7. Supplementary Material:

S1 Pharmacists' Perceptions:

Title of Survey:

Drone Delivery of EpiPen®: Do Pharmacists approve of the use of aerial drones to deliver adrenaline auto-injectors to patients?

Participant Information Sheet

Invitation paragraph:

My name is September Beck and I am a 4th year Pharmacy student at Kings College London. I am working with Dr Paul Royall to complete my research project on - The use of drones for the delivery of medicines: Stability of transported medicines.

While robotic systems are starting to be deployed to support pharmacy logistic operation within hospitals, there are many locations where the cost-effective delivery of medical materials is problematic. There has been considerable interest in the use of aerial drones to assist in the delivery of medicines. A few pilot studies have been carried out, but little discussion of the many non-engineering challenges and issues. My project seeks to address this knowledge gap.
https://doi.org/10.2146/ajhp170196

I am asking **pharmacists** to complete the attached, which explores their **perceptions** on drone usage and **EpiPen®** adrenaline autoinjectors.

What is the purpose of the survey and why have I been invited to take part?

The purpose of the survey is to explore **pharmacists' perceptions** on drone delivered adrenaline autoinjectors. I am asking **pharmacists** from a range of employment expertise to take part in this exciting survey.

Do I have to take part?

No, it is not compulsory but your participation would be much appreciated.

What will happen to me if I take part, is it confidential?

The survey will take 5 minutes of your time and yes, all information collected is confidential. The results of the survey will be used in my MPharm Research Project.

Who should I contact for further information or if something goes wrong?

If you have any questions or require more information please contact:

September Beck
September.beck@kcl.ac.uk

Dr Paul Royall – Senior Lecturer in Pharmaceutics
Paul.royall@kcl.ac.uk

Institute of Pharmaceutical Science
King's College London Franklin-Wilkins Building
150 Stamford Street SE1 9NH

Thank you for reading this and for taking part in this research.

1. **Which age demographic do you fall into?**

Age Ranges: 20-30 ☐ 31-40 ☐ 41-50 ☐ 51-60 ☐ 60+ ☐

2. **Please select your work speciality:**

GP Practice ☐ Community ☐ Hospital ☐

3. **Are you aware that medicines are currently being delivered by drones?**

Very Unfamiliar ☐ Unfamiliar ☐ Neutral ☐ Familiar ☐ Very Familiar ☐

4. **Have you experienced any logistical challenges in terms of delivery, or problems with adrenaline auto-injector availability, which may cause a delay or issue to your patient?**

If YES, please briefly describe here.

5. **How confident are you that drones are a successful way to deliver adrenaline auto-injectors such as EpiPen®?**

	Not at all Confident	**Not so Confident**	**Somewhat Confident**	**Very Confident**	**Extremely Confident**
How confident are you that drones will be able to deliver EpiPen® within an achievable range from your pharmacy to the patients' location?					
How confident are you that the quality of adrenaline will be maintained and would not suffer instability issues?					
How confident are you that EpiPen® is robust enough to survive the onboard drone conditions?					
How confident are you that the security of the drone supply would be maintained, so that the EpiPen® would not fall into the wrong hands?					
How confident are you that in the case of drone failure, that the impact on the EpiPen® and the environment would be minimal?					

6. How do you think your patients who require EpiPen® would react to the delivery of their device via drone?

Not Accepting 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ Very Accepting

7. A Medical Emergency is defined as

"the sudden onset of a medical condition with acute symptoms of sufficient severity, where the absence of instant medical attention could result in: placing the patient's health in serious risk, serious impairment and dysfunction to bodily functions and/or organs." ***Medical Dictionary 2011***

In your experience, have you encountered an emergency situation requiring an adrenaline auto-injector such as EpiPen®? YES ☐ NO ☐

8. If you dispense regularly, please fill out the following:
How often do you dispense and receive EpiPen®? Please indicate the number of occasions per month in the boxes below.

	Number of occasions per month
Dispense at the request of the Patient	
Dispense the request of the Prescriber	
Receive at your pharmacy	

9. If you have dispensed adrenaline auto-injectors before, have you encountered any stability issues?

	YES	**NO**	**If YES, state your observations**
Issues in regard to the stability of the autoinjector			
Issues in regard to the quality of the medication			
Issues in regard to the packaging			

10. Do you think the delivery of adrenaline auto-injectors by aerial drone would benefit patients in emergency situations?

