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Research Article

HOLD TIME STUDY OF CETIRIZINE DI HYDROCHLORIDE LUBRICATED GRANULES

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ABSTRACT

It is important to perform the hold time study (HTS) of a lubricated granule in order to predict the time period for which the product is on hold shall be justified with adequate data to demonstrate the product will be stable throughout the approved shelf life. During the hold time study, lubricated granules were collected and analyzed upto 45th day. The hold time of the Cetirizine dihydrochloride granules was evaluated or calculated and content uniformity (%) was determined and compared with the pharmacopoeia limits. A specification chart is designed for indication of limits of the determined results. The Content uniformity (%) in different interval i.e. initial, 30th and 45th day was analyzed and results at the pharmacopoeia limits were plotted. The probabilities of the erroneous decisions of initial, 30th, 45th days were calculated from these studies. Therefore, extremely accurate hold-time data were obtained. In light of this data the correct trends in hold-time study as a function of storage period for Cetirizine dihydrochloride granules can be established.

Keywords: Cetirizine dihydrochloride; Content Uniformity; Pharmacopoeia limits

INTRODUCTION

Sample holding times are established for bulk and in-process drug products. Data to justify the hold time can be collected during development on pilot scale batches, during process validation or as a part of a deviation with proper testing[1]. Although there are no specific regulation or guidance document on bulk product holding time, GMP practice dictates that holding time should be validated to ensure that in–process and bulk product can be held, pending the next processing step, without any adverse effect to the quality of the material[2]. The time during which the product is stored in the bulk container, prior to packing into the final immediate container, constitutes part of the approved shelf life, i.e., the date of expiry remains a function of the date of manufacture, not the date of packing[3,4]. To validate the holding time of lubricated granules under the prevailing condition, it should be ensured that the result of all process is within the limits of acceptance criteria throughout the holding time[5]. Studies must be conducted to provide data to support bulk holding times for inprocess or intermediate materials. For a stable drug product, it is generally acceptable that no formal study is needed if in-process materials are held less than 30 days. For unstable products or materials that need to be held longer than 30 days, stability studies are necessary to verify the holding times do not affect the quality of the in-process materials. The present work was performed to determine the hold time study (Stability time) of Cetirizine di hydrochloride granules are used to determine its time period.

MATERIAL AND METHOD

MATERIALS

Cetirizine di hydrochloride granules and some common excipient such as lactose monohydrate, microcrystalline cellulose, colloidal anhydrous silica, maize starch, talc, magnesium stearate.

SIFTING

All the excipient is sifted from 40 # sieve to form uniform size and they are blended and lubricated in 25 kg octagonal blender.

HOLD TIME STUDY PROTOCOL [6,7,8]

The three formulation of same batch were selected for hold time study. During development on pilot scale batches, lubricated granules withdrawn from 10 different positions at initial stage from Octagonal blender. After blending 5kg sample are collected in Intermediate product container (IPC) because in hopper minimum 2 kg granule are required. For Left hand side and Right hand side 4kg sample are required. Lubricated granules should be stored at controlled condition in well closed IPC/SS container containing double polythene bag with status label. After collection of lubricated granules assay of lubricated granule studied at different interval i.e. Initial, 30th day, 45th day & the remaining blend are compressed at 45th day.

Table 1: sampling points and sampling technique in tablet manufacturing process [9, 10]

Process stage	Equipment	Sampling tool	Sampling points
Lubrication	Octagonal blender	Sampling thief	➢ Sample withdrawn from 10 different positions at initial stage from Octagonal blender. ➢ 5 kg sample withdrawn for hold time study (for 45th day) from top, middle and bottom in small Intermediate product container (IPC).
Compression after 45th day	Compression machine	Sampling scoop	Depending upon number of station, sample withdrawn from left hand side and right hand side at initial, middle, and end stage of machine run. Mix and made a composite sample

Note: unload the blend in the IPC withdraw samples equivalent to between 1-3 units dose (XX mg to XX mg) in triplicate from Top, Middle and Bottom layers from each of the IPC.

