HOLD TIME STUDY FOR HGC DURING MANUFACTURING PROCESS

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ABSTRACT
Stability studies plays major role in the pharmaceutical industry. Guidelines to conduct Stability studies for pharmaceutical drug products are available in ICH, USFDA, EMEA, WHO guidelines. It is important to perform the hold time study of drug product, in order to predict the time period for which the product is on hold shall be shall be justified with adequate data to demonstrate the product will be stable throughout the approved shelf life. Hold samples need to store at GMP conditions i.e. where the lot or stage holds in the manufacturing area. All the regulatory agencies also may expect the hold time study at critical stages to understand the trend of degradation during holding at in-process stages. During the hold time study of hard gelatin capsules, Binder, Lubricated blend and filled capsules were collected and analyzed. Sample for hold time should be stored at the controlled condition in well-closed IPC/SS holder containing two-fold polythene bags. The hold time of the hard gelatin capsules was evaluated or calculated by comparing results of chemical and physical parameters with the pharmacopoeia limits. A specification chart is designed for indication of limits of the determined results. The chemical and physical parameters in different interval were analyzed and results at the pharmacopoeia limits were plotted. The probabilities of the erroneous decisions of initial and other interval 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 hard gelatin capsules can be established.

KEYWORDS: Hold time study, HGC, Hold time study.

INTRODUCTION

Pharmaceutical drug products stability studies are important for establishing the shelf life of the products. Stability studies can be performed for finished drug substances and drug products with the real time, intermediate and accelerated storage conditions. All stability study guidelines are mentioned in ICH, FDA, EMEA and WHO guidelines. [1]

Hold time is defined as time period in which materials (dispensing raw materials, intermediate and bulk dosage form awaiting final packing) may be held at specified condition and will remain within predefined specification. Hold time studies establish the time limit for holding the materials at different stages of production. It ensures that the quality of product does not produce results outside the acceptance criteria during the hold time. The design of study should reflect the holding time at each stage. [2]

Many times, in industry the material is kept on maximum allowable hold time which should be established for bulk and in-process drug products. 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.[3]

Hold-time studies are performed as promote information to justify the hold time deviation which happened during production.

Manufacturers should ensure that the products that they manufacture are safe, effective and of the quality required for their intended use. Systems should be in place to ensure that pharmaceutical products are produced according to validated processes and to defined procedures. Manufacturing processes should be shown to be capable of consistently manufacturing pharmaceutical products that are of the required quality and that comply with their specifications. Good manufacturing practices (GMP) require that arrangements should be made to ensure that the dispensed raw materials and packaging materials, intermediate products, bulk and finished products are stored under appropriate conditions. Storage arrangements should not have

deleterious effects on the subsequent processing, stability, safety, efficacy or quality of starting materials, intermediate products and bulk products prior to final packing. Maximum acceptable holding periods should therefore be established to ensure that intermediates and bulk product can be held, pending the next processing step, without producing results outside the acceptance criteria for the quality of the material. Normally, intermediate and bulk products should not be stored beyond the established hold time. The choice of maximum holding period should be supported by relevant data. Studies may extend beyond the chosen maximum but it is not necessary to extend testing to determine the extreme limits at which failure occurs.[2]

The risk evaluation of changes in processes, equipment, storage conditions, and starting, or packaging materials ought to incorporate an appraisal of whether additionally; hold-time studies ought to be performed. Although for products which have been already marketed retrospective risk-based, hold-time studies should be performed. The plan of the examination must reflect the holding time at each phase of the tablet production. To approve the hold time under the specific hold-time condition, results attained should be within the confinement of acceptance criteria all through the hold time.[4]

Hold Time study Flow

Hold-time studies are performed on bulk and intermediate drug products during product development phase i.e. Scale up stage and ought to be confirmed during process validation of commercial scale processing.[5]

