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FORMULATION, STABILIZATION BY LYOPHILIZATION AND TECHNOLOGY TRANSFER STUDIES ON ANTIFUNGAL INJECTION

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Abstract: The aim of present research work was to formulate intravenous powder for injection of voriconazole and to transfer the product from lab scale to commercial scale. Since voriconazole is unstable in aqueous condition and it is stable only for 24 hours at 5-6 ^{0}C. Hence lyophilization technology was adopted to increase the stability of voriconazole. Before lyophilization three trials were carried out to optimize the process parameters in which Trial 2 was considered as optimized process. Based on this trial lyophilization was carried out. The lyophilization was carried out in five different batches by varying the total cycle time, freezing and holding time, primary drying and secondary drying time by maintaining the quantities of all the active pharmaceutical ingredients constant. An optimized lyophilization cycle of 70.16 hours has been achieved. The optimized lyophilized product was subjected to *in vitro* parameters such as description, reconstitution time, pH, water content, identification, assay, purity test. In this process the batch-5 formulation was considered as an optimized formulation with the process. All the in-vitro evaluation parameters complies the limits as per the specification. Accelerated stability studies were conducted and from the result it was concluded that the optimized formulation was found to be stable. Hence the formulation 5 can be transferred from lab scale to commercial scale via scale-up batch. Finally, it is concluded that the lyophilization is a suitable technique to increase the stability of voriconazole and the optimized formulation can be successfully transferred from lab scale to commercial scale.

Keywords: Voriconazole, Hydroxypropyl beta cyclodextrin, Lyophilization, Freezing, Primary Drying, Secondary Drying, Technology Transfer.

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INTRODUCTION

The present research work was to formulate an intravenous injection of Voriconazole which is a second-generation azole antifungal agent.

The work was to transfer the product from lab scale to commercial scale. Since Voriconazole is unstable in aqueous condition and is stable only for 24 hours at 5-6 ^{0}C, lyophilization technology was adopted to increase the stability of the formulation.

Lyophilization also known as freeze drying is widely used for pharmaceuticals to improve the stability and long term storage of labile drugs. Technically, lyophilization is the vacuum sublimation of ice crystals that are formed when an aqueous solution is frozen. Left behind are the solid non-volatile solutes which may have been excipients and pharmaceutical ingredients of the liquid product. Within the box that is called a lyophilizer there is a large amount of stainless steel in the way of shelves and tubing. In use, there is also a reasonable amount of glass as vials. The remainder of the box volume is largely empty.

The fundamental process steps of lyophilization are:

1. Freezing: The product is frozen. This provides a necessary condition for low temperature drying.

2. Vacuum: After freezing, the product is placed under vacuum. This enables the frozen solvent in the product to vaporize without passing through the liquid phase, a process known as sublimation.

3. Heat: Heat is applied to frozen product to accelerate sublimation.

4. Condensation: Low temperature condenser plates remove the vaporized solvent from the vacuum chamber by converting it back to a solid. This completes the separation process.

In pharmaceutical industry “technology transfer” refers to the processes that are needed for successful progress drug discovery to product development to full scale commercialization.

Technology transfer can be divided in to 2 types

1) Tech transfer:-In tech transfer, the product is developed in lab-scale, subjected to scale-up, exhibit batch to full scale commercialization.

2) Site transfer:-In site transfer the products from the outside customer are subjected to lab-scale feasibility trials and then to commercial scale depending on customer need.

Before lyophilization three trials were carried out to optimize the compounding process. It was carried out in three different trials varying the processing parameters keeping the quantities of the entire active pharmaceutical ingredient constant. The trials are subjected to in vitro parameters like description, assay, related compounds by HPLC, pH and specific gravity.

Trial 2 is considered as an optimized compounding process. Based on this trial lyophilization is carried out.

The lyophilization was carried out in different batches by varying the total cycle time, freezing and holding time, primary drying and secondary drying time by keeping the quantities of all the active pharmaceutical ingredients constant.

An optimized lyophilization cycle of 70.16 hours has been achieved. The optimized lyophilized product was subjected to *in vitro* parameters such as description, reconstitution time, pH, water content, identification, assay, purity test.

2. MATERIALS AND METHODS:

2.1 Materials:

Voriconazole from Dr. Reddy's, Hydroxypropyl Beta Cyclodextrin from Roquette other facilities from Strides Arcolab Ltd.

30ml flint type I glass vials, siliconised chlorobutyl-isoprene 20mm rubber stoppers for lyophilization and flip of seals 20mm (polypropylene/ aluminium) were used as packing material.

2.2 Methods:

2.2.1 Preformulation of drug:

The main purpose of preformulation study is to ascertain that the drug substance complies with the standards. The preformulation studies of the drug voriconazole carried were:

Description, Solubility, Specific optical rotation, Loss on drying, Identification by IR, Residue on ignition, Heavy metals, Melting point, Particle size, Assay by HPLC, Related substance by HPLC.

2.2.2 Compatibility studies with excipients:

Conducting an excipients compatibility screen at the early preformulation stage of the development gives valuable information about potential incompatibilities between drug and excipients.

Compatibility between drug and excipients can be affected by many factors, such as moisture content, physical form, particle size, surface area, and morphology and trace impurities of either component. The stressed storage conditions used to accelerate reactions between drug and excipients, so that measurable changes occur in short time frame. Compatibility studies with voriconazole and selected excipients were studied for duration of one month.