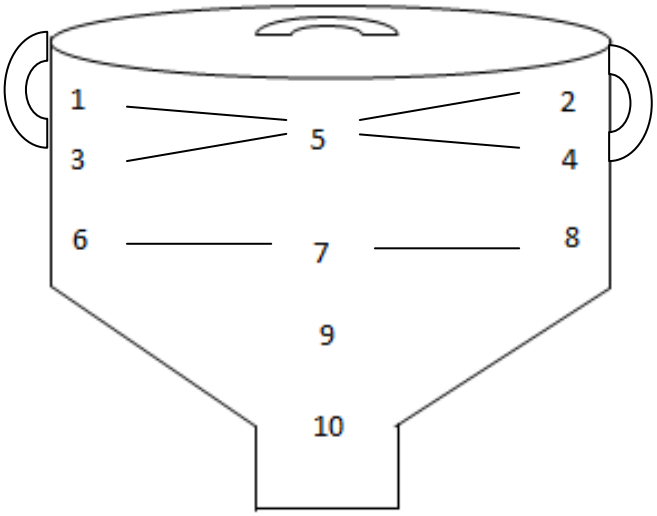

Fig 1: Samples for hold times study withdrawn from 10 different positions during development on pilot scale batches, during process validation or as a part of a deviation with proper testing.

Figure- Fig 2 sampling position:

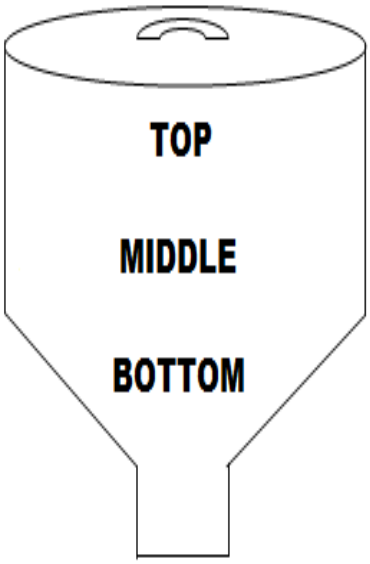

Fig 1.2: Sample for hold times study withdrawn from Top, Middle & Bottom when sample are stored in quarantine area at initial day, 30th day & 45th day

Table 2: Stages, test and study time in lubrication stage:

Stage	Test to be carried out as per specification	Study time
Lubricated granule	Description, Assay, loss on drying, particle size distribution, bulk density, tap density, angle of repose.	Initial, 30th day, 45th day
Compression after 45th day	Description, hardness, thickness, friability, disintegration, assay,	After lubrication time i.e. 45th day is over blend is compressed at 45th day

Note: sample quantity should be given in duplicate if 1st sample are fail next should be used.

ANALYTICAL PROCEDURE

Weigh accurately about 0.1 g sample of Cetirizine di hydrochloride granules; dissolve in 70 ml of a mixture of 30 volumes of water and 70 volumes of acetone. Titrate with 0.1 M sodium hydroxide to the second point of inflexion. Determine the end-point potentiometrically

RESULT AND DISCUSSION

Table 3: Stages, test and study time in lubrication stage:

Table 3.1: Initial Day

S.NO	TEST	LIMIT	BATCH A	INITIAL BATCH B	BATCH C
1	Description	White crystalline powder	complies	complies	complies
2	Loss on drying (%w/w)	2.00-5.00	3.42	3.48	3.50
3	Tap density (gm/ml)	0.60-0.80	0.71	0.77	0.71
4	Fine (%)	80-96	86.0	89.0	88.0
5	Content uniformity (%)	95-105	98.4	96.8	101.8

Table 3.2: 30th Day

S.NO	TEST	LIMIT	BATCH A	30TH BATCH B	BATCH C
1	Description	White crystalline powder	complies	complies	complies
2	Loss on drying (%w/w)	2.00-5.00	3.40	3.44	3.45
3	Tap density (gm/ml)	0.60-0.80	0.70	0.72	0.71
4	Fine (%)	80-96	88.0	85.0	87.0
5	Content uniformity (%)	95-105	97.5	96.8	98.2

