Quantifying the Effects of Vibration on Medicines in Transit Caused by Fixed-Wing and Multi-Copter Drones

Andrew Oakey 1,*, Tim Waters 2, Wanqing Zhu 3, Paul G. Royall 3, Tom Cherrett 1, Patrick Courtney 4, Dennis Majoe 5 and Nickolay Jelev 6

1 Transportation Research Group, University of Southampton, Southampton SO17 1BJ, UK; T.J.Cherrett@soton.ac.uk
2 Institute of Sound and Vibration Research, University of Southampton, Southampton SO17 1BJ, UK; t.p.waters@soton.ac.uk
3 Department of Pharmacy, Faculty of Life Sciences and Medicine, Institute of Pharmaceutical Science, King’s College London, London SE1 9NH, UK; wanqing.zhu@kcl.ac.uk (W.Z.); paul.royall@kcl.ac.uk (P.G.R.)
4 tec-connection, D78467 Konstanz, Germany; patrick.courtney@tec-connection.com
5 Motion Robotics, Southampton SO30 3DS, UK; dennis.majoe@motion-robotics.co.uk
6 Computational Engineering and Design Research Group, University of Southampton, Southampton SO17 1BJ, UK; n.d.jelev@soton.ac.uk
* Correspondence: a.oakey@soton.ac.uk

Abstract: The concept of transporting medical products by drone is gaining a lot of interest amongst the medical and logistics communities. Such innovation has generated several questions, a key one being the potential effects of flight on the stability of medical products. The aims of this study were to quantify the vibration present within drone flight, study its effect on the quality of the medical insulin through live flight trials, and compare the effects of vibration from drone flight with traditional road transport. Three trials took place in which insulin ampoules and mock blood stocks were transported to site and flown using industry standard packaging by a fixed-wing or a multi-copter drone. Triaxial vibration measurements were acquired, both in-flight and during road transit, from which overall levels and frequency spectra were derived. British Pharmacopeia quality tests were undertaken in which the UV spectra of the flown insulin samples were compared to controls of known turbidity. In-flight vibration levels in both the drone types exceeded road induced levels by up to a factor of three, and predominant vibration occurred at significantly higher frequencies. Flown samples gave clear insulin solutions that met the British Pharmacopoeia specification, and no aggregation of insulin was detected.

Keywords: drone; UAV; vibration; insulin; medicine; logistics; healthcare; dangerous goods; blood

1. Introduction

Unmanned Aerial Vehicles (referred to as ‘drones’ in this paper) are increasingly being seen as a potential new freight mode to assist health care service providers with the collection of patient diagnostic samples and the delivery of blood stocks and pharmacy to clinics and hospitals [1]. With business-as-usual logistics practices in this domain centred around van fleets, drones provide several potential benefits in terms of speed of carriage, reduced carbon footprint and the scope to respond more dynamically in a more patient-centric care structure [2,3]. This latter point is particularly relevant in relation to aseptic medicines which are often bespoke-made for the patient, and have to be administered within five hours of manufacture, a process which often leads to the treatment schedule being dictated by the capabilities of the logistics system.

The market for drone medical logistics is significant and will increase by 25% between 2019 and 2025 to a predicted USD 400 million [4,5]. More recently, the COVID-19 pandemic has brought into sharp focus the potential value of drones in delivering medical supplies when quarantine regulations and social distancing policies limit the efficiency of traditional
logistics systems [6]. Several companies have recently made advances in this domain, running a mixture of commercial services and trials to better understand the role drones could play in future medical logistics supply chains (Table 1).

Drone companies not only have to have airworthiness certification to fly but also, in the case of some medical products, dangerous goods approval for carriage. Secondary to this, and often overlooked, is the need to satisfy the health care products regulatory bodies that their platforms will be fit for purpose and through their operation, will not cause any adverse effects on the medical products being carried [7]. In terms of the United Kingdom, the Medical Healthcare Products Regulatory Agency (MHRA) would want to see such guarantees, and it is this area of research that is not currently well understood.

**Table 1.** Ongoing medical drone delivery projects. Italic lines indicate the drones used in this research. VTOL = Vertical take-off/landing, GIZ = (Gesellschaft für Internationale Zusammenarbeit). (Note: rows in italics denote studies conducted as part of this research) [8–23].

| Location            | Start Date | Company Name(s) | Drone Type | Item Type | Reported Flight Duration * | Reported Distance (One-Way) * | Reported Max. Payload * | Cargo Protection (s)                                                                 |
|---------------------|------------|-----------------|------------|-----------|---------------------------|-------------------------------|------------------------|-----------------------------------------------------------------------------------|
| Rural Virginia      | July 2015  | Flirtey         | Multi-copter Electric | Drug      | 3 min                     | Not Mentioned                 | 5.5 kg                 | Anti-drone collision system (NASA), parachute landing                             |
| Rural Madagascar    | July 2016  | Vayu            | VTOL Fixed-wing Electric | Blood transfusion units and patient sample test specimens | Not Mentioned | Up to 60 km                | 2 kg                        | Lock                                                                              |
| Rwanda and Ghana    | October 2016 | Zipline         | Fixed-wing Electric | Blood transfusion units | 30 min                     | 80 km                        | 1.8 kg (3 units) | Redundant systems: parachute landing, communication and navigation                |
| Urban Switzerland   | March 2017 | Swiss Post and Matternet | Multi-copter Electric | Blood, test specimens | 10 min                     | 3 km                         | 2 kg                        | QR code for opening the case, parachute landing                                  |
| Tanzania            | October 2018 | DHL, GIZ, GIZ and Wingcopter | VTOL Fixed-wing Electric | Snake venom antiserum, etc. | 40 min                     | 60 km                        | 6 kg                        | Thermally insulated box                                                            |
| Vanuatu             | December 2018 | Swoop Aero and Wingcopter | VTOL Fixed-wing Electric | Vaccines | 30 min                     | 45 km                        | 6 kg                        | Teardrop shape, remote control dropping, ice, temperature sensor                 |
| North Carolina, USA | December 2019 | UPS and Matternet (WakeMed) | Multi-copter Electric | Specimens | 5–10 min | Up to 12.5 miles (~20 km)—within hospital site | Up to 5 lb. (~2 kg) | Cable-controlled (20 ft/6 m) dropping, Authentication system (e.g., ID badge) |
| North Carolina, USA | October 2019 | UPS and Matternet (CVS Pharmacy) | Multi-copter Electric | Prescription only medicine | 5–10 min | Up to 12.5 miles (~20 km)—Pharmacy to patient’s home | Up to 5 lb. (~2 kg) | Cable-controlled (20 ft/6 m) dropping, Authentication system (e.g., ID badge) |
Table 1. Cont.

| Location                      | Start Date | Company Name(s)         | Drone Type       | Item Type                          | Reported Flight Duration * | Reported Distance (One-Way) * | Reported Max. Payload * | Cargo Protection (s) |
|-------------------------------|------------|-------------------------|------------------|-----------------------------------|----------------------------|-----------------------------|------------------------|----------------------|
| Bahamas, Puerto Rico, USA     | July 2020  | Volansi and Merck       | VTOL Fixed-wing Electric | Temperature sensitive medicines   | Not Mentioned              | Up to 50 miles (80 km)      | 4.5 kg                  | Temperature control devices (Details Not Mentioned) |
| Isle of Mull, Rural Scotland  | December 2020 | Skyports, Wingcopter and Soarizon | VTOL Fixed-wing Electric | Medicines, Pathology samples      | 15 min                     | 16 km, Over the Sea         | Not Mentioned          | Not Mentioned         |
| Berlin, Urban Germany (planned) | February 2021 | Matternet               | Multi-copter Electric | Pathology samples                 | Varies by site, Approx. 10 min | About 7 miles (up to 20 km), From hospitals to laboratory | 2 kg                   | Authentication system (e.g., ID badge), temperature controlled payload boxes, parachute |
| Thorny Island, England        | November 2020 | Windracers (ULTRA TDI prototype) | Fixed-wing Petrol | Actrapid (Medical Insulin)        | ~12 min                    | Manoeuvres only (no delivery taking place) | 10–20 kg in tests 100 kg max | Insulated polystyrene and cardboard based packaging/Versapak |
| Cornwall-Isles of Scilly, England | December 2020 | Motion Robotics (Arty) | Multi-copter Electric | Actrapid (Medical Insulin)        | ~20 min total              | ~7 km in tests 20 km max    | ~7 kg in tests 11 kg max | Insulated polystyrene and cardboard based packaging |

* Figures have been reported by their respective authors, however, may not have been independently validated.

