Available online on 15.06.2024 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Full Text Article

Research Article

Stabilization of the pharmaceutical finished dosages form by using various techniques

Vikas Chandel [1]*, Hemendra Pratap Singh [2], Nilesh Rarokar [3], Kamlesh Wadher [4]

[1] *DGM Formulation Development, Anthea Pharma Pvt. Ltd., Hyderabad, Telangana, India*

[2] *B N Institute of Pharmaceutical Sciences, B N University, Udaipur, Rajasthan, India*

[3] *G H Raisoni Institute of Life Sciences, Department of Pharmaceutics, Shradha Park, Hingna MIDC, Nagpur-440016, India*

[4] *BCYRC'S KDK College of Pharmacy and Research Institute , Nandanvan, Nagpur-440009, India*

Article Info:

Article History:

Received 18 March 2024
Reviewed 02 May 2024
Accepted 19 May 2024
Published 15 June 2024

Cite this article as:

Chandel V, Singh HP, Rarokar N, Wadher K, Stabilization of the pharmaceutical finished dosages form by using various techniques, Journal of Drug Delivery and Therapeutics. 2024; 14(6):44-50

DOI: http://dx.doi.org/10.22270/jddt.v14i6.6619

*Address for Correspondence:

Vikas Chandel, DGM Formulation Development, Anthea Pharma Pvt. Ltd., Hyderabad, Telangana, India

Abstract

The stabilization of pharmaceuticals means that the drug product is physically, chemically and microbiologically stable at the recommended storage condition throughout the predefined shelf life of the product. Pharmaceutical formulations irrespective of its physical states have been used for their efficacy and safety so for as its therapeutic activity is concern. Stability of dosage forms is the ability of drugs to remains unaffected by environmental condition viz. temperature, humidity and microbiological contamination. This research work is an attempt to stabilize the drug product at controlled room temperature for the drug product which is stable at refrigerated storage condition. Hence the aim of present study was development and stabilization of the drug product at room temperature. Investigation of alternate manufacturing processes for stabilization of the drug product at controlled room temperature was one of the objectives of the work.

Keywords: Stability, shelf life, lyophilization, freeze drying

INTRODUCTION

The stabilization of pharmaceuticals means that the drug product is physically, chemically and microbiologically stable at the recommended storage condition throughout the predefined shelf life of the product. The physical stability means that the drug product shall retain its original shape, size, color, particle size, globule size and texture throughout the recommended shelf life of the product. The chemical stability means that the drug product and its critical constituents e.g. Active pharmaceutical ingredient(s), preservatives, antioxidants, rate controlling excipients etc. remains within the predefined limits.

The microbiological stability means that the drug product is not contaminated with the microbes; if the drug product contains antimicrobial preservatives, then these preservatives should be in sufficient amount to prevent the growth of microbes throughout the shelf life of the product. Any changes in any of these parameters should be within the acceptable range as determined during development and finalization of the limits at various stages of product development, filing and approval process. Apart from this the specifications can be modified to some extent during the commercial run of the product, after due discussion and approval from the regulatory agencies. Stabilization of the pharmaceuticals is one of the most challenging but important task for the pharmaceutical industry this is applicable for drug products which are stable at room temperature as well as the drug products which are stable at refrigerated condition.

The drug products which are not stable at room temperature but are stable at refrigerated storage condition poses a grave challenge for maintenance of the cold chain during the manufacturing, transportation, storage and subsequent distribution for the end use of the drug product. As per the *Pharmaceutical & Medical Packaging News*, surveyed supply chain experts in 2015 and concludes these findings that amongst the temperature sensitive products shipped, 51% were ambient, 31% were refrigerated, 17% were frozen, and 32% should not be allowed to freeze[1].

