ORIGINAL RESEARCH PAPER

Pharmaceutical Science

SCIENTIFIC VALIDATION OF LOSARTAN SODIUM BY USING DRY MIXING AND GRANULATION TECHNIQUES

KEY WORDS: Losartan Potassium Tablets, Dry Mixing, Granulation, Planetary Mixer, tray drier and multi mill

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ABSTRACT

The main objective of the study is used for the validation of Losartan Potassium Tablets 50 mg manufactured at Orchid Healthcare, Alathur, with the evaluation of parameters like Dry Mixing and Granulation due find the quality of product. Dry Mixing and Granulation was performed by using Planetary Mixer and also wet granules dried by tray drier. Product size was reduced by multi mill. The assay results founded 3 batches average percentage 100.5% and which will be applicable for Good Manufacturing Process

INTRODUCTION

Granulation may be defined as a size enlargement process which converts fine or coarse particles into physically stronger and larger agglomerates having good flow property, better compression characteristics and uniformity[1]. The art and science for process and production of granules is known as Granulation Technology. Granulation is the process in which primary powder particles are made to adhere to form larger, multi particle entities called granules. Pharmaceutical granules typically have a size range between 0.2 and 4.0 mm, depending on their subsequent use. In the majority of cases this will be in the production of tablets or capsules, when granules will be made as an intermediate product and have a typical size range between 0.2 and 0.5 mm, but larger granules are used as a dosage form in their own right[2]. Granulation normally commences after initial dry mixing of the necessary powdered ingredients so that a uniform distribution of each ingredient through the mix is achieved. After granulation the granules will either be packed (when used as a dosage form), or they may be mixed with other excipients prior to tablet compaction or capsule filling[3].

Validation is an integral part of Good Manufacturing Practice (GMP) that involves the systematic study of systems, facilities and processes aimed at determining whether they perform their intended functions adequately and consistently as specified. A validated operation is one, which has been demonstrated to provide a high degree of assurance that uniform batches will be produced that meet the required specifications, and has therefore been formally approved[4]. Unlike many other requirements of GMP, validation in itself does not improve processes. It can only confirm (or not, as the case may be) that the process can been properly developed and is under control. Ideally, any development activity in the latter stages should be finalized by a validation phase[5]. This includes, in particular, the manufacture of investigational products and the scaling up of processes from pilot plant to production unit. [1] According to European community for medicinal products, Validation is action of proving, in accordance with the principle of cGMP that any procedure, process, equipment, material, activity or system actually used to expected results. Pharmaceutical manufacturing will need to employ innovation, cutting edge scientific and engineering knowledge, along with the principle of Quality Management to respond to the challenges of new discoveries and improvement of Quality attributes in the existing ones.[6]

MATERIALS AND METHODS

DISPENSING OF RAW MATERIALS

The received raw materials must meet the established quality standards and it is certified by the quality assurance team. It provides for the authorization of the release of the approved raw materials for manufacturing, and the release of the manufactured product to the market, based on actual laboratory testing[7].

Physical And Chemical Tests

Tests for appearance, colour, odour, optical rotation, specific gravity, pH, solubility, viscosity, disintegration time, hardness, friability, average weight, weight variation, content uniformity, dissolution profile, particle size, moisture content, assay for active ingredients, impurities, contaminants and degradation[8].

Biologic And Microbiologic Tests

Macro biologic or Microbiologic assays, tests for potency, safety, toxicity, pyrogenicity, sterility and preservative[9].

Dry Mixing And Granulation

Dry mixing and granulation is done so as to obtain a uniform formulation. The sifted fine powder is transferred to the planetary mixer. The agitator of the planetary mixer has planetary motion. The agitator rotates on its own axis and around the central axis so that it reaches all parts of the powder.The beater revolves 2-4 times for each revolution of the head providing double mixing action. Each revolution of the head causes the beater to complete one revolution around the bowl[1].

Drying

The wet granules are dried by using Tray Drier. The granules are loaded in the trays. Fresh air introduced through the inlet, which passes through the heaters and then the air gets heat and hot air get generated. The fan circulates the hot air. The hot air pickup the water content from the granules and it became dried. This type of drying is not suitable for material having hygroscopic in nature and the material, which undergoes oxidation and reduction in the presence of air.

