Research Report

Long-Term Stability of the Electronic Sensor Component of a Digital Pill System in Real-World Storage Settings

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Abstract

Background: Digital pill systems comprise an ingestible sensor integrated into a gelatin capsule that overencapsulates medication allowing real-time measures of medication ingestion. These systems may improve the manner in which medication adherence can be assessed and supported. **Objective:** In this investigation, we tested the durability of the ingestible sensor as part of a clinical trial to measure the feasibility and acceptability of the system to measure adherence to once daily tenofovir disoproxil fumarate/emtricitabine (NCT03842436). **Methods:** Digital pills not dispensed during the study were stored in a pharmacy. Seventeen sensors were selected from digital pills stored for at least 12 months and activated in a simulated gastric environment. A radiofrequency spectrum analyzer and the reader device used in the clinical trial to capture ingestion events were used to measure activation of emitters. A passing evaluation was defined as an energized emitter within 30 minutes of immersion, ability to broadcast a signal for 10 minutes, and successful acquisition by the reader. **Results:** All ingestible sensors passed the stability test. Mean activation time in simulated gastric fluid was 3.33 minutes (SD = 1.47); emitters remained active for a mean of 47.72 minutes (SD = 1.78). These parameters matched guidelines defined in the ID-Cap system requirements for use in patients. **Conclusions:** Ingestible sensor components of the ID-Cap system were therefore stable after long-term storage.

Keywords

stability, digital pill, ingestible sensor

Introduction

Digital pill systems (DPSs) are ingestible electronic devices that enable unobtrusive direct measurement of medication adherence.[1] These systems comprise an ingestible electronic sensor and a wearable receiver device. One available type of DPS consists of an ingestible electronic sensor integrated into a standard gelatin capsule shell and a wearable receiver device (Figure 1).[2] The gelatin capsule overencapsulates the drug with the ingestible sensor, effectively "digitizing" the medication thereby creating a digital pill. Ingestion of this digital pill activates the electronic sensor, which transmits medication ingestion data to a wearable receiver. This receiver transmits adherence data to a cloud-based server, which displays medication ingestion data to patients and clinicians. Direct measures of adherence can then be interpreted by clinicians or patients, and interventions that reinforce medication adherence or address changes in ingestion patterns can be delivered in response to DPS data.[3] Early evidence suggests that DPS are feasible and acceptable to patients and can accurately report medication ingestion events.[4-8] To date, 2 DPSs have been cleared by the US Food and Drug Administration as

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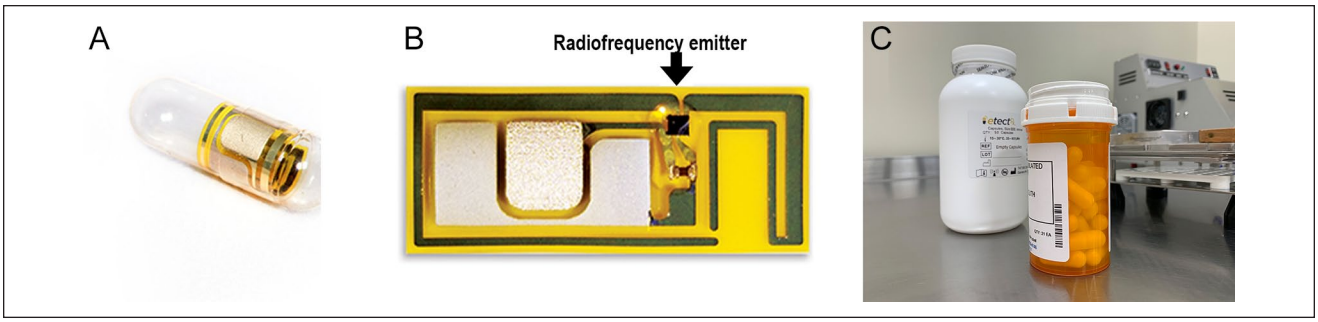

Figure 1. ID-Cap system comprising a standard gelatin capsule with integrated ingestible sensor, for example, ID-Tag (A). This ingestible sensor contains a radiofrequency emitter that is powered using a silver-magnesium battery (B). The final digital pills are dispensed in an ultraviolet light blocking standard medication bottle (C).

ingestible event markers.[9,10] In 2017, the first drug-device combination product consisting of a DPS, aripiprazole with sensor, was approved by the Food and Drug Administration.[11]

An important step in operationalizing DPS to measure medication adherence requires the integration of the digital pill capsule into the pharmacy supply chain. Medications can be overencapsulated by the digital pill capsule using a capsule-filling machine at the pharmacy, pharmaceutical company, or contract manufacturing organization level.[12] For researchers, this overencapsulation process can be completed at an investigational pharmacy level, but this process may be difficult in the United States given regulations on reformulation and repackaging of drug.[13] These digital pills are then dispensed to the patient for use. Previous investigations have demonstrated that the ingestible electronic components of DPS do not interfere with the pharmacokinetics of the overencapsulated drug.[14-16] While hard gelatin capsules have been demonstrated to be stable over long periods of time, the stability and activation of ingestible electronic sensor components of digital pills after filling with the medication dose and long-term storing in commercial dispensing pharmacies remains unknown.[12,17] Understanding the stability of these electronic components, whether they may fail when stored in these conditions for long periods of time, and their general durability can provide guidance to pharmacies around the optimal storage and dispensing strategies for DPS.