Due to advent of research and development in the arena of pharmaceuticals evolving past traditional chemical based small molecular therapeutics to more complex and more effective large molecular biologics which are sensitive to environmental condition are available as an opportunity to stabilizes from all possible destabilizing phenomenon viz. hydrolysis, Oxidation, Reduction, microbial contaminants, aggregation, etc.[2,3] The exact number of pharmaceutical products affected by prolonged storage and temperature is difficult to pinpoint. The improper exposure to temperature during storage and even in distribution chain may also leads some untoward effect

In August 2017, for instance, a shipment from a single lot of Intralipid 20% IV fat emulsion, 100 mL bags (Baxter International, Inc.), was improperly exposed to subfreezing temperatures which one is outside the labeled acceptable storage range, on its way to a distribution facility. These frozen condition leads to an enlargement of the product's emulsion droplets and forming aggregates that can obstruct pulmonary circulation, leading to serious health problems and possible death[4]. The company voluntarily recalled this parenteral-nutrition product about two months later and warned patients and the health care practitioner to dispose of their supplies to avoid the serious consequences. Hence, it would be always beneficial to stabilize more and more drug products irrespective of their physicochemical peculiarities at room temperature from their prescribed storage condition which require refrigeration or subzero temperature storage for maintaining the desired quality of the drug throughout the shelf life of the product.

The Posaconazole injection is such drug product wherein the recommended storage of the drug product is 2 - 8°C. This work will focus on stabilizing the drug product at room temperature by one or more the techniques discussed subsequently in this work. The storage temperature of the drug product is decided based on the extent of impurities generated at the stability conditions as specified by the ICH guideline Q1A (R2) "Stability Testing of New Drug Substances and Products.[5]

The RLD formulation Noxafil is available in the market which is in solution form and is stable at Refrigerator condition i.e. 2 to 8 °C. The refrigerated condition is difficult to maintain at manufacturing location, transportation and at the site of end user i.e patient or the small dispensaries in the remote areas[6-9]. This may sometimes lead to inadvertent exposure of the drug product to a higher temperature leading to degradation of the drug product thus jeopardising the efficacy of the formulation.

The aim of the present work is to stabilize the formulation at room temperature which otherwise is stable at 2-8°C or refrigerated storage condition, to achieve the same different permutation and combination of drug and the excipient were tried to develop the formulation of desired efficacy and stability.

MATERIAL AND METHODS

Posaconazole was procured from Dr. Reddy's Laboratory. Betadex sulfobutyl ether sodium (SBECD), edetate disodium, propylene glycol, dimethyl acetamide, ethanol, sodium metabisulfite (SMBS), sodium ascorbate, sodium ascorbate, polysorbate 80, arginine, L-Cysteine, hydrochloric acid, sodium hydroxide were obtained from Loba Chemie PVT. LTD.. All other reagents used in the study were of analytical grade

Formulation of posaconazole solution

About 10 formulation trials of posaconazole solution were designed based on solubility profile of posaconazole drug and its compatibility with the excipients as shown in table 1. The water for injection (80 %), purged nitrogen to achieve the dissolved oxygen content of 2 ppm or less. Continued nitrogen purging throughout the batch manufacturing. The pH of the water for injection was checked. A sodium ascorbate and sodium metabisulfite was added slowly under continuous stirring. The stirring was continued till get clear solution. This was followed by addition of propylene glycol, and ethanol with stirring. The pH was adjusted to 2.6. The posaconazole was then added slowly under stirring for 2 h and was observed for complete solubility of the API in the selected solvent system.

Table 1: Formulation trials of posaconazole solution

S.N.	Composition	RLD	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7	Trial 8	Trial 9	Trial 10
1	Posaconazole	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0
2	Betadex Sulfobutyl Ether Sodium (SBECD)	400	-	-	-	-	-	-	-	150	200	200
3	Edetate disodium	0.180	-	-	-	-	-	-	-		-	-
4	Propylene glycol	-	200	200	-	-	-	200	-	-	-	-
5	Dimethyl acetamide	-	-	-	100	150	200	-	-	-		
6	Ethanol	-	10	40	-	-	-	75	30	-		
7	SMBS	-	4	-	-	-	-	-	-	25	35	35
8	Sodium ascorbate	-	**5**	-	-	-	-	-	-	20	20	20
9	Polysorbate 80	-	-	-	-	-	-		20	40	40	40
11	Arginine	-	-				15	-	-	-		
12	L – cystiene	-	-	-			30	-	-	-		
17	HCl	Q.S to pH	Q.S to pH	Q.S to pH	Q.S to pH	Q.S to pH	Q.S to pH	Q.S to pH	Q.S to pH	Q.S to pH	Q.S to pH	Q.S to pH
18	NaOH	Q.S to pH	Q.S to pH	Q.S to pH	Q.S to pH	Q.S to pH	Q.S to pH	Q.S to pH	Q.S to pH	Q.S to pH	Q.S to pH	Q.S to pH
19	WFI	Q.S to 1 mL	Q.S to 1 mL	Q.S to 1 mL	Q.S to 1 mL	Q.S to 1 mL	Q.S to 1 mL	Q.S to 1 mL	Q.S to 1 mL	Q.S to 1 mL	Q.S to 1 mL	Q.S to 1 mL