The drug and excipients were taken in 1:2 ratios in to glass amber vials and kept at accelerated temperature of 40°C±2°C/75%±5% RH and analyzed by IR.

2.2.3 Formulation development:

Entire manufacturing process was carried out under aseptic conditions which include washing and sterilization of vials, rubber plugs and disinfections of aluminium seals. The vials were filled in class 100 laminar air cabinets.

First we studied the solubility of voriconazole in water. It is found that the drug is not soluble in water. So, we need a solvent to dissolve voriconazole in water. From literature survey we found that modified ß-cyclodextrins could be used as a solvent. The ß-cyclodextrin is not soluble in water but modified ß-cyclodextrins are soluble. There are three modified forms of ß-cyclodextrin.

1) Hydroxypropyl-β-cyclodextrin
2) Randomly methylated β-cyclodextrin (RAMEB)
3) Sulfobutylether β-cyclodextrin

Among the three Sulfobutylether β-cyclodextrin is patented (Patent No. - 5, 567, 817). So, we tried with the other two.

2.2.3.1 Solubility trial with Randomly methylated β-cyclodextrin:

Solubility of voriconazole in water with different concentrations of randomly methylated β-cyclodextrin

Table-1 Solubility trials (with RAMEB)

RAMEB Conc. (%)	2.5	5.0	7.5	10.0	20.0	30.0	40.0
Dissolved Voriconazole (mg/mL)	2.0	4.0	6.5	8.0	**12**	20.0	25.0

2.2.3.1.1 Calculation for each vial based on solubility:

Considering 20% concentration RAMEB and as per label claim of voriconazole, 200mg per vial,

Fill volume will be, 200/12= 16.6mL

For 16.6 mL RAMEB quantity will be, (16.6 × 200) = 3320mg per vial

Batch Size: 125ml

2.2.3.1.2 Composition:

Table-2 Formula for Trial (with RAMEB)

SL. No.	Ingredients	Qty/ml	Qty/125ml
1	Voriconazole	16mg	2.0gm*
2	Randomly methylated β-cyclodextrin	200mg	25.0gm
3	Water for injection	Qs to 1ml	Qs to 125ml

2.2.3.1.3 Compounding Process:

1. 90ml of water for injection was taken in a glass beaker and then hydroxypropyl-ß-cyclodextrin was added slowly under vigorous stirring into a beaker at room temperature.
2. It took 10 minutes for complete solubilisation, and then Voriconazole was added gradually into above under constant stirring. It took 5 hours for complete solubilisation.
3. Then the pH of the solution was checked.
4. The solution was then made up to the batch size with WFI and kept for stirring for 10 minutes for uniform mixing.
5. The solution was then filtered through 0.22µm PVDF membrane filter.

Note: As the process of complete solubilisation of voriconazole is time consuming (5 hours) we cannot use Randomly methylated β-cyclodextrin as a solvent.

2.2.3.2 Solubility trial with Hydroxypropyl β-cyclodextrin:

Solubility of voriconazole in water with different concentrations of hydroxypropyl-ß-cyclodextrin

Table-3 Solubility trials (with HPβCD)

HPßDC Conc. (%)	2.5	5.0	7.5	10.0	20.0	30.0	40.0
Dissolved Voriconazole (mg/mL)	3.0	5.0	7.0	9.0	**16.0**	24.0	30.0

2.2.3.2.1 Calculation for each vial based on solubility:

Considering 20% concentration HPßCD and as per label claim of voriconazole, 200mg per vial,

Fill volume will be, 200/16 = 12.5mL

For 12.5 mL HPßCD quantity will be, (12.5 × 200) = 2500mg per vial

Trial:

Batch Size: 125ml

2.2.3.2.2Composition:

Table-4 Formula for Trial 1:

SL. No.	Ingredients	Qty/ml	Qty/125ml
1	Voriconazole	16mg	2.0gm*
2	Hydroxypropyl-ß-cyclodextrin	200mg	25.0gm
3	Water for injection	Qs to 1ml	Qs to 125ml

Three trials were taken with same formula but different conditions.

Trial 1: RPM-Not specified, Temperature- room temperature

Trial 2: RPM-350 (as in commercial batch we can't go for stirring speed more than 350 RPM)

Temperature- room temperature

Trial 3: RPM-350, Temperature- 30-40 ^{0}C

2.2.3.2.3 Compounding Process:

1. 90ml of water for injection was taken in a glass beaker and kept under stirring at constant 350RPM with top end blade stirrer. Then hydroxypropyl-ß-cyclodextrin was added slowly at the vortex region into the beaker at temperature noted to be 62 ^{0}C.
2. It took 10 minutes for complete solubilisation, and then check the temp of the bulk and it was maintained between with hot plate stirrer. Then Voriconazole was added gradually into above under constant stirring.
3. It took 1 hour for complete solubilisation of voriconazole, and then dispensed quantity of sodium chloride was added and kept for stirring for 5 minutes till complete solubilisation.
4. Then the pH of the solution was checked.
5. The solution was then made up to the batch size with WFI and kept for stirring for 10 minutes for uniform mixing.
6. The solution was then filtered through 0.22µm PVDF membrane filter.

Note: Comparing the three trials we found that, though time required for complete solubilisation of voriconazole is more but all the results are within the specification limit in Trial 2.

So, **Trial 2** is considered as an optimized manufacturing procedure. This manufacturing formula is used for the optimisation of lyophilization cycle.