Not at all Beneficial 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ Extremely Beneficial

Please state your reasoning.

11. Do you approve of the use of aerial drones to deliver adrenaline auto-injectors to patients?

YES☐ NO ☐

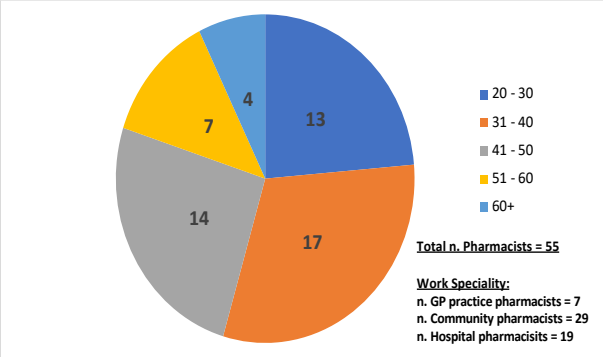


Figure S1a: Answers to Question 1-2, *Age Demographic and expertise of the Pharmacists who took part in the PPI/Audit.*

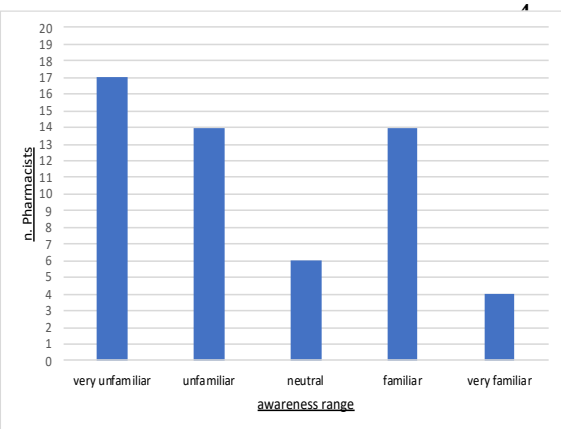


Figure S1b: Answers to Question 3, *Pharmacists awareness to drone delivery of*

Question 4, Logistical Challenges:

Direct quotes and summary of logistical challenges

- Issues in obtaining supply of all adrenaline auto-injectors brands.
- National shortages are arising due to manufacturing issues.
- Patients not getting their supply on time, unable to supply majority of patients.
- Manufactures limiting supply.
- Item seems to be in demand all the time with not enough stock availability to match.
- Patients being forced to switch to another brand of auto-injector i.e.: Jext, which had multiple recalls, but unaffected replacement stock were available.
- These are products which have a short expiry and rarely used but require pharmacies to show manufacturers evidence of the need for the auto-injector in the form of a prescription this would allow the product to get to us but take over 72hours.
- In `hospital, nation supply shortages have led to delays in discharge of patients.

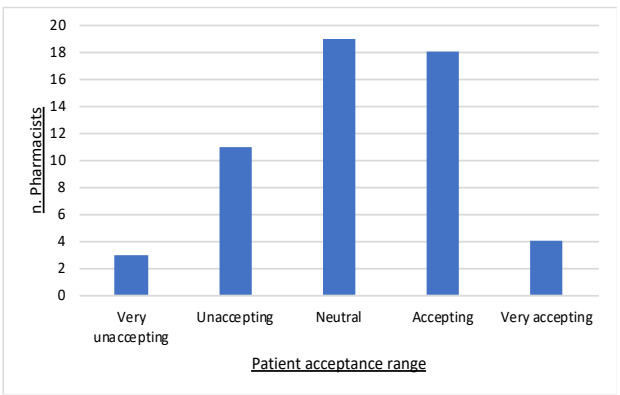


Figure S1c: Answers to Question 6, *Pharmacists perceptions on patient acceptance to the drone delivery of EpiPen®.*

Question 7:
82% of pharmacists have not encountered an emergency situation requiring EpiPen.

Answers to Question 8 omitted due to 80% of Pharmacists leaving this question unanswered

	YES	NO	If YES, state your observations
Issues in regard to the stability of the autoinjector	2	53	Jamming of Emerade Pens. When EpiPen stock was unavailable we contacted the manufacturers who said you can use 4-5months after the expiry date as it is still stable.
Issues in regard to the quality of the medication	0	55	
Issues in regard to the packaging	2	53	Outer cartons often ripped. Not enough information was available on the outer packaging.

