Drug Delivery Drone

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Abstract- *This study investigates the effects of drone transport on drug quality. The effects of temperature and vibration on insulin were investigated using pharmacopoeia methods, modeling important process parameters of drone flight. The drug Actrapid (3.5 mg / mL of insulin) sparked a quad-rotor drone. Insulin was stored between 30 minutes to 40 ° C and passed for the vibrational pharmacopoeia test (0–40 Hz, 25 LS C, 30 minutes). Dynamic light scattering identified active tetrameric and hexameric types of insulin post test. The frequency of vibration during the drone flight was between 0.1 to 3.4 Hz. There was no evidence that insulin accumulated after drone transport. The difference between the UV absorption readings between the flood act ctrapid and the controls was not negligible (P = 0.89). Drone transport showed no adverse effects on insulin. This study provides evidence that drone transport of medicinal products containing insulin is possible. The authors recommend that five tests be implemented when considering the delivery of drones. These tests will have to determine the safe flight time and range, the quality of the drug post flight, the onboard conditions experienced by the drug, the safety of the drone supply chain and the impact of the drone failure on both the drone and the environment.*

Keywords- drug delivery; Quality of insulin drugs; Drug stability; Drone delivery; Healthcare; Quality by design

I. INTRODUCTION

Unmanned aerial vehicles have historically been used exclusively by the military. Currently, the use of remotely operated aircraft systems (RPAS) and small drones to carry out civilian tasks has increased, such as support for search and rescue operations [2], weather and traffic flow distribution, and cargo. Delivery.[4,6] and certainly as a platform for aerial photography. Drones are being used as a result of climate change; A good example of this is in agriculture, where efficiency can be given by using drones to spray fields and to find a pattern of crop growth [1].

However, drone development is one of the most exciting areas of healthcare. Such applications include urgently needed medicines, vaccines [7], blood [3] and other medical supplies [10] in remote areas. Supply challenges are often caused by poor transport networks, extreme weather conditions, natural disasters or urban traffic fears. [11] Drones can be the solution to such problems. An example of this is the distribution of medical supplies from Wise County Regional Airport to a clinic in rural Virginia. With the help of the drone, the total travel miles have been reduced from 0 minutes [12]. The United Parcel Service and Zipline are working on a drone network to allow delivery of 50–150 blood and vaccines per day to 20 clinics in remote areas of Africa. California-based drone company Maternet has delivered drugs using automatic drones of up to 2 kg in Haiti []] and Dominican Republic, Lesotho, Bhutan [2], and remote areas of Papua New Guinea and Switzerland. , Which flew 10 km in 18 minutes [12]. After testing in Lesotho, the Maternet estimated that it would cost $ 900,000 to operate 50 base stations and 150 drones (24 cents / flight) in the capital Meroso, which could be more efficient than road construction (of construction Estimated cost 2 km one-lane road = $ 1 million) [2]. In Germany, three generations of DHL parcel-powered parcelcopters to send Jews (a sea island 12 km off the North Sea coast) to Bonn (1 km) to send blood samples, drugs and other immediate supplies, respectively, across the Rhine. Was tested to do. Germany) [7] And in January-March, an immediate supply of 111330 parcels (two kilograms each) was required between automated airports at Ritim Winkle and Winkelmuzulam (two Bavarian Alpine villages), reducing travel time by 0 minutes. done. In winter it is eight minutes [12].

In terms of health, timely delivery of drugs, vaccines and blood is important. [12] Drones can potentially overcome logistic challenges because they do not have traffic delays [113] and, importantly, they can reach areas where there are not enough roads. However, drones are only practical for delivery of fragile drugs, blood [14] and clinical clinical laboratory samples [1], as long as they do not adversely affect the quality of the products transported. We do. So drones should be tested as a novel method for drug transport to have an impact on drug quality.