Size Reduction

Coarser raw material has to be reduced to fine ones. This process of size reduction is called milling. The basic principles involved in size reduction are mechanical process and precipitation process. In this method, size reduction involves successive cutting or sheering the feed material with the help of sharp knives. The coarser material to be milled is filled in the hopper. The inner jacket containing the milling blades are surrounded by sieve of appropriate mesh.

The motor is switched on and the coarser material is slowly allowed to fall on the knives. By successive cutting and sheering the material is milled and minor size particles that come out of the jacket are collected.

RESULTS AND DISCUSSION

DRY MIX / GRANULATION DATA COMPILATION

Equipment : Planetary Mixer Batches: A,B,C
Speed: Optimum Batch size: 60,000 Tablets
Time: 8 minutes, 10 minutes & 12 minutes

The dispensed, sifted Active drug and excipients were dry mixed, granulated with the binding solution and checked for assay value from three different Locations as illustrated in the figure.1-3. The observed data for three batches were compiled in the table.1 The second batch sifted Active drug and the excipients were dry mixed, granulated with binding solution and checked for assay value from three different Sites as exemplified in the figure 4-6. Observed data for three batches were compiled in the table.2. The batch three sifted Active drug and the excipients were dry mixed, granulated with binding solution and tested assay value from three different performances as shown in the figure 7-9 & table.3.

Table: 1: Dry Mix/Granulation Data Compilation In 8mins

Location	Observations			Limit
	Assay of Losartan Potassium (%)			
	Batch A (A536001)	Batch B (A536002)	Batch C (A535001)	
1	99.9%	99.8%	100.1%	90.0-110.0% of Label Claim
2	101.0%	100.8%	100.3%	90.0-110.0% of Label Claim
3	100.5%	100.6%	100.4%	90.0-110.0% of Label Claim
4	99.9%	95.6%	99.7%	90.0-110.0% of Label Claim
Minimum	99.9%	95.6%	99.7%	90.0-110.0% of Label Claim
Maximum	101.0%	100.80%	101.4%	90.0-110.0% of Label Claim
Average	100.3%	99.2%	100.1%	90.0-110.0% of Label Claim
% RSD	0.5%	2.4%	0.3%	NMT 5%

Table:2: Dry Mix / Granulation Data Compilation In 10 Mins

Location	Observations			Limit
	Assay of Losartan Potassium (%)			
	Batch A (A536001)	Batch B (A536002)	Batch C (A535001)	
1	99.8%	99.7%	99.9%	90.0-110.0% of Label Claim
2	101.0%	100.3%	100.6%	90.0-110.0% of Label Claim
3	99.8%	99.1%	99.8%	90.0-110.0% of Label Claim
4	99.7%	99.3%	100.1%	90.0-110.0% of Label Claim
Minimum	99.7%	99.1%	99.8%	90.0-110.0% of Label Claim
Maximum	100.1%	100.3%	100.6%	90.0-110.0% of Label Claim
Average	99.9%	99.6%	100.1%	90.0-110.0% of Label Claim
% RSD	0.2%	0.5%	0.4%	NMT 5%

Table: 3: Dry Mix / Granulation Data Compilation In 12mins

Location	Observations			Limit
	Assay Of Losartan Potassium (%)			
	Batch A (A536001)	Batch B (A536002)	Batch C (A535001)	
1	99.7%	100.2%	100.3%	90.0-110.0% of Label Claim
2	99.9%	99.7%	99.8%	90.0-110.0% of Label Claim
3	98.0%	100.7%	100.6%	90.0-110.0% of Label Claim
4	99.8%	97.3%	100.2%	90.0-110.0% of Label Claim
Minimum	98.0%	99.5%	99.8%	90.0-110.0% of Label Claim
Maximum	99.9%	100.7%	100.6%	90.0-110.0% of Label Claim
Average	99.4%	99.5%	100.2%	90.0-110.0% of Label Claim
% RSD	0.9%	1.5%	0.3%	NMT 5%

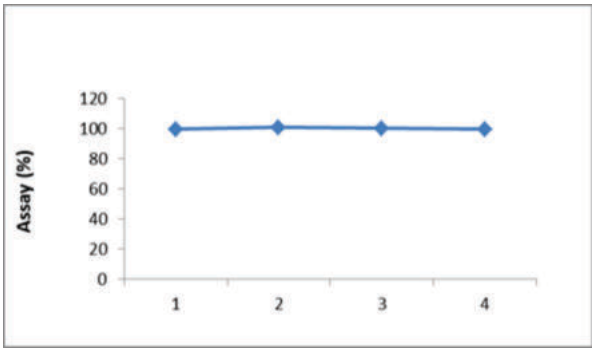

Figure:1: Dry Mix/Granulation Data For Batch-a (8 Minutes)

