RESEARCH ARTICLE

Formulation, Development and Evaluation of Highly Oxidative Degradative Drug Molecule Injectable Dosage form by Lyophilisation Techniques

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ABSTRACT

Adrenaline (ADR) It is lifesaving and is the only first-line drug for the treatment of anaphylaxis. Adrenaline (ADR) is the endogenous catecholamine with potent alpha- and beta-adrenergic stimulating properties. Alpha-adrenergic action increases systemic and pulmonary vascular resistance, increasing both systolic and diastolic blood pressure. Adrenaline is released in the bloodstream, which increases heartbeat, muscle strength, blood pressure, and glucose metabolism. Oxidation degradation of the medicinal product is the main route of degradation. Affects chemical and physical changes in drugs during the formulation development process. Physicochemical changes in the product can affect both the safety and efficacy of the drug product.

Main product development strategy to develop, a stable, freeze-dried product of epinephrine for injection. The stability of adrenaline injection is of paramount objective as it is classified as a catechol compound that is sensitive to oxidation to o-quinone and therefore can react further to form highly colored compounds. Adrenergic drugs further react to form adrenochrome, a highly colored indole derivative. The rate of this reaction increased with pH, temperature and presence of the metal ions. Aqueous solutions of adrenergic agonists decompose rapidly when exposed to air, light, or heat, turning pink due to oxidation to adrenochrome and brown due to melanin formation. Due to its strong oxidizing properties and easy decomposition in aqueous solutions. To achieve this, the aqueous solutions of adrenergic agonists decompose rapidly when exposed to air, light, or heat, turning pink due to oxidation to adrenochrome and brown due to melanin formation. Due to its strong oxidizing properties and easy decomposition in aqueous solutions.

Keywords: Endogenous catecholamine, Adrenergic for injection, Perlitol injectable, Critical quality attributes Freeze-dried, Lyophilization.

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INTRODUCTION

Adrenaline (ADR) action is very short within very few minutes, it directly counteracts all end-organ effects of immune mediators of anaphylaxis and stabilizes mast cells to prevent further degranulation and release of mediators.

ADR is an endogenous catecholamine with potent alpha- and beta-adrenergic enhancing properties. Alpha-adrenergic action increases systemic and pulmonary vascular resistance, increasing both systolic and diastolic blood pressure.[1,2] Adrenaline is released into the bloodstream, increasing heart rate, muscle strength, blood pressure, and glucose metabolism. Epinephrine is a sympathomimetic catecholamine (adrenergic agonist), chemically known as 4-[1-hydroxy-2(methylamino) ethyl]-1,2 benzenediol, that is a white, microcrystalline powder. In general, parenteral epinephrine is used to relieve respiratory distress due to bronchospasm, to rapidly reduce hypersensitivity reactions (anaphylactic or anaphylactoid reactions) to drugs, animal serum, and other allergens, and to counteract the effects of infiltrating anesthetics. Most commonly used for lengthening. In addition to the above functions, epinephrine is the main drug administered during cardiopulmonary resuscitation (CPR) to reverse cardiac arrest[3,4]

ADR is pH-dependent solubility, slightly soluble in water, DMSO. ADR must be stored in tightly closed containers, vacuum pouched, light protection at controlled room temperature between 20 to 25°C,[3] away from moisture, ADR mol. weight is 183.2 Da, its chemical formula is $C_9H_{13}NO_3$.[3,4] Figure 1 depicts the molecular structure of ADR.