In this investigation, we measured the stability of the digital pill and integrated electronic sensor component of a DPS used in a clinical trial measuring adherence to once daily tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) as pre-exposure prophylaxis (PrEP) among men who have sex with men.

Methods

We deployed a DPS (ID-Cap System, etectRx) in a pilot demonstration trial among 15 individuals to measure adherence to once daily tenofovir disoproxil fumarate/emtricitabine as PrEP against HIV infection (NCT:03842436). Digital pills were assembled at a specialty pharmacy (Curant Health) by the pharmacist who placed a single PrEP tablet within each digital pill capsule. Following assembly, PrEP digital pills were dispensed in standard ultraviolet light protected medication bottles with each containing a 30-day supply of once-daily medication. PrEP digital pills were shipped to a research pharmacy associated with a community health center (Fenway Health, Boston, MA) and stored at 15 °C to 25 °C prior to dispensing to study participants. The pharmacy monitored temperature on once daily basis.

At the end of the study period, pill bottles that were not dispensed to study participants due to participant withdrawal and that had been stored in the research pharmacy were returned to the specialty pharmacy. Next, digital pills were visually inspected by a pharmacist outside of the study team. Any defects identified, including blemishes, cracks, or disintegration of gelatin capsules, were logged. Next, digital pills were manually disassembled to remove the active medication (ie, TDF/FTC tablet), and the electronic sensor component within the capsule shell was returned to the original pill bottle and shipped to etectRx stability testing.

Ingestible Sensor Testing Protocol

A random selection of 17 ingestible electronic sensors (ID-Capsules) were chosen from the materials returned from the pharmacy. This subset was selected from ID-Capsules stored in the research pharmacy for at least 12 months. Each of these ingestible sensors were individually tested using the following procedure. A glass 500 mL beaker with 500 mL of HCl solution at 37.5 °C at a pH of 2.0 ± 0.1 to simulate gastric fluid was prepared as a test vessel. A magnetic stir rod at 50 rotations per minute was added to ensure consistent agitation of the mixture. An ID-Capsule was placed into the center of the water bath and fully immersed. A radiofrequency spectrum analyzer (Keysight Technologies) was used to detect the presence of the radiofrequency signal from the ingestible sensor. Additionally, a

Table 1. Testing Dynamics of Selected ID-Tags.

ID-Tag	Time to start (minutes)	Total run time (minutes)	Reader acquisition
1	2.35	50.22	Yes
2	4.58	50.02	Yes
3	1.50	37.72	Yes
4	5.40	40.08	Yes
5	2.68	45.38	Yes
6	5.42	44.43	Yes
7	4.67	48.55	Yes
8	2.17	50.88	Yes
9	4.72	59.67	Yes
10	2.05	48.90	Yes
11	5.25	43.68	Yes
12	2.10	40.90	Yes
13	4.13	54.25	Yes
14	2.82	61.93	Yes
15	3.95	53.65	Yes
16	1.65	41.28	Yes
17	1.42	39.67	Yes
Mean ± SD	3.33 ± 1.47	47.72 ± 7.02	

wearable reader of the model used in the pilot demonstration trial was placed less than 1 m away from the water bath. Successful acquisition of radiofrequency signal by the reader was demonstrated by a simulated recorded ingestion on a paired smartphone app. A passing evaluation on the performance test was defined as the activation of the ID-Tag within 30 minutes of immersion into the water bath, ability to broadcast for at least 10 minutes, and successful acquisition of the radiofrequency signal by the reader. Finally, we measured the total run time (time from activation of sensor to cessation of the signal) for each ID-Tag.

Data Analysis

We calculated descriptive statistics on the frequency of defects recorded during visual inspection of digital pills. Mean time with standard deviation was calculated for the time to activate ID-Tags and for the duration of the read time.

Results

During the study period, we recovered 90 PrEP digital pills that had not been dispensed to study participants. The returned digital pills were stored in a controlled environment in the research pharmacy for 400 days. On visual inspection, none of digital pills were noted to have damage. None of the ID-Tags were found to have physical damage on visual inspection.