2.2.4 Scale up batch:

Table-5 Formula for Scale-up batch

Sl. No.	Ingredients	Qty/10ml
1	Voriconazole	160g*
2	Hydroxypropyl-ß-cyclodextrin	2Kg
3	Water for injection	Q.S to 10L

(*) indicates that based on that quantity we did the potency calculation.

2.2.5 Potency calculation for API:

Assay of the API = 100.2% (on anhydrous basis)

Water content = 0.24%

$$\text{Quantity required for batch} = \frac{\text{Actual quantity} \times 100 \times 100}{\text{Assay value} \times (100 - \text{Water content})}$$

$$\text{Quantity required for lab scale} = \frac{2^* \times 100 \times 100}{100.2 \times (100\text{-}0.24)}$$

$$= 2.0008099 \text{ gram}$$

$$\text{Quantity required for scale up} = \frac{160^* \times 100 \times 100}{100.2 \times (100\text{-}0.24)}$$

$$= 160.0647 \text{ gram}$$

2.2.6 Optimization of lyophilization cycle:

Design of freeze-drying processes is often approached with a "trial and error" experimental plan but "optimized" freeze-drying process is not particularly difficult for most products, as long as some simple rules based on well-accepted scientific principles are followed.

Based on the DSC result, the recipe for lyophilization was designed.

Five batches were taken changing the freezing, primary and secondary drying temperature as follows.

2.2.6.1 Batch 1(Table-6):

Temperature(°C)	Ramp(min)	Hold(min)	Pressure(mbar)
Loading			
5	-	-	-
Freezing			
5	-	60	-
-45	100	180	-
Primary Drying			
-45	-	5	0.250
-30	25	2400	0.250
-10	100	200	0.250
Secondary Drying			
5	100	200	0.250
25	100	300	0.250

Total: 62.83 hours

2.2.6.2 Batch 2(Table-7):

Temperature(°C)	Ramp(min)	Hold(min)	Pressure(mbar)
Loading			
5	-	-	-
Freezing			
5	05	60	-
-45	100	180	-
Primary Drying			

-45	05	15	0.700
-30	30	2500	0.700
-10	100	300	0.700
Secondary Drying			
5	100	200	0.500
25	100	300	0.500

Total: 66.58 hour

2.2.6.3 Batch 3(Table-8):

Temperature(°C)	Ramp(min)	Hold(min)	Pressure(mbar)
Loading			
5	-	-	-
Freezing			
5	05	60	-
-45	120	180	-
Primary Drying			
-45	05	10	0.470
-30	30	2700	0.470
-10	100	300	0.250
Secondary Drying			
5	100	200	0.250
25	100	300	0.250

Total: 70.16 hours

2.2.6.4 Batch 4(Table-9):

Temperature(°C)	Ramp(min)	Hold(min)	Pressure(mbar)
Loading			
5	-	-	-
Freezing			
5	05	60	-
-45	120	180	-
Primary Drying			
-45	05	10	0.470
-30	30	2700	0.470
-10	100	300	0.270
Secondary Drying			
5	100	200	0.250
25	100	300	0.250

Total: 70.16 hours

2.2.6.5 Batch 5(Table-10):

Temperature(°C)	Ramp(min)	Hold(min)	Pressure(mbar)
Loading			
5	-	-	-
Freezing			
5	05	60	-
-45	120	180	-
Primary Drying			

-45	05	10	0.470
-30	30	2700	0.470
-10	100	300	0.270
Secondary Drying			
5	100	200	0.270
25	100	300	0.250

Total: 70.16 hours

2.2.7 Evaluation of the products:

The bulk and final lyophilized products are evaluated by description, assay, related compounds by HPLC, pH, water content and description, reconstitution time, pH, water content, identification, assay purity test respectively.

2.2.8 Stability Studies:

Accelerated testing studies were designed to increase the rate of chemical or physical degradation of the drug substance/product by using exaggerated storage conditions as per USFDA, and a rapid detection of deterioration of the drug in different formulations can be known in short time. The stability studies were carried out as per ICH guidelines. The accelerated study was carried at the temperatures of 40 °C±2 °C/75%±5% RH and the sample was withdrawn at one month interval and analyzed for evaluation parameters such as description, assay, pH, water content, reconstitution time.

3. RESULTS AND DISCUSSION:

3.1 Preformulation of the drug:

As a primary step the drug was subjected to preformulation studies. The description of the drug was found to be white crystalline powder, which complies with the standard. The solubility was determined and it was found that the drug was soluble in methanol and chloroform. The drug was identified by IR spectrum and which complies with standard drug spectrum. The assay was carried out by HPLC method which was found to be 100.2% and relative substances TAP, Deschloro VOR-5, VOZ-2 diasteromer, VOZ-1, VOZ-2 diasteromer were not detected. and the total impurity was found to be 0.01%. The specific optical rotation was found to be (-)61^0, which

was within the limits. The drug exhibits a loss on drying of 0.24%w/w, and melting point of 128 ^{0}C. Residue on ignition was found to be .07% w/w and heavy metal content less than 10 ppm. These results were found to be within the specification limits.