Lyophilization

The prepared solution was filled in a glass vials, the vials were half stoppered and were loaded on the precooled shelf in the lyophilizer. During the secondary drying the cycle time at step 40°C was 1000 minutes. The total duration of cycle was 66 hours.[2]

Evaluation of lyophilized powder and or Cake

The lyophilized powder or cake was evaluated for physical appearance, moisture content and reconstitution time

Physical appearance

The physical appearance i.e description and color of the lyophilized powder was determined.

Moisture Content

Moisture content was determined using Karlfisher titration. The cake was weighed approximately 400 mg and was added to the KF titrator [3].

Reconstitution time

The Vial having lyophilized powder was taken and removed flip off seal. The 17 mL of water for injection was taken in 20 ml disposable syringe and injected in to the vial. Then the vial was shaken till the lyophilized powder and or cake was completely dissolved. The time at which the solution becomes clear colourless solution recorded.

RESULT AND DISCUSSION

Development of the Lyophilization Cycle

Lyophilization cycle depends upon the number of parameters viz. freezing point, critical temperature and vapor pressure of the formulation. To optimize all these 13 trials were done and results are summarized in table no.2.

Fixing of Freezing Stage

The shelves of the lyophilizer were pre-cooled to 5°C before loading the vials into the lyophilizer; this was done in order to minimize the rate of degradation due higher temperature. As discussed above, the freezing temperature was finalized as -45°C since the drug formulation was aqueous based. The ramp rate selected was neither too high e.g. 1°C per minute or neither too slow of 0.1°C per minute, but optimum ramp rate of 0.35°C per minutes was chosen for freezing step. The complete freezing was ensured by providing sufficient time for freezing.

Development of Primary Drying

After freezing the product to -45°C, the product was slowly heated to -30°C at the ramp rate of 0.35°C per minute. Since conservative approach was adopted for the initial development of lyophilization cycle, the temperature of -30°C (critical temperature -25°C) was selected as the primary drying temperature which was in-line with the literature references which indicates that the primary drying temperature shall be lower than the critical temperature [10-12]. After carrying out the drying for 20 hours (1200 minutes) at -30°C, the product was slowly ramped to 20°C at rate of 0.11°C per minute to -20°C at this temperature product was hold for 10 hours (600 minutes) after completing the hold, the product was ramped to 10°C slightly at a higher rate of 0.6°C per minute, at the temperature of 10°C the product was held for 16.67 hours before proceeding for secondary drying. During the entire primary drying at all the temperature condition vacuum of 100 mtorr was maintained.

Secondary Drying

After completion of the primary drying stage the product was heated to 40°C at the slow ramp rate of 0.3°C per minute, at this temperature the product was held for 33.33 hours at the vacuum of 50 mtorr to ensure complete drying. After completion of the lyophilization cycle the lyophilizer was back filed partially with nitrogen and the vials were stoppered and unloaded from the lyophilizer. The cycle of the trial was illustrated in the table 2.

Table 2: Lyophilization cycle of the Trial 1

Trial 1			
Temperature	**Ramp**	**Hold time**	**Vacuum**
5	50	60	-
-45	140	600	
-30	50	1200	100
-20	85	600	100
10	50	1000	100
40	100	2000	50
Total Time	475	5460	minutes
Total Time (R+H)	5935	99	Hours

The vials were observed for physical appearance, reconstitution time and moisture content and the results were given in the table 3.

