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RESEARCH ARTICLE

Formulation Development and Evaluation of Injectable Dosage form for Stabilization of Adrenergic Drug Molecule.

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Abstract

Adrenaline (ADR) is the endogenous catecholamine with potent α and β adrenergic stimulating properties. The α adrenergic action increase systemic and pulmonary vascular resistance increasing both systolic and diastolic blood pressure. Adrenaline to be release in blood stream, which increase heart rate, muscle strength, blood pressure and sugar metabolism.

Oxidation degradation of the drug product is the major route of degradation. It's impact the Chemical and physical changes of pharmaceutical drug product in the formulation development process. Physicochemical changes in the product can affect both the safety and efficacy of drugs product.

The creation of a novel, stable lyophilized version of adrenaline for injection was the main goal of this work. The stability of Adrenaline is of utmost importance due to its classification as a catechol compounds that are sensitive to oxidation to o-quinones, which can thus react further to form highly colored compound. Adrenergic drug further react to form adrenochrome, highly colored indole derivative. Rate of this reaction increased with pH, temperature and presence of the metal ions. Adrenergic drug aqueous solution deteriorate rapidly on exposure to air or light or heat and discolour to pink from oxidation to adrenochrome and to brown from formation of melanin. Due to its highly oxidation property and its susceptibility to degradation in aqueous solutions. To achieve this, the Adrenaline injection was processed using freeze-drying technology to avoid its aqueous solution instability. The addition of Glycine, serving as a bulking agent, within an aqueous solvent system. The choice of bulking agent was based on factors such as the drug substance's solubility, stability, and feasibility in the manufacturing process. During the development of the formulation, the bulk solution underwent evaluation to assess the effects of process time, temperature, and compatibility with the materials it came into contact with.

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Keywords: endogenous catecholamine, Adrenargic for injection, Glycine, Injectable, Critical quality attributes Freeze dried, Lyophilization

INTRODUCTION:

Adrenaline (ADR) is the endogenous catecholamine with potent α and β adrenergic stimulating properties. The α adrenergic action increase systemic and pulmonary vascular resistance increasing both systolic and diastolic blood pressure [1,2]. Adrenaline to be release in blood stream, which increase heart rate, muscle strength, blood pressure and sugar metabolism. Adrenaline, is a sympathomimetic catecholamine (adrenergic agent) designated chemically as 4-[1-hydroxy-2 (methylamino) ethyl]-1,2 benzenediol, a white, microcrystalline powder.

In general, the most common uses of parenteral adrenaline are to relieve respiratory distress due to bronchospasm, to provide rapid relief of hypersensitivity (anaphylactic or anaphylactoid) reactions to drugs, animal serums and other allergens, and to prolong the action of infiltration anesthetics . In addition to the above functions, epinephrine is the primary drug administered during cardiopulmonary resuscitation (CPR) to reverse cardiac arrest 3, 4

ADR is pH dependant solubility, slightly soluble in water, DMSO. ADR must be stored in tightly closed containers, vacuum pouched, light protection at controlled room temperature between 20°C to 25°C,[3] away from moisture, ADR molecular weight is 183.2 Daltons and its chemical formula is $C_9H_{13}NO_3$.[3] Figure 01 depicts the molecular structure of ADR.

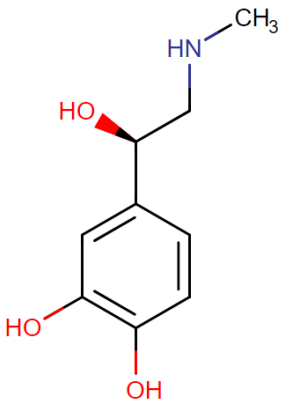

Figure 1 shows the synthetic form of ADR. Chemical structure (Adrenaline)

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1.) MATERIALS AND METHODS:

Adrenaline (ADR) was provided as gift sample by PAR Pharmaceutical ltd. Glycine was procured from Merck. Other excipients were of analytical grade. The main aim of proposed study is to develop stable dosage form of Adrenaline for injection using Glycine as bulking agent and as antioxidant property. Pre-formulation activity, bulk solution solubility and stability in the presence of Glycine, bulk solution hold time evaluation at various temperatures prior to lyophilization, compatibility of bulk solution of drug product with various contact material, optimization of lyophilization cycle with desired water contented and other critical quality attributes (CQA) are all included in the total development work.