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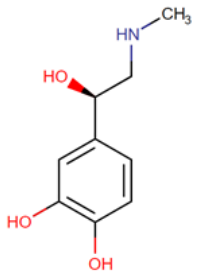

Figure 1: Chemical structure of ADR

MATERIALS AND METHODS

ADR was received as a gift sample by PAR Pharmaceutical Limited. Perlitol received procured from Roquette. The main aim of the mentioned study to develop, evaluate and stabilise highly oxidative drug molecule injectable dosage form by lyophilization techniques i.e., ADR for injection using perlitol as bulking agent property. Preformulation activity, solubility and stability of bulk solutions in the presence of Parlitol, evaluation of retention time of bulk solutions at different temperatures before freeze-dried, compatibility of bulk solutions of pharmaceutical products with different contact parts, lyophilization cycle optimization desired moisture content and other (CQAs) are covered throughout the development effort.

Ingredient Selection for Formulation

The available literature and references and some commonly used excipients were evaluated for their specific functionality for the proposed injectable formulation (Table 1.).[5,6]

Mentioning innovative injectable formulation, parlitol as a diluent agent and sodium chloride 7 as a tonicity adjusting agent were selected, as well as other pH-adjusting components (HCL and NaOH). Water acts as a vehicle. The risks of all listed substances were assessed as part of the QbD development. Through development studies, the amounts of every ingredient were optimized. Based on the literature review and scientific findings, important material properties of every ingredient were determined..[7-9]

Parlitol is mostly used as a diluent and antioxidant in lyophilization technology.[7] Parlitol is important its activity to prevent ice crystal development, stabilize drug molecules, prevent oxidation, and help control drying. These characteristics make it an important ingredient in the development of lyophilized pharma and biologics.[8] This helps maintain the stability, potency, and quality of the ADR throughout the freeze-drying process.

Manufacturing Process Development

Development efforts were aimed at creating new pharmaceutical formulations that meet. The formulation was developed to meet the final product specifications and general requirements for injectable dosage forms. Process components were selected for manufacturing feasibility and compatibility with bulk epinephrine injection solutions. As formulation development, the compatibility of product solutions with contact parts such as SS vessels, glass, and membrane filters was evaluated. The heat sensitivity of the bulk formulation was evaluated. The results are mentioned in the results below.

Table 1: Material evaluated for below developmental work

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

Active ingredient solubility

The proposed active (ADR) is sparingly soluble in water. It has pH-dependent solubility. Water was selected as the vehicle system for the mentioned formulation the active ingredient is slightly soluble in a vehicle. The solubility of the drug in vehicle, ethanol, and acetonitrile was evaluated. The solubility of AVP was evaluated at the following concentrations 1-mg/mL in water with 100 mg/mL perlitol concentrations, 9 mg/mL sodium chloride concentration- and HCl as pH adjusting agent. Table 3 a summary of the research results is presented

Drug product chemical stability and compatibility

Mass homeostasis was assessed using peritol sodium chloride at a concentration of 100 mg/mL, and epinephrine at a concentration of 1-mg/mL in HCl at 9 mg/mL as pH modifiers. Most were stored in SS vessels or glass containers at standard internal temperatures (RT) of 2 to 8°C. Study samples were collected after defined time periods, 0, 6, 12, and 24 hours, and CQAs were examined in comparison to the results of the 0 hours-control sample. Tables 4 and 5 mention a summary of the results.

Compatibility of adrenaline stock solution and filter membrane

Interaction of the filter membrane with the bulk solution is a main consideration when choosing filtration techniques for a variety of uses, suitability on factors such as the chemical content of the membrane, the characteristics of the main solution, and the intended purpose of filtration. We prepared the main solution of the ADR for injection and collected various washout volumes on time to confirm the compatibility of the drug solution and select a suitable filter membrane. The results are mentioned in Table 6.

Freeze-drying cycle development and optimization

The product is freeze-dried, and water is removed under room temperature and pressure without changing its state from solid to liquid. Pharmaceutical formulations must be carefully prepared before lyophilization to handle cold stress and achieve stability and attractive appearance.[10,11] During freeze-drying, it is important to maintain the product temperature well below the critical level. Differential scanning calorimetry (DSC) is an efficient way to evaluate lyophilized products when developing them

Differential scanning calorimetry

To accurately determine the critical process temperature, it was important to gather more information about the characteristic physicochemical aspects of the components in the product during the freezing process. These results have significant implications for the design of freeze-drying processes. DSC becomes important in this situation as it is necessary to measure the TG of the lyophilized product. DSC analysis was performed on the proposed formulation for freeze-drying recipe optimization. DSC equipment was used to examine the proposed solution samples while exposing them to different temperatures. The details of the DSC study results are mentioned in Figure 2.

