity.^{6,7} Developing strategies to improve adherence is a national priority for addressing asthma and other chronic diseases, particularly in high-risk patient groups.^{8,9} Studying adherence in asthma ideally depends on the ability to detect and record when a dose of ICS is inhaled. Electronic monitoring, which records when the inhaler is actuated or used, comes closest to achieving this ideal, providing more reliable data than other methods such as patient report.^{4,8,10}

Dry powder inhalers (DPIs) are now widely used, but no electronic monitor is available for studying adherence with these medications. A monitor is needed that can capture both the time and date of DPI use because it provides information not only on the use of an inhaler over the course of the day but also on the deliberate actuation of an ICS inhaler unaccompanied by inhalation, sometimes called *dumping*.¹¹ Although the DPI inhalers have built-in dose counters that display the number of doses left in the inhaler, this counter lacks time and date information and thus cannot provide sufficient details of use or dumping.

The new DPIs are popular for several reasons. They do not use the chlorofluorocarbon-containing propellants of most of the older metered-dose inhalers, scheduled to be removed from the market according to the terms of the Montreal Accord.¹² Some of these new DPIs contain long-acting β -agonist in addition to ICS, simplifying the medication regimen for many patients. The addition of the long-acting β -agonist also provides some immediate relief of symptoms, unlike the older metered-dose inhaler ICS formulations. This ability to relieve symptoms and improved convenience may result in these newer inhalers having different adherence characteristics.³

The goal of this project is to develop and test an electronic monitor for a dry powder inhaler that will provide information on the time and date of use.

METHODS

Described here is an electronic monitor to record the use of the Advair Diskus DPI (GlaxoSmithKline, Brentford, Middlesex, United

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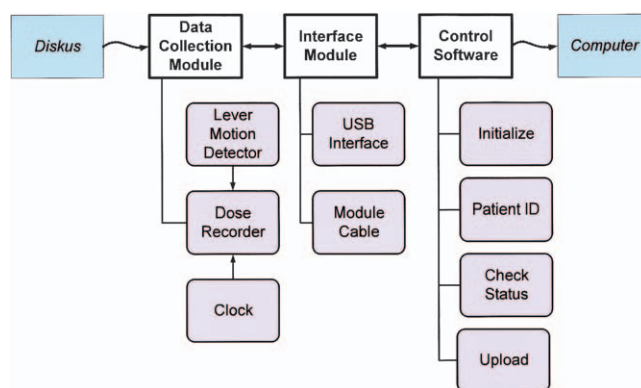


FIG 1. System diagram of the DAL device. Diagrammed are the 3 major subsystems, along with their primary subcomponents or functions. The data collection module is attached to the DPI and records the time and date of drug doses. The interface module connects to the data collection module to allow stored data to be uploaded to a computer. The control software is used to initialize the data collection module and upload data.

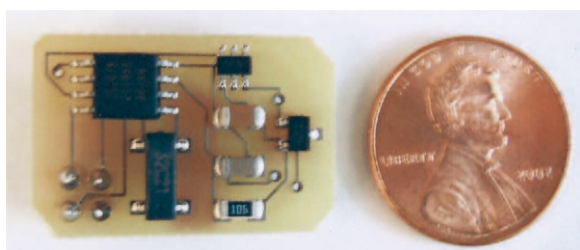


FIG 2. Photograph of DAL (data collection) module. Battery and connector are on back side of circuit board. The tiny black chip adjacent to the penny is the magnetic (Hall effect) sensor that detects the forward position of the drug delivery lever.

Kingdom), currently the most widely used DPI. Advair, a combination ICS (fluticasone propionate) and long-acting bronchodilator (salmeterol xinafoate), is delivered through a disk-shaped inhaler, the Diskus, containing 60 doses. Drug delivery requires 3 operations: “open” (the case), “click” (the lever that advances a dose of dry powder into the mouthpiece), and “inhale” (which draws the dry powder into the pulmonary airways). Because the electronic monitor has been constructed specifically for the Diskus inhaler, we refer to it as the Diskus Adherence Logger (DAL). Technical details, particularly those related to electronic design and operation, are available in the Journal’s Online Repository (www.mosby.com/jaci).