Table-11: Preformulation data of the drug

Sl. No.	TESTS	SPECIFICATION	RESULT
1.	Description	White to off-white crystalline powder	A white crystalline powder
2.	Solubility	Soluble in methanol and chloroform	Complies
3.	Specific optical rotation	Between (-)55^0 and (-)65^0	(-)61^0
4.	Loss on drying (at 105^{0}C for 3 hrs)	Not more than 0.50% w/w	0.24%w/w
5.	Identification by IR	Comply with reference standards	Passes
6.	Residue on ignition	Not more than 0.10% w/w	0.07% w/w
7.	Heavy metals	Not more than 10 ppm	Less than 10 ppm
8.	Melting point	128-130^{0}C	128^{0}C
9.	Particle size D(0.5)	Not more than 25µm	9µm
10.	Assay by HPLC (On dried basis)	Not less than 98.0% and Not more than 102.0% w/w	100.2%w/w
11.	Related substances by HPLC		
	8.1) TAP	Not more than 0.12%	Less than LOQ (LOQ

		is 0.005%)
8.2) Deschloro VOR-5	Not more than 0.12%	Not detected
8.3) VOZ-2 diasteromer	Not more than 0.12%	Not detected
8.4) VOZ-1	Not more than 0.12%	Not detected
8.5) VOZ-2 diasteromer	Not more than 0.12%	Less than LOQ (LOQ is 0.015%)
8.6) Any other impurity	Not more than 0.10%	Not detected
8.7) Total impurities	Not more than 0.50%	0.01%

TAP: 2, 4- triazole acetophenone

Deschloro VOR-5: 6-Ethyl-5-fluoro pyrimidine

VOZ-1: (2R,3S / 2S,3R)-2-(2,4-difluoropyrimidin-6-yl)-2-(2,4-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol.

VOZ-2 diasteromer: (2R,3R/2S,3S)-2-(2,4-difluorophenyl)-3-(5-fluoropyridin-4-yl)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol

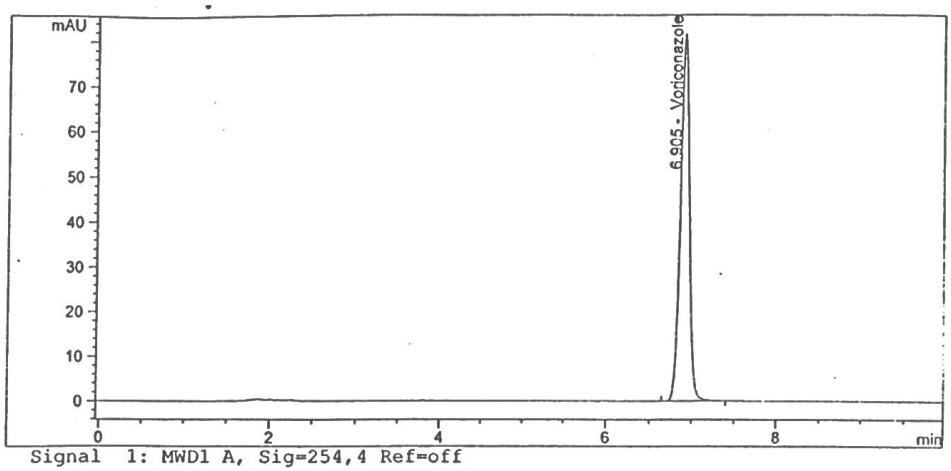

Fig.-1: HPLC of the pure drug (Voriconazole).

3.2 Compatibility data for the drug and excipients:

Drug excipient compatibility studies were carried out with the excipient selected in 1:2 ratio for one month at accelerated stability conditions. The results from the IR spectra as shown in fig no-2, 3 & 4 confirmed that the selected excipient was compatible with the drug.

Lyophilization technique was adopted to formulate parenteral dosage form of voriconazole and based on the physicochemical properties of the drug and excipient. As the drug is not soluble in water we needed a suitable solvent. Through literature survey we found that modified beta cyclodextrins could be used as solvent. Firstly we tried Randomly methylated beta cyclodextrin but with it the process became time consuming as it required around 5 hours for complete solubilisation of the dispensed drug. So, we tried with Hydroxypropyl beta cyclodextrin (HPßCD) with which it was found to be feasible. Finally HPßCD was used as solvent and water for injection as vehicle.

Table 12: Compatibility data for the drug and excipients

Sl. No.	Samples	Results
1	Voriconazole	Complies
2	HPßCD	Complies
3	Voriconazole + HPßCD	Complies