Evaluation of Lyophilized Adrenaline Injection

Parlitol was used as a bulking agent since the therapeutic substance was found to be sensitive to oxidation and temperature and degrades significantly in the presence of oxidation and temperature. The lyophilization procedure also helped to remove water from the lyophilized drug and avoid further oxidation of the drug substance during formulation. To achieve the desired results, it was important to combine perlite with pharmacological ingredients as suggested. Fourier transform infrared spectroscopy (FTIR) and X-ray diffraction (XRD) were performed to assess the extent to which pharmacological substances bind with parlitol. FTIR (Figure 3) and XRD (Figure 4) will be presented in the results and discussion session.

RESULTS AND DISCUSSION

Bulk solution showed interaction with various materials used in pharmaceutical preparation, including examples: Stainless steel vessels, membrane filters made of polyethersulfone (PES) and polyvinylidene difluoride (PVDF). In particular, no significant changes in important quality attributes were observed, drug's main solution was kept refrigerated for up to 24 hours. The preset acceptance criteria of the QTPP are successfully met by the optimized lyophilized product.[12,13]

The incorporation of parlitol resulted in bulk solution stability for up to 24 hours before lyophilization when stored at temperatures between 2 and 8°C. Additionally, increased stability was observed after lyophilization. The lyophilization process has been precisely optimized taking into account important quality characteristics description, active ingredient content, reconstitution time, pH of the reconstituted solution, content of water and absorption color.

Injectable epinephrine was successfully stabilized by performing a freeze-drying process using peritol as a bulking agent. The proposed injectable formulation was not only proven to be safe but also demonstrated economy, These results strongly support the utility of lyophilized formulations as a technically viable solution to ensure the stability of epinephrine as a drug substance in lyophilized injectable dosage forms. This preparation requires further study as it has the potential to treat cardiac arrest patients as a vasoconstrictor in shock conditions and as a bronchodilator and antispasmodic agent in bronchial asthma. Possible uses also include combating hypotension in hemorrhagic, allergic, or anaphylactic shock.

Solubility and Stability

Results mentioned on Table 2, the active component is sparingly soluble in water and has pH dependant solubility, dilute HCl acts as a dissolution agent and pH adjusting agent, Sodium chloride act as a tonicity modifying agent, perlitol as a bulking agent practically insoluble in acetone. The active was soluble in water when dissolved in the presence of HCl, sodium chloride, and peritol. After storing the mass in the refrigerator for 48 hours, no odd physical changes were observed. This represents the worst-case solubility evaluation.

ADR Bulk Solution Stability and Compatibility

Typical analysis results of the stability of drug solutions at various processing temperatures (5 ± 3°C and standard internal temperature (RT)) for the proposed solvent composition are presented in Table 4.

The stability data of the bulk solution shows that there are no drastic changes in the pH, appearance, and contents of the bulk solution for up to 6 hours under at both storage conditions (5 ± 3°C and RT). When the main solution is stored at room temperature for 12 and 24 hours, the color of the solution changes significantly from colorless and transparent to pink, and the pH and pH decrease compared to when stored at 5 ± 3°C test. This shows the thermal sensitivity of the active ingredient and the instability of the main solution within 12 hours at room temperature. Therefore, it is recommended to keep the main solution at 5 ± 3°C to complete the manufacturing process. Comparing the data showed no obvious differences in the results, so it was concluded that the bulk solution is stable with both SS vessel and glass.

