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ORIGINAL ARTICLE

Process Validation of Solid Oral Dosage Form of Levofloxacin Tablet I.P 500mg

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ABSTRACT

Objectives: This study focused on the process validation of levofloxacin tablet I. P 500 mg. The objective is to validate the critical process variables to ensure that manufacturing processes consistently produce products of the desired quality. **Methods:** Validation studies were conducted in three consecutive batches intended for commercial use, making this a concurrent validation study. Process validation was performed according to the approved process validation protocol and the sampling plan. All individual processes, including sifting, dry mixing, granulation, drying, lubrication, compression, coating, and packing, were fully monitored, and the samples were collected according to the sampling plan. The in-process parameters and process variables were checked throughout, ensuring that they remained within the specified limits. **Findings:** The validation showed that all in-process parameters and process variables were within acceptable limits. No significant deviations or changes in process parameters were observed. The results for individual process validation were as follows: Carr's index (5-20%), Moisture content (2-3%), Angle of repose (25-30), Thickness (6.0 mm $\pm$ 0.1 mm), Hardness (not less than 4 kg/cm^2), Average weight (784 mg to 816 mg), Disintegration (not more than 10 minutes), Dissolution (not less than 80% of label claim), Friability (not more than 1% w/w), and Assay (not less than 90% and not more than 110%). All the results were within the specified limits. **Novelty :** Based on validation data from three consecutive batches, the manufacturing process consistently produces a stable product that meets predetermined specifications and quality attributes. Thus, the method employed in the manufacture of model drugs can be routinely followed with suitable modifications.

Keywords: Carr's Index; Friability; Process Validation; Levofloxacin tablet

INTRODUCTION

The main aim of designing a dosage form is to obtain predictable medicinal responses to the drug from the dosage form. The product should be a quality product, quality assessment is the most important part for any product, and the product should confirm all the criteria given in the pharmacopoeia; it should be reproducible when manufactured on a large scale. For the assurance of quality, many features are required, which are related to the chemical and physical stability of the drug and formulation, preservation from microbial contamination, and content uniformity of the drug, and should be well accepted by physicians and patients[1].

Validation is an essential part of good manufacturing practices (GMP). Therefore, validation is an element of quality assurance which confirms the quality of a product, equipment, manufacturing steps, and analytical test procedures[2]. From an economic point of view, validation is very important, as it helps in decreasing rejection and retesting, which minimises waste and cost. Validation is a prerequisite for product approval from various regulatory bodies such as the USFDA and CGMPs, Validation can be for a process, equipment, and analytical method[3].

Levofloxacin[(-)-(S)-9-fluoro-2,3-dihydro-3-methyl10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate] is a laevorotatory isomer of ofloxacin.[4] It is a synthetic fluoroquinolone antibiotic with molecular formula C18H20FN3O4. $\frac{1}{2}$ H_2O, and a molecular weight of 370.38[5]. It exerts broad-spectrum antibacterial activity against both Gram-positive and Gram-negative bacteria such as Streptococcus pneumoniae, Streptococcus haemolytic, Streptococcus pyogenes, Escherichia coli, Salmonella, Klebsiella, Serratia etc.[6,7] It has also antibacterial activity

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against Chlamydia trachomatis[8].

Fluoroquinolones are a group of synthetic, broad-spectrum antibiotics with bactericidal activity. Levofloxacin is a third-generation fluoroquinolone with enhanced activity against gram-positive organisms and is the active S-enantiomer of D-ofloxacin. Levofloxacin binds to the A subunit of deoxyribonucleic acid (DNA) gyrase and DNA topoisomerase IV in bacteria, and causes defective supercoiling of DNA and also irnpai1ment of relaxation of supercoiling in chromosomes and plasmids. It exhibits high potency in vitro and a long elimination half-life, thus pe1mitting once daily dosing. Although the rate of resistance to other antibiotic classes has increased, levofloxacin has maintained efficacy with generally ve1y low rates of resistance worldwide[9].

METHODOLOGY

Raw Materials

Each tablet has 530.5 mg of Levofloxacin Hemihydrate I.P, 8 mg of Colloidal Silicon Dioxide I.P, 8 mg of Magnesium Stearate I.P, 5 mg of Polyvinyl Pyrrolidone I.P K-30 (PVP K30), 8 mg of Talc I.P, 20 mg of Sodium Starch Glycolate I.P, 40 mg of Pre-gelatinised Starch I.P, 60.5 mg of Microcrystalline Cellulose I.P, and an additional 120 mg of microcrystalline cellulose I.P, making a total of 800 mg per tablet. For a batch size of 350,000 tablets, the required quantities were 185.675 kg of levofloxacin hemihydrate I.P, 2.800 kg of colloidal silicon dioxide I.P, 2.800 kg of magnesium stearate I.P, 1.750 kg of polyvinyl pyrrolidone I.P K-30, 2.800 kg of talc I.P, 7.000 kg of sodium starch glycolate I.P, 14.000 kg of pre-gelatinised starch I.P, 21.175 kg of microcrystalline cellulose I.P, and 42.000 kg of microcrystalline cellulose I.P, totalling 280 kg for the entire batch.

