Subscription Agency
Exploring and Distributing Knowledge Globally

International Journal of Research in Pharma & Pharmaceutical Sciences
Volume 1 Issue 2

A Review on Memantine Tablets

Ramkishor[1*], Praveen Kumar Ashok[2], Nidhi Semiwal[3]
[1]M. Pharm 2nd Year (Quality Assurance), [2]Guide, [3]Co-Guide
Gyani Inder Singh Institute of Professional Studies, Dehradun, Uttarakhand, India
Corresponding Author
E mail Id: rkishor_1980@rediffmail.com

ABSTRACT

Process validation is the process for improving the safety and quality of the dosage form which is manufactured in the pharmaceutical industry. Basically, Process validation emphasize the role of objective measure and statistical tools and analyses knowledge, detection ,and control of variability and give assurance on consistent of quality/productive throughout life cycle of product. Result from Process validation method can be used to judge the quality and consistency of analytical result. The purpose of this review to cover need of process validation, principle of process validation, type of process validation, phase of process validation, strategy for process validation. In this review article we discussed about the importance and strategy of validation of tablet manufacturing.

Keywords: *Memantine Tablets, Development, Validation Process, Dosage Formulation.*

Introduction

The most vital aim of any pharmaceutical industry is to manufacture products of requisite attribute and quality consistently, at the lowest possible cost. The concept of validation was first come into light by Food and Drug Administration (FDA) officials, Ted Byers and Bud Loftus, in the mid 1970 s in order to improve the quality of pharmaceuticals [1].

According to the European Agency for the Evaluation of Medicinal Products (EMEA), "Validation is the act of demonstrating and documenting that a procedure operates effectively." In other words Validation is the documented act of demonstrating that a procedure, process, and activity will consistently lead to the expected results [2].

It often includes the qualification of systems and equipment. It is an essential requirement for good manufacturing practices and other regulatory requirements. Since a wide variety of procedures, processes, and activities need to be validated, the field of validation is divided into a number of subsections including the following:

Process Validation

Pharmaceutical process validation is the most important and recognized parameter of CGMP's. It is, therefore, an element of the quality assurance program associated with a particular product or process. "Process validation is a documented program which provides a higher degree of assurance that a specific process will produce a product meeting its predetermined specifications and quality attributes." The basic principles of quality assurance have as their goal the production of products that are fit for their intended use.

These principles are as follows:

1) Quality, safety and efficacy must be designed and built into the product.
2) Quality cannot be inspected or tested into the product.
3) Each critical step of the manufacturing process must be validated. Other steps

in the process must be under control to maximize the probability that the finished product consistently and predictably meets all quality and design specifications.

Validation of processes and systems is fundamental to achieving these goals. It is by design and validation that a manufacturer can establish confidence that the manufactured products will consistently meet their product specifications [2].

Importance of Process Validation

1) Assurance of quality
2) Time bound
3) Process optimization
4) Reduction of quality cost.
5) Minimal batch failures, improved efficiently and productivity.
6) Reduction in rejections.
7) Increased output.
8) Avoidance of capital expenditures
9) Fewer complaints about process related failures.
10) Reduced testing in process and in finished goods.
11) More rapid and reliable start-up of new equipment.
12) Easier scale-up form development work.
13) Easier maintenance of equipment.
14) Improved employee awareness of processes.
15) More rapid automation
16) Government regulation (Compliance with validation requirements is necessary for obtaining approval to manufacture and to introduce new products) [5].

Approaches to Process Validation

There are two basic approaches to process validation-one based on evidence obtained through testing (prospective and concurrent validation), and one based on the analysis of accumulated (historical) data (retrospective validation). Whenever possible, prospective validation is preferred. Retrospective validation is no longer encouraged and is, in any case, not applicable to the manufacturing of sterile products.

Both prospective and concurrent validation may include:

1) Extensive product testing, which may involve extensive sample testing (with the estimation of confidence limits for individual results) and the demonstration of intra- and inter-batch homogeneity;
2) Simulation process trials;
3) Challenge/worst case tests, which determine the robustness of the process.
4) Control of process parameters being monitored during normal production runs to obtain additional information on the reliability of the process [6].