In the United Kingdom, Nesta's Flying High report reported in July 2018 that drone delivery [5] has the potential to flourish. The Flying High Challenge investigated the use of drones in urban areas and assessed the technical and economic feasibility of providing blood samples or medical supplies to hospitals (St and St. Thomas'). Several challenges were identified, in particular, laws requiring aerial drones flying in sight [18,19]. In addition to such regulatory and security issues, drones show some technical limitations battery life,

payload capacity, and maximum attractive distance [12]. In addition, the misuse of drones to deliver illegal drugs to prisons reduced the general public's trust and this technique was adopted [12,20]. Critically, however, the report did not provide any information about the quality of drone-assisted drugs, which underscores significant gaps in knowledge. Few pilot studies have been conducted about the supply of drones in remote areas, but no attention has been paid to the effect of flight conditions on the quality of drugs delivered by drones. Therefore, the feasibility of administering a drug that is highly sensitive to the environment has been studied in this study.
Current unmanned aerial vehicles (UAS) or drones can usually be classified into fixed-wing or rotary-wing aircraft. Fixed-wing UASs are more efficient, have longer life and higher payloads; However, rotary-wing drones take flight and land vertically with the ability to fly during flight. While rotor-based drones are more applicable to drone drone delivery in urban conditions, rural areas benefit from a greater range associated with fixed wing aircraft. Udroy and Blaze (201) have incorporated tilting wing technology and have made a compelling case for the design of value take-off and landing (VTOL) drones to combine the benefits of rotors and fixed-wing aircraft. The equally important process parameters related to flight for all drone configurations affect the stability of the drugs transported by this mechanism.

Insulin was chosen as a model drug in this study as it is one of the most important drugs of life for the treatment of type 1 diabetes [21]. In addition, insulin is a sensitive peptide-based drug, easily exposed to environmental stresses [22] such as high temperature and vibration / agitation. Changes in the structure of insulin will affect its biological efficiency [22]. This study underscores the importance of maintaining insulin quality during drone transport. Any compromise in drug quality can be detrimental to the health and well-being of the patient.

The aim of our study is to investigate the effect of drone transport on the form of human insulin used by diabetic patients. We opted for a pharmaceutical product, Actrapid, and mixed the glass vials with the original packaged product into a cardboard box by small, commercially available drones.

Under the design, the QBD, Framework, (International Council for Harmonization, Q8 [2], a set of critical quality attributes (CQA) has been established to ensure the quality, safety, and efficacy of the patient's medication. Critical content characteristics (CMA) represent a set of properties of the input material to ensure the desired quality of the output material that must be within range. In the study, we have selected the formation of irreversible groups as indicators of insulin instability [2]. Analyst-grade insulin was used for the development and standardization of stability-signaling tests applied in this study. Critical Procedure The set of parameters (CPP), whose variability affects the CQA, can be monitored or controlled to ensure that the desired quality Manufactured by Rkriya. In this study, as well as the parameters of temperature and vibration of the primary important process of interest selected air pressure and relative humidity (RH%) were Table 1.

Table 1. Important process parameters and critical material properties for drone blown insulin.

	Test Scenario	**Parameter**	**Conditions**	**Time Course**
CPP process parameter	Lab stresstest	Temperature	−20 . . . 100 °C	24 hours, 30 minutes
	Lab stresstest	Vibration	3–40 Hz	30 minutes
	Drone flight	Duration, pressure, RH%	Ambient	9 ± 2 minutes
	Parameter	**Measurement**	**British Pharmacopoeia (BP) Method [24]**	
CMA material attribute	Aggregation	Clarity (turbidity)	Visual inspection, UV/Vis spectroscopy	
	Aggregation	Particle size (diameter)	Dynamic light scattering	

To date, there has been no published work on the effect of drone delivery on insulin quality. Obtaining this information will help determine the feasibility of drone transport of highly sensitive drugs.

II. MATERIALS AND METHODS

The methods chosen for this study were first run qualitatively by pharmacopoeia and drug stability [23,24] was investigated by a design framework used by the pharmaceutical industry and the pharmaceutical industry. When drones applied these methods to fly insulin, five studies emerged from our study. The first three tests, which address flight time, drug quality, and ship condition, were performed using the following methods. The safety of the supply chain and the consequences of the failure of drones will be studied in subsequent studies.