Figure S1d: Answers to Question 9, *addressing the stability issues of adrenaline auto-injectors.*

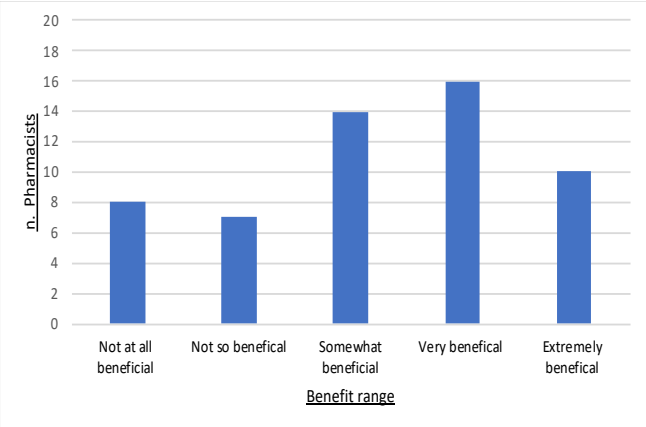


Figure S1e: Answers to Question 10, *Pharmacists perceptions on whether the delivery of adrenaline auto-injectors by drone would be beneficial for patients in emergency situations.* ***Direct quotes and reasonings for and against are discussed below.***

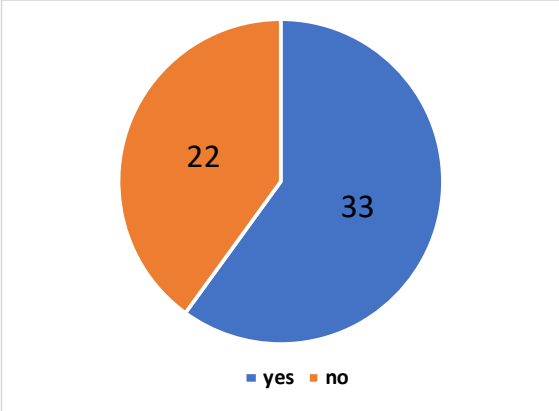


Figure S1f: Answers to Question 11, *Pharmacists approval of the use of drones to deliver adrenaline auto-injectors to patients.*

YES, beneficial:

- Drone delivery will improve supply chain function
- Drone delivery seems to be cost-effective
- Drone delivery will avoid London traffic
- Drones enhance practicality for patients with physical disabilities, especially those who are unable to collect their prescriptions from their local pharmacies.
- Drones are a quick way to reach patients in any scenario/environment.
- If a patient needs an auto-injector and they cant get it by other means, then drone delivery may save a life.
- For certain destinations where it would difficult to get the medication to the patient, e.g. in war zones, provided that the stability of the medication is maintained, the medication reaches the correct patient, does not fall into the wrong hands and does not pose a safety risk to the patient or the public. I feel that the patient should have to agree to this delivery method before going ahead with it so it would be by patient choice.
- If there is no alternative, then this is a novel option. Clearly there would need to be safeguards in place and in my previous answers, I speak from a standpoint of relative inexperience (e.g. likely stability or susceptibility to damage of adrenaline on drones). Given the potential catastrophic consequences of not having adrenaline to hand, then any solution is worth exploring, with the right infrastructure and safeguards to support. An interesting idea!
- An amazing concept but may make some people complacent thinking they do not need to carry one if they know a drone could deliver it.
- Self injecting adrenaline is a holding measure and short-lived therapy until an ambulance with paramedics arrive to deliver care. Anaphylaxis kills. The drone must be able to beat the speed of ambulances but patients must see a healthcare professional after as further treatment is often required. First experience of anaphylaxis patients must be reviewed and treated in a hospital.

NO, not beneficial:

- Is it safe? Worried about needles being transferred to the wrong patients.

- The nature of drones in terms of air space, no fly areas, negative public perception "snooping"/privacy, where to deliver to – especially in densely populated areas/high rise apartment type accommodation.

- How do you ensure it reaches the right patient and the right distance? Also depends on the patients state, are they well enough to retrieve the EpiPen from the drone?

- How would the issue of downed/crashed drones and security of medicines be assured?

- Drones may affect the current aerial dimension ie: planes, has this been considered?

- Have you considered time? A drone probably wont get to a patient in anaphylaxis quick enough.

- Locations would need to be assessed as to suitability from drone delivery – landing area, cables/wires, public safety, space – could not have a guaranteed delivery point in an emergency.