Bulk Solution Compatibility with Filter Membrane

The primary ADR injection solution was prepared and various washout volumes were collected over a period of time. The results are shown in Table 5.

Table 2: Active drug substance solubility

Active (mg/mL)	*Solvent*	*Excipient*	*Observation*	
			Initial	*After 48 hours at 2–8°C*
1	Water	None	Sparingly soluble	Slight hazy solution
1	Water	HCL	Soluble clear solution	Soluble clear solution
1	Water	HCL+ NaCL	Soluble clear solution	Soluble clear solution
1	Water	HCL+ NaCL+ Perlitol	Soluble clear solution	Soluble clear solution
1	Acetone	None	Practically insoluble	Practically insolubel

Table 3: SS vessel with ADR injection hold stability at different temperature

Test parameters	*Initial*	*6 hours*		*12 hours*		*24 hours*	
		5 ± 3°C	*Room temperature*	*5 ± 3°C*	*Room temperature*	*5 ± 3°C*	*Room temperature*
Description	CCS	CCS		CCS	Pink solution	CCS	Pink solution
pH of bulk	3.1	3.1	3.5	3.2	3.6	3.2	3.9
Drug content (By % of label amount)	100.1	101.1	100.1	101.3	92.3	100.5	75.2

CCS: Clear colourless solution values mentioned as mean ± SD (n = 3).

Table 4: ADR injection stability at different temperature when solution hold in glass beaker

Test parameters	*Initial*	*6 hours*		*12 hours*		*24 hours*	
		5 ± 3°C	*Room temperature*	*5 ± 3°C*	*Room temperature*	*5 ± 3°C*	*Room temperature*
Description	CCS	CCS		CCS	Pink solution	CCS	Pink solution
pH of bulk	3.1	3.1	3.3	3.1	3.4	3.2	3.6
Drug content (By % of label amount)	100.1	101.1	100.9	101.1	98.3	101.1	80.1

CCS: Clear colourless solution Values mentioned as mean ± SD (n = 3).

Table 5: Adrenaline injection bulk solution with filter compatibility

S. No.	*Filter sample volume in mL*	*Filter type and drug content in %*			
		observation		*%Assay*	
	Initial un-filtered bulk	CCS*		101.3%	
	Bulk solution filter (mL)	Polyethersulfone (PES) filter		Polyvinylidene difluoride (PVDF) filter	
		Description	Active content (%)	Description	Active content (%)
1	0–10	CCS*	101.2	CCS*	100.1
2	10–20		101.3		100.5
3	20–30		101.5		100.7
4	30–40		101.6		101.3

*CCS: Clear colourless solution Values mentioned as mean ± SD (n = 3).

In Table 6, it can be seen that the mentioned filters have no odd physical changes or discoloration. The initial active ingredient content before filtration was 101.3%. After the first 10 mL mass filtration through the PES membrane filter, the content was 101.2%. Using the PVDF filter membrane, the initial drug content in 10 mL was 100.1%, so there was no absorption of the drug within the first 10, and 20 mL blob, but after filtering the 40 mL blob. The content was 101.6%. This study concludes that PES and PVDF membrane filters are compatible in terms of description and active ingredient content.

Product Freeze Drying

DSC study

DSC is a robust thermal measurement method to study heat transfer phenomena associated with physical and chemical changes inside materials, where these occur due to differences in temperature or time. It is an analytical method.[14,15] The basis of DSC is the measurement of the heat difference enthalpy change that is observed when a sample and a reference material are exposed to the same controlled temperature system. DSC studies were conducted on drugs.