Of particular interest is to better understand what adverse effects vibration might have on certain medical products that are potentially susceptible. This paper addresses this area, looking into the current evidence on how vibration from drones affects the carriage of medical products, and quantifying this through live trials using both fixed-wing and multi-copter drones carrying insulin cargoes.

1.1. The Effects of Vibration on Medical Cargoes during Transit

Despite work being undertaken to demonstrate that cold chain temperatures can be adequately maintained during drone flights, little work has seemingly been undertaken to quantify the potential effects of vibration from drone platforms on the stability of medical cargoes [10]. The logistics of sensitive medical goods transportation is not usually a topic of academic research and thus not frequently challenged, but increasingly, a viable role is seen for UAVs to help speed up the process in a more sustainable way compared to the road-based business-as-usual case.

When delivering medicines, the influence of temperature has usually been thoroughly considered [24]. Conditions according to the International Council for Harmonisation [25] are recommended as the basis for stability testing, with the effects of exact temperature and humidity on the properties of drugs examined over different periods before releasing to the market [26]. It is therefore necessary to account for the temperature and humidity conditions imposed on the cargo during transit when stability testing pharmaceutical products [27]. In contrast, published research articles on the effects of vibration are generally only carried out on medicines if problems are likely to occur during administration. This usually concerns low frequency processes centred around stirring or shaking [28].

Insulin is known to be sensitive to vibration, and when transported at therapeutic concentrations, is not regarded as a dangerous good, unlike diagnostic blood samples [29,30]. Insulin therefore offers potential as a candidate biopharmaceutical for the investigation
of drone flight effects on medicine stability. Like blood, this medicine’s stability is governed primarily by physical processes, with aggregation and eventual precipitation during storage central to the loss of efficacy [31].

The mechanism of aggregation and eventual precipitation of human insulin has been simplified in Figure 1. It should be noted that when administered as a subcutaneous depot, small soluble aggregates are exploited within the controlled release mechanism, but during transit and storage, the formation of larger insoluble aggregates or fibrils must be avoided [32]. Their precursors, and the fibrils themselves, are large enough to scatter light, thus turbidity measurement is a pharmacopeial recommended test used for insulin quality control [31].

Figure 1. Schematic display of insulin fibrillation [32].

The presence of an air-water interface contributes to insulin’s sensitivity towards vibration, as this hydrophobic surface stabilizes the intermediates in fibril formation. Rotation and stirring, (used to mimic shaking), at a rate of 160 rpm, has been shown to induce insulin aggregation, but it should be noted that these experiments exposed products to these conditions over several hours [29]. Interestingly, removing the air-water interface by overfilling vials, and thus purging headspace, was key to improving the stability of monoclonal antibody (IgG1) preparations against vibration [33]. More work is required to investigate the effect of shorter exposure periods and the higher frequencies associated with drone propeller operation.

Ohno et al. [34] reported a frequency dependency towards the stability of aqueous insulin solutions where, at a very low stimulation of 0.5 Hz, no loss of stability was seen, however after 24 h of constant vibration at approximately 14 Hz at 37 °C, a significant increase in the turbidity was observed. Drone delivery services are typically of a much shorter duration, but flight times to distant islands, (e.g., isolated communities in the South Pacific) that require larger drones powered by combustion engines, may generate the exposure times reported in the insulin laboratory studies described by Ohno et al. [34].

Rapid acting insulin formulations are used for patients who require an alternative to daily injections, whereby their insulin is delivered by continuous subcutaneous infusion. Thus, any precipitation caused by vibration will not only lower the efficacy of the formulation but also has the potential for blocking the catheters and causing secondary health issues. Kerr et al. [35] conducted a systematic review of 24 studies and found that mechanical agitation, ranging from 35 to 100 oscillations per minute (0.6–1.7 Hz) at 37 °C showed no loss of activity from 2 to 14 days. This further supports the hypothesis that insulin-based medicines are robust towards low-frequency vibrations.

1.2. Packaging and Carriage Requirements Regarding Medical Cargoes during Transit

The carriage of medicines is governed by the EU Good Distribution Practice (GDP) guidelines for medicinal products for human use [36]. These describe the minimum standards that must be met by a wholesale distributor of medical products to ensure that the quality and integrity of medicines is maintained throughout the supply chain journey. The wholesaler is obliged to: (i) protect medicinal products against breakage, adulteration and theft, and to ensure that temperature conditions are maintained within
acceptable limits during transit and; (ii) demonstrate that the medicines have not been exposed to conditions that may compromise their quality and integrity regardless of the mode of transport used. The wholesaler is also required to regularly calibrate any temperature monitoring equipment used with temperature-controlled goods. Of relevance to this research is that there is no official requirement to understand whether the transport mode generates any adverse effects on the integrity of the medical cargo resulting from vibration, nor to monitor vibrations during transit. The key monitoring focus centres around temperature control, but there are other aspects which can affect medicine quality during transit such as humidity, avoidance of light, vibration/shock, and dramatic pressure changes [37].

In terms of carriage and packaging regulations related to medicines, several classifications exist (Table 2).

Table 2. Carriage and packaging regulations related to medicines with illustrative examples [30,38,39].

| Regulation: | Details/Description | Illustrative Examples: |
|------------|--------------------|------------------------|
| ID8000–Y963 | Non-toxic medicines which are treated as consumer commodities. | Aspirin tablets; Adrenaline and Insulin ampoules containing aqueous solutions for injection. |
| UN3248–PI352 Y341 | Liquid medicines which are toxic and flammable and within Class 3 dangerous goods carriage regulations. | Topical sprays—Pain Relief Heat Spray—containing ethyl nicotinate, methyl salicylate, racemic camphor—in denatured ethanol, butane, isobutane, propane—a liquid formulation in a pressurised container. |
| UN1851–PI654 Y641 | Liquid medicines which are toxic and within Class 6.1 dangerous goods carriage regulations. | Hydroxyurea solution for injection. |
| UN3249–PI669 Y644 | Solid medicine which are toxic and come under Class 6.1 dangerous goods carriage regulations. | Azacitidine lyophilized powder and Pentamidine isethionate powder for solution for injection. |

All products under these categories have to be packed according to their specific packing instruction (PI) which usually dictate multi-layer containment (primary receptacle and secondary bagged containment layers) before being placed in a sealed box with a coolant system (if temperature controlled) [30,40]. Temperature monitoring equipment should be placed within the secondary containment layer and may or may not provide live updates during transit.

The packaging group depends on the toxicity of the medical cargo. For example, cytotoxic medicines are strictly controlled when carried by air, with limitations on the volumes per container. Of interest here is the potential susceptibility of cytotoxic medicines to vibration and to what extent different frequencies might affect their stability when transmitted through the packaging layers during different stages of transit. It appears that the current regulations do not specifically cover this area.

1.3. Sources of Vibration Emanating from Drones and Road Transportation

Understanding the sources of vibration emanating from UAVs is very important if the negative effects on medical cargoes are to be successfully mitigated. Generally, aircraft using rotary propulsion systems for vertical take-off record higher levels of vibration compared to their fixed-wing counterparts due to the lift being generated by one or more high-speed rotors being uneven [41]. The core advantages of a multi-rotor UAV over a typical helicopter are their enhanced agility and reliability, with most UAV plat-
forms utilising fixed-pitch propellers which control the flight by changing their individual rotational velocities.

Li et al. [42] measured the triaxial vibration of a T-lion quadcopter during steady-state hover. Strong in-plane vibration was observed at the rotor speed of 50 Hz, and also at 40 Hz due to resonant response of the payload swaying on its mounting. The highest vibration levels occurred above 100 Hz. These were successfully suppressed by mounting the sensor on a vibration isolating gel sheet although the 50 Hz peak was consequently amplified. All of these frequencies are much higher than those featured in literature studies concerning the vibration stability of sensitive medicines [28].

In contrast, cargoes being transported by road going freight vehicles are reported to be exposed to much lower frequency vibration. Chonhenchob et al. [43] used tri-axial accelerometers to measure vibration caused by vertical, lateral and longitudinal movements across five different types of small and medium package delivery vehicles. The lateral and longitudinal levels of vibration recorded across all the delivery vehicles was much lower than in the vertical direction, and the authors suggested that due to the extremely low G\text{rms} levels recorded, damage to the cargoes was considered negligible. The vertical vibration response (1–10 Hz) in the vehicle suspension was found to be higher in interstate articulated truck shipments compared to the other vehicle types. However, higher frequency responses (10–20 Hz), were found to be more severe in the van and small truck.