System overview

The DAL device consists of 3 subsystems: (1) the data collection module, which detects and records DPI doses; (2) an interface module, which allows the electronic dose record to be uploaded to a computer; and (3) computer software for initializing the data collection module and uploading data from it. Fig 1 displays the overall system design, indicating its 3 subsystems and their key functions. The data collection module (also referred to as the *DAL module*) is a postage stamp-size electronic device that is directly mounted on the Diskus and continuously records data. The interface module is used only briefly to set up the data collection module for recording and to upload data from it. The interface module is approximately the size of a package of chewing gum. It inserts into the Universal Serial Bus port of a computer at 1 end and supplies a connecting cable to the data collection module at the other end. Finally, the computer software allows the data collection module to

be initialized with the correct time and the patient’s identification, and to upload the dose history from the module. Each of the 3 subcomponents is described in detail here.

Data collection module

The DAL unit operates by sensing the motion of the dose delivery lever and then recording and storing the time at which the lever motion is sensed. Thus, there are 2 major functions to be achieved: (1) the generation of a “lever moved” signal, and (2) the recording of that signal. In this design, the “lever moved” signal is generated by a miniature, low-power magnetic sensing system, and the electronic recording uses a miniature, low-power event-recording chip specifically designed for data logging applications. The dose recorder stores the time and date at which lever motions were observed, and hence, the time and date of drug use. These 2 components provide the basis for the miniature low-power DAL.

Lever sensing. Photographs of the device are shown in Figs 2 and 3. The DAL operates by sensing and recording when the Diskus lever (which delivers the powder) is moved forward to its “click” position. Sensing is achieved by attaching a miniature magnet to the lever itself, and a magnetic field sensor (A3212 Hall effect switch, Allegro Microsystems, Worcester, Mass) on the stationary body of the Diskus. When the lever is pushed forward, the magnet is carried toward the sensor, which is contained within a 16 mm × 25 mm × 7 mm electronic module attached to the thumb grip of the Diskus. The proximity of the magnet causes a voltage output change in the sensor, which is then recorded by the dose recording electronics. When the Diskus case is closed, the lever, along with the magnet, is automatically pulled back, and the voltage output of the magnetic sensor returns to its normal state.

Dose recording electronics. The dose recording electronics consist of 2 subsections: a signal conditioning section and a time stamping section. The signal conditioning section, or *bounce filter*, filters out the effect of lever vibrations, or *bounces*, which may lead to extra sensor output pulses when the lever is moved. The bounce filter ensures that there is only a single voltage change for each movement of the lever. The output of the bounce filter, a voltage signal indicating the position of the lever, is connected to the time stamping section of the electronics. This portion is based on a Dallas DS1678 event recorder chip (Dallas Semiconductor Corp, Dallas, Tex). The DS1678 event recorder chip has a built-in real-time clock and electronic data storage, along with a control structure that records the time and date at which a voltage transition (event) occurs on its input. The dose recording section also includes a connector that

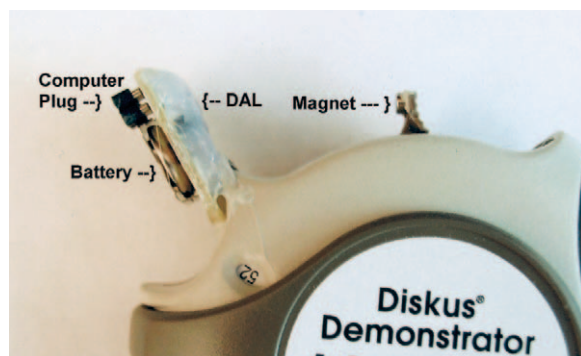


FIG 3. Attachment of DAL to Diskus. The DAL unit is mounted on the thumb groove of the Diskus case, and the magnet is glued to the drug delivery lever. The battery and connector are shown exposed for clarity. In clinical use, they would be coated with a vinyl rubber casing.

accommodates the cable from the interface module. This allows the interface module to communicate with the event recorder chip for control and data uploading to a computer.

The event recorder chip can be operated in different modes. In this application, it is programmed so that it will record the time and date of every lever actuation, recording as many as 1025 such events. It records only when the lever is pushed forward, not when it is pushed back when the Diskus case is closed. The event recorder time stamp resolution has been set to 1 second, allowing deliberate dose dumping (by rapid, repetitive lever activation) to be detected.