- Whilst I recognise it can assist in an emergency situation, I would require far more information about the quality assurance that the drone would be able to maintain in order to deliver the product intact. There would also need to be standards in place to deal with a situation where the drone malfunctioned/did not reach target destination or patient intact and assurances that it did not fall into the wrong hands. I do not know enough at this stage to feel the risks outweigh the benefits as most patients I come across have at least 2 EpiPen® auto-injectors with them at any one time and look to replace one when it has either been administered or expired.

- Extremely allergic patients should be taking with them at all times. If one was not available how could a drone help this ?

- Anaphylaxis episodes are a medical emergency and need medical attention - Drone delivery is not a substitute.

- This is not appropriate for first issuing of adrenaline when patients need counselling.

- Drone security and EpiPen security would be a huge negative, Drone could be a target to capture and resell EpiPen illicitly.

S2 Buffer Preparation and Model Formulations:

A 500mL buffer solution was formulated based upon the EpiPen® (1mg/mL) formulation itself and stored in the fridge – 6g sodium chloride (Acros Organics, extra pure, LotN#A0290430, Code:194090010), 1.67g sodium metabisulfite (Sigma Aldrich, LotN#SLCB1165, PCode:102162351, >99%), 0.1M HCl (diluted with 85mL water from 37% HCl, Sigma Aldrich) and distilled water, pH2.8 maintained.
For more information on the EpiPen: https://www.medicines.org.uk/emc/product/4289/smpc

Adrenaline 1mg/mL solution for injection ampoules (Macarthys Laboratories Ltd T/A Martindale Pharma PL01883/6118R) were purchased and diluted to 0.5mg/mL with a buffer solution based upon this ampoule – 4.6g sodium chloride, 0.2g sodium metabisulfite, 0.1M HCl and distilled water, pH3.1 maintained.
For more information on the injection ampoule: https://www.medicines.org.uk/emc/product/3673/smpc

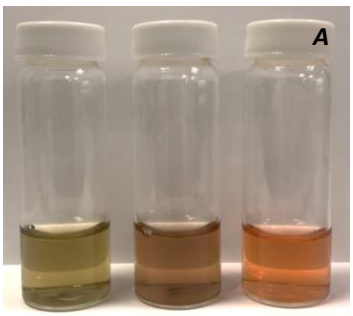
Amber vials were not used since the EpiPen® vial and ampoules were glass.

S3 Skyports:

SkyPorts are a UK based company determined to advance the future aerial dimension. They are the first company who have designed and marketed a connected network infrastructure to increase urban air mobility services and opportunities, for both passengers (commercial air taxi services “Volocopter”) and cargo (medical, e-commerce and logistical) globally.
For more information: https://skyports.net

S4 Stability Investigation:

CD is the difference in absorbance of left and right-handed circularly polarized light. CD spectra magnitude and sign are derived from a chiral chromophore which is able to make optically active electronic and magnetic dipole transitions. Adrenaline ellipticity signals due to chiral sensitivity were observed at 230nm and thus the study parameters were set.



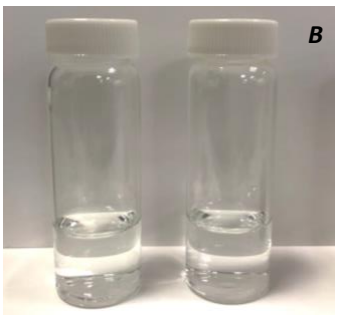
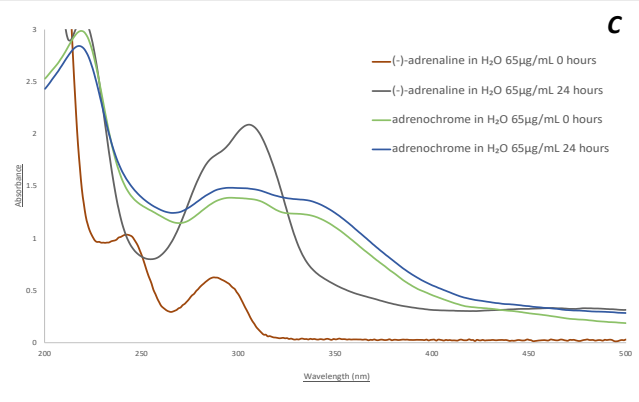