The various types of process validation are outlined below:

Prospective Validation (Pre Marketing Validation)

This type of validation activity is normally completed prior to the introduction of new drug and their manufacturing process &prior to the distribution and sale of the drug product. It is undertaken when a new formula, process or facility must be validated. It is generally considered acceptable that three consecutive batches runs within the finally agreed parameters, giving product of the desired quality would constitute a proper validation of the process. It is preferred that the validation batches made should be of the same size as the intended production scale batches, when this is not practical, a reduced batch size corresponding to at least 10% of the intended batch size for full scale production can be considered.

Concurrent Validation

This type of validation is carried out during routine production activity and in exceptional cases [low volume product]. It is similar to the prospective validation except the operating firm will sell the product during the qualification runs, to the public at its market price. The document requirements are same as prospective validation. The decision to carry out concurrent validation must be justified, documented and approved by authorized person. It involves in process monitoring of critical processing steps and product testing, this helps to generate the document evidence to show that the production process is in a state control.

Retrospective Validation

Retrospective validation is defined as the establishment of documented evidence that a system does what it purports to do based on review and analysis of historical data achieved by the review of historical manufacturing testing data to prove that the process has always remained in control. This type of validation is acceptable only for well-established processes, without any change in the composition of the product, operating procedures, equipment. The source of data for this type of validation may be include batch documents Process control chart, maintenance logbooks, process capability studies, Finished product data, including trend data and stability data. Batches selected for retrospective validation should be representative of all batches made during the review period including any batches that fail to meet the specification. The data generated from 10 to 30 batches should be examined to assess process consistency.

Revalidation

Revalidation is the repetition of a validation process or a specific part of it. Revalidation provides the evidence that changes in a process-introduced intentionally/unintentionally; do not adversely affect process characteristics and product quality. Revalidation may be required in following cases: Change in formulation, procedure or quality of pharmaceuticals ingredients, change in equipment, addition of new equipment and major breakdown [Maintenance which affect the performance of the equipment].Major change of process parameters, change in site, batch size change [1].

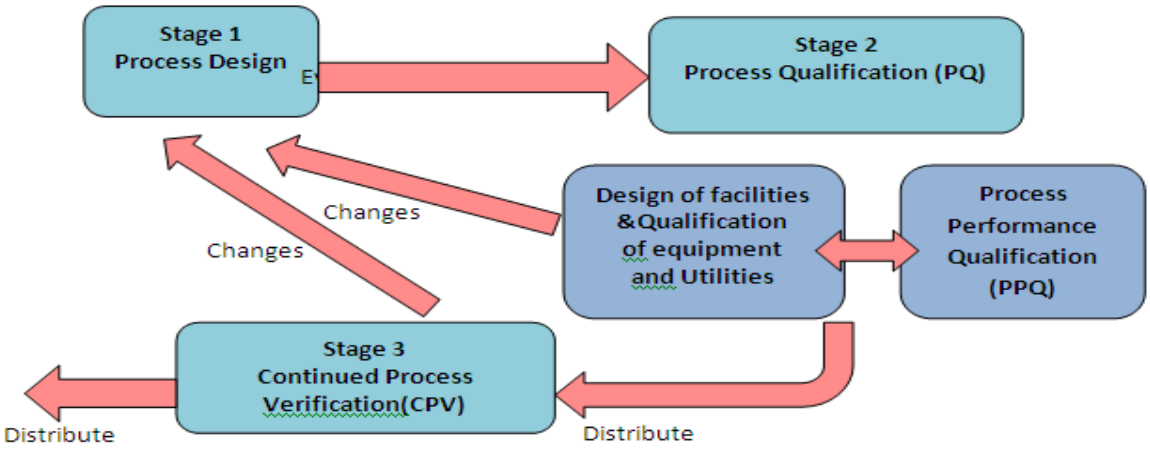

Fig.1. Stages of Process Validation [11]

Need for Process Validation

The possible reasons for performing process validation may include

1) New product or existing products for,
   - Change in site of manufacturing
   - Change in batch size
   - Change in equipment
   - Change in process
   - Change in composition or components
   - Change in the critical control parameters
   - Change in vendor/manufacturing site of API
   - Change in vendor of critical excipients
   - Change in specification of input material
   - Abnormal trends in quality parameters of product through review during annual product review.