Interface module

The interface module provides the connection between the data collection module and a computer. The connector portion consists of a USB port connector at 1 end (which plugs into a computer) and a 4-wire cable at the other end (which plugs into the 4-pin connector on the data collection module. The electronic portion consists of circuitry that translates between the communication signals used by the DS1678 event recorder and the USB communication signals used by the external computer. The interface module is controlled by software.

Control and upload software

The control and upload software initializes the DAL for recording at the beginning of the logging period, terminates the logging operation, retrieves the data at the end of the logging period, and then stores it as a file on the computer. The software is written in Visual Basic 6 (Microsoft, Redmond, Wash) and is operated through a user interface window, shown in Fig 4. All of the software functions are indicated by the user interface, whose functions are listed in Table I.

Battery life

The data collection module is powered by a small lithium coin-cell battery (BR1225, 3V lithium). The expected battery life is 5.8 months. The interface module requires no batteries because it is powered directly by the USB port.

RESULTS

Two initial verification tests were performed to demonstrate the operation of the DAL system. The first verification was designed to demonstrate the overall

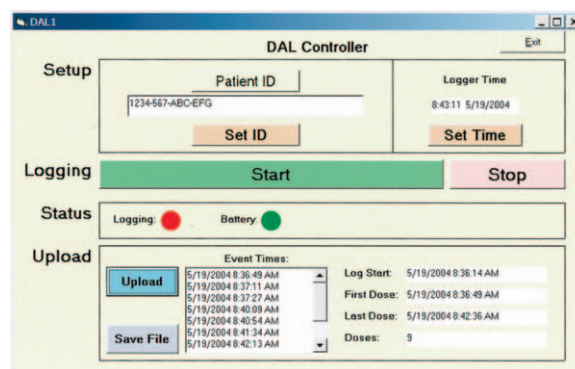


FIG 4. User interface window for control and upload software.

operation of the entire system, including the data collection module, the interface module, and the software. The second verification was designed to demonstrate the reliability of the lever sensing system.

System verification

In this test, a DAL module was mounted on a Diskus Demonstrator unit (that is, a Diskus that did not contain drug), and the Diskus was subjected to simulated use over a 3-day period. Simulated use consisted of opening the Diskus unit, pushing ("clicking") the lever forward, inhaling through the mouthpiece, and then closing the Diskus. Simulated use was performed 22 times over the 3-day period—much more frequently than the Diskus would actually be used for drug delivery—to supply more frequent observation points. The instrumented Diskus was also carried around in a briefcase during the day; thus, although this did not constitute a strenuous vibration test, the unit was tested under somewhat realistic out-of-laboratory conditions. The time and date of each simulated use were recorded on a paper log. At the end of the test, the data (the list of times and dates when the doses were delivered) were retrieved, stored on the computer, transferred into an EXCEL spreadsheet (Microsoft), and compared with the paper log (Fig 5).

Every simulated dose was recorded by the DAL. There were no missed doses, nor were there extra dose recordings that did not correspond to actual doses. Thus, there were no false positives or false negatives. The time records, DAL versus paper log, all agreed to within 1 minute.

Reliability testing

The system verification test demonstrates the overall operational capability of the DAL but does not directly examine the portion of the system most likely to malfunction or exhibit less than perfect performance: the lever motion detector. Malfunction of the other portions of the system would be highly unlikely unless 1 of the electronic components failed, which would be highly unusual. However, the lever motion detector conceivably could fail to detect lever motion if the snap action of the lever failed to bring the magnet close enough to the

TABLE I. List of functions available in the control and upload software interface

Function	Description
Patient ID	"Set ID" button stores patient identification, entered in the text window, into the DAL. When the DAL unit is reconnected to the computer for data retrieval, the patient's identification is retrieved from the DAL unit, displayed at the top of the user interface window, and subsequently stored with the data collection files on the computer.
Start logging	Begins the data collection process.
Stop logging	Stops the data collection process.
Status	Logging indicator shows whether the DAL is currently in logging mode. Battery indicator shows whether the battery is good.
Logger time	DAL clock time is continuously displayed; verifies operation of DAL. "Set time" button sets DAL clock with correct time.
Upload	When "upload" button is pressed, the following operations occur: If the logging operation has not yet been stopped, then logging is stopped. All of the time and date information is then retrieved from DAL memory. As the information is retrieved, it is displayed in the "event times" window on the display for immediate review. Also displayed is a log summary, consisting of the time and date of log start, the first and last logged dose, and the total number of logged doses. Data remain in the DAL memory and can be re-retrieved until logging is restarted. Whenever logging starts, previous memory contents are cleared.
Save file	Saves the list of "event times" as a text file, along with the patient identification.

