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Hold time study for pharmaceutical binders, lubricated granules, compressed tablets, coating suspension and coated tablets during manufacturing process

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ABSTRACT

Although there are no specific regulations of guidance document on bulk product holding times, good manufacturing practice dictates that holding 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. 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. 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. The conclusions from this article may lead to guidelines on sampling, storage and holding times for Pharmaceutical Tablet and during manufacturing process. Most appropriate storage and preservation protocol should be based on the specific study objectives and focus.

Key words: Hold time study; Binders, Lubricated Granules, Tablets and Coated tablets.

INTRODUCTION

Many times, in industry the material is kept on maximum allowable hold time which should be established for bulk and in-process drug products [1]. Although regulatory agencies expect manufacturers to document and address hold times, they do not describe a process for establishing hold time practice of sampling, storage for pharmaceutical tablet and injection during manufacturing process. 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 [2, 3]. In such case the manufacturer shall produce sufficient data demonstrating that the product is stable for said period of time before processing to the next stage and it will meet the acceptance criteria for the finished product as well as stability specifications. 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 [4]. Bulk products, which are stored for a period of time prior to packing into the final containers for 25% or more of the approved shelf life, should be tested, with stability indicating methods, prior to packaging [5]. Hold time study establish the time limits of holding the materials at different stages of production by assuring that the quality of the product does not deteriorate during the hold time. To validate the holding time of binders, lubricated granules, tablets, coating suspensions and coated tablets 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 [6].

Figure 1: Hold time study Flow chart in tablet manufacturing process.