Stress Testing

Temperature

The glass vial (7 mL) was filled with 0.2 mL human insulin solution (10 mg / mL, Sigma-Alderic I 9278) and stored for 24 hours. Storage temperatures from 20 (C (freezer), 4 to C (control, freeze), 25 to C (thermostatically controlled chamber, memoratummomontrol, relative humidity 60%), 40 to C (thermostatically controlled chamber, ordnance 75)%) And 65) C (GenLab E3 dry cabinet, temperature measured by

standard thermocol) and 100 ° C (pixel) tone oven thermometer measured temperature). After 24 hours, the samples were diluted to 0.2 mg / mL using ultra-pure water for analysis. The tests were performed using equivalent concentrations of a drug (10 mg / mL Sigma-Ledleric sample diluted with ultra-pure water) diluted with 10 mL 3.5 mg / mL and stored at, 20, C, 4 to C, 25 C. I went. And 40 30 C for 30 minutes.

The vibration

A vortex mixer was used to mimic the range of vibrations a drone can experience during launch, flight, and landing. The vibration generated at each movement frequency of the vortex mixer (MS1 MiniShacker, IKA) was measured using a vibrochecker (ACE Stoßdßmpfer GmbH) to establish a relationship between vibration and movement frequency.
Glass jars (7 mL) were filled with insulin samples (5 mL, 0.5 mg / mL), diluted to 10 mg / mL with ultra-pure water and placed on a vortex mixer for agitation (25 30 C 30 minutes). Speeding speeds were 200 rpm (3 Hz), 1400 (23 Hz) and 2400 rpm (40 Hz) with the corresponding versions. A control (0 Hz) was made for comparison under similar atmospheric conditions [25]. After 30 minutes, the samples were analyzed. The tests were repeated with a concentration equal to 10 mL of drug 3.5 mg / mL insulin.

Assessment of degree of opacity by visual inspection and UV spectrophotometry

Insulin opacities were compared with a freshly prepared reference suspension (British Pharmacopoeia [224] and Supplementary Material, S1), using a black background and certified laboratory lighting [26]. The rate of anemia was 35050 nm using a UV / Vis spectrophotometer (using Perkin Elmer, Lambda) as an ultra-pure water vacuum. Reference suspension I - IV and insulin samples were recorded in triplicate of absorbent readings for the samples after each stress test and their average was increased. The results obtained from visual inspection were compared with the instrumental method (absorbance at 350 nm).

Dynamic Light Scattering (DLS) Particle Size Analysis

Large amounts of insulin were removed from the capsule after each stress test. The results show that, prior to analysis, the samples were filtered (Fisherbrand, PES 0.45 err m) to avoid misintegrating effects caused by the dispersion of large range particles, for example dust particles [2, 2]. Measurements were performed in 2 mL semi-microscope visible cuvettes at a temperature of 25 ° C using a Zetasizer Nano ZS (Material on Materials). Size distribution curve obtained.

Drone Test

Commercially available drones (DJI Mavic Air, 430 g, 168 × 184 × 64 mm when unveiled) [228] were used. It was powered by a 2970 mAh lithium polymer battery [2] and was controlled using a remote controller connected to a smartphone application (DJI Go 4, iOS iPhone 7). The Mavic air drone weighs 430 grams. However, no data were provided regarding maximum take off or payload weight. Thus, a set of experiments failed to determine a safe flight time as a function of load, with the maximum test being just under 200 grams. This primary indoor and outdoor test with a test payload was used to define the test flight protocol used in the study with a flight time of 0.8190.18 km with a flight time of 9 minutes 2 minutes. During testing, the game mode was avoided, and the drone was operated using its standard settings. The quad drone landed vertically from a height of 10 m and then rotated around a fixed point with a radius of 5 m and a constant speed of 1.5 m / s.