1.1 SELECTION OF INGREDIENT IN FORMULATION:

Based on available literature and references, some of commonly used excipients were evaluated for proposed injectable formulation with their specific functions.[5,6]

In the proposed novel injectable formulation Glycine was selected as bulking agent,[7] Sodium chloride selected as tonicity modifying agent,[7] in addition to other pH modifying ingredients (hydrochloric acid & sodium hydroxide). Water work as solvent. All the listed materials had their risk evaluated as part of the QbD process. Throughout the development study, the quantity of each ingredient was optimized. Based on research in the literature and scientific understanding, the critical material characteristics for each material were determined.[7]

Glycine is commonly used as a bulking agent and antioxidant freeze-drying (lyophilization) technology.[7] Glycine is a valuable bulking agent in drying technology due to its ability to prevent ice crystal formation, stabilize drug molecule, reduce oxidation, and aid in controlled drying. These properties make it an essential component in the formulation of freeze dried pharmaceuticals and biologics.[8] It helps ensure that the ADR maintain their stability, efficacy, and quality throughout the freeze-drying process and during storage.

Table 1 lists the materials used in the medicinal formulation. The product's material was chosen in accordance with global pharmacopeial standards.

Table#01: Material evaluated for below developmental work:

Ingredients	Manufacturer	Function
Glycine	Merck	Antioxidant Bulking agent
Sodium chloride		Tonicity modifying agent
Hydrochloric acid		pH adjustment
Sodium hydroxide		pH adjustment
Water*	-	Solvent

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*Water will be removed after lyophilization from final drug product

1.2 MANUFACTURING PROCESS OPTIMIZATION

The development efforts aimed to create a new pharmaceutical formulation matching the desired quality target product profile (QTPP). Both the quantitative and qualitative compositions were established through literature review and preliminary experimental trials. This drug product was designed to meet finished product specifications and general requirements for injectable dosage forms. Process components were chosen to align with manufacturing feasibility and compatibility with the adrenaline injection's bulk solution. As part of process development, the interaction of the product solution with materials like stainless steel, glass, and filters was evaluated. Temperature sensitivity of the bulk formulation was assessed. The outcomes are summarized in the results section.

1.2.1 Solubility study of active drug substance:

The proposed drug substance (ADR) is sparingly soluble in water, It has pH dependant solubility. Water was chosen as the solvent system for the suggested medication formulation since drug substance is sparingly soluble in water. The drug substance's solubility in water, ethanol, and acetonitrile was assessed. AVP's solubility was assessed at a concentration of 1mg/mL in water with 50mg/mL Glycine concentrations, 9 mg/mL sodium chloride concentration- and Hcl as pH adjusting agent. Table 03 provides a summary of the study's findings.

1.2.2 Drug product solution stability & compatibility:

By using a concentration of 1mg/mL of adrenaline in 50mg/mL concentrations of Glycine, Sodium chloride 9mg/mL, Hcl as pH adjusting agent bulk constancy was assessed. The bulk was kept in stainless steel and glass vessels, respectively, at standard interior temperature (RT) and 2°C-8°C. After defined time period, 0hr, 6hours, 12 hours and 24hours, study samples were collected and examined for CQA against 0hrs (control) sample results. Tables 04 and 05 provide a summary of the study's findings.

1.2.3 Adrenaline bulk solution compatibility with filter membrane:

The compatibility of a filter membrane with a bulk solution is an important consideration when selecting a filtration method for various applications, such as laboratory research, pharmaceutical manufacturing, and industrial processes. The compatibility depends on factors, ike membrane chemical composition, characteristics of the bulk solution, and the

intended purpose of the filtration. The bulk solution of ADR for injection was made, and various flush out volumes were collected over time in order to confirm the compatibility of the drug solution and make an acceptable filter membrane selection. The results were summarized in table 06

1.2.4 Development and Optimization of Freeze-drying Cycles.

When a product is lyophilized, water is taken under controlled temperature & pressure without changing its condition from solid to liquid. Pharmaceutical formulations require careful preparation before freeze-drying to manage cold stresses and achieve storage stability and visual appeal. Keeping product temperature well below the critical level during freeze-drying is crucial. Differential Scanning Calorimetry (DSC) is efficient for assessing this during freeze-dried product development.