Coating materials for manufacturing Levofloxacin tablet I P 500mg

Each tablet required 114.2857 mg of isopropyl alcohol I.P, amounting to 40.000 L per batch. Additionally, 214.2857 mg of methylene chloride I.P is needed per tablet, total 75.000 kg per batch. The coating also included 1.028 mg of Instaglow White IG 001 per tablet, with a batch requirement of 0.360 kg, and 16 mg of Instacoat Sol Pink (IC-S-3751) per tablet, with a batch requirement of 5.600 kg.

Packing materials for manufacturing Levofloxacin tablet I P 500mg

The required packing materials and their quantities per batch were 44.000 units of 5PLY CBB 20×1140 ml containers, 3,500.000 units of CRT PTD Levofloxacin tablets 500 mg 10×10's (KGHS), 70.000 kg of BLST PVC film amber 174 mm, 15.000 kg of BLST AL foil PTD 170 mm for levofloxacin tablets 500 mg, and 45.0 units of SCL Levofloxacin tablets 500 mg.

In process checks and controls variables of Levofloxacin Tablet I P 500mg

During the sifting process, the particle size was controlled to ensure the easy flow of materials, with no specific sampling plan required. In the mixing stage, variables such as the mixing speed, mixing time, and solvent addition rate were controlled to maintain optimal flow properties, with samples taken from the top, middle, and bottom of the mix. The drying process involved controlling the drying temperature and drying time, and moisture content analysis was performed on samples from the top, middle, and bottom. During lubrication, the blending time, blending speed, and amount of lubricant are controlled to ensure uniformity of the content and flow properties, with samples taken from the top, middle, and bottom.

In the compression stage, high-speed, low-speed, and hopper levels were monitored, with checks on tablet appearance, average weight, hardness, friability, thickness, disintegration, and dissolution. Sampling was performed at different powder levels in the hopper (full, half, and almost empty) and various RPMs (18, 20, 22). For coating, variables such as spray rate, coater load, air temperature, pan speed, tablet flow, and concentration and viscosity of the coating solution were controlled, with samples collected after coating to check the average weight, thickness, disintegration, and dissolution. Finally, in the packing stage, the flow of tablets into the blister cavities was monitored through visual inspection and leak tests, with samples collected after packing.

Process Description

Processing was performed in a clean environment. All equipment parts coming in contact with the material were made from stainless steel SS 316, thoroughly washed, and dried as per SOP before being used in processing. When handling the raw materials, all operators wore gloves and face masks.

Sieving

The material was sieved through a 12# sieve using 30 diameter sifter and divided into two equal lots.

Preparation of binder

In a 200-liter stainless steel vessel, 90 kg of purified water and polyvinyl pyrrolidone were added under continuous stirring for 20 min to obtain a clear solution. (Divide the solution into two equal lots, lot A and lot B).

Table 1: Results of mixing, drying, blending, compression of manufactured Levofloxacin tablet I.P. 500 mg

Results of flow properties after mixing

Batch number	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)
5000816	0.688	0.796	13.567
5000916	0.655	0.764	14.26
5001016	0.692	0.774	10.59

Results of moisture content determination of Levofloxacin Tablet I.P. 500 mg validation batches

Batch number	Sampling points	Temp (°C)	Laps time (min)	Moisture content (%w/w) (Limit: 2-3%W/W)
5000816	Top	101	3.6	2.60
	Middle	103	3.8	2.68
	Bottom	102	3.2	2.71
5000916	Top	102	3.4	2.56
	Middle	101	4	2.78
	Bottom	104	3.1	2.79
5001016	Top	103	4.2	2.31
	Middle	101	3.5	2.77
	Bottom	102	3.9	2.81

Flow properties after blending

Batch number	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Angle of repose (⊠⊠ ϕ)
5000816	0.660	0.762	13.38	26.71
5000916	0.666	0.775	14.06	27.11
5001016	0.656	0.769	14.69	28.31

