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Optimization and validation of process for formulation of duloxetine hydrochloride capsules

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ABSTRACT

Process validation is a requirement of the current good manufacturing practices (cGMP) regulations for finished pharmaceuticals. Validation is defined as a documented program that provides a high degree of assurance that a specific process, method or system will constantly produce a result meeting pre-determined acceptance criteria. In this study formulation and development of capsules containing drug Duloxetine Anti-depressant drug belongs to Class-II Bio pharmaceutics Classification. Coating was done using sugar spheres and these pellets were filled in capsules. Validation of process for formulation of Duloxetine hydrochloride capsules were done. The objectives of this study were determine critical process parameters for coating and capsule filling operation, to establish boundary limits for critical process parameters which influence the product, process quality and performance and to evaluate coated pellets and filled capsules. This paper deals with the Process performance qualification of Duloxetine hydrochloride capsules 60mg, 30mg.During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing. Validation study will be initiated on 3 batches. During this study the process design will be evaluated to determine its capability to manufacture reproducible commercial batches of Duloxetine hydrochloride capsules 60mg, 30mg.The process understanding and process knowledge gained from the product developmental study, exhibit batch and process evaluation studies in the commercial batches will be leveraged. Data shall be generated during this study is used to establish documented evidence that the process is capable of manufacturing reproducible commercial batches and consistently deliver quality product.

Keywords: Process validation; Optimization; Duloxetine; Coating

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INTRODUCTION

The prime objective of any pharmaceutical plant is to manufacture products of requisite attribute and quality consistently, at the lowest possible cost. Validation is a concept that has evolved in United States in 1978.Validation is founded on, but not prescribed by regulatory requirements and is best viewed as an important and integral part of cGMP. The word validation simply means assessment of validity or action of proving effectiveness. This principle incorporates the understanding that the following conditions exist: Quality, safety, and efficacy are designed or built into the product. Quality cannot be adequately assured merely by in-process and finished product inspection or testing each step of a manufacturing process is controlled to assure that the finished product meets all quality attributes including specifications. The development of a drug product is a lengthy process involving drug discovery, laboratory testing, animal studies, clinical trials and regulatory registration. Process controls include raw materials

inspection, inprocess controls and targets for final product. The purpose is to monitor the online and off-line performance of the manufacturing process and then validate it. Even after the manufacturing process is validated, current good manufacturing practice also requires that a well-written procedure for process controls is established to monitor its performance. Validation mainly based on, FDA regulations describing current good manufacturing practice (cGMP) for finished pharmaceuticals are provided in 21 CFR parts 210 and 211. The cGMP regulations require that manufacturing processes be designed and controlled to assure that in-process materials and the finished product meet predetermined quality requirements and do so consistently and reliably. Process validation is required, in both general and specific terms, by the cGMP regulations [1].

Definitions:

European medicines agency Definition "The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes."[4]

US FDA Definition "process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product."[2]

ICH Definition "Process Validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes."[6]

WHO Definition "Process validation is associated with the collection and evaluation of data, from the process design stage through commercial production, which provides scientific evidence that a process is capable of consistently delivering a quality product. Process validation provides documented evidence that a process is capable of reliably and repeatedly rendering a product of the required quality. [6]"

Approach to Process Validation

Process validationis defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves a series of activities taking place over the lifecycle of the product and process.

Process validation activities are in three stages.

Stage 1 – Process Design:

The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.

Stage 2 – Process Qualification:

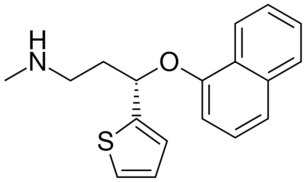
During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

Stage 3 – Continued Process Verification:

Ongoing assurance is gained during routine production that the process remains in a state of control. [2]

Drug Profile:

Duloxetine hydrochloride is a white to slightly brownish white solid, which is slightly soluble in water. Duloxetine is an Anti-depressant drug belongs to Class-II Bio pharmaceutics Classification. It is serotonin-norepinephrine reuptake inhibitor (SNRI).It is mostly prescribed for major depressive disorder and generalized anxiety disorder (GAD) fibromyalgia and neuropathic pain.[3]



Uses:
The main uses of duloxetine are in major depressive disorder, general anxiety disorder, urinary incontinence, neuropathic pain, and fibromyalgia.