Differential Scanning Calorimetry (DSC):

In order to properly and exactly identify the critical formulation temperature, it was necessary to collect further information on the distinctive physicochemical behavior of the ingredient in the mixture throughout the freezing process. These results significantly affect the design of the freeze-drying procedure. Glass transition temperature (Tg) of the lyophilized product must be determined in this situation, hence DSC is crucial. On the suggested formulation for recipe optimization for lyophilization, a DSC analysis was conducted. Using a DSC instrument, the proposed bulk solution sample was examined while being subjected to a series of temperatures. The details DSC study results were summarized in fig. 02.

1.3 CHARACTERIZATION OF FREEZE DRIED ADRENALINE INJECTION:

In the proposed formulation, Glycine was utilized as a bulking agent and antioxidant because it was discovered that the therapeutic substance is sensitive to oxidation and temperature and significantly degrades in the presence of oxidation and temperature. Lyophilization procedures also helped to eliminate water from the lyophilized medicinal product and avoid the further oxidation of the drug substance in drug product formulation. It was crucial to combine the pharmacological ingredient with glycine as suggested in order to achieve the intended outcome. For the purpose of assessing the degree to which a pharmacological substance forms a compound with glycine, Fourier-transform infrared spectroscopy and X-ray diffraction were conducted. FTIR (fig.03) and XRD (fig.04) is presented in result and discussion session.

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2) RESULTS AND DISCUSSION

The incorporation of glycine, led to the stability of the bulk solution for up to 24 hours before lyophilization when stored at temperatures between 2°C and 8°C. Moreover, enhanced stability was observed post freeze-drying. The lyophilization process was precisely optimized, taking into account critical quality attributes such as description, active drug content, pH of the reconstituted solution, reconstitution time, moisture content, and color absorption percentage.

The bulk solution demonstrated compatibility with various materials employed in the manufacturing of the drug product, such as stainless-steel vessels, polyethersulfone (PES) & Polyvinylidene difluoride (PVDF) membrane filters. Notably, when the drug product bulk solution was kept refrigerated for up to 24 hours, there were no appreciable changes in the critical quality features found. The quality target product profile (QTPP)'s preset acceptance criteria are successfully met by the optimized freeze-dried product.

Conclusions: The stabilization of Adrenaline for injection was successfully achieved through the implementation of the lyophilization process with Glycine as the bulking agent. The envisaged injectable formulation not only proves to be safe, but also showcases its economic viability, convenience, and overall safety in the preparation methods. These findings strongly support the viability of the freeze-dried formulation as a technically sound solution for ensuring the stability of adrenaline as a drug substance within the freeze-dried injectable dosage form. This formulation warrants more research due to its potential to treat cardiac arrest patients as a vasoconstrictor in shock, and as a bronchodilator and antispasmodic in bronchial asthma. Uses also include examples are combating low blood pressure during hemorrhagic, allergic or anaphylactic shock [2]

Solubility and Stability:

Table 02: Solubility of Active drug substance:

Drug substance	Solvent	Excipient	Observation	
			Initial	After 48 hrs at 2°C-8°C
1mg/mL	Water	None	Sparingly soluble	Slight hazy solution
1mg/mL	Water	HCL	Soluble clear solution	Soluble clear solution
1mg/mL	Water	HCL+ NaCL	Soluble clear solution	Soluble clear solution

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1mg/mL	Water	HCL+ NaCL+ Glycine	Soluble clear solution	Soluble clear solution
1mg/mL	Acetone	None	Practically insoluble	Practically insolubel

The results are reported in Table 2, the medicinal component is sparingly soluble in water and has pH dependant solubility, dilute Hcl acting as dissolution agent and pH adjusting agent, Sodium chloride act as tonicity modifying agent, Glycine as bulking agent practically insoluble in acetone. It was also noted that the medicinal material showed solubility in water when dissolved in the presence of Hcl, Sodium chloride, and glycine. After 48hrs holding of bulk in refrigerator condition, no unexpected physical changes were noticed, which is the worst-case situation for solubility assessment.

Stability and compatibility of ADR bulk formulation:

The typical analytical result of drug product solution stability at different processing temperature (5°C±3°C & standard interior temperature (RT)) in proposed solvent composition is shown in table 4.

Table 3: Stability of ADR Injection at different temperature when solution hold in Stainless steel vessel.

Test parameters	Initial	6 Hrs.		12 Hrs.		24 Hrs.	
		5°C±3°C	Room temperature	5°C±3°C	Room temperature	5°C±3°C	Room temperature
Description	Clear solution	Clear solution		Clear solution	Pink solution	Clear solution	Pink solution
pH of bulk	3.0	3.1	3.3	3.1	3.4	3.2	3.6
Drug content (By % of label amount)	101	101.1	100.1	101.2	95.4	100.9	80.2

Values represented as mean ± SD (n = 3).