Levofloxacin Tablet I.P. 500mg-blend sample Assay

Lubrication time	Sampling points	Batch number		
		5000816	5000916	5001016
15 mins	Top(mg)	522.86	521.23	520.36
	Middle(mg)	519.83	520.01	512.65
	Bottom(mg)	519.73	507.25	513.52
17 mins	Top(mg)	520.91	515.32	516.21
	Middle(mg)	523.40	510.24	512.23
	Bottom(mg)	508.05	510.54	509.31
20 mins	Top(mg)	522.43	521.41	518.23
	Middle(mg)	522.54	522.52	522.23
	Bottom(mg)	513.65	521.64	514.24

Dissolution comparison of Levofloxacin Tablet I.P. 500mg

Batch number	Average % drug release
5000816	99.53
5000916	101.185
5001016	102.155

Table 2: Variables monitored during compression

Compression at different RPM and hopper level of Batch No- 5000816							
RPM	Powder level in hoper	Average weight 784mg-814mg	Thickness 6.0mm + 0.1 mm	Hardness 4.0Kg/cm2	NLT	Friability NMT 1.0%W/W	Disintegration time NMT 10 mins
	Full	799	6.0	7		0.22	5
18 RPM	Half	801	5.9	8		0.25	4.5
	Almost empty	798	6.0	8		0.52	4.3
	Full	800	6.0	7		0.78	4
20 RPM	Half	798	6.1	7		0.45	5
	Almost empty	802	6.1	7		0.34	5.2
	Full	797	6.0	8		0.28	5
22 RPM	Half	801	6.0	7		0.36	5
	Almost empty	803	6.0	7		0.50	4
Compression at different RPM and hopper level of Batch No- 5000916							
RPM	Powder level in hoper	Average weight 784mg-814mg	Thickness 6.0mm + 0.1 mm	Hardness 4.0Kg/cm2	NLT	Friability NMT 1.0%W/W	Disintegration time NMT 10 mins
	Full	795	6.1	8		0.44	5.4
18 RPM	Half	800	6.0	8		0.22	4.2
	Almost empty	799	6.0	8		0.85	4
	Full	800	5.9	7		0.45	4.5
20 RPM	Half	797	6.0	8		0.53	5.1
	Almost empty	801	6.1	7		0.63	5
	Full	799	6.0	8		0.35	5
22 RPM	Half	801	6.1	7		0.78	5.2
	Almost empty	802	6.0	7		0.49	5.1
Dissolution of Levofloxacin Tablet I.P. 500mg coated tablet - Batch No- 5001016							
RPM	Powder level in hoper	Average weight 784mg-814mg	Thickness 6.0mm + 0.1 mm	Hardness 4.0Kg/cm2	NLT	Friability NMT 1.0%W/W	Disintegration time NMT 10 mins
	Full	800	6.0	7		0.54	5.1
18 RP M	Half	804	6.0	8		0.66	5
	Almost empty	801	5.9	8		0.31	4.4
	Full	801	6.0	8		0.64	5
20 RP M	Half	796	6.0	8		0.84	5.1
	Almost empty	802	6.0	7		0.78	5.4
	Full	804	5.9	8		0.46	4.5
22 RP M	Half	795	6.1	8		0.64	5.1
	Almost empty	800	6.0	7		0.34	5.2

Dissolution comparison of Levofloxacin Tablet I.P. 500mg

Batch number	Average % drug release
5000816	100.513
5000916	102.47
5001016	101.218

Mixing and granulation

All sieved raw materials were loaded into a rapid mixer granulator and mixed for 5 min, after which the binding solution was added and mixed for another 10 min to obtain a uniform wet mass.

- Determination of powder flow properties of bulk density, tapped density, drying, FBD, lubrication and blending, angle of repose, compression, and dissolution of the product were determined.

Preparation the coating solution

200 L of isopropyl alcohol was added to a clean stainless-steel tank attached to a stirrer (100-200 RPM). Methylene chloride was added with continuous stirring for 45 mins. 0.360 kg Triturate Insta glow white, 5.6 kg of Instacoat solution pink with 40 L isopropyl alcohol was added with stirring to obtain a smooth paste. Methylene chloride (75 kg) was added to this mixture with constant stirring. The coating solution was passed through a colloidal mill and filtered through a 60# mesh nylon cloth.

Coating procedure

The tablets were loaded onto a coating pan, and the coating solution was sprayed on warm tablets at a rate of 500 g/ml, keeping both hot air and exhaust. Spraying was continued until the coating solution was exhausted, and the tablets were dried for at least 30 min. After the completion of coating, 20 tablets were taken, and the average weight was noted. The increase in the average weight of core tablets should be between 8 and 10 mg. The tablets were unloaded and stored in double-polyethene lines plastic drums. After coating, several critical parameters were monitored to ensure the tablet quality.