magnetic sensor to be detected, leading to false negatives. Another theoretical possibility is that when the Diskus case is shut and the lever is moved backward, there might be lever bounces that would not be eliminated by the bounce filter, leading to false positives. To test whether either false-positive or false-negative conditions might occur, we repetitively actuated the lever 300 times to test for false recordings. Each repetition consisted of the normal Diskus operation: the Diskus case was swiveled open, the lever was moved forward, and then the case was closed. In this 300-repetition test, the first 100 repetitions were performed over a 6-minute period. There was then a 7-minute pause, and the next 200 repetitions were performed over a 17-minute period. In this test, all 300 lever actuations were recorded without error.

Cost

The cost of parts for the data collection module is less than \$10.

DISCUSSION

Design constraints

The DAL described here satisfies several important design constraints, including the need for (1) extremely small size; (2) noninterfering operation, so that the patient operates the Diskus in a normal fashion; (3) external attachment, so that the DAL can be attached without disassembling the Diskus and possibly interfering with drug delivery; (4) extended battery life; (5) simplicity, to promote reliability; and (6) low cost, to make large-scale clinical studies using the DAL feasible.

Performance

In the system verification and reliability tests, the DAL performed flawlessly, with 100% accuracy. This is not

unexpected, because the DAL performs a very simple function by using a simple design with few components. In general, measurement errors could arise from either electrical or mechanical malfunction. Electrical malfunction is highly unlikely in the DAL. Almost all of the electronic functions are performed by special purpose chips, such as the DS1678, which have been in production for an extended period. Outright chip failure is also unlikely, given the mild operating conditions (temperature and vibration) for the DAL.

The only potential electronic performance limitation we can identify currently is battery life. The DAL has been designed with an expected battery life of about 6 months, but with the additional expectation that the DAL units will be returned to the physician within 2 months of being activated. Should the battery be prematurely depleted, recording will stop, but data will remain stored in the DAL. Only when the battery is severely depleted will the data be lost. The simple precautions of putting a fresh battery into the DAL just before it is to be used and retrieving the DAL soon after the data has been acquired should avoid problems related to battery life.

Mechanical malfunction is a more likely occurrence. The DAL itself has no intrinsic moving parts. The moving part that allows the DAL to operate is the Diskus lever. Should the lever not move to a fully forward position, thus not bringing the magnet close enough to be detected, the DAL would not correctly record lever movement. Such a mechanical malfunction could conceivably occur with repetitive actuation of the Diskus, causing the plastic Diskus mechanism to deform and degrade with extended use. However, the Diskus is designed for only 60 doses, or 60 lever motions. This small number of movements should not affect the operation of the lever in any appreciable way. In the reliability test described here, 300 doses were delivered without deterioration in DAL function, making this kind of mechanical malfunction unlikely.

Another possibility is mechanical malfunction arising from mechanical overloading of the Diskus, such as stepping on it. In this case, it might be possible for the Diskus to operate well enough to deliver drug but still interfere with the operation of the DAL. We cannot eliminate this possibility but judge that it would be an infrequent occurrence. Other concerns are failures of the adhesives holding the magnet and circuit board to the Diskus. Because the magnet is not mechanically loaded, it is unlikely that it could come off unless it were not properly bonded to begin with. With the electronics module, however, disbonding is a more significant concern, because the electronics module acts as a physical extension of the finger groove that is used to open and close the Diskus case. The electronics module acts as a convenient handle for opening and closing the case, and in fact, the electronics module was used as the handle to open and close the Diskus during the tests described. However, the electronics module remained securely attached during the hundreds of Diskus operations involved in testing. Thus, it seems unlikely that the module could separate after only the 60 doses stored in the Diskus. Nevertheless, we will observe how the DAL functions in the field and how it performs when exposed to rough handling or other unanticipated events.