Duloxetine is recommended as a first line agent for the treatment of chemotherapy-induced neuropathy by the American Society for Clinical Oncology, as a first-line therapy for fibromyalgia in the presence of mood disorders by the German Interdisciplinary Association for Pain therapy, as a Grade B recommendation for the treatment of diabetic neuropathy by the American Association for Neurology and as a level A recommendation in certain neuropathic states by the European Federation of Neurological Societies.

A 2014 Cochrane review concluded that duloxetine is beneficial in the treatment of diabetic neuropathy and fibromyalgia but that more comparative studies with other medicines are needed. The medical journal Prescribe (based in France) concluded that duloxetine is no better than other available agents and has a greater risk of side effects. Thus they recommend against its general use.

EXPERIMENTAL SECTION

MATERIALS:
Manufacturing formula:
The quantities of various ingredients required for manufacturing the commercial batch are

a) Drug Loading
1. Sugar Spheres
2. Duloxetine
3. Hypromellose
4. Glycine
5. Purified Water

b) Sub Coating
1. Hypromellose
2. Sucrose
3. Talc
4. Purified Water

c) Enteric Coating
1. Hypromellose
2. Triethyl citrate
3. Talc
4. Isopropyl alcohol
5. Methylene chloride

d) Lubrication
1. Talc

e) Capsule filling
1. Empty hard gelatin capsules of Size ‘3’

METHOD&PROCESS FLOW:

Screening
1. Screen the ingredient 1 through # 24 mesh.(Passes to be collected) 2. Pass the material of above step through #35 mesh.(Retains to be collected)

↓

Preparation of Drug Dispersion
1. With the help of steam, Heat the Purified water up to 60-70°C. 2. Stir the above step ingredient with the help of Pneumatic stirrer / Remi stirrer. Until vortex is formed. 3. Dissolve Hydroxypropyl methylcellulose until a clear solution is formed. 4. Allow to cool the above step solution to room temperature (30°C). 5. Dissolve Glycine in the above step with the help of Pneumatic stirrer / Remi stirrer. 6. Stir the solution until a clear solution is formed. 7. Add Duloxetine Hydrochloride USP into the above step with continuous stirring till the homogenous dispersion is formed.

↓

Drying (Fluid Bed Processor - 500 liters)
Dry the drug loaded pellets at temperature 40 ±3°C inlet air temperature, till LOD is Less than 2.0 %w/w at 105°C.

↓

Screening (Fluid Bed Processor - 500 liters)
1. Screen the pellets through # 18 mesh and collect the # 18 passes. 2. Pass the # 18 mesh pellets through # 24 mesh and collect the # 24 mesh retains.

↓

Drug loading & Coating (Fluid Bed Processor - 500 liters)
Load the screened Sugar spheres to FBP (500 liters bowl) and spray the drug dispersion and coating to be done at spray rate 35 – 200 gm/min/gun.

↓

Preparation of Sub-Coating Dispersion
1. Take Purified water in a vessel stir the solution until a vortex is formed. 2. Add Hydroxypropyl methylcellulose into the above solution Avoid the formation of lumps and foam. 3. Add Sucrose into the above step stir till Sucrose goes into solution. 4. Add Talc to the above step Continue stirring till homogenous and uniform dispersion is formed.

↓

Sub-Coating (Fluid Bed Processor - 500 liters)
Load the drug loaded pellets to FBP 800 lts and spray the sub-coating dispersion and coating to be done at spray rate 40 - 200 gm/min/gun.

↓

Drying (Fluid Bed Processor - 500 liters)
Dry the sub coated pellets at temperature 40 ±3°C inlet air temperature till LOD is Less than 2.0 %w/w at 105°C

↓

Screening (Fluid Bed Processor - 500 liters)
1. Screen the pellets through # 18 mesh and collect the # 18 passes. 2. Pass the # 18 mesh pellets through # 24 mesh and collect the # 24 mesh retains.

↓

Preparation of Enteric Coating Dispersion
1. Take Isopropyl alcohol in a SS vessel stir the solution until a vortex is formed. 2. Add Hypromellose phthalate into the above step Avoid the formation of lumps and foam. 3. Add Methylene chloride into the above step stir till a clear solution is formed. 4. Add Triethyl Citrate to the above step Continue stirring till a clear solution is formed. 5.Take Isopropyl alcohol in SS vessel 6. Add Talc to the above step. 7. Pass the above solution through colloidal mill for 20 minutes. 8. Add step no 7 to step no 5 and stir for 45 minutes or till the uniform dispersion is formed.