Using a similar approach with tri-axial accelerometers, Ranathunga et al. [44] evaluated the effects of vibration on the transportation of 128 boxes of tomatoes (3250 kg) using a Mitsubishi Canter FE535B6R truck (5500 kg GVW) over a 68 km road leg between Illukkumbura and Dambulla in Sri Lanka. The accelerometers were mounted in the truck bed and vertically on the cargo to measure vibration horizontally and vertically across the cargo (tomato boxes). The heavily loaded truck induced less vertical acceleration and therefore generated less vibration energy, and the observed damage to the tomatoes was minimal compared to the lightly loaded truck. In this case, vertical acceleration in the frequency range below 10 Hz caused most damage to the cargo. The rear section of the truck’s cargo bay produced a power spectral density (PSD) 10 times higher compared to that recorded towards the front and a greater PSD was also observed in the topmost boxes of stacked cargo, suggesting that those fruit were at risk of greatest damage. The damage caused by vibration on the top layer of the cargo by the rear axle was made considerably worse when travelling over poorly maintained roads, even at lower speeds.

Considering both road vehicles and drones, the learnings from the studies of road transport are not transferrable to drone deliveries, as these quite different systems appear to generate vibrations at distinct ranges of frequencies. In addition, vibration is location dependent on board both groups of vehicles, all of which show the need for more research within this space. From the available literature concerning the generation of vibration and its effect on the stability of medicines, a simple hypothesis is clear, i.e., that the vibrations applied to medical goods transported by drone are different from those generated by road-based transportation, but these are not significant enough to affect the quality of an example biopharmaceutical medicine, namely insulin.

To investigate this hypothesis, the aim of this paper is to determine to what extent vibration emanating from fixed-wing and multi-copter drones might negatively affect the stability of the medical cargoes they carry, focussing on a case study involving insulin. The work also addresses the fundamental question as to whether drone transportation induces any greater vibration issues compared to road-based transportation. The specific experimental objectives are to; (i) measure the vibration environment onboard a fixed-wing and multi-copter drone and subsequent transmission through packaging to a medical product; and (ii) quantify the effects of vibration on cargoes of insulin during a series of routine and severe aerial manoeuvres and compare to the road-based transport situation.
2. Methodology

This research used a series of real-world drone test flights transporting 10 mL vials of ‘Actrapid’ (human insulin solution for injection, 3.5 mg/mL, Novo Nordisk) and dummy blood products in different packaging types to quantify to what extent vibration caused by the drone was transferred through the packaging to the cargoes.

In terms of the Actrapid, 24 vials of insulin were used (sample 1–6 Batch No.: JT6K794 (EXP: 04/2021); sample 7–24 Batch No.: KT6W795 (EXP: June 2022), carried in packaging used for the transportation of chilled cytotoxic chemotherapy drugs. Dummy blood products consisting of 340 mL (360 g) saline bags filled with water, mirroring those used for blood transfusion products were also used to understand the vibrational effects on a different product. A series of accelerometers were fitted to the fuselage of the drones and in the packaging to record the transfer of vibration during flights. Calibrated temperature gauges (data loggers) were also used to record the temperatures of the cargoes during the trials.

2.1. Drones Used in the Trials

Two different drones were used in this research. The first was a large fixed-wing drone, the ‘ULTRA TD1’ first generation prototype, built by the University of Southampton for Windracers, Figure 2. It is an advanced technology demonstrator designed to carry 100 kg over 1000 km and is powered by two, four stroke engines, each directly connected to a two bladed wooden propeller. The engines have a V-twin configuration, whose normal operating range is between 1100 and 3400 RPM and are attached to the airframe using four industrial vibration isolators in a cantilever configuration. The payload is secured into the loading bay using a cargo net and straps (Figure 3).

The second was a smaller, battery powered hexacopter drone with offset motor positioning for directional flight called ‘Arty’, developed by Motion Robotics, (Figures 4 and 5). This platform has six, 3 kW, 100 KV electric motors, coupled to 3008, 30-inch propellers, producing a maximum lift of 948 N in ideal conditions. These are suspended from the carbon fibre central chassis with carbon tubing and jointed with hinged, machined aluminium mounting points. With a typical 5 kg payload, the motors run between 35–50 % or 2000–2500 rpm.

Figure 2. Windracers ULTRA TD1 prototype: the fixed-wing drone used in flight tests.
Figure 3. Medical carriers loaded into the Windracers ULTRA TD1 prototype using cargo netting during flight testing. (Hold width was 2 m).

Figure 4. Motion Robotics Arty: the copter UAV used in flight testing.

Figure 5. Medical carrier loaded underneath Arty using a mechanised release system.
2.2. Containment Packaging Used and Cargo Monitoring Equipment

A polystyrene-insulated cardboard box (dimensions $32 \text{ cm} \times 37 \text{ cm} \times 36 \text{ cm}$, empty weight, inc. cool packs $6 \text{ kg}$) commonly used by the NHS for the transportation of cytotoxic chemotherapy drugs (Figure 6) was used for the trial of the Actrapid. The box was set up in an arrangement similar to that used in actual shipments of drugs containing nine cooling packs to maintain chilled temperatures ($2–8 \degree \text{C}$); three on either side of the cargo, and three above the cargo. Across a series of three trials (detailed in the next section), the box was set up to contain either $3 \times 10 \text{ mL}$ of Actrapid insulin, placed inside a Blue Bio-bottle or $4 \times 10 \text{ mL}$ vials of Actrapid insulin, split between $2 \times$ Blue Bio-bottles (3:1 split). The packaging configuration can be seen in Figure 6.

The other packaging used in the trials was a medium-sized Versapak ($46 \text{ cm} \times 26 \text{ cm} \times 31 \text{ cm}$), typically used in the carriage of diagnostic specimens between GP surgeries and hospitals, and chemotherapy drugs within hospitals (Figure 7). The UN3373 compliant bag which is manufactured from softer plastic-coated foam carried $5 \times$ mock blood/saline bags of approximately $360 \text{ g}$ each. This packaging and cargo configuration was used to enable a comparison of the vibration transmission effects of different packaging types and loads. The Versapak was only flown in ULTRA due to the drone’s larger hold enabling simultaneous carriage of both packaging types.

Vibration of the medical cargoes within the packaging was measured by an Axivity AX3 3-axis logging accelerometer [45]. The sensor was set to acquire data at a sampling frequency of $1.6 \text{ kHz}$, with a sensitivity of $\pm 8 \text{ g}$. In the Cytotoxic Drug Box, sensors were attached to insulin vials (Figure 6) or inserted in place of a vial in the standard manufacturer’s packaging. In the Versapak, a sensor was attached to a dummy blood product (Figure 7). Additional sensors, attached using cable ties and adhesive tape, monitored the cargo hold of the ULTRA TD1 prototype, and near the cargo attachment point on Arty. Temperature
monitoring of flown samples was undertaken using a RS PRO PRO-USB-1 Temperature Data Logger stick [46]. The sensor was set to record at 1-min intervals. Control samples were monitored using a Lascar Electronics USB-2-LCD Temperature Logger [47].

Figure 7. (a): Versapak carriers in three sizes (centre = medium). (b): Packaging configuration of the medium Versapak: 5× dummy blood bags (1 with attached vibration sensor). Approximate dimensions of the medium carrier = 46 cm × 26 cm × 31 cm. Loaded weight ~9 kg.

Acceleration signals were centred, i.e., the mean subtracted, thereby removing non-oscillatory components such as gravitational acceleration. Overall vibration levels were obtained from the standard deviation of the magnitude of the resultant acceleration vector, i.e., the square-root of the sum of the variances of the signals in the three orthogonal directions. Power spectral densities (PSD) were computed which represent the contributions to the variance by different frequencies. Welch’s method was chosen which computes the spectra of many short, overlapping segments of data and averages them to obtain a statistical estimate for their frequency content [48]. Segments of 2-s duration were used to obtain a frequency resolution of 0.5 Hz. A Hamming window was chosen, and the segments were overlapped by 50% [49]. The PSDs were plotted in deciBels with a reference of 1 g^2/Hz whereby 20 dB represented a factor of 10 on acceleration. Octave band spectra were synthesised by summing the area under the PSD curves in each octave range.