Table 4: Stability of ADR Injection at different temperature when solution hold in glass Beaker.

Test parameters	Initial	6 Hrs.		12 Hrs.		24 Hrs.	
		5°C±3°C	Room temperature	5°C±3°C	Room temperature	5°C±3°C	Room temperature
Description	Clear solution	Clear solution		Clear solution	Pink solution	Clear solution	Pink solution
pH of bulk	3.0	3.0	3.2	3.1	3.3	3.2	3.5

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Drug content (By % of label amount)	101.0	101.0	100.9	101.1	98.5	101.1	89.3

Values represented as mean ± SD (n = 3).

Bulk solution stability data reveals no significant changes in pH, appearance, and content of the bulk solution up to 6 hours at both storage conditions (5°C±3°C & standard interior temperature). However, when stored for 12 hours and 24 hours at ambient room temperature, the bulk solution experiences a notable change in the colour of the solution clear colourless to pink colour and pH and assay reduction compared to the 5°C±3°C storage. This highlights the heat sensitivity of the active drug and the bulk solution's instability at room temperature within 12 hours. Consequently, it's recommended to maintain the bulk solution at 5°C±3°C throughout the manufacturing process. Since there was no discernible difference in the results when the data was compared, it was also concluded that the bulk solution was compatible in both stainless steel and glass material.

Compatibility of bulk solution with Filter membrane:

The bulk solution of ADR injection was prepared and different flush out volumes collected over a period and result were tabulated in below table 5.

Table 5: Filter compatibility data with adreanline injection bulk solution

S. No.	Sample flush out volume in mL	Filter Type and drug content in %			
		Description		% Assay	
	Initial unfiltered bulk	CCLS*		101.5%	
	Filtered bulk solution	Polyethersulfone (PES) filter		Polyvinylidene difluoride (PVDF) filter	
		Description	Drug content (%)	Description	Drug content (%)
1	0mL-10mL	CCLS*	101.1	CCLS*	100.2
2	10mL-20mL		101.3		100.6
3	20mL -30mL		101.6		100.9
4	30mL -40mL		101.5		101.2

* Clear, colorless liquid solution; values shown as means standard deviations (n = 3).

Based on the information in Table 6, it is evident that the selected filters exhibit no noticeable physical changes or discoloration. Throughout the filtration process of the bulk solution, there

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was no evidence of fibre formation or filter shedding. The initial active drug content was 101.5% before filtration. After the first 10mL bulk filtration using a PES membrane filter, the content measured 101.1%. When utilizing a PVDF filter membrane, there initial 10 mL drug content was 100.2% there was as such no drug absorption within the first 10mL, 20mL of bulk, after filtering 40mL of bulk, the content measured 101.5%. and 101.2% This study concludes that the PES and PVDF both membrane filter is compatible, with respect to description and drug content.

PRUDUCT LYOPHILIZATION:

Differential Scanning Calorimetry (DSC) study:

Differential Scanning Calorimetry (DSC) stands as a robust thermal analysis method utilized for investigating the heat transfer phenomena linked with physical and chemical transformations within materials, as these phenomena evolve concerning variations in temperature or time. The foundation of DSC is the measurement of the heat difference (enthalpy change) that occurs when a sample and a reference material are put through the same controlled temperature program. The DSC study was performed on drug product.