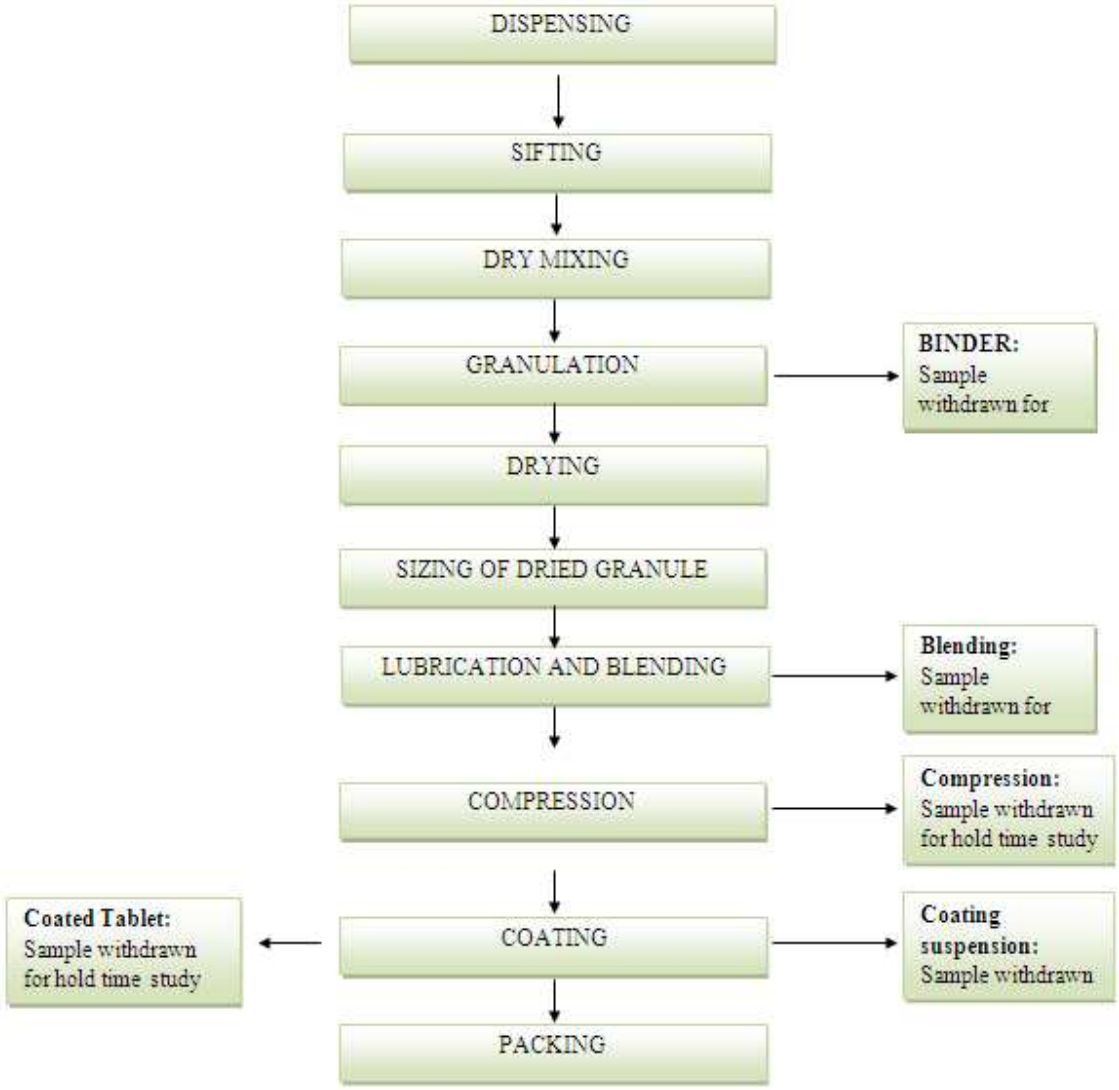

Table 1: Sampling points and sampling technique in tablet manufacturing process [7, 8].

Process stage	Equipment	Sampling tool	Sampling points
Binder	Steam kettle	S.S container	Discharge ports of steam kettle [3].
Lubrication	Octagonal blender	Sampling thief	10 points at initial stage from O'blender. 5 kg sample withdraw from top, middle and bottom in small Intermediate product container (IPC) [7].
Compression	Compression machine	Sampling scoop	Depend upon number 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 [8].
Coating Suspension	Steam kettle	S.S Container	Discharge ports of steam kettle [3].
Coating	Auto coater	Sampling scoop	Samples are collected from pan at initial, middle, and end portion [3].

Note:

1. On the basis of processing time at each individual stage and subsequent stage we can find the time interval for numbers of test to be performed.

2. After blending 5kg sample are collected in Intermediate product container (IPC) because in hopper 2 kg granule are required. For LHS and RHS 4kg sample are required.

Table 2: Stages, test and study time in tablet manufacturing process [4, 6].

Stage	Test to be carried out as per specification	Study time
Binder preparation	Microbial counts	Initial, 2hrs, 5hrs, 8hrs. in case of starch initial, 2hrs, 5hrs.
Lubricated granule	Description, Assay, loss on drying, water content, 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, dissolution or dissolution profile, related substance, uniformity of dosage units and microbial limits.	After lubrication time i.e. 45th day is over blend is compressed at 45th day.
Compression	Description, hardness, thickness, friability, disintegration, assay, dissolution or dissolution profile, related substance, uniformity of dosage units and microbial limits.	Initial, 30th day, 60th day & 90th day
Coating suspension	Physical appearance, viscosity, sedimentation, pH, microbial counts	Initial, 12, 24, 36, 48, 60, 72 hours
Coated tablets	Description, hardness, thickness, friability, disintegration, assay, dissolution or dissolution profile, related substance, uniformity of dosage units and microbial limits.	Initial, 30th day, 60th day & 90th day

Sample quantity required in each stage in tablet manufacturing process:

Table 3: Lubricated Granules

Average weight of standard compressed in gm.	0.160

Sample Quantity required for Hold Study

Test	Sample quantity in gm	Duplicated	Total Quantity for each test to be mentioned in Technical information sheet	For initial day	For 30th day	For 45th day
Description	0	0	0	12	10	12
Water content	2	2	4			
Assay	3.2	2	6			
Related substance/ degradation product	1	2	2			
Bioload	5	2	10	10	NA	10
Lubricated granules compressed at 45th day						
Test	Description	Water content	Assay	Related substance/ degradation product	Dissolution/ dissolution profiling	Bio-load
Sample quantity	0	6×2=12	20×2=40	3×2=6	6×2=12	16×2=31