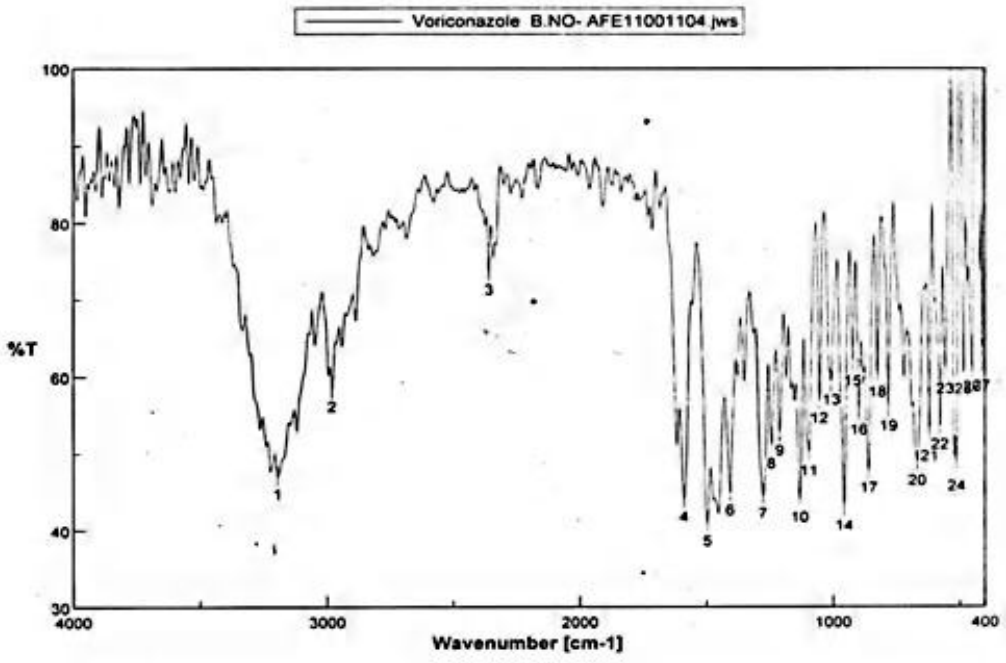

Fig.-2: IR spectrum of pure drug (Voriconazole)