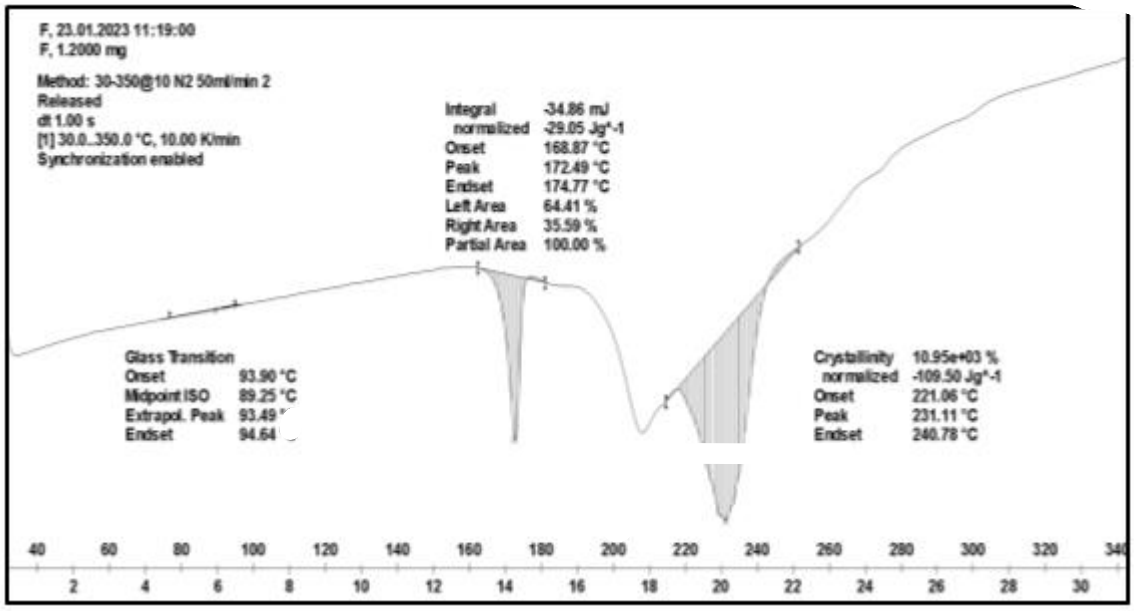

Fig. 02: DSC graph is depicted in fig which clearly shows that the phenomenon of freezing and onset of collapse.

According to the DSC study shown in Figure 2, the curve exhibits a baseline glass transition on set -93.90 °C and end set -94.64 °C, signifying a "glass transition." DSC helping the measurement of the heat flow associated with transition within a material across a specified

temperature range. These changes in the heat flow can provided evidence of physical and chemical changes within the material such as glass transitions, crystallisations and melts.

Lyophilization cycle optimization data:

Based on DSC study and available literature information, several lyophilization cycles were examined in order to optimise the desired cycle to obtain a consistent result by adjusting the vacuum and drying temperature. Amongst the various trials water content was observed to be diverse with different trial. With an adjusted lyophilization cycle, the water content and cake appearance were determined to be satisfactory.

Optimized lyophilization cycle for proposed formulation

Table 6 presented finalized optimized lyophilization cycle after various trial taken using with different value & time of freezing temperature, sublimation & secondary drying with respective vacuum.

Common problem in Lyophilisation cake formulation are lyo cake collapse, it is a phenomenon which occurs in amorphous solids when the product reaches a higher temperature than the collapse temperature, Tc (closer to the glass transition temperature Tg'). The amorphous phase of the solid experiences internal movement without reaching the melting point, with the crumbling or collapse of the dried cake as a result. It can resolve by maintain the product temperature below the collapse temperature during all the primary drying time (while there is still presence of ice in the product). Avoid the formation of a "dried skin" at the top of the surface.

Table 6: Optimized lyophilized cycle for Adrinaline injection

Lyophilization steps	Temperature	Ramp	Hold	Vacuum
-	5	-	30 min	Off
Freezing	-45°C	120 min	150 min	Off
	-3°C	90 min	150 min	Off
	-45°C	90 min	360 min	Off
Primary drying	-0°C	180 min	2700 min	150 mT
	40°C	540 min	-	50 mT
Secondary drying	40°C	-	900 min	0 mT

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In the optimized lyophilization cycle from Table 6, freezing was conducted at -45°C, considering the bulk solution's freezing point, scalability, and uniform freezing across all vials in the lyophilizer. Following freezing, sublimation occurred below 40°C to prevent collapse, beginning at 0°C. A stepwise sublimation process with controlled temperature increments was used for efficient and safe drying. The driving force is the temperature and vapor pressure difference between the sample's sublimation surface and the ice layer on the condenser, with a higher difference leading to faster drying. Vacuum was selected based on vapor pressure requirements; 150mT to 50mT was chosen to match a 0°C ice layer, preventing melt-back during sublimation. The desorption temperature for solid cake drying was set at 40°C. This comprehensive freeze-drying cycle effectively removed water from the drug product, resulting in a stable, lyophilized formulation with desired moisture content and consistent product quality.

Optimized lyo cycle cake structure image shown in below figure 3. Packaging components containing 10mL and 1mL clear glass type I plus tubular vial with 20mm and 13 mm neck with Lyo rubber stoppers, Each vial contains 10mg of ADR in 10 mL vial and 1mg of ADR in 1mL vial reapectively.