Table 3: Results of evaluation of lyophilized powder and or cake

Sr. No	Test parameters	Results
1	Physical appearance	White to off white intact cake or powder
2	Reconstitution time	180 seconds
3	Moisture content	2.8%

Table 4: Lyophilization cycle of the Trial 2

Trial 2			
Temperature	**Ramp**	**Hold time**	**Vacuum**
5	50	60	-
-45	133	600	
-30	50	1200	100
-15	83	600	100
10	50	1000	100
40	100	2000	40
Total Time	467	5460	minutes
Total Time (R+H)	5927	99	Hours

The vials were observed for physical appearance, reconstitution time and moisture content and the results are given in table 5.

Table 5: Results of evaluation of lyophilized powder and or cake

Sr. No	**Test parameters**	**Results**
1	Physical appearance	White to off white intact cake or powder
2	Reconstitution time	180 seconds
3	Moisture content	2.8%

Table 6: Results of evaluation of lyophilized powder and or cake (Trial 3)

Sr. No	**Test parameters**	**Results**
1	Physical appearance	White to off white intact cake or powder
2	Reconstitution time	145 seconds
3	Moisture content	2.5%

Table 7: Results of evaluation of lyophilized powder and or cake (Trial 4)

Sr. No	**Test parameters**	**Results**
1	Physical appearance	White to off white intact cake or powder
2	Reconstitution time	163 seconds
3	Moisture content	2.68%

In the further trials from 6 to 13 the focus will remain on the temperature optimization and reducing the cycle time. The freezing step was kept same as the previous trial; The following changes were done in the primary drying stage:

a. The step of -10°C was removed (which was there in Trial 6).

b. After completion of freezingstep the temperature was raised to -5°C from -45°C slowly at the ramp rate of 0.235°C per minute.

c. The overall duration of primary drying was decreased from 51.72 hours to 40.33 hours.

d. The overall cycle time was reduced from 101 hours to 89 hours

After completion of the lyophilization cycle, the vials were stoppered, unloaded from the lyophilizer and sealed. The observation of the lyophilized vials is given in table 8.

Table 8: Results of evaluation of lyophilized powder and or cake (Trial 5)

Sr. No	**Test parameters**	**Results**
1	Physical appearance	White to off white intact cake or powder
2	Reconstitution time	147 seconds
3	Moisture content	2.47%

In this trial (Trial 7) the primary drying temperature was further increased to 0°C from -5°C and to +20°C from +10°C respectively, as compared to the previous trial 7. The primary drying duration was kept unchanged. The vials were stoppered unloaded and sealed. The observation of the sealed vials is given in table 9.

Table 9: Results of evaluation of lyophilized powder and or cake (Trial 6)

Sr. No	Test parameters	Results
1	Physical appearance	White to off white intact cake or powder
2	Reconstitution time	150 seconds
3	Moisture content	2.39%

Table 10: Results of evaluation of lyophilized powder and or cake (Trial 7)

Sr. No	Test parameters	Results
1	Physical appearance	White to off white intact cake or powder
2	Reconstitution time	139seconds
3	Moisture content	2.47%

In the trial 8 all the parameters were kept constant and the hold time during the primary drying (20°C) and secondary drying (40°C) was reduced by 400 minutes and 500 minutes respectively. The total cycle time was reduced by 900 minutes i.e. 11 hours when compared with the trial 9. After completion of the lyophilization cycle, the vials were stoppered, unloaded, sealed. The drug product was evaluated for parameters given in table 11.

Table 11: Results of evaluation of lyophilized powder and or cake (Trial 8)

Sr. No	Test parameters	Results
1	Physical appearance	White to off white intact cake or powder
2	Reconstitution time	139seconds
3	Moisture content	2.47%

Following success of this trial one more trial (Trial 9) was planned in which the temperature at the primary drying stage was increased to +10°C from the 0°C, during the cycle slight melt back was observed through the watch glass hence, the cycle was aborted in between.

The Lyophilization cycle in trial 9 is given in table 12.