Drone flight involving pharmaceutical insulin

Four doses of insulin glass (Aktripid mg. Mg mg / ml, Novo Nordisk) were brought to the flight site (The Griffin Sports Ground). The glass bucket (23.8 grams each) in its original cardboard packaging was transported to the flight site in an insulated container within an hour. The vials were left in cardboard packaging for flight testing. One coupe served as a control, while the remaining fare flew from 0.81 to 0.88 km 9 92 minutes. Polypropylene-based sealing tape was used to fix the original box packaging of acrylic glass on top of the drone. Flight protocol was followed and the drone was kept under control. The ambient temperature is 1 to 0 during C during the experimental window. Other parameters include wind speed 2 mph, relative humidity 93% and air pressure 1021–1010 MB [29]. After the flight, the capsule was brought back to the laboratory for analysis. Flight vibrations were measured using the same Vibrocatur app described in Section 2.2.2. In this experiment, the iPhone was fixed with the same polypropylene-based sealing tape on top of the drone used to carry aprotopid samples. Vibrations at take-off, flight, and landing were measured following the mission used for anthracite samples.

Statistical analysis

Statistical analysis was performed using Excel 2010. The two-tailed non-tailed test was used to determine

statistically significant differences, assuming equal differences. P <0.05 was considered significant.

Initial payload and flight time test

Initial tests were conducted to provide guidance for maximum payload, range, and flight time and formed the basis of the test flight protocol used in this study. Sight was always monitored. Using polypropylene-based sealing tape. The masses of G G (low), .21.2 G (medium) and 194.6.6 G (high) were safely attached to the drone. The battery level was set as> 30% safe working limit. Before each payload test, the battery was fully charged (100%).

For initial indoor testing, loaded drones were launched and allowed to hover at a height of 1.2 meters. The time required to lower the battery level was reported to be 100% to 30%. For initial field test (0 ◦ speed C wind speed 1 hour m per hour, relative humidity 100–100%, 10, test 26 MBR)

The loaded drone climbed to a height of 10 m at test height and was asked to revolve around a fixed pole (radius = 5 m, constant speed 1.5 m / s) [14]. As soon as the battery level reached 30%, the drone was instructed to step down. The time taken to lower the battery level was reported. These tests were performed to determine the edge of failure in battery life.

As the load increased, the time required to reach 30% of the battery level decreased rapidly (Fig. 6). When moving indoors with high loads, the load was reduced by 40% compared to no load, and a warning was shown indicating maximum motor speed before the battery level reached 30%. Therefore, the maximum payload for safe use was set to be <200 g. When traveling indoors, the battery life was longer than when traveling indoors, but the difference was lower for medium (P = 0.07) and high mass (P = 0.08) loads but lower for mass and load. Without (P <0.05).

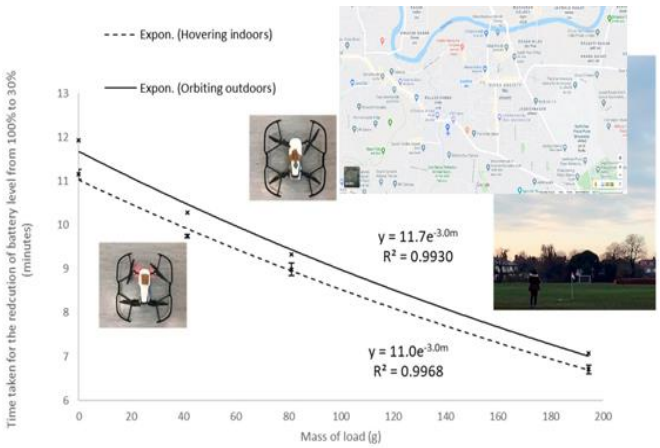

Figure 6. Time taken to reduce the battery level from 100% to 30% (min) (large load in kg). Exponential regression to rotate the drone indoors: time = 11.0 e - 3.0 m (r 2 = 0.9968). The data points shown are the mean of the n = 3 measurements, indicating the standard deviation of these values along with the error values. Exponential regression for outdoor drones: time = 11.7 e - 3.0 m (r 2 = 0.9930). The data points shown are n = 1. Performance of drone flying at altitude outside the house = 10 m, radius = m, speed = 1. M / s at Griffin Sports Ground, Flight Site, London, SE 21 AL AL. United Kingdom.