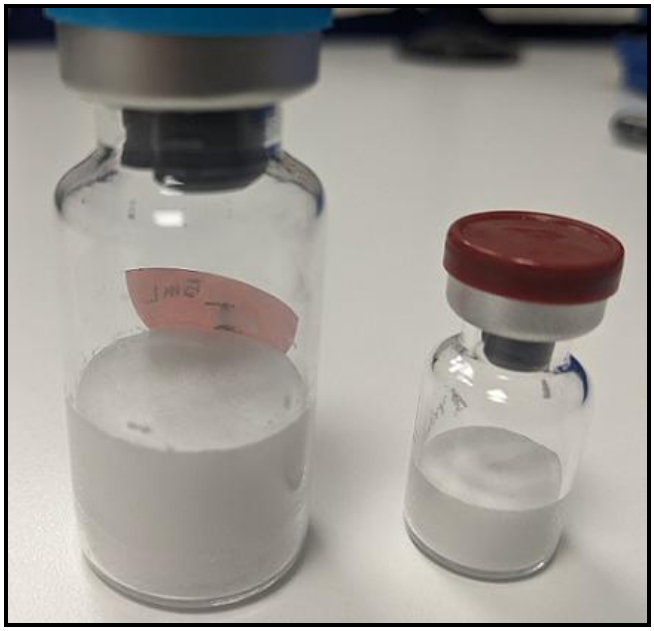

Fig 3: Showing Adrenaline for Injection lyo cake structure. 10mL and 1mL vial.

Additional characterization data for Lyophilized drug product:

The Fourier-transform infrared spectroscopy (FTIR):

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To assess the suitability of the freeze-drying process, samples from the freeze-dried medication were subjected to FTIR analysis. To gain deeper insights into the complexation process between the drug substance and drug product finished form, FTIR spectra were collected (see Figure 3) using the individual drug material and the lyophilized drug product.

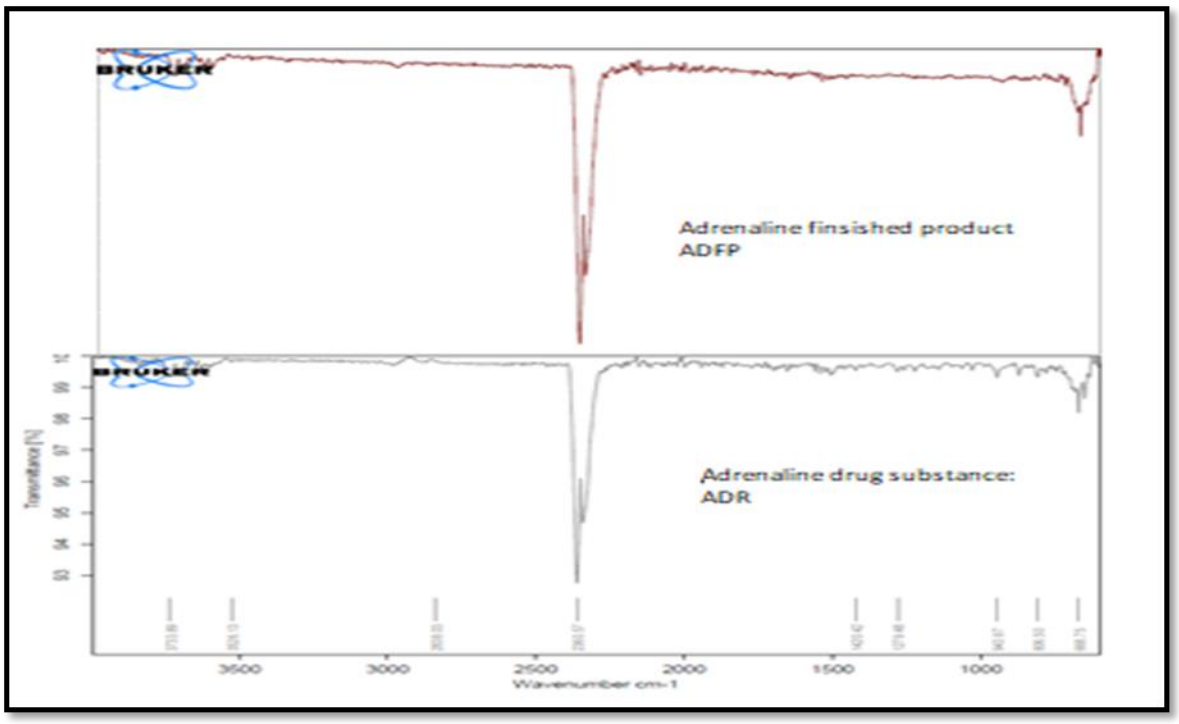

Fig. 04: FTIR graph for drug substance and freeze-dried product of Adrenaline injection