Table 12: Lyophilization cycle of the Trial 9

Trial 9			
Temperature	**Ramp**	**Hold time**	**Vacuum**
5	50	60	-
-45	133	600	
0	170	1200	100
20	50	800	100
40	100	1500	50
Total Time	503	4160	minutes
Total Time (R+H)	4663	78	Hours

Since, the above trial (Trial 9) resulted in melt back when the temperature was raised to +10°C from 0°C; another trial (This trial 10) was planned in which primary drying temperature was set at 5°C without any other changes. After completion of the lyophilization cycle(table No. 5.12). The vials were stoppered, unloaded and sealed. The drug product was evaluated for the parameters given in the table No. 5.12.

Table 13: Lyophilization cycle of the Trial 10

Trial 10			
Temperature	**Ramp**	**Hold time**	**Vacuum**
5	50	60	-
-45	133	600	
10	170	1200	100

Table 14: Results of evaluation of lyophilized powder and or cake

Sr. No	Test parameters	Results
1	Physical appearance	White to off white intact cake or powder
2	Reconstitution time	152seconds
3	Moisture content	2.73%

The success of trial 10 gives assurance that the trial 9 can be further optimized with respect to time without causing melt back or any other cake defects. The primary drying temperature of 0°C also have required cushion in trial 9 also

have the required Based on this trial it was decided to further optimize the lyophilization cycle of trial 9.

The first and second step of primary drying i.e. 0°C and 20°C respectively was finalized in the trial 9. This cycle (Trial 11) and further trials will be executed for optimization of cycle time with the aim to reduce the duration of cycle so as to make the product more cost effective.

In this trial the duration of cycle was reduced during the step by 200 minutes and 300 minutes at step of 20° and 40°C respectively, thereby decreasing the cycle time by 9 hours i.e. from 78 hours to 69 hours.

The observations of the lyophilized vials are given below in Table No. 5.14

Table 15: Lyophilization cycle of the Trial 11

Trial 11			
Temperature	**Ramp**	**Hold time**	**Vacuum**
5	50	60	-
-45	133	600	
0	170	1200	100
20	50	600	100
40	100	1200	
Total Time	503	3660	minutes
Total Time (R+H)	4163	69	Hours

Table 16: Results of evaluation of lyophilized powder and or cake

S. N.	**Test parameters**	**Results**
1	Physical appearance	White to off white intact cake or powder
2	Reconstitution time	147seconds
3	Moisture content	2.50%

In this trial during the secondary drying the cycle time at step 40°C was reduced by by 200 minutes i.e. the cycle time was reduced from 1200 minutes to 1000 minutes. The total duration of cycle was reduced by 3 hours as compared to previous trial i.e. from 69 hours to 66 hours. The observations of the lyophilized vials are given below in table

Table 16: Lyophilization cycle of the Trial 12

Trial 12			
Temperature	**Ramp**	**Hold time**	**Vacuum**
5	50	60	-
-45	133	600	
0	170	1200	100
20	50	600	100
40	100	1000	
Total Time	503	3460	minutes
Total Time (R+H)	4163	66	Hours

Table 17: Results of evaluation of lyophilized powder and or cake

Sr. No	**Test parameters**	**Results**
1	Physical appearance	White to off white intact cake or powder
2	Reconstitution time	133 seconds
3	Moisture content	2.67%

In this trial the cycle time was reduced at the following steps as compared with the previous cycle:

a. 0°C : Cycle time was reduced from 1200 minutes to 1000 minutes.

b. 20°C: Cycle time was reduced from 600 minutes to 400 minutes.

c. 40°C: Cycle time was reduced from 1000 minutes to 800 minutes

The total duration of Lyophilization cycle was reduced by 600 minutes i.e. 10 hours hence, the cycle was reduced from 66 hours as in trial 12 to 56 hours in trial 13. The observations of the lyophilized vials are given below table 18.

Table 18: Results of evaluation of lyophilized powder and or cake

S. N.	**Test parameters**	**Results**
1	Physical appearance	White to off white intact cake or powder
2	Reconstitution time	173seconds
3	Moisture content	3.54 %

From the above observations it is evident that the further reduction in the cycle time would not be feasible as this would result in increase in moisture content which may lead to degradation of the drug product over stability and other product related issues hence, further stability batches will be manufactured using the Lyophilization cycle.