↓

Enteric Coating (Fluid Bed Processor - 800 liters)
Load the Sub- coated pellet to FBP 800 lts and spray the Enteric coating dispersion and coating to be done at spray rate 40 - 200 gm/min/gun.

↓

Drying (Fluid Bed Processor - 800 liters)
Dry the enteric coated pellets at temperature 45 ±3°C inlet air temperature till LOD is Less than 2 %w/w at 105°C.

↓

Screening (Fluid Bed Processor - 500 liters)
1. Screen the pellets through # 16 mesh and collect the # 16 passes. 2. Pass the # 16 mesh pellets through # 24 mesh and collect the # 24 mesh retains.

↓

Lubrication (Fluid Bed Processor - 800 liters)
1.Load the Enteric coated pellet to FBP 800 lts 2.Add Talc to the above step 3. Fluidize the above step for 15 to 20 min.

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Capsule filling
1. Filling of lubricated pellets into EHG capsules on Bosch capsule filling machine.

RESULTS AND DISCUSSION

The following parameters were observed during the processing of these three process performance qualification Batches.

Table 1. Analytical Results of Common Drug Loaded Pellets and Sub coated pellets

Drug Loading Pellets		**Batch 1**	**Batch 2**	**Batch 3**
In-process test	**Specification limits**	**Results**	**Results**	**Results**
Description	White to off-white spherical pellets	Off-white spherical pellets	White spherical pellets	White spherical pellets
LOD	NMT 2.0%	0.5% w/w	0.2% w/w	0.4% w/w
Assay	NLT 32.14 % w/w and NMT 39.28 % w/w of labeled amount of Duloxetine	35.09 %w/w	35.62 %w/w	34.8 %w/w
Sub coated pellets				
In-process test	**Specification limits**	**Result**	**Result**	**Result**
Description	White to off-white spherical pellets	Off-white spherical pellets	White spherical pellets	White spherical pellets
LOD	NMT 2.0% w/w	0.2 % w/w	1.2 % w/w	0.5% w/w
Assay	NLT 25.22 % w/w and NMT 30.84 % w/w of labeled amount of Duloxetine	28.63 % w/w	28.08 % w/w	28.36% w/w

Table 2. Analytical Results of Enteric Coated Pellets

In-process test	**Specification limits**	**Batch 1**				**Batch 2**				**Batch 3**			
		Lot-1		**Lot-2**		**Lot-1**		**Lot-2**		**Lot-1**		**Lot-2**	
		Results		**Results**		**Results**		**Results**		**Results**		**Results**	
LOD	NMT 2.0 % w/w	0.3 % w/w		0.4 % w/w		1.0 % w/w		1.6% w/w		1.20 % w/w		1.5% w/w	
Assay	NLT 21.95 % w/w and NMT 26.82 % w/w of labeled amount of Duloxetine	25.31 % w/w		25.25 % w/w		25.50%w/w		25.27 % w/w		25.750% w/w		25.51 % w/w	
Residual solvents*	Isopropyl alcohol :7500 PPM	IPA: 2052 PPM		IPA: 2615 PPM		IPA: 2116 PPM		IPA: 2728 PPM		IPA: 3320 PPM		IPA: 3163 PPM	
	Methylene chloride: 597 PPM	MDC: BLD		MDC BLD		MDC BLD		MDC: BLD		MDC: BLD		MDC: BLD	
Drug release in Acid Stage	NMT 10% of labeled amount of Duloxetine is dissolved in 2 hours	Cap.No.	% release	Cap.No	% release	Cap. No.	% release	Cap.No.	% release	Cap.No.	% release	Cap.No.	% release
		1	0	1	1	1	3	1	4	1	3	1	2
		2	1	2	3	2	3	2	2	2	0	2	2
		3	1	3	2	3	2	3	3	3	0	3	1
		4	0	4	1	4	4	4	2	4	2	4	0
		5	2	5	2	5	2	5	3	5	2	5	3
		6	1	6	3	6	3	6	2	6	4	6	3
Drug release in Buffer Stage	NLT 70% (Q) of labeled amount of Duloxetine is dissolved in 60 minutes	Capsule No.	% release	CapNo.	% release	Capsule No.	% release	Capsule No.	% release	Capsule No.	% release	Capsule No.	% release
		1	89	1	89	1	93	1	90	1	91	1	91
		2	91	2	91	2	90	2	90	2	91	2	93
		3	90	3	91	3	90	3	92	3	92	3	91
		4	91	4	90	4	90	4	90	4	88	4	91
		5	90	5	90	5	94	5	89	5	92	5	92
		6	88	6	91	6	90	6	90	6	93	6	92