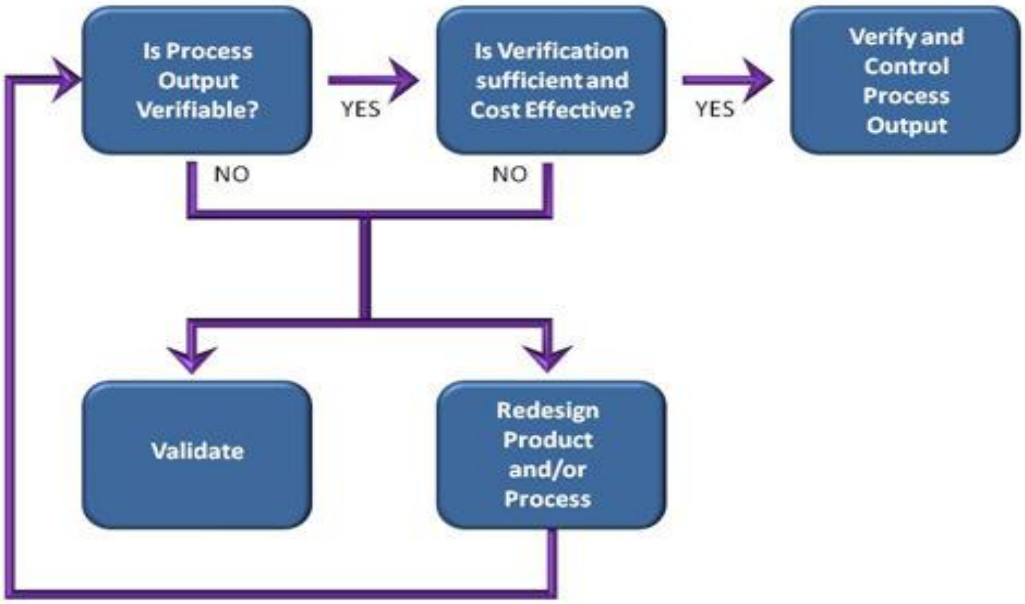

Fig. 2: *Process Validation Decision Tree [11]*

Tablets

Tablets are the solid unit dosage forms containing a medicament or mixture of medicament and excipients compressed or molded into solid cylindrical shape having either flat or convex surfaces. They offer the greatest capabilities of all oral dosage forms for the greatest dose precision and the least content variability.

Steps for the formulation of tablets

1) Granulation
2) Compression
3) Coating
4) Packaging

Granulation

The manufacture of granulations for tablet compression may follow one or a combination of three established methods-

Direct Compression

There are few crystalline substances, such as sodium chloride, sodium bromide, and potassium chloride that may be compressed directly. Direct compressible materials, in addition to possessing good flow and compressibility, must be inert, tasteless, re-workable, able to disintegrate, and inexpensive. Even though direct compression has some important advantages (low labor input, a dry process,

and fewest processing steps) there are some limitations to the techniques. Differences in particle size and bulk density between the drug and diluent may lead to stratification within the granulation. The stratification may then result in poor content uniformity of the drug in the compressed tablet. The stratification and resultant content uniformity problems are of special concern with low-dose drugs. A large-dose drug may present problems with direct compression if it is not easily compressible by itself. In some instances, the direct compression diluent may interact with the drug. Because of the dry nature of direct compression, static charge buildup can occur on the drug during routine screening or milling and mixing, which may prevent a uniform distribution of the drug in the granulation.

Dry Granulation (Compression Granulation)

It is a valuable technique in situations where the effective dose of a drug is too high for direct compaction, and drug is so sensitive to heat, moisture or both, which precludes wet granulation. It involves the compaction of the components of a tablet press or specially designed machinery, followed by milling and screening, prior to final compression into a tablet.