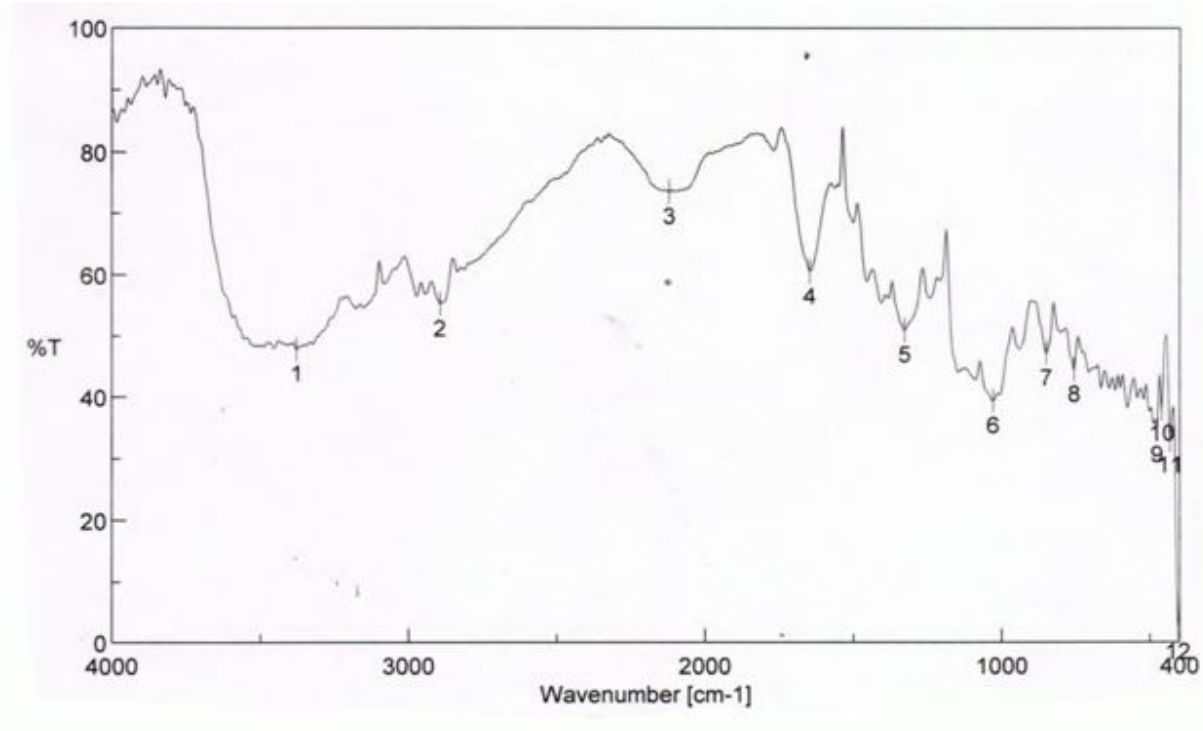

Fig.-3 IR spectrum of HPßCD

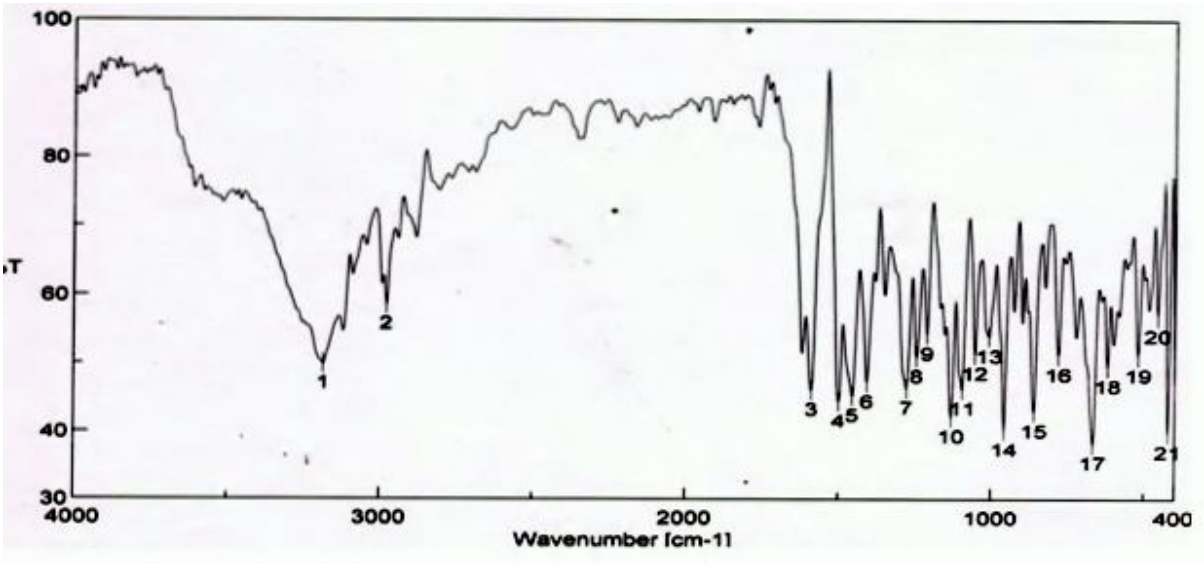

Fig.-4: IR spectrum of Voriconazole + HPßCD

3.3 Evaluation of the Bulk Product:

Three batches were prepared to develop the compounding process. In the Trial 1 the RPM was more (room temperature). As we can't go with the RPM more than 350 in commercial batches so we have gone for another batch with 350RPM. In Trial 2 the compounding process was done in room temperature and it took 3hrs for the complete solubilisation of the drug. So, in Trial 3 30-40^{0}C was maintained throughout the process to enhance solubilisation process. The time required for the complete solubilisation of the drug is less but assay was coming less.

Table 13: Evaluation of the bulk

Sl. No.	Evaluation Parameters	Trials			Specifications
		Trial 1	Trial 2	Trial 3	
1	Description	Clear colourless solution	Clear colourless solution	Clear colourless solution	Clear colourless solution
2	Assay	94.5%	101.9%	84.3%	Between 95%-105%

3	Related compound by HPLC				
	TAP Impurity				
	By Product 8	BDL	BDL	BDL	NMT 0.05%
	By product 7	BDL	BDL	BDL	NMT 0.15%
	Any unidentified impurity	BDL	BDL	BDL	NMT 0.15%
	Total Impurities	BDL	BDL	BDL	NMT 0.10%
		BDL	BDL	BDL	NMT 0.5%
4	pH	6.41	6.468	6.787	For information
5	Specific gravity	1.071	1.088	1.076	For information

From the results it is clear that assay was coming within the limits in Trial 2.

So, **Trial 2** is considered as an optimized manufacturing formula. This manufacturing formula is used for the optimisation of lyophilization cycle.

3.4 Optimisation of lyophilization cycle:

Batch 1:

Observation: The cake appearance was not satisfactory. There was powder ejection during primary drying.

Conclusion: This may be due to less primary drying period i.e. drying the lyophilate too quickly & strong vapour flow out of cake. And the vacuum is very high. This needs to be overcome by increasing the primary drying hold time.

Batch 2:

Observation: cake appearance was not satisfactory. Drying was not good. However powder flying was not observed at primary drying stage.

Conclusion: The probable cause may be due to less vacuum. This needs to be overcome by increasing the vacuum and increasing the primary drying hold time.

Batch 3:

Observation: cake appearance was satisfactory, no melt back, no collapse or any other defect. However powder flying was observed at -10°C of primary drying stage.

Conclusion: This may be due to high vacuum which causes the dried lyophilate to force out of the vial. So, vacuum must be decreased further to prevent the powder ejection. So, vacuum is decreased from 0.250 to 0.270 m bar.

Batch 4:

Observation: cake appearance was satisfactory, no melt back, no collapse or any other defect. There was no flying at end of primary drying but there was flying at the beginning of secondary drying.

Conclusion: So, the same cycle was followed while changing the vacuum at beginning of secondary drying to 0.270 m bar

Batch 5:

Observation: cake appearance was good. There was no melt back or collapse or any other defect. There was no powder ejection. So, this lyophilization cycle is said to be optimised for 200mg/vial voriconazole.

3.5 Evaluation of the Finished Lyophilized Product:

Table 14: Evaluation data of the Finished Lyophilized Product

S. N	Evaluation Parameters	Batches					Specifications
		Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	
1.	Appearance	Lyophilized cake	Lyophilized cake	Lyophilized cake	Lyophilized cake	Lyophilized cake	Lyophilized cake
2.	Colour	White	White	White	White	White	White
3.	Reconstitution time	54 Seconds	52 Seconds	42 Seconds	38 Seconds	32 Seconds	NMT 90 seconds
4.	PH	6.4	6.2	6.3	6.4	6.2	4-7
5.	Moisture content	0.56%	0.60%	0.66%	0.67%	0.60%	≤2%
6.	Identification	Conforms	Conforms	Conforms	Conforms	Conforms	By HPLC
7.	Assay	200.4mg (100.2%)	202.0mg (101%)	201.5mg (100.75%)	199mg (99.5%)	204.5mg (102.25%)	190mg/vial-210mg/vial (95-105%)
8.	Purity test TAP impurity	0.10%	0.02%	0.04%	0.03%	0.01%	≤0.1%
	Any unidentified	0.06%	0.06%	0.07%	0.06%	0.05%	≤0.1%

impurity						
Total impurities	0.20%	0.14%	0.16%	0.13%	0.11%	≤0.2%

From the results it is seen that in Batch 5 assay is coming more than other two trials and impurities are also less in Batch 5. So, Batch 5 is taken as the optimized lyophilisation cycle.