Table 3. Results of Finished product (30mg)

S. No	Parameter	Specification				Results	
1	Description	White to off white spherical enteric coated pellets filled in size '3' hard gelatin capsules with opaque blue colored cap and opaque white colored body, imprinted 'RDY609' on cap & '30 mg' on body with golden yellow ink.				White to off white spherical enteric coated pellets filled in size '3' hard gelatin capsules with opaque blue colored cap and opaque white colored body, imprinted 'RDY609' on cap & '30 mg' on body with golden yellow ink.	
2	Weight of 10 filled capsules (g)	10 x [Actual fill weight(mg) + Avg. Weight of 50 empty capsules) / 1000] ± 4.0%	Theoretical	Batch No.	Actual	Lot-1	Lot-2
			1.64-1.77	C404107	1.71-1.85	1.762	1.783
				C404109	1.66-1.79	1.72	1.747
				C404111	1.66-1.79	1.724	1.745
3	Weight variation of capsule content (mg)	Actual fill weight ± 10 %	111-135	C404107	117-141	124	132
				C404109	111-135	115	129
				C404111	111-135	119	128
4	Weight variation of filled capsule (mg)	[Actual fill weight(mg) + average weight of 50 empty capsules] ± 10.0%	154-188	C404107	161-195	169	184
				C404109	156-190	164	179
				C404111	156-190	167	181
5	Height (locked length of filled capsule) (mm)	15.8 ± 0.4 mm (15.4 – 16.2 mm)	15.4 – 16.2 mm			15.5	15.9

Table 4. Results of Finished product (60mg)

S.No	Parameter	Specification				Results	
1	Description	White to off white spherical enteric coated pellets filled in size '1' hard gelatin capsules with opaque blue colored cap and opaque green colored body, imprinted 'RDY610' on cap & '60 mg' on body with white ink.				White to off white spherical enteric coated pellets filled in size '1' hard gelatin capsules with opaque blue colored cap and opaque green colored body, imprinted 'RDY610' on cap & '60 mg' on body with white ink.	
2	Weight of 10 filled capsules (g)	10 x [Actual fill weight(mg) + Avg. Weight of 50 empty capsules) / 1000] ± 4.0%	Theoretical	Batch No.	Actual	Lot-1	Lot-2
			3.08 - 3.33	C404596	3.092 - 3.348	3.203	3.244
				C404597	3.12 - 3.38	3.227	3.275
				C404598	3.072 - 3.328	3.184	3.227
3	Weight variation of capsule content (mg)	Actual fill weight ± 10 %	222 - 270	C404596	223 - 271	239	256
				C404597	226 - 276	238	261
				C404598	221 - 269	235	256
4	Weight variation of filled capsule (mg)	[Actual fill weight(mg) + average weight of 50 empty capsules] ± 10.0%	289 - 353	C404596	290 - 354	312	334
				C404597	293 - 357	315	335
				C404598	288 - 352	308	330
5	Height (locked length of filled capsule) (mm)	19.3 ± 0.4 mm (18.9-19.7 mm)	18.9 - 19.7 mm			18.9	19.5

CONCLUSION

The process performance qualification study has been performed on three batches of Duloxetine hydrochloride capsules 60mg, 30mg. The observations were recorded, samples were analysed and the results found to meet the specifications in acceptance criteria. The method depicted the different process controls and variables to be monitored during the manufacturing process of a capsule dosage form and a comparative study was done on the three consecutive batches. The batch execution and results show that that all the established limits of critical process parameters are valid and within the limits and meets pre-determined specification and quality attributes. Hence it is concluded that the process for manufacturing of Duloxetine hydrochloride capsules 60mg, 30mg. is deemed validated.

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