When the initial blend of powders is forced into the dies of a large capacity tablet press and is compacted by means of flat-faced punches, the compacted masses are called slugs, and the process is referred to as “slugging”. The slugs are then screened or milled to produce granular form of tablet material, which now flows more uniformly than the original powder mixture. When a single slugging process is insufficient to confer the desired granular properties to the material, the slugs are sometimes screened, slugged again, and screened once more.

Wet Granulation

Wet granulation process involves the wet massing of powders, wet sizing or milling, and drying. This process forms the granules by binding the powders together with an adhesive instead of by compaction. The wet granulation technique employs a solution, suspension, or slurry containing a binder, which is usually added to the powder mixture; however, the binder may be incorporated dry in to the powder mix, and the liquid may be added by itself. During granulation the particles and agglomerates are subjected to consolidating forces by action of machine parts and of inter-particulate forces. Granulation in large blenders requires 15 min to an hour.

The next stage is wet screening, which involves converting the moist mass in to coarse, granular aggregates by passage through a hammer mill or oscillating granulator, equipped with screens having large perforations. After drying the granulation is screened again. The size of the screen depends upon the grinding equipment and the size of the tablet to be made.

Spray Granulation

Spray granulation is the drying of liquid (solution, suspension, melt) while simultaneously building particle size. It is generally performed on Fluid bed processor, so it is also called Fluidized bed granulation. In spray granulation, mixing of an active ingredient with a carrier in the liquid phase is done, and is sprayed on to the fluidized powder bed (granules/seeds) , so as the active ingredient will be encapsulated in a matrix of carrier after the spray granulation process. Seeds for the granulation can be charged in to the granulator (external seeds) or they are formed within the Fluid bed by abrasion

(internal seeds). The sprayed liquid is coated on to the seed and is dried.

Types of Tablets According to Route of Administration

1) Tablets ingested orally
   a) Standard compressed tablet, *e.g.* Paracetamol tablet
   b) Multiple compressed tablet
   c) Repeat action tablet
   d) Delayed release tablet *e.g.* Enteric coated Bisacodyl table
   e) Sugar coated tablet *e.g.* Multivitamin tablet
   f) Film coated tablet *e.g.* Metronidazole tablet
   g) Chewable tablet, *e.g.* Antacid tablet

2) Tablets used in oral cavity
   a) Buccal tablet, e.g. Vitamin-C tablet
   b) Sublingual tablet, *e.g.* Vicks Menthol tablet
   c) Troches or lozenges
   d) Dental cone

3) Tablets administered by other route
   a) Implantation tablet

4) Tablets used to prepare solution
   a) Effervescent tablet, *e.g.* Dispirin tablet (Aspirin)
   b) Dispensing tablet, *e.g.* Enzyme tablet (Unienzyme)
   c) Hypodermic tablet
   d) Tablet triturates *e.g.* Enzyme tablet (Digiplex).

Excipients in Tablet Formulation

Conventional oral tablets for ingestion usually contain the same classes of components in addition to the active ingredients, which are one or more agents functioning as 1) a diluent, 2) a binder or an adhesive, 3) a disintegrant, and 4) a lubricant.

All nondrug components of a formula are termed excipients.

1) Diluents: Diluents are fillers designed to make up the required bulk of the tablet when the drug dosage itself is inadequate to produce this bulk. The dose of some drugs is sufficiently high that no filler is required (*e.g.*, aspirin and certain antibiotics). Examples- Lactose USP, Microcrystalline cellulose NF, Mannitol USP, Sorbitol, Directly compressible starches, hydrolyzed starches, sucrose USP powder, Dextrose & Calcium sulfate dehydrate NF.

2) Binders and adhesives: These materials are added either dry or in liquid form during wet granulation to form granules or to promote cohesive compacts for directly compressible tablets. Examples- Acacia, pre-gelatinized starch, cellulose derivatives, gelatin, glucose, sorbitol, polyvinylpyrolidone (PVP), Starch paste, Sodium alginate, Alginate derivatives and Tragacanth.