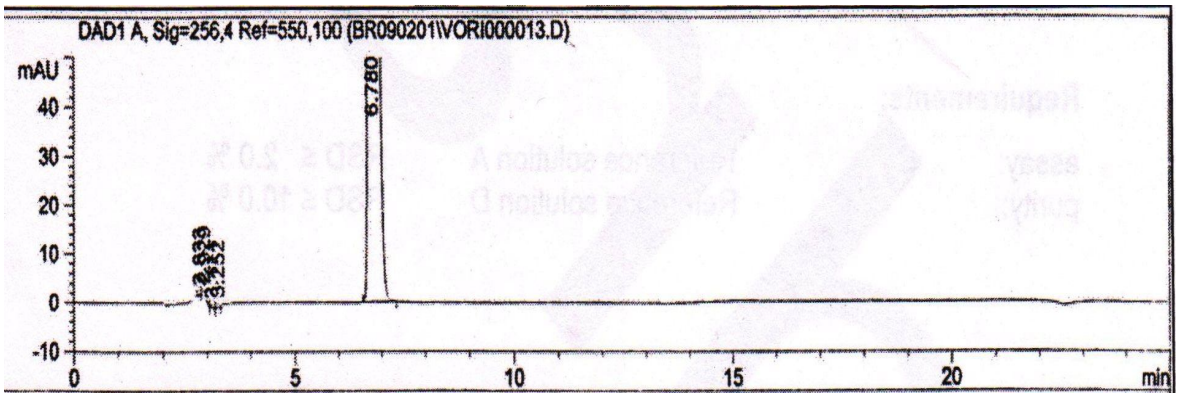

Fig.-4: HPLC for optimized formulation Batch 5

3.5.2 Stability studies:

The optimized lyophilized formulation under stability studies were analyzed at time interval of one month. The formulations were analyzed for all the evaluation parameters such as appearance, colour, reconstitution time, pH, moisture content, identification, assay, purity test. In both 1st & 2nd month stability analysis, the colour of the product was same as the initial product and no colour change was observed and other parameters also within the limit (Table-15).

Table-15: Stability data for lab-scale formulation Batch 5

Duration	1st Month	2nd Month
Stability condition	40^{0}C ±2^{0}C / 75% RH	40^{0}C ±2^{0}C / 75% RH
Appearance	lyophilized cake	lyophilized cake
Colour	White	White
Reconstitution time	40 Seconds	52 Seconds
pH	6.3	6.4

Moisture content	0.50%	0.52%
Identification (By HPLC)	Conforms	Conforms
Assay	101%	100.5%
Purity test		
TAP impurity	0.02%	0.04%
Any unidentified impurity	0.06%	0.07%
Total impurities	0.13%	0.15%

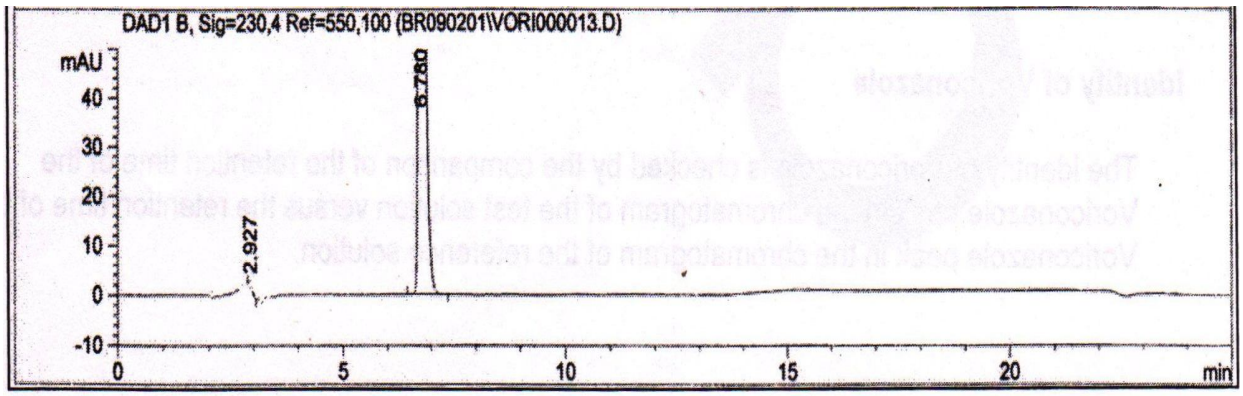

Fig.-5: First month stability HPLC peak area at 40^{0}C ±2^{0}C / 75% RH for lab scale Batch 5.