Drone Flight Involving Pharmaceutical Insulin (Actrapid)

All three ectropid samples were swept at 0.81 km at 0.18 km and their original packaging was clear and the formation of a minor bubble led to a BP turbidity test (Figure 7B, C). There was a significant difference in absorption between the control (flight site) and flying air samples (p = 0.54) as well as the control (flight site) and control (fridge) (p = 0.89 absorbed). In DLS measurements, a main peak below 10 nm (d = 4.19.4.85 nm) was observed for all controls and flight samples (Figure 7D) indicating the presence of insulin tetramer. Samples were exposed prior to analysis with analytical grade insulin to avoid any peaks in the 1000 nm size induced by shear forces related to the filtration process or method. However, low intensity peaks above 1000 nm were observed, which were stable in all samples and controls, thus they were originally and did not form as a result of drone transport. All samples passed pharmacopoeia stability tests, thus the quality of insulin, or in particular the drug product, acetropidmg .. mg / ml was not affected by the launch of the drone.

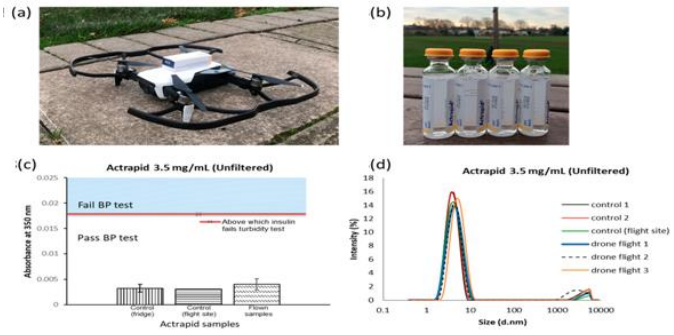

Figure 7. (a) Acetrapide in its original packaging was securely attached to mavic air. (B) Presence of ectrapids after flight (9, 2 min, n = 3 left controls). (C) The action of absorbing 350 350 nm on an average is carried out not on the flight of N scrapid but on the flight. Data points shown are flow samples for n = 2 measurement controls (fridges), n = 1 measurement controls (flight site) and n = 3 measurements, with error bars indicating standard deviations at these values to the data points. have been shown. (D) Intensity (%) was plotted against

particle diameter, distributed in nm (DMN) with three flying ectropid samples, one control (brought to the flight site) and two controls (from the freezer).

III. CONCLUSION

In recent years, there has been increased interest in supplying drones to remote areas. However, little has been said about the feasibility and effects of drone delivery on drugs, so this study is needed. Tests on human insulin have shown that insulin quality is maintained after 30 minutes of drone delivery (temperature from -20 to +40 ° C, vibration frequency 0–40 Hz). There was no adverse effect after drone transport Flight after little bubble formation on uprights. To the best of the author's knowledge, this is the first successful test of drone-flying insulin quality, proving that drone transport of insulin is possible in terms of drug stability and drug quality. Therefore, this research serves as a model for future studies investigating other types of drugs, environmental conditions, or different drones.

IV. RESULTS AND RECOMMENDATIONS

The authors recommend that the next five trials be implemented when considering drug delivery. (1) Keeping in mind the total weight of medicines required for transportation, it is necessary to set safe flight times and safe limits. For the selection of the most suitable drone, it is necessary to examine the edge of failure keeping in mind the possible variation in environmental conditions. (2) Pharmaceutical quality check after delivery is necessary for the drug product to be stable. Theoretically it should be non-destructive, easy to perform and, if possible, based on pharmacopoeia recommendations, and based on QBD considerations, such as significant physical quality properties. ()) According to the Board's rules for monitoring the environment of drugs during drone flight, the manufacturer's recommendations should be ignored. Critical process parameters such as temperature, pressure, vibration frequency and g-force must be monitored. ()) Safety of drugs should be ensured in the supply chain of drones, for example on-board anti-tamper monitoring and receiver authentication. ()) To understand the consequences of drone failure during flight, it is necessary to consider the effects on both medicine and the environment. The work presented here has led to the successful completion of the first three of these tests, and future work and the previous two developments together with drone manufacturers will be allowed.

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