Table 3.2: 45th Day

S.NO	TEST	LIMIT	BATCH A	45TH BATCH B	BATCH C
1	Description	White crystalline powder	complies	complies	complies
2	Loss on drying (%w/w)	2.00-5.00	3.41	3.41	3.49
3	Tap density (gm/ml)	0.60-0.80	0.71	0.71	0.72
4	Fine (%)	80-96	88.40	85.20	87.80
5	Content uniformity (%)	95-105	98.00	96.10	98.10

Table 4: Granule Compressed after 45th Day (Average Weight: 180 mg)

S.NO	TEST	LIMIT	45TH BATCH A	BATCH B	BATCH C
1	Description	White uncoated capsule shaped tablet.	Complies	Complies	Complies
2	Hardness	45-112 Newton (N)	67	80	72
3	Thickness	3.00-3.60 mm	3.20	3.48	3.46
4	friability	NMT 1.00 (%w/w)	0.11	0.14	0.09
5	Disintegration	NMT 15 min	1.35	1.22	1.40
6	Assay	95-105	98.4	97.5	97.4

BULK PROPERTIES

The first three batches of Cetirizine di hydrochloride granules were studied for hold time study, Table no. 03 summarize the stages and test of lubricated granules. Table no. 03 also includes the limit of each test.

HOLD TIME OF LUBRICATED GRANULES [11, 12]

H.T.S studies were continued upto 45th days in quarantine area at 22±2⁰ c. None of the batches showed significant change based on the ICH condition. All three batches showed acceptable results. Table 3 shows all the test within the limit at initial, 30th and 45th day for all three batches.

PRECAUTION AND RECOMMENDATION

Lubricated Granules

Lubricated granules should be stored at controlled condition in well closed IPC/SS container containing double polythene bag with status label.

Compressed Tablets

Compressed tablets should be stored at controlled condition in well closed IPC/SS container containing double polythene bag with status label.

CONCLUSION

Present study indicates that the result of lubricated granules of Cetirizine di hydrochloride which was stored for 45th days found within limit and uniform throughout the batch. After completions of 45th day the lubricated granule of Cetirizine di hydrochloride was compressed and the results were analyzed, it was found that it passes all the test and found within limit. From the data it can be concluded that the lubricated granules of Cetirizine di hydrochloride were stored upto 45th day and it is recommended to follow the instruction in guideline and batch manufacturing record.

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REFERENCES

1. Agalloco JP, Carleton FJ, Validation of pharmaceutical processes, 3rd ed. Informa Healthcare: New York; 2007, 444-446.
2. Pawar DP, Shamkuwar PB, Hosmani AH. Hold time study for pharmaceutical binders, lubricated granules, compressed tablets, coating suspension and coated tablets during manufacturing process. Der Pharmacia Sinica, 2012;3(2):300-304,
3. http://www.setac New Orleans.
4. QC Bulk Pharmaceuticals Work Group, "PhRMA Guidelines for the Production, Packing, Repacking or Holding of Drug Substances," Quality Steering Committee, PhRMA Science and Regulatory Section, Part I and Part II, *Pharmaceutical Technology*, December 1995 and January 1996.
5. PMA Committee on Guidelines for Bulk Pharmaceutical Chemicals, PMA Guidelines for the Production, Packing, Repacking, or Holding of Bulk Pharmaceutical Chemicals, Second Edition, Revised - June 1978.
6. International Conference on Harmonization (1997) Q1C: Stability testing for new dosage forms; EU: adopted by CPMP, December 96, issued as CPMP/ICH/280/95; FDA: Published in the Federal Register, 1997, 62, (90), 25634–25635.
7. Grimm W Extension of the international conference on harmonization tripartite guideline for stability testing of new drug substances and products to countries of climatic zones III and IV. Drug Dev Ind Pharm.1998, 24,313–325.
8. www.fda.gov/cder/guidance/index.htm
9. Hopkins M, Jenkins J, Louge M. Advances in Micromechanics of Granular Materials, 20th ed. Elsevier Science Publisher; 1991.
10. http://www.pharmatech.com.
11. Huynh K. editors. Hand book of stability testing in pharmaceutical development.17th ed. springer; 2009,389.
12. Prescott JK, Garcia TJ.A Solid Dosage and Blend Content Uniformity Troubleshooting Diagram. Pharm. Technol. 2001; 25 (3):68-88.