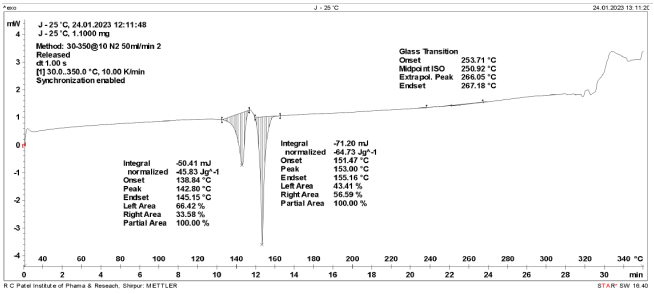

Figure 2: DSC graph is depicted in Fig which clearly shows the phenomenon of freezing and the onset of collapse

Figure 2, the curve exhibits a baseline glass transition on set -253.71 and end set -267.18°C, signifying a "glass transition." DSC helps the measurement of the heat flow associated with a transition within a material across a specified temperature range.[16] These changes in the heat flow can provide evidence of physical and chemical changes within the material such as glass transitions, crystallisations and melts.

Table 6: Optimized freeze-dried cycle for ADR injection

Freeze drying steps	*Temperature (°C)*	*Ramp (minutes)*	*Hold (minutes)*	*Vacuum*
-	5	-	30	Off
Freezing	-45	120	150	Off
	-3	90	150	Off
	-45	90	270	Off
Primary drying	-0	180	2700	150 mT
	40	200	-	50 mT
Secondary drying	40	-	420	0 mT

Freeze drying optimization cycle

DSC studies and literature information, multiple freeze-drying cycles were studied to optimize the targeted cycle and achieve constant results by adjusting the vacuum and drying temperature. In various experiments, it was observed that the water content varied from experiment to experiment. Due to the adjusted freeze-drying cycle, the moisture content and appearance of the cake were found to be good.

Optimized freeze-dried cycle for proposed formulation

A common problem in lyophilization cake formulation is cake collapse. This is a phenomenon that occurs in amorphous solids when the product reaches a temperature higher than the collapse temperature Tc (a temperature close to the glass transition temperature Tg`). The solid amorphous phase undergoes internal motion without reaching its melting point, resulting in the dry cake crumbling or crumbling. This problem can be solved by maintaining the product temperature below the collapse temperature during the primary drying period (while there is still ice in the product). Avoid the formation of "dry skin" on the surface.

In the freeze-dried cycle shown in Table 6, lyophilization was performed at −45°C considering the freezing point, scale-up, and uniform freeze-drying of all vials in the main solution lyophilizer. After freezing, sublimation is done from 0 to below 40°C to prevent collapse. A stepwise sublimation step with controlled temperature steps was used for effective and safe drying, driving force is the difference in temperature and vapor pressure between the sublimated surface of the sample and the ice on the condenser. The greater the difference, the faster the drying will occur. Vacuum selected based on vapor pressure requirements. 150 to 50 mT was chosen to correspond to an ice layer at 0°C and to prevent melting back during sublimation. The secondary drying temperature for solid cake drying was set at 40°C. This lyophilization cycle effectively removes water from pharmaceutical products, resulting in stable freeze-dried formulations with desirable moisture content and stable product quality.

The optimized lyophilization cycle cake structure image is shown in Figure 3. Packaging components containing 10 and 1-mL clear glass type I plus tubular vial with 20 and 13 mm neck with Lyo rubber stoppers, each vial contains 5 mg of ADR in 10 mL vial and 1-mg of ADR in 1-mL vial, respectively.

Characterization Data Additional for Freeze Dried Drug Products

Fourier-transform infrared spectroscopy

The available literature and references and some commonly used excipients were evaluated for their specific functionality for the proposed injectable formulation and drug product finished form, fourier-transform infrared (FTIR) spectra were collected (Figure 4) using the active material and the lyophilized drug product (Figure 3).

In the FTIR spectrum of ADR, 3526 and 2836 cm^{-1} are stretching vibrations of -OH due to CH_3 on the benzene ring.