In the FTIR spectra of ADR, 3526 cm −1 and 2836 cm −1 are the stretching vibrations of -OH with CH3 on the benzene ring

The ADR peak was clearly seen at 2360 cm (C-O stretching) -1. The FTIR spectra of ADR showed C-N stretching at 1278cm-1, C-O stretching at 1612.38 cm-1, C-H stretching at 3010.01 cm-1, and C=C stretching at 1639.38 cm-1. The spectra of ADR drug product showed that C-N stretching at 1278cm-1, C-O stretching at 1612.38 cm-1, C-H stretching at 3010.01 cm-1, and C=C stretching at 1639.38 cm-1. In the lyophilized drug sample, this peak was clearly sean at 2360 cm.

From the FTIR spectrum of ADR, ADR lyophilized drug product, it can be concluded that chemical integrity of ODH was preserved.

X-ray diffraction (PXRD) study:

Powder X-ray diffraction studies have been widely used to understand crystallinity of solids. This uses Bragg's equation to study the crystal structure of solids by fallowing equation.

$n\lambda = 2\ d \sin\theta$ (29)

Where 'n' is order of diffraction, λ = wave length of X-rays,

d= d spacing distance between two planes of crystal, θ = angle of diffraction,

By knowing the θ, the angle of diffraction d spacing can be calculated where d spacing gets changed significantly. It is considered that polymorphic changes have taken place or crystal habit has changed. But with same 2θ peak intensity has been reduced then it is interpreted as reduction of crystallites of the solids. The PXRD pattern of ADR drug substance and ADR finished drug product form has showed in the (Figure 4) slight reduction in the crystalinity of drug molecules same peaks have been observed in ADR finished product with slight reduced intensities. These findings suggest the retention of the crystallinity of drug substance in drug product formulation, crystallization due to drug substance behaviour during the freeze drying process, which coincides with the conclusion of Fernandes and Veiga. 91, 92

When different substances are solubilized in any suitable solvent & mix and then lyophilized, few changes can affect the crystallographic characteristics of lyophilized drug. Freeze-dried drug product charged for PXRD study. PXRD spectrum figure 4 was created utilizing ADR single pharmacological ingredient, and lyophilized ADR finished drug product.

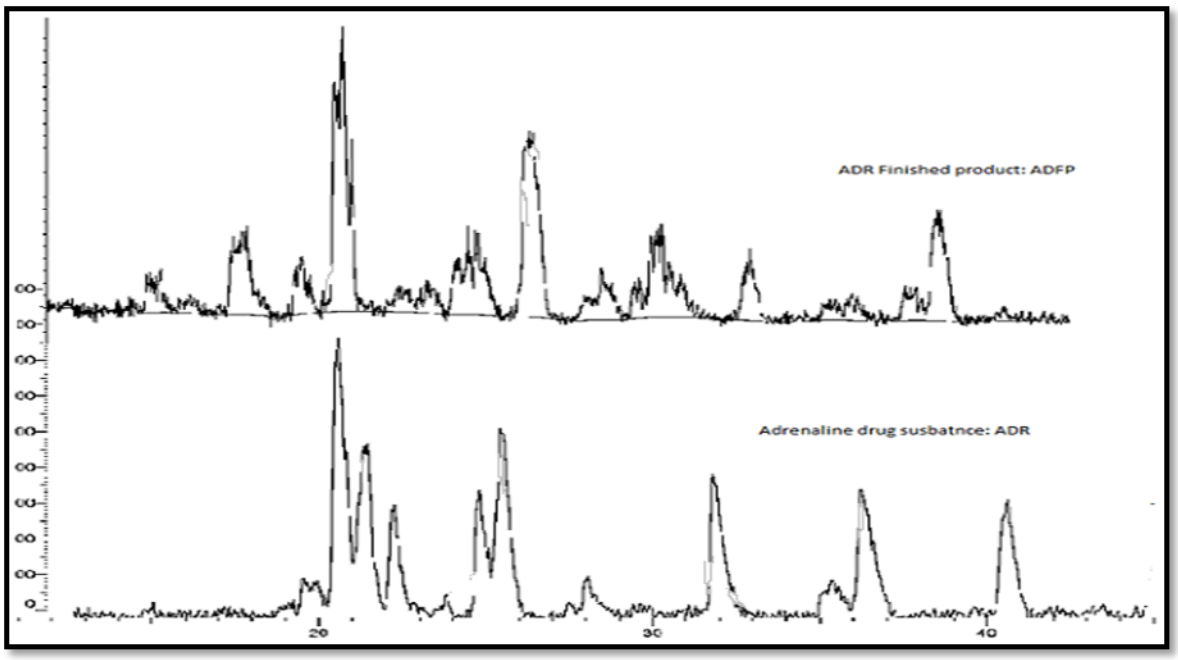

Figure 5: PXRD data for pure ADR drug substance and finished drug product of Adrenaline injection