2.3. Experimental Design

Three flight trials (experiments) were conducted in this research:

2.3.1. Trial 1: Fixed-Wing Mixed Manoeuvres (12 November 2020)

The first trial investigated the effects of vibration from flying Actrapid in the hold of the fixed-wing ULTRA TD1 prototype drone at Thorney Island, England. Two separate flights made up of multiple ascents and descents without landing took place on a single day to test the drone’s autonomous control systems (Figure 8). The trial involved the engines being operational for 1 h 51 min 26 s in two intervals of 1 h 08 min 43 s and 42 min 43 s, respectively. The craft was flying for 50 min 17 s in the first flight, and 22 min 18 s in the second. During this time, the ULTRA TD1 prototype completed multiple left-hand turns climbing to a height of ~280 m, followed by multiple approaches over the runway (descending to 25 m) before throttling up to ascend to around 180 m (Figure 9).
2.3.2. Trial 2: Multi-Copter Evasive Manoeuvres (10 December 2020)

The second trial quantified vibration levels and investigated their effects on the insulin cargoes when flown by the multi-copter, Arty, during shorter flights with some evasive manoeuvres; what may be deemed typical of a localised drone delivery service (Figure 10). Working with Motion Robotics, a flight plan schedule was developed (Table 3) which would re-create all of the conditions that could reasonably be expected during a flight. This included steady state flight, multiple take-offs and landings, and evasive actions in which fast and sharp changes in direction occurred. The flights took place on a private estate in West Wellow, England, over a period of approximately 2 h.

Table 3. Arty manoeuvre plan.

| Battery 1                                                                 | Battery 2                                                                 |
|---------------------------------------------------------------------------|---------------------------------------------------------------------------|
| 1. 0.75 km lap with evasive action (time = 1 m 23 s).                     | 5. Short, aggressive manual flight (time = 1 m 02 s)                      |
| 2. 1.5 km (2 × 0.75 km laps) with evasive actions and landing/take-off between laps (time = 4 m 12 s). | 6. 2.25 km (3 × 0.75 km laps) with evasive actions (time = 4 m 53 s). |
| 3. 0.75 km lap with evasive actions, (single motor failure part-way through lap, completed on 5 motors) (time = 2 m 01 s). |                                                             |
| 4. 1.5 km (2 × 0.75 km laps) with evasive actions and landing/take-off between laps (time = 4 m 05 s). |                                                             |
2.3.3. Trial 3: Fixed-Wing Long Distance Flight (15 December 2020)

The third trial quantified vibration levels and investigated their effects on the insulin cargoes when flown over longer distances by the ULTRA TD1 prototype as part of a test flight from Land’s End Airport, Cornwall to the Isles of Scilly, England (Figure 11). In this experiment, the outward flight duration (to the Scilly Isles) was 38 min 14 s, whilst the return flight duration (to Cornwall) was 23 min 31 s, with the disparity being a result of the strong outward headwind/return tailwind. The mission included a routine taxi, take-off and landing at each airport, in addition to a steady state cruise at an altitude of approximately 600 m. The engines were on for a duration of 1 h 22 min.

Figure 11. Fixed-wing (Cornwall to Scilly Isles) flight path map [50]. The approximate distance between the take-off and landing sites is 31 miles/49 kilometres.

2.3.4. Trial Management and Analysis Process

The medical products used in each trial along with the packaging types used for containment are described in Table 4.
Table 4. Packaging arrangements and placement of vials during the three experiments.

| Packaging Layer 1 | Packaging Layer 2 | Packaging Layer 3 | Trial 1 * | Trial 2 | Trial 3 |
|-------------------|-------------------|-------------------|-----------|---------|---------|
| Bio-bottle 1      | 3 × 10 mL Vial Actrapid (in manufacturer’s box) | ✓ (vials 7, 8, 9) | ✓ (vials 15, 16, 17) | ✓ (vials 21, 22, 23) |
|                   | 1 × RS Pro Temperature Logger                   | ✓                   | ✓               | ✓       | ✓       |
|                   | 1 × 10 mL Vial Actrapid (unboxed)                | ✓ (vial 18)         | ✓ (vial 24)     |         |         |
|                   | Bio-bottle 2                                        |                     |                   |         |         |
|                   | 1 × 10 mL Vial Actrapid (unboxed)                | ✓ (from vial 18)    | ✓ (from vial 24) |         |         |
|                   | 2 × Axivity AX3 Vibration Sensor (1 attached to unboxed vial, 1 in vial box) | ✓                   | ✓               | ✓       | ✓       |
|                   | 1 × RS Pro Temperature Logger                    | ✓                   | ✓               | ✓       | ✓       |
| Medium Versapak   | 3 × 10 mL Vial Actrapid (in manufacturer’s box)  | ✓ (vials 10, 11, 12)|                     |         |         |
|                   | 1 × RS Pro Temperature Logger                    | ✓                   | ✓               | ✓       | ✓       |
|                   | 5 × Dummy blood bags                              | ✓                   | ✓               | ✓       | ✓       |
| Small Versapak    | 1 × 10 mL Vial Actrapid (in manufacturer’s box)  | ✓ (vial 2 *)        | ✓ (vial 14)     | ✓ (vial 20) |         |
| (Control—travels to site—not flown) | 1 × Lascar USB-2-LCD Temperature Logger | ✓                   | ✓               | ✓       | ✓       |
|                   | No packing (Control—remains in fridge at lab site) | ✓ (vial 1 *)       | ✓ (vial 13)     | ✓ (vial 19) |         |

* additional vials (1–6) from a different batch with known storage issues were also used in trial 1 (Thorney Island) to validate the analysis. These results are detailed in Appendix A.

The insulin products used in the trials were transported by land from a laboratory in London to Southampton for set-up using a small chilled Versapak (see Figure 7) with a temperature data logger. They were then stored overnight in a domestic refrigerator to maintain the insulin’s recommended temperature of 2–8 °C. Prior to flight testing, the vibration sensors were attached (Figure 6), and the samples were placed into the appropriate packaging alongside the cool packs with temperature sensors (Table 4). The test products were then transported by road to their respective test site. The samples were then flown and subsequently returned to London by land transport for immediate analysis. In the case of trial 3 (Cornwall), the samples were set-up and transported prior to overnight refrigeration before the flight day. Due to the drive distance (292 miles) and time (5 h) between the London laboratory and the Cornwall take-off site, a two-day delay was also incurred in trial 3 between the flight completion and the final analysis. Samples were refrigerated throughout this process to maintain the recommended temperature of 2–8 °C. The mean kinetic temperature (MKT) is calculated in the analysis to ensure the sample’s storage was acceptable during the experiment.

To account for any possible damage during the land logistics legs, each experiment featured two control samples; one which remained at the laboratory (vials 1, 13, 19), and one which travelled to the test site but did not fly (vials 2, 14, 20).

In the analysis of the insulin after flight, different concentrations of Formazin reference suspensions (I–IV) were prepared and used as the standard of turbidity (Table A1) as recommended by the British Pharmacopoeia (BP) [51]. For the products to be fit for use, the insulin solutions (the Actrapid samples) should remain ‘clear’ (Opalescent Values NTU ≤ 3) after exposure to the potential vibration. A light scattering calibration curve was then built by a UV/Vis spectrophotometer (Perkin Elmer, Lambda 2S) based on measuring the absorbance at 350 nm of 4 reference suspensions plotted against their NTU, using ultra-pure water as blanks to provide a robust assignment of the category of opalescence for subsequent turbidity assessment. The Actrapid samples from the trials could then be compared with the reference suspensions using their UV absorbance. All measurements were recorded in triplicate and averaged; 3 significant digits have been kept. A two-tailed
unpaired t-test was performed to determine the significant differences, with $p < 0.05$ being considered significant.

3. Results and Discussions
3.1. Temperature Analysis (Trials 1, 2, 3)

During all the experimental flights, the MKT of the cargo was found to be within the required specification ($2\,^\circ\text{C}$ to $8\,^\circ\text{C}$, Figure 12), based on calibrated sensor data [52].

![Figure 12. Mean Kinetic Temperatures for each trial. (Trial 1 = Thorney Island fixed-wing, trial 2 = New Forest multi-copter, Trial 3 = Cornwall to Isle of Scilly fixed-wing). Based on temperature from laboratory departure to return.]

For trial 1 (Thorney Island fixed-wing), temperatures were not affected by flights. Weather conditions were $13\,^\circ\text{C}$ with cloud and light winds [53]. Sensors detected one instance of conditions being too cold (max. deviation of $4\,^\circ\text{C}$), and two instances where temperatures were too warm (max. deviation of $12\,^\circ\text{C}$).

In the case of trial 2 (multi-copter), cargo temperatures were also not affected by flights. Weather conditions were $8\,^\circ\text{C}$ with cloud and light winds [54]. During the experiment there were two instances of conditions being too cold (max. deviation of $1\,^\circ\text{C}$), and four instances of conditions being too warm (max. deviation of $6\,^\circ\text{C}$).