3) Disintegrants: A disintegrates is added to most tablet formulations to facilitate breakup or disintegration of the tablet when it contacts water in the gastrointestinal tract. Disintegrate may function by drawing water in to the tablet, swelling, and causing the tablet to burst apart. Such tablet fragmentation may be critical to the subsequent dissolution of the drug and to the attainment of the satisfactory dug bioavailability. Examples: Starch, Starch derivatives, cellulose, cellulose derivatives, clays, alginates and cross-linked PVP.

4) Lubricants, Antiadherents, and Glidants: These three classes of materials are typically described together because they have overlapping functions. Lubricants are

intended to reduce the friction during tablet ejection between the walls of the tablet and walls of the die cavity in which the tablet was formed. Antiadherents have the purpose of reducing the sticking or adhesion of any of the tablet granulation or powder to the faces of the punches or to the die wall. Glidants are intended to promote flow of the tablet granulation or powder materials by reducing friction between the particles. *Examples*- Lubricants: Stearic acid, Stearic acid salts, Surfactants, Talc, Waxes and, Polyethylene glycols. Glidants and Flow promoters: Silica derivatives, Talc, Cornstarch

5) **Colors, Flavors & Sweeteners:** The use of colors & dyes in the tablet manufacturing has served three purposes: disguising of off-color drugs, product identification, and production of a more elegant product. Flavors are usually limited to chewable tablets or other tablets intended to dissolve in the mouth. In general, flavors that are water soluble have found a little acceptance in tablet making because of their poor stability. Flavor oils are added to tablet granulations in solvents, are dispersed on clays and other adsorbents, or are emulsified in aqueous granulating agents. Various dry flavors are also available for pharmaceutical products. Examples- FD & C and D & C dyes and lakes, Spray dried and other flavors, Natural sweeteners, artificial sweeteners.

Table 1: Problems Arising During Manufacturing of Tablets:

Problem	Definition	Causes	Solutions
Picking& Sticking	When the surface material of the tablet is removed by the punch, it is called picking. In sticking the granules adhere to the dye wall and there by the lower punch cannot move freely.	**Tooling**: ✓ Wrong design of embossing or break line. ✓ Punch faces having pitting marks. **Machine**: ✓ Less compression pressure. ✓ Compression too fast ✓ Concaving too deep for granulation. ✓ Too much heat generation due to wrong setting of feed frames/ gears/turret etc. **Granules**: ✓ Oily or Waxy materials ✓ Too much binder. ✓ Excessive moisture. ✓ - Insufficient lubrication	✓ Change embossing design ✓ Increase pressure ✓ Improve Granulation
Lamination	It is a separation of a tablet into two or more distinct layers.	**Tooling**: Concave edges of punches turning claw shaped. ✓ Greater radius of curvature of punch face. ✓ Dies developing a wear ring shape. ✓ Improper adjustment of sweep off blade. ✓ Less rise of lower punch during	✓ Checking of punches & replacing them ✓ Proper checking and replacing them. ✓ Turning the die over so that compression occurs in an unworn area above ring. ✓ Proper setting of

		ejection of tablet. **Machine**: Improper/Deep concave punches **Granules**: ✓ Air entrapment in the granular material. ✓ Low levels of binding agent ✓ - Over dried granules (due to lack of cohesion).	sweep off blade & lower punch rise. ✓ Better to use flat punches. ✓ By pre-compression, reducing final compression, minimizing tableting rate. ✓ By maintaining moisture levels using hygroscopic materials.
Mottling	It is an unequal distribution of colour on a tablet with light and dark areas standing out in an otherwise uniform surface.	**Granules**: ✓ Difference in the color of drug and excipients. ✓ Dye may migrate to the surface of granulation during drying. ✓ Adhesive gel solutions may not distribute well. ✓ Improper mixing of granular material. ✓ - Dirt in the granular material or on punch faces; oil spots by using oily lubricant.	✓ Use of colorants. ✓ Change the solvent and binder system. ✓ Reduce the drying temperature. ✓ Grind to a smaller particle size. ✓ Use fine powder adhesive. ✓ Disperse a dry color additive during powder blending.
Capping	It is partial or complete separation of the top or bottom crown of the tablet from the main body of the tablet. This problem may occur after hours or even days later.	**Tooling**: ✓ Die bores having ring ✓ Too much depth of concavity in punches. **Machine**: ✓ Excessive pressure. ✓ Compression taking place at lower side of the die. ✓ Too much of vibration. **Granules**: ✓ Excessive lubrication ✓ Too dry granules. ✓ Less binder in granules.	✓ Replace dies if found defective. ✓ Reduce compression pressure. ✓ Improve granulation.
Weight variation	It is unequal distribution of weight in tablets	**Tooling**: ✓ Non uniform punch working length. ✓ Non-uniform Head-flat or Head thickness. ✓ Die height is above the standard limit. **Machine**: ✓ Defective feed frame or improper setting. ✓ High machine speed. ✓ Excessive vibration ✓ Worn out weight dosser ✓ Wrong anti-turning device setting. **Granules**:	✓ Replace/rectify tools, if found defective ✓ Reduce machine speed, replace worn out parts and feed frame. ✓ Provide uniform granules.