Packing

After inspection and finished product testing of the manufactured product, all the materials from the packing area were removed and the inspection labels were stamped on carton boxes with batch no, manufactured date, and expiry date.

RESULTS AND DISCUSSION

All the pharmaceutical dosage forms were validated to determine their quality. Without validation, there is a chance of low-quality products, more cost, more rejection of batches, more in-process and finished product testing, and reworks. It cannot ensure that the blend and content uniformity are significant, consistency between batches, or release of batches. Thus, we could not ensure the quality of the final product. Hence, the present work was undertaken with the goal of conducting a study on the process validation of solid oral dosage form of levofloxacin tablet I. P 500 mg for three consecutive batches to prove that the system remains in control and that the process is capable of consistently producing tablets that meet the predetermined process variable, acceptance criteria, and quality attributes.

Validation of sifting

Sifting was performed as per the BMR. All sieve screens were found to be intact before and after use in all three batches. Sift Levofloxacin Hemi hydrate IP # 12, Micro-Crystalline Cellulose #12, Pre-Gelatinised Starch I.P #12, Talc, Magnesium Stearate #40, Colloidal silicon dioxide I.P #40, Sodium Starch Glycolate by vibratory 30" diameter sifter.

Validation of Dry Mixing and Granulation process

Levofloxacin Hemihydrates, Micro-Crystalline Cellulose, Pre-Gelatinized Starch were added to Rapid Mixer Granulator and mixed for 5 mins for all 3 bathes. A binder solution (water {90 kg} + polyvinyl pyrrolidone) was added to the RMG and mixed for 5 min at a slow impeller speed and for 3 min at a high impeller speed with a chopper to form granules. Carr's index was found to be well within the limit (5 – 15) so it showed excellent flow.

Validation of Drying process

Drying was carried out in FBD for about 2 hours at NMT 60°C of inlet air temperature for all three batches. The LOD was within the limit (2–3%).

Validation of Blending and Lubrication process

All lubricants were added and blended for 20 min in all three batches. All assay results for all three batches fell within the specified limit [90(450 mg) — 110(550 mg) %]. Carr's index was found well within the limit (13 – 20) so it showed good flow. The angle of repose was found to be well within the limit (25 – 30); therefore, it showed good flow.

Validation of Compression process

In-process testing was carried out for all three batches during compression at different speeds (18, 20, and 22 RPM) and stages (initial, middle, and end). Description: Average weight [784–816 mg (± 2% of 800 mg)], Thickness (6.0 mm±1), Hardness (NLT 4 kg/sq. cm), friability (NMT 1%w/w), and disintegration time (NMT 5 min) were found to be well within the limits. The dissolution test was performed after compression for all three batches and met the acceptance criteria (NLT 80%).

Validation of Coating process

All processing parameters for all three batches, such as the pan speed, inlet air temperature, outlet temperature, tablet bed temperature, peristaltic pump speed, compressed

Table 3: Variables monitored during coating

Sl. No	Parameters	Specification	Observation			Results
			5000816	5000916	5001016	
1	Appearance	Light orange colored capsule shaped tablet	Light orange colored capsule shaped tablet	Light orange colored capsule shaped tablet	Light orange colored capsule shaped tablet	Complies
2	Average weight	800mg [(+2%of 800mg)784mg to 816mg]	805	810	812	Complies
3	Hardness	NLT 4.0kg/cm2	7	8	7	Complies
4	Thickness	6.0+0.1mm	6.01	6.0	6.05	Complies
5	Disintegration	NLT 4 min	5.2	4.9	5.20	complies
6	Dissolution	NLT 80%	101.51	102.47	101.218	complies

air pressure, and spray rate, were monitored during the coating process. For all three batches in process tests like Description, Average weight [784mg-816mg (± 2% of 800mg)], Thickness(6.0mm±1), Hardness (NLT 4 kg/sq.cm), Disintegration time (NLT 4 min) and Dissolution (NLT 80%) was carried out and was found meeting the acceptance criteria.

Validation of packing

The blisters were inspected, and the tablets were free from defects, such as improper sealing, empty pockets, labelling defects, blisters, or strips of less than 10 tablets. The finished product assay results for all three batches were carried out and found to be within the limit (90–110%). The leak test was performed for all three batches because none of the tablets were wet or there was no ingress of indicator/water into the cavity, and all the blisters passed the leak test.

CONCLUSION

The API used was found to meet all the predefined acceptance criteria. No significant deviation in any process parameter was observed during the entire validation study. No changes in process parameters were observed during the batch manufacturing operation. The validation data for three batches of levofloxacin tablet I.P 500 mg consistently produced a stable product that met its predetermined specification and quality attributes. Hence, the method employed in the manufacture of drugs should be validated and can be routinely followed.

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