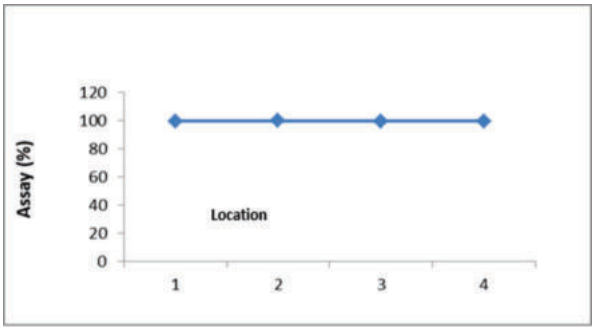

Figure:2: Dry Mix/Granulation Data For Batch-a (10 Minutes)

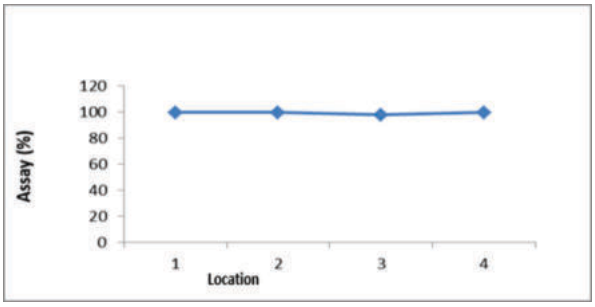

Figure:3: Dry Mix/Granulation Data For Batch-a (12 Minutes)

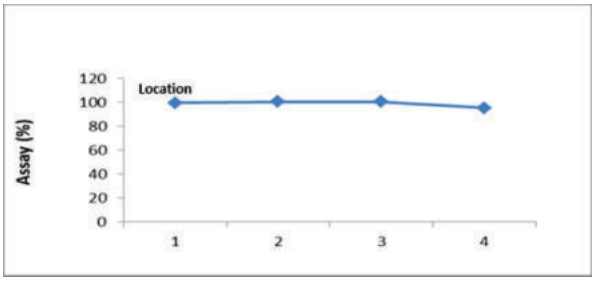

Figure:4: Dry Mix / Granulation Data For Batch-b (8 Minutes)

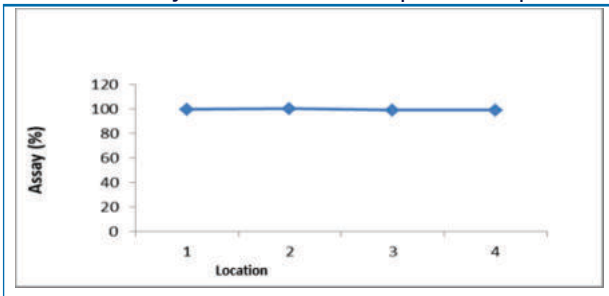

Figure:5: Dry Mix/Granulation Data For Batch-b (10 Minutes)

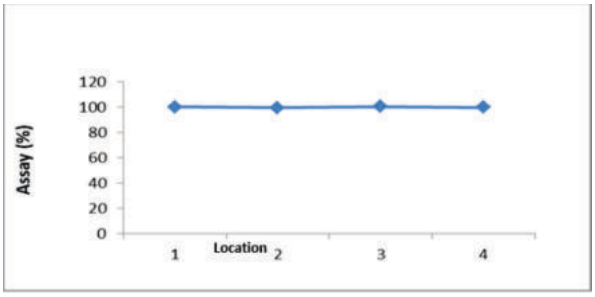

Figure:6: Dry Mix / Granulation Data For Batch-b (12 Minutes)

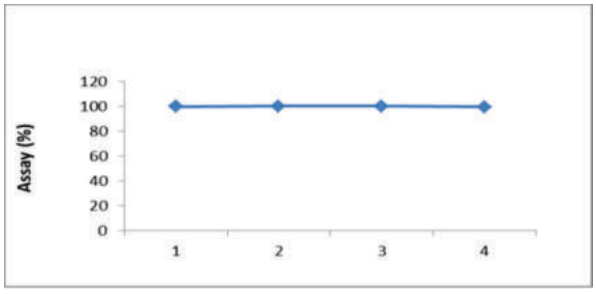

Figure:7: Dry Mix/Granulation Data For Batch-c (8 Minutes)