		✓ Non-uniform, too big, too fine granules. ✓ Granules sticking to the lower punch.	

CONCLUSION

Validation is the most widely used word in the areas of drug development, manufacturing and specification of finished products. The consistency and reliability of a validated process to produce a quality product is the very important for an industry. From the study it can be stated that Pharmaceutical Process Validation is the most important and recognized parameters of cGMP. Quality assurance techniques must be used to build the quality into the product at every step and not just tested for at the end. Process validation involves a series of activities taking place over the lifecycle of the product.

REFERENCES:

1) Parida RK (2010) Overview of Pharmaceutical Validation and Process Controls in Drug Development, *Der pharmacia Sinica*, 2010 1(1): 11-19.
2) Guidance for Industry. Process Validation: General Principles and Practices. U.S. Department of Health and Human Services, Food and Drug Administration, CDER/CBER/CVM. Current Good Manufacturing Practices (CGMP). Revision 1; January 2011.
3) Raghunandanan R (2009) Validation Aspects of Solid Dosage Form Pharma Time 41(4).
4) Patel VB, Rathwal MR and Patel K, studies in prospective Process Validation of cimitidine tablet dosage form, *International Journal of Research in Pharmaceutical and biomedical Sciences*, *Vol.* 2 (4) Oct-Dec 2011, pp 1823-1836.
5) Surbhi G, Seema S, Gurpreeet S, Rana AC (2012) International Process Validation of Tablet Dosage Form, International Research Journal of Pharmacy,3(3), pp 48-54.
6) Vivek G, Bonde CG (2009) The Statiscal Assurance of Process Validation by Analytical Method Development and Validation For Levofloxacin IR Tablets, 1(3): pp 921-924.
7) Chandan S, Rana AC, Rajni B Nirmata S (2013) Process Validation as an Industrial Practice, *IRJP*, 4(2), pp 25-28.
8) National Institute of Neurological Disorders and Stroke. Dementia: hope through research. Bethesda, MD: Office of Communications and Public Liaison, National Institute of Neurological Disorders and Stroke, US National Institutes of Health. Published online; version last updated June 26th, 2013, accessed November 1st, 2013. Summary information.
9) Alzheimer's Association. The role of plaques and tangles. Published online, accessed November 1st, 2013.
10) Alzheimer's Association. Alzheimer's disease: Risk factors. Published online, accessed November 1st, 2013.
11) Alzheimer's Association. Traumatic Brain Injury. Published online, accessed November 1st, 2013.
12) Hyman BT, Phelps CH, Beach TG, and others. National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease, *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, 2012, volume 8, issue 1, pages 1-13 (DOI: 10.1016/j.jalz.2011.10.007).
13) DeFina PA, Moser RS, Glenn M, Lichtenstein JD and Fellus J.

Alzheimer's disease clinical and research update for health care practitioners. *Journal of Aging Research*, volume 2013 (e-publication, September 4th, 2013), article ID: 207178.

14) McKhann GM, Knopman DS, Chertkow H, and others. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's and Dementia*, 2011, volume 7, issue 3, pages 263-269.