In trial 3 (Cornwall to Isle of Scilly fixed-wing), temperatures were also not affected by flights. Weather conditions were $6\,^\circ\text{C}$ with some cloud and strong winds [55]. During the experiment there were several instances of conditions being too cold (max. deviation of $4\,^\circ\text{C}$), and five instances of conditions being too warm (max. deviation of $8\,^\circ\text{C}$).

In all of the trials, subsequent detailed investigation of the time stamps associated with the temperature breaches showed that the upper limit exceedances were all associated with cargo being transferred between packaging and storage environments and not related to the individual flights. Some deviations to the recommended storage regime are permitted, for example the package leaflet for Actrapid informs patients that when a vial is carried as a spare it may be kept at room temperature, below $25\,^\circ\text{C}$, for up to 6 weeks [56]. This recommendation from the manufacturer would have required regulatory approval. The deviations observed in this study were very brief, and much lower than the $25\,^\circ\text{C}$ described in the patient leaflet, and none of these occurred during the drone flight.

3.2. Vibration Analysis—Fixed-Wing (Trial 3)

Frequency analysis was performed on vibration data from sensors onboard the 24-min Isles of Scilly to Cornwall fixed-wing flight on 15 December 2020. Table 5 lists the positions of four sensors placed in the cargo hold of the drone, three of which were mounted within standard medical packaging solutions. An additional sensor monitored vibration during a four-hour road journey by passenger car that preceded the flights.
Table 5. Positioning of the sensors for testing of the fixed-wing drone.

| Mode  | Packaging Box                        | Notes                                                                 |
|-------|--------------------------------------|----------------------------------------------------------------------|
| 1 Car | Cytotoxic Drug Box                    | Alongside vials in boxes, within the Bio bottle                      |
| 2 Drone| Cytotoxic Drug Box                    | Attached to a vial removed from its manufacturer’s box, outside the insulin box, within the Bio bottle |
| 3 Drone| Cytotoxic Drug Box                    | Inside manufacturer’s box from vial used for sensor position 2, within the Bio bottle |
| 4 Drone| Versapak (medium)                     | Attached to a dummy blood bag                                        |
| 5 Drone| Cargo hold floor (near front, port side) |                                                                      |

The on-board vibration environment during the flight is characterised by a spectrogram, shown in Figure 13, which depicts the spectrum of vertical acceleration as a function of time. The striations, indicating the predominant components of vibration, occur at multiples of about 25 Hz, owing to the periodic excitation induced by the two-cylinder, four-stroke internal combustion engines. Small variations in engine speed and consequently frequency of vibration occur, particularly whilst simultaneously climbing and manoeuvring (t < 300 s) during which the vibration level was up to 50% higher than in cruise (graph omitted for brevity).

Figure 14 shows PSDs of the resultant accelerations at the five sensor positions, averaged over the complete journey times. The plots have been restricted to 300 Hz, above which most of the signals descend into the noise floor of the data acquisition system. The strongly harmonic nature of the cargo holds vibration response manifests itself as equally spaced peaks which are even more evident inside the medical packaging. Below about 20 Hz, there is little vibration. In contrast, vibration during the road journey is predominantly below 20 Hz. Distinct peaks can be seen at about 1 Hz and 13.5 Hz which are consistent with the two primary resonances expected from a passenger car’s suspension [57]. Above these resonances, vibration transmission to the car’s luggage compartment steadily reduces to much lower levels than experienced on the drone.
Figure 14. Fixed-wing: Power spectral densities for the resultant acceleration at the five sensor locations. 20 dB corresponds to a factor of 10 on acceleration. (Anomalous, equally spaced peaks above 150 Hz in the two of the sensors are signal processing artefacts introduced by the data logging system.).

The transmission of vibration from the drone to within the medical packaging can be quantified by subtracting the PSD of the former from the latter, where both are expressed in dB, and is equivalent to expressing their ratio in dB. Transmission ratios from the cargo hold floor of the ULTRA TD1 prototype fixed-wing drone to three different packages are shown in Figure 15.

Figure 15. Fixed-wing: The level difference between the PSDs of all packaged sensors and the reference sensor mounted on the cargo hold floor. The dashed line at 0 dB indicates that the vibration amplitude is the same as that in the cargo hold. A positive dB value indicates a higher value than the cargo hold floor. Conversely, a negative dB value indicates a lower frequency than the cargo hold floor. 20 dB corresponds to a factor of 10 on acceleration.

Below about 125–150 Hz, the vibration is higher in both the Cytotoxic Drug Box and Versapak than in the cargo hold. Conversely, above these frequencies the vibration is lower
than in the cargo hold. This behaviour is consistent with classical vibration isolation theory in which vibration is amplified at low frequencies and reduced at high frequencies. The onset of isolation is dependent on the mass of the packaged product and the mechanical flexibility of the packaging. Whether such packaging is well suited to isolating medical payloads from drone vibration, or whether drone vibration is more damaging than road vehicle vibration, will depend on the frequency sensitivity of the product in transit. To the authors’ knowledge no such data have been published in the literature.

3.3. Vibration Analysis—Multi-Copter (Trial 2)

Similar frequency analysis was performed on vibration data obtained from a flight test of the multi-copter and the positions of the sensors are detailed in Table 6.

Table 6. Positioning of the sensors for testing of the multi-copter drone.

| Mode  | Packaging Box              | Notes                                                                 |
|-------|-----------------------------|----------------------------------------------------------------------|
| 1     | Drone Cytotoxic Drug Box    | Attached to a vial removed from its manufacturer’s box, outside insulin box, within Bio bottle |
| 2     | Drone Cytotoxic Drug Box    | Inside manufacturer’s box from vial used for sensor position 1/2, within the Bio bottle |
| 3     | Drone                       | Mounted at drone’s (X–Y) centre of gravity                           |

Figure 16 shows the spectrogram for a four-minute flight which is in stark contrast to the fixed-wing drone (Figure 13). If driven at constant speed, the excitation due to a single rotor is expected to produce excitation at the blade passing frequency (rotor speed times the number of blades) and its harmonics. However, when driven at differing speeds (typically 2000–2500 rpm), the six rotors generate a broader band of excitation corresponding to fundamental frequencies in the range of 66 to 83 Hz. The striations are smeared as a consequence.

![Figure 16](image1.png)

Figure 17 shows the PSDs of the resultant acceleration signals. The peak at 5 Hz is believed to be due to a resonance of the package vibrating rigidly within its harness, shown in Figure 5. If confirmed through future measurements, then the mounting arrangement provides significant vibration isolation from 10–30 Hz. This was not seen in the fixed-wing drone in which the package was secured to the cargo hold floor. The broad peak centred at about 70–80 Hz corresponds to vibration at the blade-passing frequencies and this was transmitted effectively to the payload, perhaps due to other resonances associated with the mounting or medical packaging. There was significant broadband vibration on the airframe above 80 Hz, but this was weakly transmitted to the contents of the packaging.
3.4. Comparison of Vibration Effects between Transport Modes

Figure 18 compares the resultant vibration levels for the fixed-wing and multi-copter drones alongside the road transport in the form of octave spectra. The sensor was contained in comparable packaging for the two drone flights and the car journey, except that the car journey sensor was not attached to a vial, but rather just placed alongside the vial boxes. The multi-copter drone caused the highest overall vibration level, predominantly at the blade passing frequency which fell within the 63 Hz octave band. The overall vibration level of the fixed-wing drone was about 25% lower, most of which was due to the fundamental excitation frequency associated with the internal combustion engines that sits in the 32 Hz octave band. Transportation by car returned the lowest overall vibration level, although vibration was considerably higher than either drone in the 2, 8 and 16 Hz octave bands. This is caused by random road surface inputs which get amplified by vehicle resonances arising from flexibility of the vehicle’s suspension springs and tyres.

Figure 18. Octave spectra of the resultant acceleration. Levels are expressed as linear acceleration values; the sum of the squares over all octave bands gives the square of the overall value.
3.5. Insulin Analysis (Trials 1, 2, 3)—Understanding the Effects of Vibration

Across all three trials, the Actrapid samples (7–24) from Batch No.: KT6W795 (EXP: June 2022) were clear and passed the BP turbidity test (Figures 19–21). No significant differences in absorbance at 350 nm ($p = 0.29$) were observed in the flown samples regardless of packaging type (vials 7, 8, 9—Cytotoxic Drug Box vs. vials 10, 11, 12—Versapak) in trial 1 (Thorney Island—Figure 19), with no insoluble aggregates forming. In trial 1, it was not possible to compare the absorbances observed for the “not-flown” vials to the vials flown in the Cytotoxic Drug Box and Versapak, even though the samples transported in both of these types of container all passed the BP quality test. However, in the case of trial 2, (New Forest Multi-copter—Figure 20), it was possible to compare “not-flown” with flown and no significant differences were observed ($p > 0.05$) indicating that human insulin solutions were not significantly affected by flying.