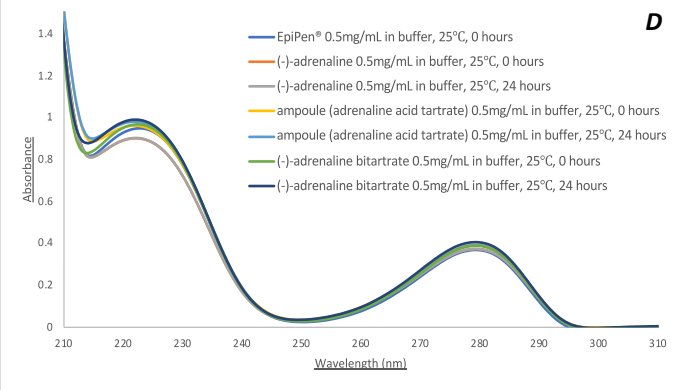
Figure S4a) *Picture taken against a white background after a 24 hour storage period at 25°C. L→R adrenochrome 65 µg/mL in 0.1M HCl, adrenochrome 65 µg/mL in water, (-)-adrenaline 65 µg/mL in water.*

Figure S4b) *Picture taken against a white background at 25°C. (-)-adrenaline in 0.1M HCl 65 µg/mL at 0 hours (L) and after 24 hours (R).*

Figure S4c) *UV Spectra comparing (-)-adrenaline and adrenochrome in water at 65ug/mL for 0 and 24 hours.*

Figure S4d) *UV Spectra of adrenaline "modified" formulations at 0.5mg/mL, 25°C at 0 and 24 hours – EpiPen® and in-vitro (-)-adrenaline, ampoule and bitartrate formulations. There were no significant changes in concentration after 24 hours (p>0.05).*





S5 The effects of light:

Borosilicate glass vials (7mL) containing 2mL in-vitro model solution (0.5mg/mL) were subjected to light (artificial light with visible and UV outputs and natural laboratory light) for 0.5 hours, 3 hours, 24 hours at 25ºC. A control sample (0 hours) covered in silver foil for light protection was prepared for comparison. The UV and CD spectra for all in vitro epinephrine samples after exposure to light at different intervals overlapped seamlessly with absorption peaks at both 280nm and 221nm and CD negative signal at 230nm. All samples remained visually clear throughout the specified time interval and there were no significant differences between the samples and the control samples ($p>0.05$) where for UV 0.5 hours ($p=0.97$), 3 hours ($p=0.89$) and 24 hours ($p=0.96$) and for CD 0.5 hours ($p=0.79$), 3 hours ($p=0.40$) and 24 hours ($p=0.79$). All samples were within the proposed range conforming to the BP % label claim. Daylight becomes pertinent in countries with warm climates ie: Australia, where light radiation can cause an increase in heat on the drone compartment box, emphasising the need for drones to have cooling machinery and technology to monitor the temperatures onboard.

S6 The effects of vibration:

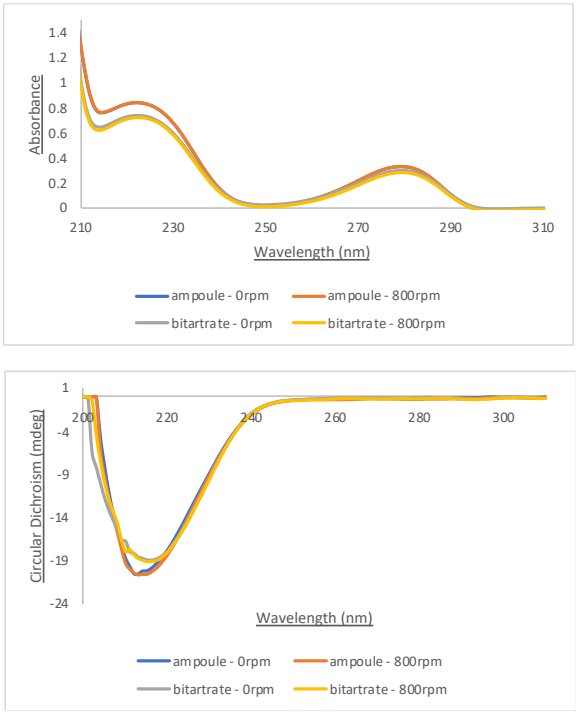
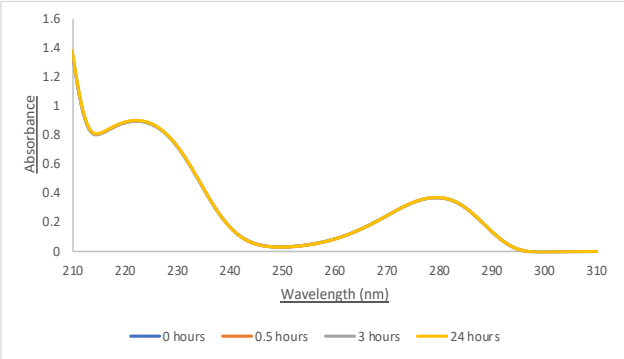
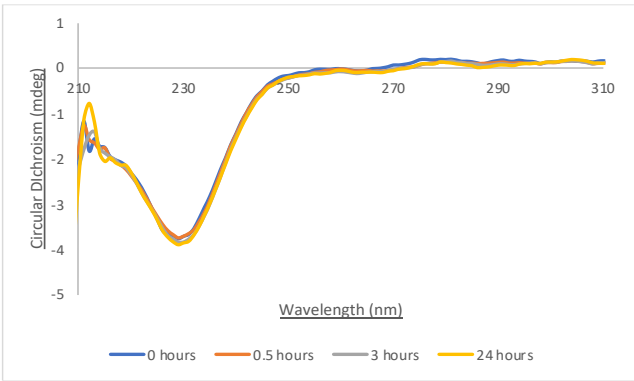