As shown in Figure 04, the standard drug substance appears in an amorphous state, while the standard mannitol is in its crystalline form. Fluctuations in intensity values are likely due to the significant presence of amorphous mannitol in sample. Absence of mannitol hydrate form's distinctive peaks confirms its absence at 10.5, 15.1, 23.6, and 27.0° (2θ) in the freeze-dried, assayed samples of the final adernargic injection product.

Characterization of developed freeze-dried product

Batch sample was characterized throughout a 6-month period while being stored at 25°C/60 %RH and under accelerated circumstances at 40°C/75 %RH. Table 7 below lists the results of physicochemical testing and stability characteristics.

Table 7: Evaluation of physico-chemical parameter of freeze-dried Adrenaline injection

Drug Product Name: Adrenaline for injection				
Sr No	**Parameter**	**Results**		
		Initial	6M 25°C/60 %RH	6M 40°C/75 %RH
1	Description before reconstitution	WCLC	WCLC	WCLC
2	Description after reconstitution with water	CCS	CCS	CCS
3	Reconstitution time	< 5 sec	< 5 sec	< 5 sec
4	pH of reconstituted freeze-dried cake	3.0	3.0	3.2
5	Colour absorption of reconstituted drug product solution	0.00	0.00	0.01
6	Active drug content (%)	101.5	100.6	100.1
7	Water content (%)	0.7	0.9	1.1

* Values are shown as mean SD (n = 3), with WCLC standing for white color lyophilized cack and CCS for clear colorless solution.

The stability data shows that the completed lyophilized medication product complies with general injectable standards and the anticipated quality profile for adrenaline injection. Rapid reconstitution, controlled moisture level, and no melt-back in the lyophilized cake are all characteristics of the product. These results attest to the effectiveness of the suggested lyophilization cycle. While samples are subjected to stability testing, the drug concentration drastically decreases from 101% to 80.2% with change in colour of the bulk solution and pH while kept at room temperature. This demonstrates the oxidation and heat sensitivity of the formulation. However, when lyophilized materials are kept at 40°C/75 %RH for up to 6 months, there is no discernible alteration. In invention of this, it may be concluded that although the Oxidation sensitivity of the newly developed lyophilized medicinal product

allows for long term storage condition at 25°C/60 %RH and Accelerated condition up to 6 month.

CONCLUSION:

A new and reliable parenteral formulation of adrenaline injection was intended. Adrenaline (ADR) is the endogenous catecholamine with potent α and β adrenergic stimulating properties

Indicated to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock. For emergency treatment of allergic reactions (Type 1), including anaphylaxis. (1.2) was goal of this formulation. Oxidation degradation of the drug product is the major route of degradation. It's impact the Chemical and physical changes of pharmaceutical drug product in the formulation development Due to the drug's poor aqueous stability, efforts were made to enhance its stability through the process of lyophilization, with the addition of a glycine as diluent and antioxidant in the formulation. The chosen glycine was found to have no adverse interactions with the drug and demonstrated compatibility with all aspects of the formulation. The bulk solution demonstrated solution stability and compatibility with various materials employed in the manufacturing of the drug product. Notably, when the drug product bulk solution was kept refrigerated for up to 24 hours, there were no appreciable changes in the critical quality features found. By employing a carefully optimized lyophilization cycle, a consistent and effective product was achieved, characterized by the appropriate water content. Further analytical characterization studies, such as DSC, FTIR and PXRD, provided insights indicating the formation of a stable complex drug product. In the presence of glycine, this complex was essential for maintaining the stability of adrenaline in its lyophilized form. The resulting adrenaline injection formulation met all the criteria outlined in the quality target product profile. In conclusion, the developed novel freeze dried formulation, incorporating glycine, successfully stabilized the adrenaline drug substance in a freeze-dried dosage form.

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