![Figure 19](image1.png)

**Figure 19.** Mean absorbance at 350 nm plotted against Actrapid samples for trial 1 (Thorney Island fixed-wing: 7, 8 and 9 flown in Cytotoxic Drug Box; 10, 11 and 12 flown in Versapak). Data points shown are the mean of $n = 3$ measurements, with error bars indicating the standard deviations on these values.

![Figure 20](image2.png)

**Figure 20.** Mean absorbance at 350 nm plotted against Actrapid samples for trial 2 (New Forest multi-copter: 13 and 14 not flown controls; 15, 16, 17 and 18 flown in Cytotoxic Drug Box). Data points shown are the mean of $n = 3$ measurements, with error bars indicating the standard deviations on these values.
An interesting variation was found in trial 3 (Cornwall to Isle of Scilly fixed-wing—Figure 21), where, whilst all vials passed the BP test, the differences in absorbance readings between all travelled samples (vials 20, 21, 22, 23, 24) and control sample 19 (remained at laboratory site) were significant ($p < 0.05$). This observation shows that the longer drone and road trip associated with trial 3 had made an impact on the turbidity, but not enough to cause the insulin to fail its BP quality test, and so was still fit for use. Although very short in its duration and with only small temperature fluctuations, that trial 3 suffered the most temperature deviations during transportation. The current study was focused on vibration, however future work should include an investigation into permitted temperature deviations on the quality of insulin, modelling small temperature spikes which may occur during combined air and road transportation.

In addition, the UV tests for trial 3 were conducted 3 days after the drone flight, and as in the case for all the UV testing, the spectrometer performance would be expected to contribute to the assay’s accuracy. This accuracy is usually determined by comparative replicate measurements of a certified reference material (CRM) whereby the mean of absorbance must be ±0.005 from the certified value, for absorbance values below 1.0 absorbance units [58]. In further measurements of both the formazin suspensions and Actrapid control samples, the maximum variation was ±0.003 absorbance units, which was regarded as acceptable. Therefore, considering the accuracy of the spectrometer, and the additional experiments with formazin and Actrapid, it can be said that insulin quality, or more specifically the quality of the medicinal product, Actrapid, was not affected by drone transport.

4. Conclusions

This research used a series of real-world drone trials transporting 10 mL vials of ‘Actrapid’ (human insulin solution for injection, 3.5 mg/mL, Novo Nordisk) and dummy blood products in different packaging types to quantify the levels of vibration inside the cargo packaging and identify any evidence of adverse effects on product quality in the specific case of the Actrapid.

Two drones were used for the trials: (i) A fixed-wing drone (‘ULTRA TD1 prototype’), powered by twin four-stroke engines, each directly connected to a two bladed wooden propeller and operating between 1100 and 3400 RPM; (ii) a battery powered hexacopter drone (‘Arty’), utilising six, 3 kW, 100 KV electric motors, coupled to 30-inch propellers running between 2000–2500 RPM, and producing a maximum lift of 948 N.
A series of accelerometers were fitted to the fuselage of the drones and in the packaging (rigid foam insulated box, used for the carriage of aseptic medicines, and a soft foam insulated Versapak, used for the carriage of patient diagnostic samples). These were used to record the transmission of vibration during flights alongside calibrated temperature gauges to record the temperatures of the cargoes. Three trials were undertaken using the drones to better understand what adverse effects vibration might have on the cargoes. Road transport was used to move the goods between sites.

In all three trials, the mean kinetic temperature of the cargoes was found to be within the required specification (2 °C to 8 °C) with all temperature breaches being associated with the cargo being transferred between packaging, and the storage environments themselves, and were not related to the individual flights. All Actrapid samples passed the BP turbidity test with no significant changes in absorbance at 350 nm level being observed, indicating no insoluble aggregates had been formed.

Overall vibration levels were higher for the hexacopter than the fixed-wing drone and both were significantly higher than for road transport. However, road-induced vibration occurred predominantly below 20 Hz where drone vibration was largely absent. Therefore, stability of medicines with respect to vibration cannot be routinely extrapolated to delivery by drone. Establishing the frequency dependent sensitivity of medicines to vibration is a prerequisite to planning new missions for medicines not previously delivered by a drone, and when new aircraft platforms are deployed.

The standard medical packages chosen were found to be ineffective at isolating medicines from drone-induced vibration, and significant amplification was observed in the case of the fixed-wing drone. This effect was less evident in the hexacopter, possibly because the package was slung-mounted rather than being fixed to the airframe. Tailoring flexible mounting systems to the vibration signature of each platform may be a more effective way to improve isolation than redesigning the packaging, particularly when delivery involves multi-modal transport.

5. Recommendations

Two sets of recommendations have been identified by the authors. The first relates to further research which should be carried out to improve the wider understanding of how vibration from transport affects sensitive healthcare cargoes, and how variations in packaging may affect this:

1. This paper identified that current medical grade packaging amplified the vibration of drone transport significantly more than car transport in specific frequency ranges. Further work to characterise the vibration isolation of medical packaging through bench tests should be undertaken. Subsequent assessment of the potential to optimise the packaging for multiple modes of transport should then be made.

2. In the review of existing work, it was identified that there is limited research which quantifies the effects of vibration frequency, amplitude, and duration on sensitive liquid healthcare products. Controlled bench tests to identify these effects should be undertaken.

3. Many drones are likely to operate delivery systems which connect with land-based transport, and as such further work investigating other possible modes should take place to enable a comparison of their detrimental effects on sensitive cargoes. Part of this research may take the form of a transport simulation study [59].

4. This study was focused on vibration, however future work should include an investigation of permitted temperature deviations on the quality of insulin, modelling the small temperature spikes which may occur during combined air and road transportation.

The second relates to a proposed method for mission/operation planning which should be considered in the deployment of UAVs and alternative transport modes in the transportation of sensitive healthcare cargoes:
1. Identify the product’s regulatory packaging restrictions based on ICAO (air transport), IMRG (maritime transport), RID (rail transport), and ADR (road transport) guidance. Where classed as dangerous by these documents, the regulations must be followed.

2. Select appropriate packaging to protect the proposed product and any parties involved in its carriage. Label as needed.

3. Test the packaging in the proposed craft/vehicle using 3-axis (or greater) accelerometers to quantify the vibration transferred to potential products.

4. Make adjustments to the packaging and/or craft/vehicle and repeat step 3, as needed, to ensure that cargoes are not exposed to damaging levels of vibration.

5. In line with the EU GDP, where uncertainties may be present, flight tests matching the intended operations (including cargoes) are required, with associated analysis of the product post-flight to ensure that the quality and integrity of the medicine has not been affected by vibration in-flight.

Additionally, mission planning aids and guidance, such as Eichleay et al.’s [60] ‘UAV delivery Decision Tool’, which assesses the feasibility and effectiveness of using UAVs in medical logistics settings, should be adapted to consider the potential risk to medical cargoes from vibration when carried by UAV, over what would be experienced in traditional transport modes.

Author Contributions: The authors named in this paper made the following contributions: Conceptualization A.O., T.C., P.G.R. and T.W.; Methodology A.O., T.C., P.G.R., T.W. and W.Z.; Formal Analysis T.W., W.Z., A.O. and P.G.R.; Investigation A.O., T.C., P.G.R., T.W., W.Z., D.M. and N.J.; Resources A.O., T.C., P.G.R., T.W., W.Z., D.M. and N.J.; Data Curation A.O., T.C., P.G.R., T.W. and W.Z.; Writing Original Draft Preparation A.O., T.C., P.G.R., T.W. and W.Z.; Writing Review and Editing A.O., T.C., P.G.R., T.W., W.Z. and P.C.; Writing Review and Editing A.O., T.C., P.G.R., T.W., W.Z. and P.C.; Visualization T.W., W.Z. and A.O.; Supervision, A.O.; Project Administration T.C. and A.O.; Funding Acquisition T.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received funding from the EPSRC and was completed as part of the e-Drone project under grant no. EP/V002619/1.

Institutional Review Board Statement: Not Applicable for this study.

Informed Consent Statement: Not Applicable for this study.

Data Availability Statement: The data used in this study are not publicly available due to commercial sensitivities of the involved parties. Contact the corresponding author for further information.

Acknowledgments: The authors would like to thank the teams at Windracers (www.windracers.org, accessed on 3 February 2021) and Motion Robotics (www.motion-robotics.co.uk, accessed on 3 February 2021) for their help facilitating the experiments featured in this paper.