Finally, it is important to point out that the DAL does not in any way interfere with the operation of the Diskus and the delivery of drug to the patient. No portion of the DAL is in contact with the delivery mechanism contained inside the Diskus. Neither electrical nor mechanical failure of the DAL could have any effect on drug delivery; thus, use of the DAL does not pose any conceivable risk for the patient.

Detection of malfunction and tampering

The Diskus mechanical dose counter allows DAL malfunctions, or deliberate attempts to interfere with its operation, to be detected. The miscount is directly given by the discrepancy between the number of doses recorded by the mechanical counter and the number of doses recorded by the DAL. Dose dumping is detected by observing a large number of doses over a short time, particularly when there is not sufficient time between doses to allow inhalation.

Limitations and future work

Although the DAL performed flawlessly in our initial tests, we are cognizant that unanticipated problems might occur when the DAL units are in the hands of patients. In the next round of clinical testing, we will determine whether the DAL performs as well after it has been subjected to more severe and frequent environmental conditions such as extremes of temperature, being dropped, being placed under weighty objects, and so forth. In addition, we will need an extended testing period to assess battery life properly.

We anticipate further reductions in the size of the DAL module. Although we used miniature, surface-mount electronic components in the DAL module, to make

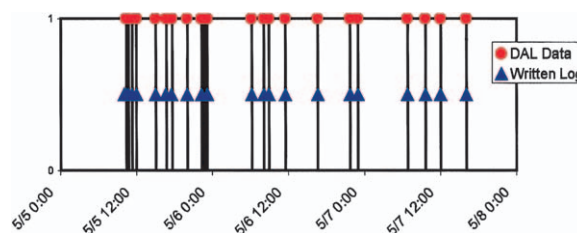


FIG 5. System test. Twenty-two simulated doses were delivered over 3 days, with the actual dose times recorded in a paper log. Shown *above* are the dose events expressed in the form of a time line. There is consistent agreement between the DAL record (red circles) and the paper log (blue triangles).

construction easier we chose not to use the smallest components available for the initial version of the DAL. Likewise, we expect that some improvements in battery life will become possible as lower-power components become available and we substitute them for the higher-power versions in the current design.

Generalizability

Finally, we have developed a monitor for only 1 specific DPI, the Advair Diskus. The device design takes advantage of the drug delivery lever that forms part of the Diskus mechanism. The use of a similar magnetic sensing approach may also be possible with other DPI devices, including DPI for conditions other than asthma, depending on the particular construction of the DPI. In particular, it appears that adapting the DAL mechanism for use with the Pulmicort Tubuhaler and Symbicort Tubuhaler (AstraZeneca, London, United Kingdom) DPIs is feasible, although we have not yet tried this. The Tubuhaler has a rotating grip that advances the medication into the mouthpiece, “clicking” into position when fully advanced. The most straightforward adaptation would be to place the data collection module on the grip, with the magnet on the body of the Tubuhaler.

Cost and clinical feasibility

The simplicity of construction and operation of the DAL helps to make the clinical dissemination of this technology feasible. Device fabrication is relatively simple because there are no mechanical mechanisms or moving parts to produce. The cost of parts for the data collection module is less than \$10; moreover, the data collection module is reusable. In our initial version of the DAL, the module is attached to the Diskus with hot-melt glue. Thus, the module is detached by heating and can be reattached to another Diskus. A commercial version of the device might use an attachment system with a mounting plate and double-sided tape to allow the module to be attached in a few seconds and then detached easily with a demounting tool.

From the clinician’s standpoint, use of the DAL is quite simple. To start logging, the clinician presses the “set time” button, types in the patient’s identification, and then

hits the “start” button on the program interface. To upload data, the clinician simply presses the “upload” button, followed by “save file.” This simple, rapid operation makes the acquisition of adherence data a practical undertaking within a busy clinical practice.

CONCLUSION

We have developed a device to record the use of the Advair Diskus DPI, a technology that should be adaptable to other DPIs. This device should enable researchers and clinicians to monitor adherence to this new formulation of an important asthma medication in the same way that adherence monitors have been used previously with metered-dose inhalers.

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