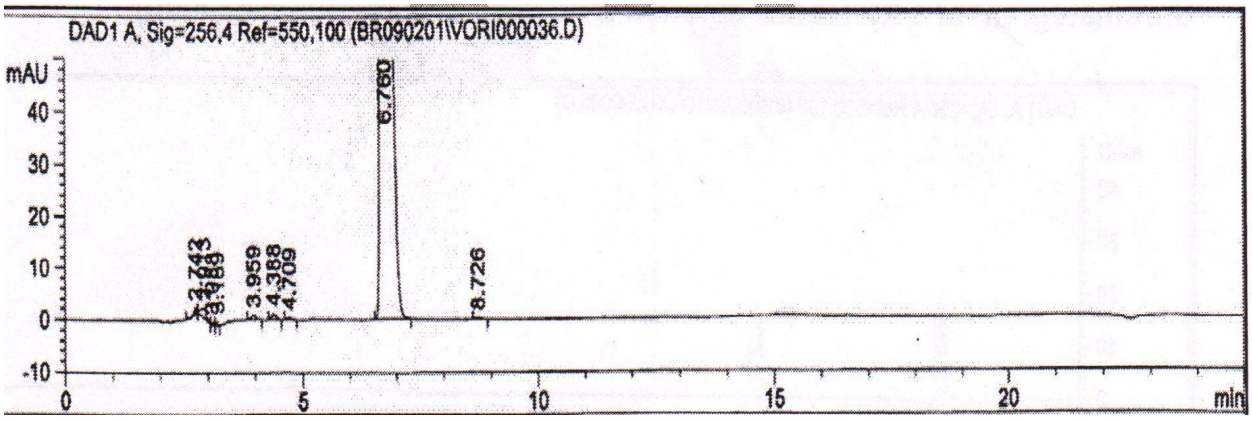

Fig.-6: Second month stability HPLC peak area at 40^{0}C ±2^{0}C / 75% RH for lab scale Batch 5

Finally, it was concluded that the batch number 5 was the best formulation. The optimized formulation was subjected to large scale production by taking scale-up batch of batch size 10.0 L.

3.6 Evaluation of the formulation in scale-up batch:

Table-16: Evaluation of the formulation in scale-up batch

Evaluation Parameters	Results
Appearance	Lyophilized cake
Colour	White
Reconstitution time	35 Seconds
pH	6.2
Moisture content	0.55%
Identification (By HPLC)	Conforms
Assay	102.5%
Purity test	
TAP impurity	0.02%
Any unidentified impurity	0.05%
Total impurities	0.11%

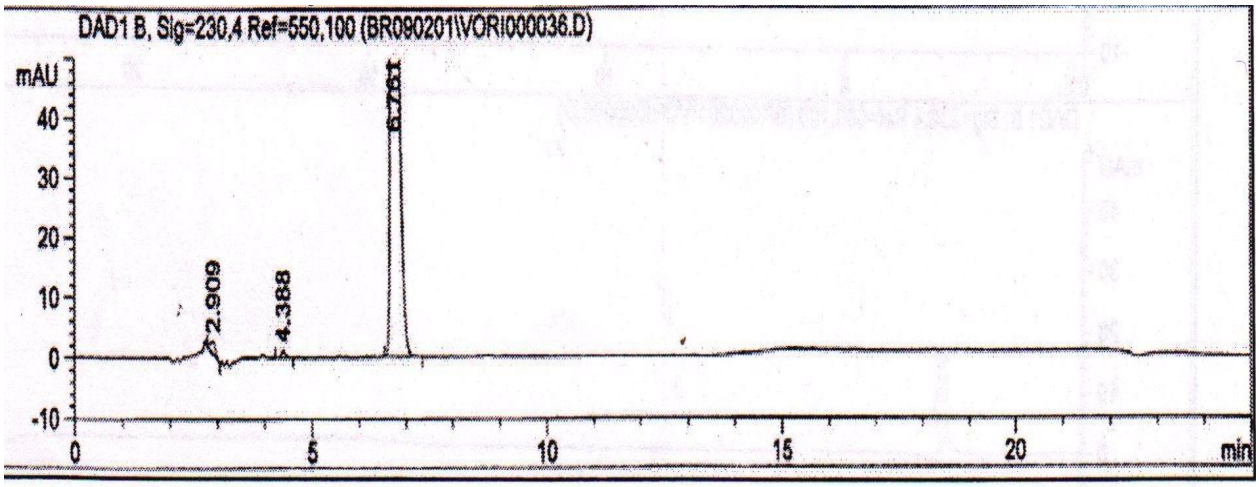

Fig.-7: HPLC for scale-up batch:

All the analysis done was found within the limit as per Table-16.

Hence Batch 5 can be transferred from lab scale to large scale.

4. CONCLUSION:

The present research work was designed to develop a novel injectable dosage form of a second generation antifungal drug, voriconazole. The drug is insoluble in water. So, hydroxypropyl-beta-cyclodextrin (HPßCD) is used as a solvent. The drug is unstable if dispensed as liquid dosage form. It is stable only 24 hours at 5-6^{0}C in aqueous solution. Hence the present project was envisaged to overcome the drawbacks associated with voriconazole and to formulate a stable formulation by lyophilization technique.

Solubility trials were done to determine the solubility of voriconazole in water with different concentrations of HPßCD is done. 20% HPßCD is taken as the optimized concentration. Based on this three trials are taken with same formula but different process parameters. . The bulk products are evaluated for description, pH, relative compounds by HPLC, assay, specific gravity. Based on the results Trial 2 was taken as optimized process. Then optimization of lyophilization cycle was carried out.

The Batch-5 of total duration of 70.16 hours was considered as the best formulation because it exhibited a good cake formation and the assay, pH, reconstitution time, percentage water content, impurities was found to be within the limits. Stability studies were conducted for the optimized formulation in lab scale as per ICH guidelines for a period of two months which revealed the stability of the formulation. Based on lab scale stability data scale up batch was

taken with the optimized lyophilization cycle. The accelerated stability data of scale up batch was found to be within the specification limits.

From the above results it was concluded that lyophilization technique proves to be an advantage for development of stable injectable dosage form of voriconazole. The Batch-5 was considered to be an optimized formulation and the same can be transferred from lab scale to commercial scale.

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