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

The stock formazin solution, standard of opalescence was prepared according to BP. The reference suspensions I–IV were prepared according to Table A1.

Table A1. Preparation of reference suspensions.

| Reference Suspension | Opalescent Values (NTU) | Component (mL) | Degree of Opalescence |
|----------------------|-------------------------|----------------|-----------------------|
|                      |                         | Standard of Opalescence | Ultra-Pure Water |                      |
| I                    | 3                       | 5               | 95                   | Clear (≤ Ref I)     |
| II                   | 6                       | 10              | 90                   | Slightly Opalescent (≤ Ref II) |
| III                  | 18                      | 30              | 70                   | Opalescent (≤ Ref III) |
| IV                   | 30                      | 50              | 50                   | Very Opalescent (≤ Ref IV) |
After preparation, build the UV spectra on the region of 500–300 nm and turbidity could be measured as absorbance at 350 nm with suspension I–IV as shown in Figure A1.

![Figure A1. Formazin Standard Suspensions UV Calibration Curve.](image)

For the purposes of in-house validation of the BP test, a set of vials close to expiry were investigated and were compared to in date samples from trial one. As seen in Figure A2, Actrapid samples 1–6 (Batch No. JT6K794, EXP 04/2021) slightly aggregated (absorbance > 0.015) and so may have lost some biological efficacy. It is understood that the likely cause of degradation is poor conditions of storage prior to the experiment, however this could also occur with patients, when the medicines are kept at home. These results prove that the UV spectroscopy used in this research is sensitive enough to detect any aggregates by light scattering.

![Figure A2. Mean absorbance at 350 nm plotted against Actrapid samples in different flight conditions (ULTRA TD1 prototype, Thorney Island). Data points shown are the mean of n = 3 measurements, with error bars indicating the standard deviations on these values.](image)

References

1. Hiebert, B.; Nouvet, E.; Jeyabal, V.; Donelle, L. The Application of drones in healthcare and health-related services in north america: A scoping review. *Drones* 2020, 4, 30. [CrossRef]
2. O’Keeffe, D.T.; Johnson, K.; Maraka, S. Provision of bidirectional remote patient care with an unmanned aerial vehicle. *Mayo Clin. Proc.* 2020, 95, 830. [CrossRef] [PubMed]
3. Mateen, F.J.; Leung, K.H.B.; Vogel, A.C.; Cissé, A.F.; Chan, T.C.Y. A drone delivery network for antiepileptic drugs: A framework and modelling case study in a low-income country. *Trans. R. Soc. Trop. Med. Hyg.* 2020, 114, 308–314. [CrossRef] [PubMed]
4. Desloovere, W. An Evaluation of the Potential to Use Drone Deliveries as Last-Mile Logistics. Master's Thesis, Mid Sweden University, Sundsvall, Sweden, 2020.

5. Ilancheran, M. COVID-19, Medical Drones, & The Last Mile of The Pharma Supply Chain. 2020. Available online: https://www.pharmaceuticalonline.com/doc/covid-medical-drones-the-last-mile-of-the-pharma-supply-chain-0001 (accessed on 15 January 2021).

6. Skorup, B.; Haaland, C. How drones can help fight the coronavirus. SSRN Electron. J. 2020. [CrossRef]

7. Bishara, R.H. Cold Chain Management—An Essential Component of the Global Pharmaceutical Supply Chain. Am. Pharm. Outsourcing 2006, 9, 14–22.

8. Cerba Healthcare and The Drone Office. Drones in Medical Logistics; Cerba Healthcare: Issy-les-Moulineaux, France, 2019.

9. Choi-Fitzpatrick, A.; Chavarria, D.; Chchosz, E.; Dingers, J.P.; Duffey, M.; Koebel, K.; Siriphanh, S.; Tulen, M.Y.; Watanabe, H.; Juskaukas, T.; et al. Up in the Air A Global Estimate of Non-Violent Drone Use 2009–2015; University of San Diego: San Diego, CA, USA, 2016. [CrossRef]

10. Amukele, T.; Ness, P.M.; Tobian, A.A.; Boyd, J.; Street, J. Drone transportation of blood products. Transfusion 2017, 57, 582–588. [CrossRef] [PubMed]

11. Güner, S.; Rathnayake, D.; Ahmadi, N.B.; Kim, B. Using Unmanned Aerial Vehicles—Drones—As a Logistic Method in Pharmaceutical Industry in Germany; Heilbronn University of Applied Sciences: Heilbronn, Germany, 2017.

12. Haidari, L.A.; Brown, S.T.; Ferguson, M.; Bancroft, E.; Spiker, M.; Wilcox, A.; Ambikapathi, R.; Sampath, V.; Connor, D.L.; Lee, B.Y. The economic and operational value of using drones to transport vaccines. Vaccine 2016, 34, 4062–4067. [CrossRef] [PubMed]

13. Direct Relief. Long-Range Drone Delivers Cold-Chain Medicines, Vaccines Between Islands in Caribbean. 2019. Available online: https://www.directrelief.org/2019/07/long-range-drone-delivers-cold-chain-medicines-vaccines-between-islands-in-caribbean/ (accessed on 15 January 2021).

14. CNN Business. CVS just Delivered its First Prescriptions via Drone—CNN Video. 2019. Available online: https://edition.cnn.com/videos/business/2019/11/06/ups-cvs-drone-delivery-prescription-orig.cnn-business (accessed on 15 January 2021).

15. Cohen, J.K. WakeMed Health and Hospitals joins forces with UPS, FAA for drone pilot. Modern Healthcare, 26 March 2019. Available online: https://www.modernhealthcare.com/care-delivery/wakemed-health-hospitals-joins-forces-ups-faa-drone-pilot (accessed on 15 January 2021).

16. Brown, A. Skyports and thales partner to conduct drone delivery trial for NHS in Scotland to support UK COVID-19 Response. Skyports, 25 May 2020. Available online: https://skyports.net/2020/05/skyports-and-thales-partner-to-conduct-drone-delivery-trial-for-nhs-in-scotland-to-support-uk-covid-19-response/ (accessed on 15 January 2021).

17. Pressroom UPS. UPS partners with matternet to transport medical samples via drone across hospital system in Raleigh, N.C. UPS Pressroom, 26 March 2019. Available online: https://pressroom.ups.com/pressroom/ContentDetailsViewer.page?ConceptType=PressReleases&id=1553546776552-986 (accessed on 15 January 2021).

18. sUAS News. Matternet launches drone delivery operations at labor berlin in Germany. sUAS News, 08 December 2020. Available online: https://www.suasnews.com/2020/12/matternet-launches-drone-delivery-operations-at-labor-berlin-in-germany-2/ (accessed on 15 January 2021).

19. Volansi. Volansi Launches Commercial Drone Delivery Program to Deliver Cold Chain Medicines in Rural North Carolina. Volansi, 20 October 2020. Available online: https://volansi.com/volansi-launches-commercial-drone-delivery-program-to-deliver-cold-chain-medicines-in-rural-north-carolina/ (accessed on 15 January 2021).

20. Zipline. Zipline—Vital, On-Demand Delivery for the World. 2020. Available online: https://flyzipline.com/ (accessed on 10 September 2020).

21. Pressroom UPS. UPS flight forward, CVS To Launch residential drone delivery service in Florida retirement community to assist in coronavirus response. UPS Pressroom, 27 April 2020. Available online: https://www.pressroom.ups.com/pressroom/ContentDetailsViewer.page?ConceptType=PressReleases&ReleaseId=1587995241555-272 (accessed on 15 January 2021).

22. Stradling, R. WakeMed in Raleigh is the spot as UPS makes its first deliveries with drones in the U.S. Raleigh News & Observer, 26 March 2019. Available online: https://www.newsobserver.com/news/local/article228373214.html (accessed on 15 January 2021).

23. Kesteloo, H. Matternet drones to deliver COVID-19 tests in Berlin. DroneXL.co, 25 November 2020. Available online: https://dronexl.co/2020/11/25/matternet-drones-to-deliver-covid-19-tests-berlin/ (accessed on 27 January 2021).

24. Badurina, G.; Majić, Z.; Pavlin, S. Evaluation of air transportation under controlled room temperature for pharmaceuticals. Promet Traffic Transp. 2011, 23, 121–130. [CrossRef]

25. ICH. ICH harmonised tripartite guideline—Stability testing of new drug substances and products. Q1a (R2) Curr. Step. 2003, 4, 1–24.