Figure S6: *UV and CD Spectra of ampoules and bitartrate formulations (0.5mg/mL), after agitation for 30 minutes, at 800rpm at 25°C (n=3).*

S7 The effects of temperature:

A





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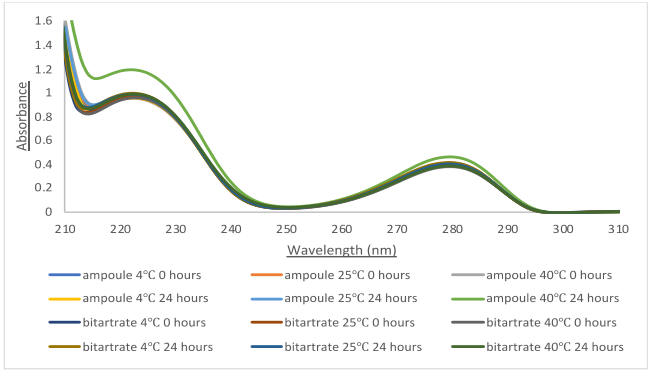


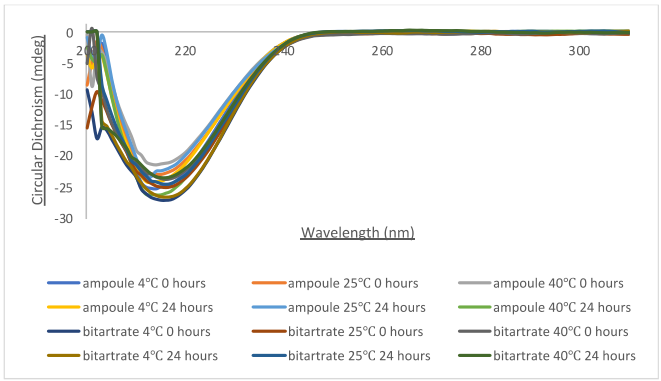
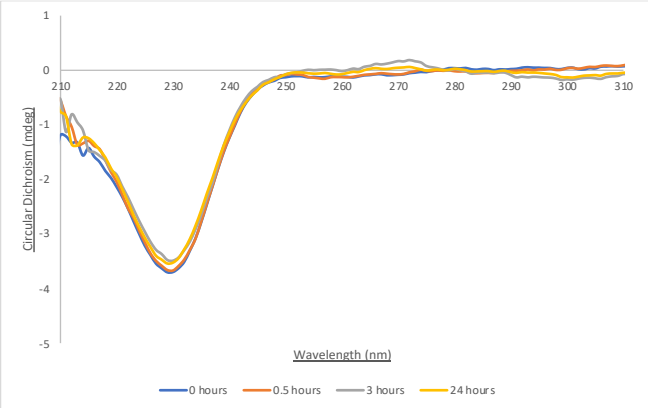
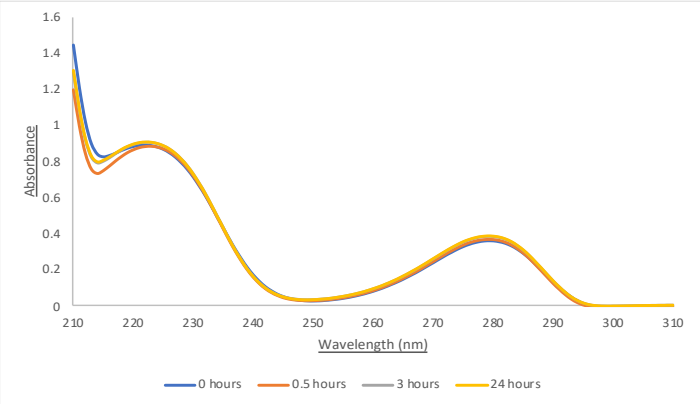