Seventeen ID-Capsules were selected for testing (Table 1). The 17 ID-Capsules were stored in the research pharmacy for 400 days. These ID-Capsules were manufactured by etectRx 2 months prior to the start of the pilot demonstration trial and were within their labeled shelf-life for the product. Using the ingestible sensor testing protocol, the mean start time for ID-Tags was 3.33 ± 1.47 minutes. ID-Tags actively broadcasted within device specifications for a mean of 47.72 ± 7.02 minutes, similar to their preprogrammed setting prior to initial integration in the gelatin capsule shell and distribution. Based on standards set within the ID-Cap System, ID-Tag start time occurred 18 standard deviations below the maximum allowed start time of 30 minutes, and 5.4 standard deviations over the minimum run time of 10 minutes.

Discussion

In the implementation of DPS to measure adherence, defining the stability of electronic components of the digital pill will help develop guidelines for dispensing pharmacies to ensure safe, widespread use of these systems in research settings and routine clinical practice. Unlike other hard gelatin capsule dosage forms containing only pharmaceutical components, the integration of an electronic sensor within the digital pill creates concerns leading to the safe storage of these systems and maximal useable lifespan.[12] This investigation demonstrates that the integrity of the electronic components of the digital pill are stable for over 12 months in real-world storage environments and usual handling procedures. The implications of this investigation are that the addition of an ingestible electronic sensor to a standard hard gelatin capsule in the form of a DPS should not change storage recommendations for pharmacies.

Researchers and clinicians who wish to use DPS to objectively measure adherence or medication ingestion

patterns will likely need to collaborate with a pharmacy, pharmaceutical manufacturer, or contract development and manufacturing organization to assemble and dispense digital pills.[12,18] The DPS manufacturer ships empty gelatin capsules with electronic components already integrated in a tentatively joined state similar to how other bulk gelatin capsule shells are supplied. The final step to assembly of the digital pill is overencapsulation of the desired drug, which can be achieved by a pharmacy or at the source of drug manufacturing at a pharmaceutical company. Our investigation suggests that these assembled digital pills can be stored at room temperature similar to standard hard gelatin capsule formulations. Additionally, the stability of the electronic components of the digital pill suggests that long-term storage of digital pills does not affect their ability to report ingestion data. Importantly, our investigation demonstrates that not only is the ingestible sensor stable in real-world storage environments, but transmission frequencies of the ingestible sensor remain stable over time. This is important because it indicates that the wearable reader device that patients must use to record ingestion events does not need adjustment to account for the age of digital pills dispensed.

Digital pills do not require special storage instruction unless dictated by the drug contained within them. This study suggests that researchers, pharmacists, or pharmaceutical manufacturers could purchase digital pills in bulk and store them at room temperature prior to overencapsulating the desired drug in quantities necessary for dispensing or distribution. This implies that bulk ordering and storage at a central facility will not change the effectiveness of digital pills. The ability to purchase digital pills in bulk may provide economy of scale across the supply chain and potentially improve the adoptability of DPS in the future. From the perspective of ingestible sensor stability, dynamic dispensing techniques such as on-demand overencapsulation at local pharmacies at the request of a patient wishing to use a DPS, or overencapsulation for a new, short-term medication as prescribed by a physician or researcher are feasible and will not require special storage by a patient. Additionally, varying dispensing techniques for digital pills will not impact the ability of ingestible sensors to transmit data; for long-term chronic disease medications like antihypertensives, oral antidiabetic agents, or antiretroviral agents for which up to a 3-month supply will be dispensed at a time, DPS can be incorporated into these dispensation patterns without concerns for impacting the performance of the ingestible sensor.

This investigation has several limitations. First, this study was conducted at a community health center with a strong research infrastructure including an investigational drug pharmacy, which permitted climate-controlled storage and quality assurance of digital pills during the course of drug receipt and dispensation to study participants. Stability and storage among other pharmacies may vary depending on available resources. Second, we randomly selected a subset of ingestible sensor tags from the final group of digital pills that were stored in the pharmacy. Although all digital pills including ingestible sensor tags were inspected at the end of the study, there may be subtle damage to these components that was not detected. Third, while we tested activation of the ingestible sensor using a static reader device, acquisition of the radiofrequency signal in the real world may be confounded by the ability of individuals to operate the DPS; these considerations are currently being investigated in the parent clinical trial, NCT03842426.

Conclusion

Ingestible sensor components of a DPS deployed in the real-world are stable over 1 year and continue to reliably activate and emit a radiofrequency signal in the preprogrammed range. They are therefore unlikely to be affected by ambient conditions in normal storage conditions. Future studies to demonstrate durability in diverse clinical settings are required.

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: SLB and EB are employees of eTectRx Inc. The remaining authors have no conflicts of interest to disclose.

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