26. Rignall, A. ICHQ1A(R2) stability testing of new drug substance and product and ICHQ1C stability testing of new dosage forms. In ICH Quality Guidelines; Teasdale, A., Elder, D., Nims, R.W., Eds.; Wiley: Hoboken, NJ, USA, 2017; pp. 3–44.

27. Kommanaboyina, B.; Rhodes, C.T. Trends in stability testing, with emphasis on stability during distribution and storage. Drug Dev. Ind. Pharm. 1999, 25, 857–868. [CrossRef]

28. Mahler, H.-C.; Friess, W.; Grauschopf, U.; Kiese, S. Protein aggregation: Pathways, induction factors and analysis. J. Pharm. Sci. 2009, 98, 2909–2934. [CrossRef] [PubMed]
29. Sluzky, V.; Tamada, J.A.; Klibanov, A.M.; Langer, R. Kinetics of insulin aggregation in aqueous solutions upon agitation in the presence of hydrophobic surfaces. *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 9377–9381. [CrossRef] [PubMed]

30. International Civil Aviation Organization. *Technical Instructions for the Safe Transport of Dangerous Goods by Air*; International Civil Aviation Organization: Montreal, QC, Canada, 2019.

31. Hii, M.S.Y.; Courtney, P.; Royall, P.G. An evaluation of the delivery of medicines using drones. *Drones* **2019**, *3*, 52. [CrossRef]

32. Akbarian, M.; Yousefi, R. Human αB-crystallin as fusion protein and molecular chaperone increases the expression and folding efficiency of recombinant insulin. *PLoS ONE* **2018**, *13*, e0206169. [CrossRef]

33. Kiese, S.; Pappenberger, A.; Friess, W.; Mahler, H.-C. Shaken, Not stirred: Mechanical stress testing of an IgG1 antibody. *J. Pharm. Sci.* **2008**, *97*, 4347–4366. [CrossRef] [PubMed]

34. Ohno, Y.; Seki, T.; Kojima, Y.; Miki, R.; Egawa, Y.; Hosoya, O.; Kasono, K.; Seki, T. Investigation of factors that cause insulin precipitation and/or amyloid formation in insulin formulations. *J. Pharm. Health Care Sci.* **2019**, *5*, 1–11. [CrossRef]

35. Kerr, D.; Wizemann, E.; SensiStus, J.; Zacho, M.; Ampudia-Blasco, F.J. Stability and performance of rapid-acting insulin analogs used for continuous subcutaneous insulin infusion: A systematic review. *J. Diabetes Sci. Technol.* **2013**, *7*, 1595–1606. [CrossRef]

36. European Commission. Guidelines of 5 November 2013 on Good Distribution Practice of Medicinal Products for Human Use; European Commission: Brussels, Belgium, 2013. Available online: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2013:343:0001:0014:EN:PDF (accessed on 15 January 2021).

37. PCI Services. EU-GDP-Implications-for-Shipping-Clinical-Materials-European-Market; PCI Services: Erie, PA, USA, 2019. Available online: https://pciservices.com/wp-content/uploads/2019/10/EU-GDP-Implications-for-Shipping-Clinical-Materials-European-Market.pdf (accessed on 15 January 2020).

38. Department of Health. Safe Management of Healthcare Waste: Environment and Sustainability; Department of Health: London, UK, 2007.

39. Murrif, S.J. *Safety and Health Handbook for Cytotoxic Drugs*; Government Institutes: Lanham, MD, USA, 2012.

40. Beck, S.; Bui, T.T.; Davies, A.; Courtney, P.; Brown, A.; Geudens, J.; Royall, P.G. An Evaluation of the Drone Delivery of Adrenaline Auto-Injectors for Anaphylaxis: Pharmacists’ Perceptions, Acceptance, and Concerns. *Drones* **2020**, *4*, 66. [CrossRef]

41. Verbeke, J.; Debruyne, S. Vibration analysis of a UAV multicopter frame. In *Proceedings of the of ISMA 2016 International Conference on Noise and Vibration Engineering*, Leuven, Belgium, 9–21 September; pp. 2329–2337.

42. Li, Z.; Lao, M.; Phang, S.K.; Hamid, M.R.A.; Tang, K.Z.; Liu, F. Development and Design Methodology of an Anti-Vibration System on Micro-UAVs. In *Proceedings of the International Micro Air Vehicle Competition and Flight Competition (IMAV)*, Toulouse, France, 18–21 September 2017; pp. 223–228.

43. Chonhencob, V.; Singh, S.P.; Singh, J.J.; Stallings, J.; Grewal, G. Measurement and analysis of vehicle vibration for delivering packages in small-sized and medium-sized trucks and automobiles. *Packag. Technol. Sci.* **2012**, *25*, 31–38. [CrossRef]

44. Ranathunga, C.L.; Jayaweera, H.H.E.; Suraweera, S.K.K.; Wattage, S.C.; Ruvinda, K.K.D.L.; Ariyaratne, T.R. Vibration Effects in Vehicular Road Transportation. *Vidyodaya Sci. J.* **2013**, *18*, 13–25.

45. Axivity. AX3 3-Axis Logging Accelerometer. 2020. Available online: http://www.axivity.com/product/1 (accessed on 15 January 2021).

46. RS online. RS PRO PRO-USB-1 Data Logger for Temperature Measurement. 2020. Available online: https://uk.rs-online.com/web/p/data-loggers/1799535/ (accessed on 15 January 2021).

47. Lascar Electronics. EL-USB-2-LCD Temperature & Humidity USB Data Logger—Lascar. 2020. Available online: https://www.lascarelectronics.com/easylog-el-usb-2-lcd (accessed on 27 January 2021).

48. Welch, P. The use of fast Fourier transform for the estimation of power spectra: A method based on time averaging over short, modified periodograms. *IEEE Trans. Audio Electroacoust.* **1967**, *15*, 70–73. [CrossRef]

49. Harris, F.J. On the use of windows for harmonic analysis with the discrete Fourier transform. *IEEE Trans. Audio Electroacoust.* **1978**, *26*, 51–83. [CrossRef]

50. Esri. “Imagery Hybrid” [basemap]. *Scale Not Given. World Imagery Hybrid Map*. Jan. 06, 2020. Available online: https://www.arcgis.com/home/item.html?id=28f49811a6974659988fd279de5ce39f (accessed on 6 January 2021).

51. Medicines and Healthcare products Regulatory Agency. *British Pharmacopoeia—Appendix IV: A. Clarity of Solution*; British Pharmacopoeia Commission: London, UK, 2020.

52. Desai, K.G.; Colandene, J.D.; Adams, M. Comprehensive temperature excursion management program for the commercial distribution of biopharmaceutical drug products. *J. Pharm. Sci.* **2020**, *109*, 2131–2144. [CrossRef] [PubMed]

53. Weather Underground. Emsworth, United Kingdom Weather History | Weather Underground. 2020. Available online: https://www.wunderground.com/history/daily/gb/west-thorney/IWESTT6/date/2020-11-11 (accessed on 16 January 2021).

54. Weather Underground. Southampton, United Kingdom Weather History | Weather Underground. 2020. Available online: https://www.wunderground.com/history/daily/EGHI/date/2020-12-10 (accessed on 15 January 2021).

55. Weather Underground. Penzance, United Kingdom Weather History | Weather Underground. 2020. Available online: https://www.wunderground.com/history/daily/ISENNEN2/date/2020-12-15 (accessed on 15 January 2021).

56. Novo Nordisk Ltd. Actrapid 100 international units/ml, solution for injection in a vial—Summary of product characteristics (SmPC)—(emc). *Medicines*, 09 October 2020. Available online: https://www.medicines.org.uk/emc/product/3849/smpc (accessed on 27 January 2021).
57. Sayers, M.W. *The Little Book of Profiling: Basic Information About Measuring and Interpreting Road Profiles*; University of Michigan Transportation Research Institute: Ann Arbor, MI, USA, 1998.

58. Burgess, C.; Hammond, J.P. *Specifying Accuracy and Precision Criteria for Ultraviolet Spectrometers*; Spectroscopy Europe: Florence, Italy, 2019.

59. Hutchinson, G.; Littlefield, D.J. Safe Transportation of COVID-19 Vaccines: Challenges and Solutions 2020. Available online: http://www.pharmoutsourcing.com/Featured-Articles/571355-Safe-Transportation-of-COVID-19-Vaccines-Challenges-and-Solutions/?ctid=1&cid=25400 (accessed on 26 January 2021).

60. Eichleay, M.; Evens, E.; Stankevitz, K.; Parker, C. Using the unmanned aerial vehicle delivery decision tool to consider transporting medical supplies via drone. *Glob. Health Sci. Pract.* 2019, 7, 500–506. [CrossRef]