Figure S7a: *UV and CD Spectra of in-vitro (-)-adrenaline formulations 0.5mg/mL at 25°C for 0, 0.5, 3, 24 hours at 0.5mg/mL (n=3).* ***Figure S7b:*** *UV and CD Spectra of ampoules and bitartrate formulations at 4°C, 25°C, 40°C for 0 and 24 hours at 0.5mg/mL (n=3). The small graphical differences in CD intensity for the same temperature over time are due to the smoothing application and high noise to signal ratio, because the data reveals there were no real significant differences (p>0.05).*

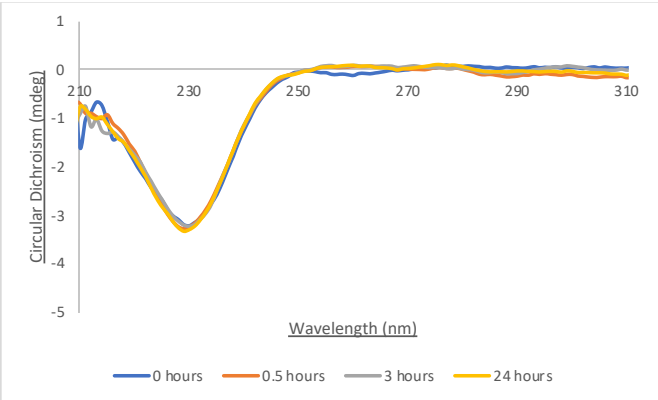
4°C c)



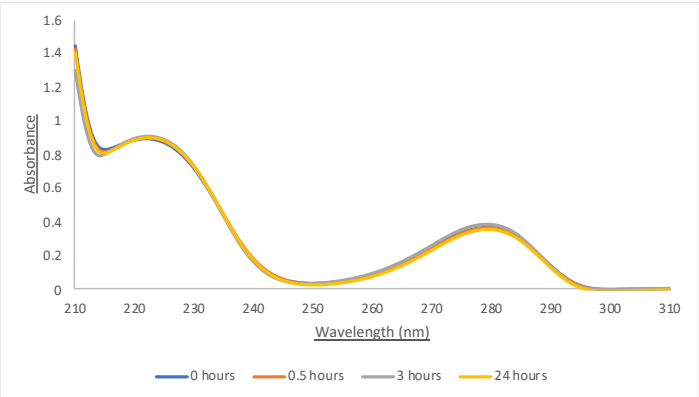
4°C d)



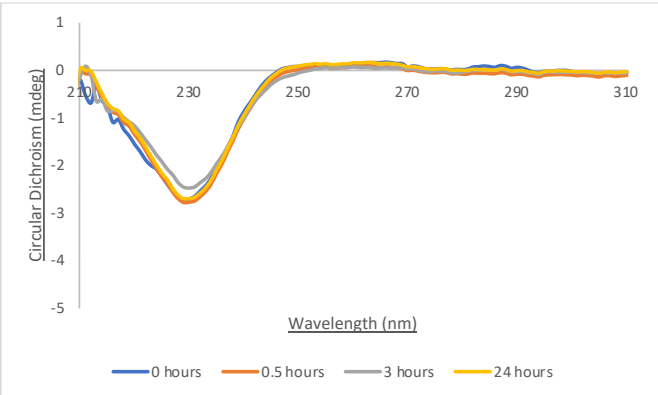
40°C e)



40°C f)



65°C g)



65°C h)