Stability study

Based on the various trials carried out in order to optimize the lyophilization cycle – The lyophilization cycle of trial 12 was finalized. The same cycle is presented below:

Table 19: Stability data

Stability Batch No. 1& 2			
Temperature	**Ramp**	**Hold time**	**Vacuum**
5	50	60	-
-45	133	600	
0	170	1200	100
20	50	600	100
40	100	1000	
Total Time	503	3460	Minutes
Total Time (R+H)	3963	66	Hours

Evaluation of lyophilized powder and or cake

The cake obtained after lyophilization were subjected to evaluate for its physical appearance, moisture content and reconstitution time. The cake is white, free flowing granular dry powder moisture content of cake was ranges in between. The cake was completely dissolved in few min. Same type of results were obtained in previously published literature[13]. Based on the physical test results it was depicted that the lyophilized product was within the acceptance criteria.

CONCLUSION

The results obtained in this study demonstrated the drug product stability upto 12 months at real time stability condition and 6 months at accelerated stability condition. Hence, it can be inferred that by adding suitable excipients and by subjecting the drug product to lyophilization has helped to stabilize the drug product at room temperature which was originally stable at refrigerated condition.

REFERENCES

1. USP. Temperature-sensitive packaging snapshot. 2015. [Accessed January 23, 2018]. Available at: https://solvers.ups.com/assets/UPS_temp_sensitive_packaging_snapshot_infographic.pdf.
2. Markarian J. Understanding risks in pharmaceutical shipping. [Accessed January 23, 2018];Pharmaceutical Technology. 2015 39(8):52–54.
3. Tennermann J. Cold chain for beginners. Vaisala; Jun 20, 2012. [Accessed January 23, 2018]. Available at: www.pharmpro.com/article/2012/06/cold-chain-beginners.
4. Baxter International, Inc. Baxter initiates voluntary nationwide recall of one shipment of Intralipid 20% IV fat emulsion due to product being exposed to subfreezing temperatures. Oct 5, 2017. [Accessed January 23, 2018]. Available at: www.baxter.com/news-media/newsroom/press-releases/2017/10-05-17-intralipid-recall.page
5. Q1A(R2): Stability Testing Of New Drug Substances and Products.
6. Timothy J., Snape., Alison M., Astles., and Janice Davies., 'Understanding the chemical basis of drug stability and degradation' The Pharmaceutical Journal, Vol. 285, p416.
7. Panda BP, Patnaik S and Maharana RL. Trends in Design and Development of Nanopharmaceutical Dosage Forms. Bioequivalence & Bioavailability International Journal.1,1:2017. https://doi.org/10.23880/BEBA-16000104
8. Adepu S, Ramakrishna S. Controlled Drug Delivery Systems: Current Status and Future Directions. Molecules. 2021 Sep 29;26(19):5905. https://doi.org/10.3390/molecules26195905
9. Waterman KC, Adami RC, Alsante KM, Hong J, Landis MS, Lombardo F, Roberts CJ, Pfizer Global Research and Development, Eastern Point Road,Groton, CT 06340
10. Dave P., The Role of Pharmacists in Opioid Addiction Management. Asian Journal of Dental and Health Sciences, 2024;*4*(1):51–56. https://doi.org/10.22270/ajdhs.v4i1.71
11. Xiaolin (Charlie) Tang and Michael J. Pikal. Design of Freeze-Drying Processes for Pharmaceuticals: Practical Advice *Pharmaceutical Research, 21;2: 2004.* https://doi.org/10.1023/B:PHAM.0000016234.73023.75 PMid:15032301
12. Zimmermann CM, Baldassi D, Chan K, Adams NBP, Neumann A, Porras-Gonzalez DL, Wei X, Kneidinger N, Stoleriu MG, Burgstaller G, Witzigmann D, Luciani P, Merkel OM. Spray drying siRNA-lipid nanoparticles for dry powder pulmonary delivery. J Control Release. 2022 Nov;351:137-150. https://doi.org/10.1016/j.jconrel.2022.09.021 PMid:36126785 PMCid:PMC7613708
13. Gatto MS, Najahi-Missaoui W. Lyophilization of Nanoparticles, Does It Really Work? Overview of the Current Status and Challenges. Int J Mol Sci. 2023 Sep 13;24(18):14041. https://doi.org/10.3390/ijms241814041 PMid:37762348 PMCid:PMC10530935