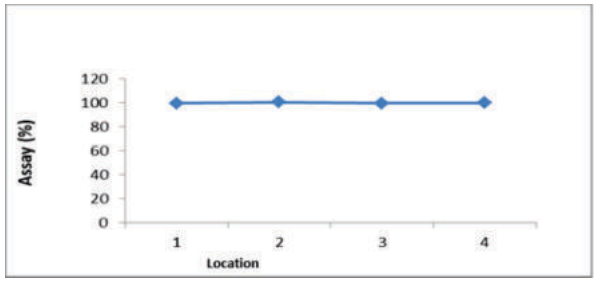

Figure:8: Dry Mix/Granulation Data For Batch-c (10 Minutes)

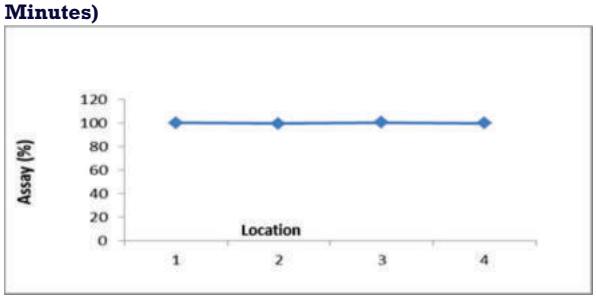

Figure:9: Dry Mix / Granulation Data For Batch-c (12 Minutes)

Table:4:Values Are Within Specifications Limits Specified By The Industry.

Batches	Granular RPM	
	Low	High
Batch A	20	40
Batch B	20	40
Batch C	20	40

Drying Data Compilation

Equipment: Tray Drier Batches: A,B,C
Temperature: 60°C Batch size: 60,000 Tablets

The granulated mass was dried in Tray Drier and the samples were observed for Loss on Drying at specific time interval. The observed data's for the three batches were compiled in the table4. The observed data's from the three batches , Batch A, Batch B, Batch C implies that the Loss On Drying was found to be within the specified limits (2.0 – 3.0%), which was set forth during the prospective validation phase. Hence the specified parameters drying at 60°C was acceptable during the concurrent validation phase also.

Table:4: Drying Data Compilation

Batches	Drying Time	% LOD (2.0 to 3.0 %)
Batch A	1 Hour 44 Minutes	2.4%
Batch B	1 Hour 55 Minutes	2.4%
Batch C	2 Hour 40 Minutes	2.4%

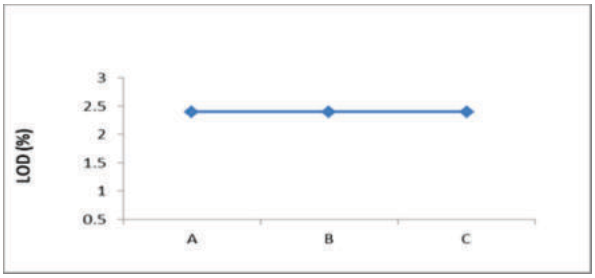

Figure:10: Drying Time Compilation Datalocation

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Conflict of Interest

No potential conflict of interest was reported by the authors

SUMMARY AND CONCLUSION

To obtain uniform mixing at dry mixing stage, samples were drawn from four different locations of the Planetary Mixer and the observed data are compiled. From the observed data, it was confirmed that, the uniformity was good after dry mixing for 12 minutes. After dry mix / Granulation, that wet mass was spread on the trays of Tray Drier and dried at 60°C. From the observed data, it was confirmed that, the drying time was 115 Minutes to attain 2.0-3.0% Loss on Drying at a temperature of 60°C. Pharmaceutical products are processed all over the world using the direct compressing, wet-granulation, or dry granulation methods. Which method is chosen depends on the ingredients individual characteristics and ability to properly flow, compresses, eject, and disintegrate. Choosing a method requires thorough investigation of each ingredient in the formula, the combination of ingredients, and how they work with each other. Then the proper granulation process can be applied. A judicial selection of appropriate technology for carrying out the granulation process is the key to achieve a targeted granulation and final product parameters. In depth knowledge of the processing techniques and their merits and demerits is required to adopt during development stage of product. A systematic approach should be followed for selecting the suitable granulation process.

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