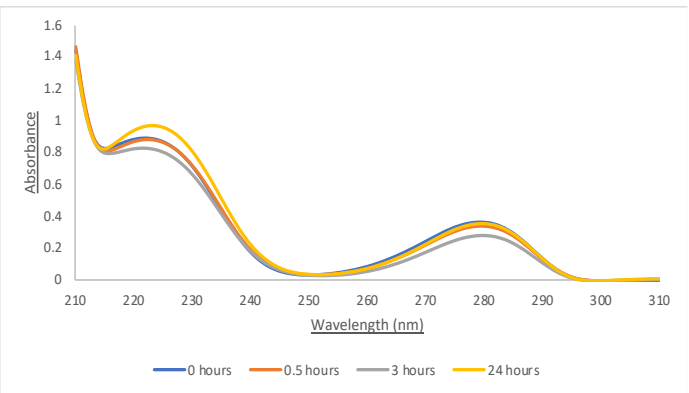


Figure S7e-h): *UV and CD spectra of (-)-adrenaline in buffer solutions at 4°C, 40°C, 65°C for 0, 0.5, 3, 24 hours at 0.5mg/mL (n=3). Pharmacopeia temperature maxima for stability testing is 40°C, however this is not representative of countries with warmer climates, thus 65°C was also used.*

S8 Drone Flight:

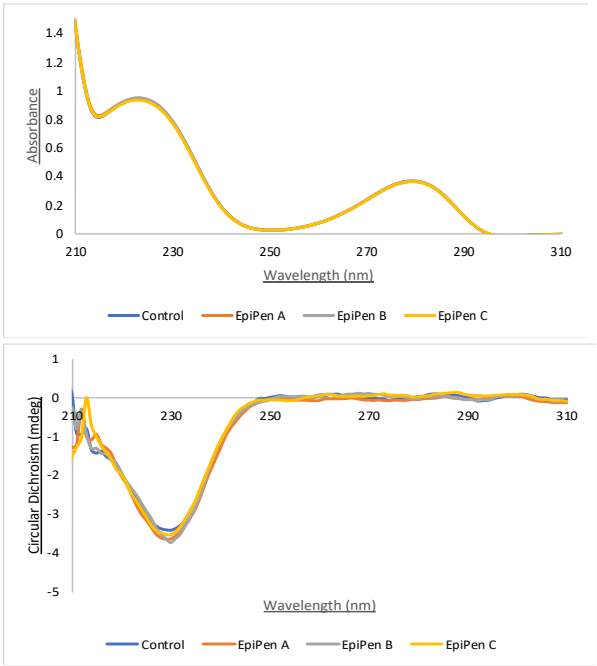


Figure S8: *UV and CD Spectra of EpiPen® after drone flight of 10732m, at 12m/s, 1.82g (±0.23), 10.70°C (±0.32), 47.74%rh (±0.29).There were no significant differences observed in terms of UV: EpiPen® A (p=0.97), EpiPen® B (p=0.98), EpiPen® C (p=0.99) and CD: EpiPen® A (p=0.55), EpiPen® B (p=0.11), EpiPen® C (p=0.73).*

S9 Medical-Specific Payload Box:

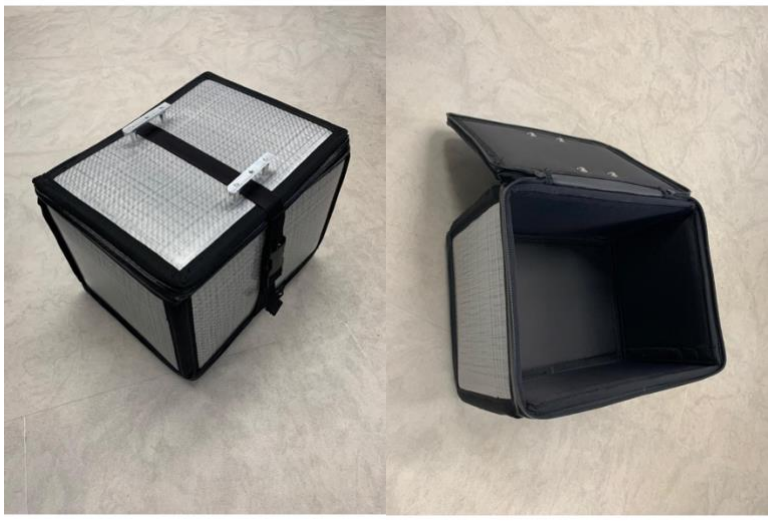


Figure S9: *The novel medical-specific payload box which can be attached for future investigations.*

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