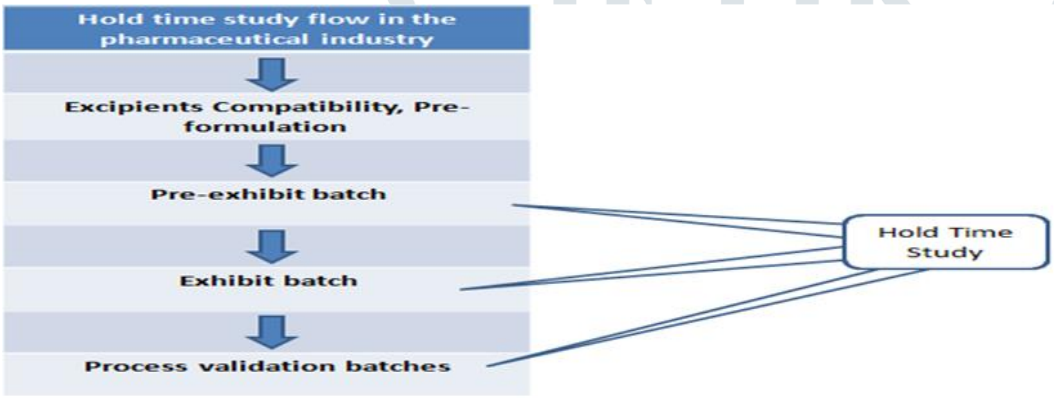

FIG : 1 FLOW OF HOLD TIME STUDY

Capsules are widely used as a highly flexible drug product vehicle. Capsules can be filled with powders, granules, pellets, tablets, mini-tablets, etc. The two main types of capsules are available 1. Hard-shelled capsules, which are normally used for dry, powdered ingredients or miniature pellets; 2. Soft-shelled capsules, primarily used for oils and for active ingredients that are dissolved or suspended in oil.[6]

Hold time study Steps

i. Selection of critical steps;

ii. Hold study time points and tests;

iii. Hold study protocol;

iv. Hold study results evaluation and report.

Selection of critical steps

The selection of hold time stability study conditions is very important for starting the hold study. These conditions are same with the manufacturing area/hold area conditions, so these conditions may vary with the product to product. Based on the manufacturing process of the capsule dosage form, hold study stages can be decided. Hold study required stages are summarized in the table 1.

Table 1: Hold study required stages for hard gelatine Capsules.

Stage	Hold study required stages
1	Binder solution
2	Dried Granules
3	Lubricated Blend
4	Filled Capsules

Hold study time points and tests

After gathering of samples physical and chemical parameters are considered at various interim. The selection of hold study stages are important for the evaluation of hold study, after selecting the stage then time points and tests need to select. Hold study time points are generally in Hours: 1, 3, 5, 7, 12, 24, 36, 48, 72 hours and Days: 1, 7, 15, 30, 45, 60, 75, 90 days.[5]

Hold stages, time points and required test for hard gelatin Capsules are discussed in detail in Figure-2 and Table-2:

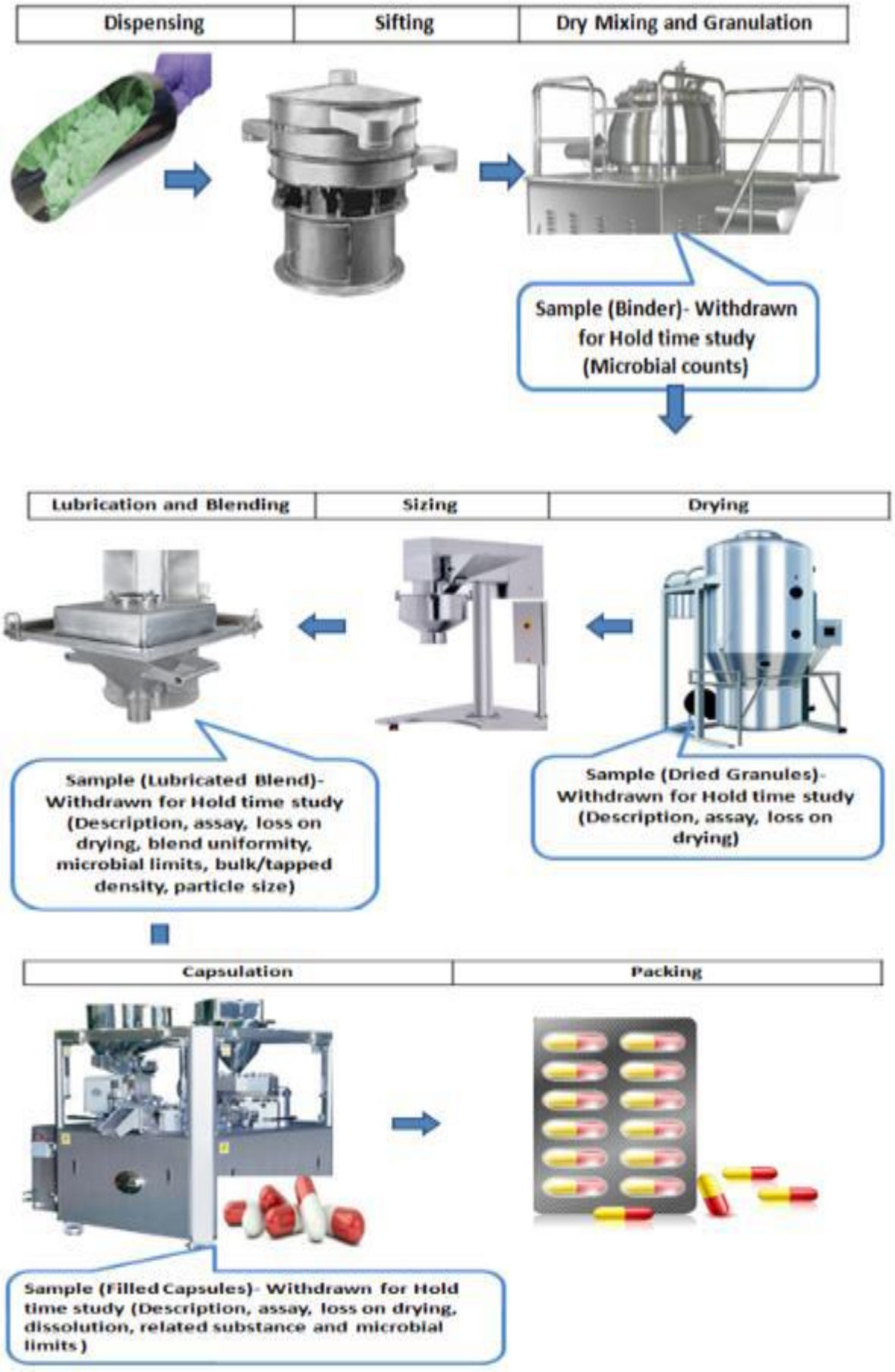

Figure-2: Hold stages, time points and required test for HGC.

Table 2: Hold study time points and test required for HGC.

Hold study required stages	Hold study time points	Tests required*
Binder solution	Initial, 2, 5 , 8 hours In case of starch Initial, 2, 5 hours	Microbial Limit Test
Dried Granules	Initial, 30th day, 45th day	Description, LOD or water content, Related Substances and assay.
Lubricated Blend	Initial, 30th day, 45th day	Description, LOD or water content, Related Substances and assay.
Filled Capsules	Initial, 7, 15 and 30, 45 and 60days	Description, LOD or water content, assay, Related Substances, dissolution and Microbial Limit Test.

***these tests may vary depend on the requirement.**

Hold Time study protocol

A written protocol, procedure or programme should be followed which includes elements and test parameters appropriate to the material or product under test. The protocol and report should include a title, reference number, version, date, objective, scope, responsibility, procedure, description of the material/product, sample quantities, sampling method and criteria, acceptance limits, frequency for sampling, sampling locations, pooling of samples, storage conditions, type of container, methods of analysis, results, conclusion, recommendation, signatures, dates, etc.[2]

Hold study results evaluation and report

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. Statistical calculations are required to estimate a reliable holding time. To validate the holding time of binders, lubricated granules and capsules 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.[7]

Hold time study results are passing the 60 days time interval then 45 days limit is good for general practice. In the same way if the stage is passing the 72 hours interval then 48 hours limit is general practice.[3]

Precautions: Sample for hold time should be stored at the controlled condition in well-closed IPC/SS holder containing two-fold polythene bags.

CONCLUSION

Hold study evaluation plays a main role for manufacturing the new products in GMP conditions. Based on the hold time study establishment and shelf life product manufacturing plan can be decided. Hold time study results are passing the 60 days time interval then 45 days limit is good for general practice. In the same way if the stage is passing the 72 hours interval then 48 hours limit is general practice. 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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