The ADR peak was clearly visible at 2360 cm^{-1} (C-O stretch). The IR spectrum of ADR shows C-N stretching at 1278 cm^{-1}, C-O stretching at 1612.38 cm^{-1}, C-H stretching at 3010.01 cm^{-1}, and C=C stretching at 1639 and 38 cm^{-1}. The spectrum of the ADR drug showed a C-N stretch at 1278 cm^{-1}, a C-O stretch at 1612.38 cm^{-1}, a C-H stretch at 3010.01 cm^{-1}, and a C=C stretch at 1639, 38 cm^{-1}. For the freeze-dried drug sample, this peak was clearly visible at 2360 cm.

From the FTIR spectrum of ADR, ADR lyophilized drug product, it concluded that the chemical integrity of ADR was preserved (Figure 4).

Powder X-ray diffraction study

Powder X-ray diffraction (PXRD) studies have been widely used to understand the crystallinity of solids. This uses Bragg's equation to study the crystal structure of solids by following the equation.[17]

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

Where 'n' is order of diffraction, λ = wavelength 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 the same 2θ peak intensity has been reduced then it is interpreted as a reduction of crystallites of the solids. The PXRD pattern of ADR drug substance and ADR finished drug product form has shown in Figure 5 slight reduction in the crystalinity of drug molecules same peaks have been observed in ADR finished product with slightly reduced intensities. These findings suggest the retention of the crystallinity of drug substances in drug product formulation, and crystallization due to drug substance behavior during the freeze-drying process, which coincides with the conclusion of Fernandes and Veiga. 91, 92

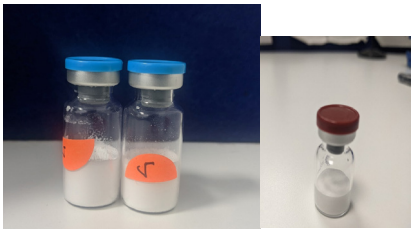

Figure 3: Showing adrenaline for injection Lyo cake structure 10 and 1-mL vial

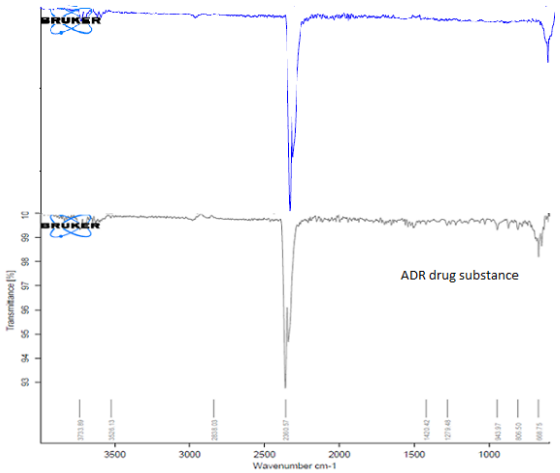

Figure 4: FTIR graph for the active substance and lyophilized product of adrenaline injection

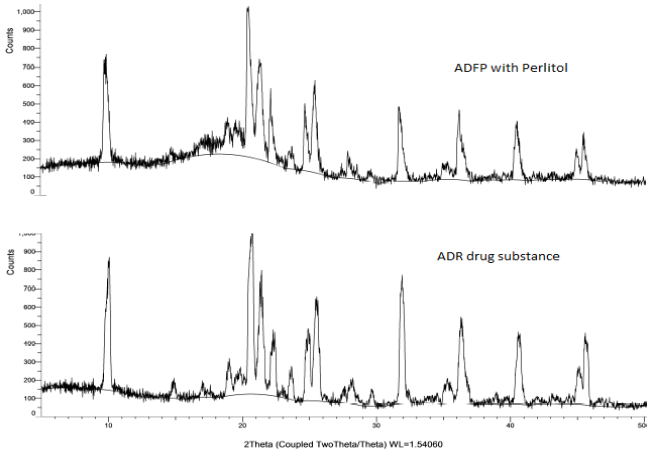

Figure 5: IR data for pure ADR active substance and FP drug product of ADR injection