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

Table 4: Compressed tablets

Average weight of standard compressed in gm.	0.350

Sample Quantity required for Hold Study

Test	Sample quantity in gm	Duplicated	Total Quantity for each test to be mentioned in TI sheet	For initial day	For 30th day	For 60th day	For 90th day
Description	0	0	0	89	51	51	89
Water content	6	2	12				
Assay	20	2	40				
Related substance/ degradation product	3	2	6				
Dissolution/ dissolution profiling	6	2	12				
Uniformity of dosage units	10	2	20				
Bioload	14	2	29	10	NA	NA	10
For physical parameter							
Weight variation	10	2		20	20	20	20
Thickness variation	10	1		10	10	10	10
Friability	21	2		42	42	42	42
Disintegration test	6	2		12	12	12	12
Total tablets required for hold time study				674			

Table 5: Coated tablets

Average weight of standard compressed in gm.	0.320

Sample Quantity required for Hold Study

Test	Sample quantity in gm.	Duplicated	Total Quantity for each test to be mentioned in TI sheet	For initial day	For 30th day	For 60th day	For 90th day
Description	0	0	0	71	53	53	71
Water content	6	2	12				
Assay	20	2	40				
Related substance/ degradation product	3	2	6				
Dissolution/ dissolution profiling	6	2	12				
Bioload	16	2	31	31	NA	NA	31
Total tablets required for hold time study				309			

Table 6: Binder preparation

Sample Quantity required for Hold Study

Test	Sample quantity in ml	Duplicated	Total Quantity for each test to be mentioned in TI sheet	For initial hrs	For 2hrs	For 5hrs	For 8hrs
Bioload	100	2	200	200	200	200	200
Total quantity required for hold time				1200			

Table 7: Coating suspensions

Test	Physical appearance	viscosity	sedimentation	pH	Bioload
Sample quantity in ml	100×2=200	100×2=200	100×2=200	100×2=200	100×2=200
Initial hrs	100×2=200	100×2=200	100×2=200	100×2=200	100×2=200
12 hrs	100×2=200	100×2=200	100×2=200	100×2=200	100×2=200
24 hrs	100×2=200	100×2=200	100×2=200	100×2=200	100×2=200
36 hrs	100×2=200	100×2=200	100×2=200	100×2=200	100×2=200
48 hrs	100×2=200	100×2=200	100×2=200	100×2=200	100×2=200
60 hrs	100×2=200	100×2=200	100×2=200	100×2=200	100×2=200
72 hrs	100×2=200	100×2=200	100×2=200	100×2=200	100×2=200
Total	1400 ml	1400 ml	1400 ml	1400 ml	1400 ml

Precaution and recommendation [2]:

1. The maximum storage period for each category of material should be established and specified on the basis of a study by keeping the material in a simulated container used in production.

2. Period of storage material should be as follows.

2.1 Binders:

Binders should be stored at controlled condition for not more than 8 hrs in well closed SS container with status label. If a binder is made up of starch it should be stored not more than 5 hrs. If storage period exceeds, then retesting should be performed.

2.2 lubricated granules

Lubricated granules should be stored at controlled condition for not more than 45 days in well closed IPC/SS container containing double polythene bag with status label. If storage period exceeds, then retesting should be performed.

2.3 Compressed Tablets:

Compressed tablets should be stored at controlled condition for not more than 90 days in well closed IPC/SS container containing double polythene bag with status label. If storage period exceeds, then retesting should be performed

2.4 Coating suspension:

Coating suspension should be stored at controlled condition for not more than 72 hrs in well closed SS container with status label. If storage period exceeds, then retesting should be performed.

2.5 coated Tablets:
Coated tablets should be stored at controlled condition for not more than 90 days in well closed IPC/SS container containing double polythene bag with status label. If storage period exceeds, then retesting should be performed.

3. Environmental condition:
For the storage of sample the environmental condition should be same as that of quarantine area /manufacture stage.

CONCLUSION

Present study indicate guidelines on sampling, storage and holding times for Pharmaceutical Binders, Lubricated Granules, Compressed Tablets, Coating Suspensions and Coated Tablets during manufacturing process. Most appropriate storage and preservation protocol should be based on the specific study objectives and focus. Statistical calculations are required to estimate a reliable holding time which is an area of growing concern, with analytical monitoring studies, appearing more frequently in the literature.

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