Table 7: Physico-chemical evaluation parameter of lyophilized adrenaline injection

Drug product name: Adrenaline for injection				
S. No.	*Parameter*	*Results*		
		Initial	*6M 25°C/60 %RH*	*6M 40°C/75 %RH*
1	Description after reconstitution with water	CCS	CCS	CCS
2	Description before reconstitution	WCLC	WCLC	WCLC
3	pH of reconstituted freeze-dried cake	3.1	3.1	3.2
4	Reconstitution time	< 5 sec	< 5 sec	< 5 sec
5	Colour absorption of reconstituted drug product solution	0.00	0.00	0.01
6	Active drug content (%)	101.2	100.7	100.2
7	Water content (%)	0.5	0.7	1.0

*Values are shown as mean SD (n = 3),

When various substances are dissolved in appropriate solvents and mixtures and freeze-dried, there are few changes that can impact the crystallographic properties of the freeze-dried drug.[18-20] Freeze-dried formulations for PXRD studies. PXRD spectra (Figure 4) were generated using a single pharmacological ADR component and the lyophilized ADR final product.

Figure 4, standard active is in amorphous state, and standard parlitol in crystalline state. The variation in intensity values ay be due to the presence of a large amount of amorphous peritol in the sample. The absence of characteristic peaks of the peritol hydrate form indicates the absence of those peaks at 16.5, 17.9, 25.7 and 27.0° (2θ) in the lyophilized sample of the final adrenergic injectable product tested.

Characterization of Lyophilized product

Batch samples were stored at 25°C/60% RH and characterized under accelerated conditions of 40°C/75% RH for 6 months. Table 7 shows the physicochemical test results and stability properties.

WCLC standing for white color lyophilized cack and CCS for clear colorless solution.

Stability data indicate that the finished lyophilized drug meets common injection std. and the quality profile expected for epinephrine injections.[21] Rapidly reconstitution, controlled moisture content, no meltback of freeze-dried cakes are all characteristics of the product. These results demonstrate the importance of the proposed freeze-drying cycle. When the sample undergoes stability testing, the drug concentration drops dramatically from 100.1 to 75.2%, and the main solution changes color and pH while being kept at room temperature. This indicates the sensitivity of the formulation to oxidation and heat. However, storage of freeze-dried materials at 40°C/75% relative humidity for up to 6 months does not result in any noticeable changes. It can be concluded that the oxidation sensitivity of the developed freeze-dried drug allows long-term storage at 25°C/60% relative humidity and accelerated storage for up to 6 months.

CONCLUSION

A novel parenteral formulation of epinephrine injection was intended. Epinephrine (ADR) is an endogenous catecholamine with potent alpha- and beta-adrenergic stimulating properties.

Increases 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 the purpose of this formulation. Oxidation degradation of the drug product is the major route of degradation. It impact the chemical and physical changes of pharmaceutical drug product in the formulation development Due to the poor stability of this drug in water, efforts have been made to improve its stability through the freeze-drying process by adding peritol to the formulation as a diluent and antioxidant. The selected parlitol was found to have no adverse drug interactions and was compatible with considering all formulation aspects. The main solution showed solution stability and compatibility with various materials used for drug preparation. In particular, no significant changes in important quality attributes were observed when the drug's main solution was kept refrigerated for up to 24 hours. By using a carefully optimized freeze-drying cycle, a consistent and effective product characterized by an appropriate moisture content is obtained. Different analytical characterization studies such as DSC, FTIR, and PXRD provided insights indicating the formation of a stable composite formulation. In the presence of perlitol this complex was essential for maintaining the stability of adrenaline in its lyophilized form. The resulting epinephrine injection formulation met all criteria listed in the quality target product profile. In conclusion, the developed novel lyophilized formulation containing parlitol stabilized the epinephrine active substance in the lyophilized formulation.

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