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PROCESS VALIDATION FOR SELECTED SOLID DOSAGE FORM AS PER FDA GUIDELINES

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ABSTRACT

An ultimate goal for science and technology should be the betterment of humanity and the welfare of human beings. In view of pharmaceutical industry, process validation is very important to deliver quality product for human beings. As per US Food and Drug Administration (FDA) guideline "Process Validation: General Principles and Practices" Process validation involves the collection and evaluation of data from the process design stage throughout commercial production that establishes scientific evidence that a process is capable of consistently delivering a quality drug substance. The purpose of this work is to present an introduction and general overview on process validation of pharmaceutical manufacturing process (CPP-Critical process parameters) with special reference to the requirements stipulated by the US Food and Drug Administration (FDA) of selected solid dosage form (Paracetamol).

KEYWORDS: Validation, Process validation, Oral solid dosage form, critical process parameters, US-FDA, Paracetamol.

INTRODUCTION

The U.S. Food and Drug Administration (FDA) has proposed guideline for process validation of harmaceutical product with the definition as "*To establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes*". According to the FDA, assurance of quality is derived from careful and systemic attention to a number of important factors, including selection of quality attributes and material, adequate process, product design & tactical control of the process through in-process and end-product testing. According to the FDA‟s cGMP 21 CFR 211.110 "*Control procedures shall be establish to monitor output & to validate performance of the manufacturing processes that may be responsible for causing variability in the characteristics of In-process material & the drug product*".

A. Oral solid dosage form

The oral route of drug administration is the most important method of administering drug for systemic effects. Drugs that are administered orally, solid oral dosage forms represent the preferred class of product. Tablets and capsules

represent unit dosage forms in which usual dose of drug has been accurately placed.

B. Tablets

Tablets are defined as solid dosage forms each containing a single dose of one or more active ingredients, obtained by compressing uniform volumes of particles.

Advantages

01. They are unit dosage forms and they offer the greatest capabilities of all oral dosage forms for the greatest dose precision and the least content variability.
02. Their cost is lowest of all oral dosage forms.
03. They are the lightest and most compact oral dosage forms.
04. They are in general the easiest and cheapest to package.
05. They lend themselves to certain special release profile products such as enteric or delayed release products.
06. They are better suited to large scale production than other unit oral forms etc.

Disadvantages

01. Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low density character.
02. Drugs with poor wetting, dissolution properties, intermediate to large dosages, optimum absorption high in the gastrointestinal tract or any combination of these features may be difficult to impossible to formulate and manufacture as a tablet that will still provide adequate full drug bioavailability.

C. Process Validation

The FDA, in its document entitled "Guideline on general principles of process validation", which was published final form in 1987, defines process validation as follows: "Process Validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics".

According to the FDA, assurance of product quality is derived from careful and systemic attention to a number of important factors, including: selection of quality components and materials, adequate product and process design, and statistical control of the process through in- process and end-product testing.

This guidance describes process validation activities in three stages (Which is shown in Figure 1) which represent stage 1, stage 2 and stage 3.

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:** On-going assurance is gained during routine production that the process remains in a state of control.

Figure 1: Process validation lifecycle approach between the three stages.

D. Process validation of oral solid dosage form (Tablets)

A tablet is a most known solid pharmaceutical dosages form and comprises of a mixture of active substances and suitable excipients. Binders, glidant, lubricants etc are some the popularly used excipients in the tablets.

Process steps of Formulation

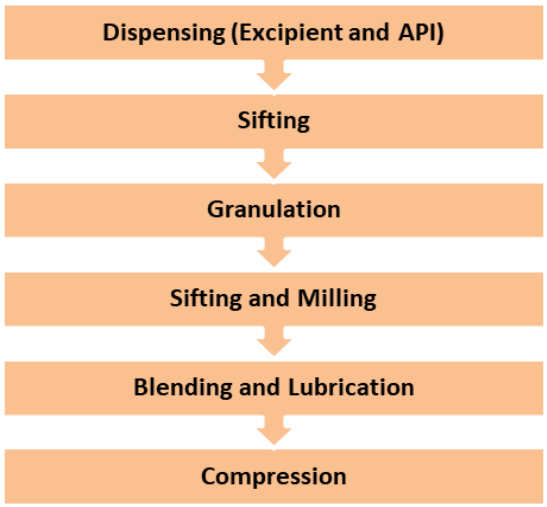


Figure 2: Process steps involved in tablet formulation.

E. RESULT AND DISCUSSION

01. Pre-compression parameters

Table no.1: Pre-compression parameters for the Formulation.

Batches	Angle of Repose (θ)	Bulk density	Tapped density	Hausner's Ratio
B232211	32.21	0.6	0.82	1.36
B232212	33	0.6	0.83	1.38
B232301	31.23	0.6	0.82	1.36

Discussion

The blend was analysed for parameters such as Angle of Repose, Bulk Density, Tapped Density and Hausner's Ratio. Batch 1,2 and 3 all showed good flow ability.

02. Post-compression parameters

Table no.2: Post-compression parameters for the formulation.

Batches	Weight Variation (Avg.SD)	Hardness (kg/cm2)	Friability (%)	Disintegration Time
B232211	661.2±0.45	4.8 kg	0.83%	3 min 6 sec
B232212	655.3±0.50	5 kg	0.79%	3 min 14 sec
B232301	659.2±0.35	4.8 kg	0.81%	3 min 30 sec

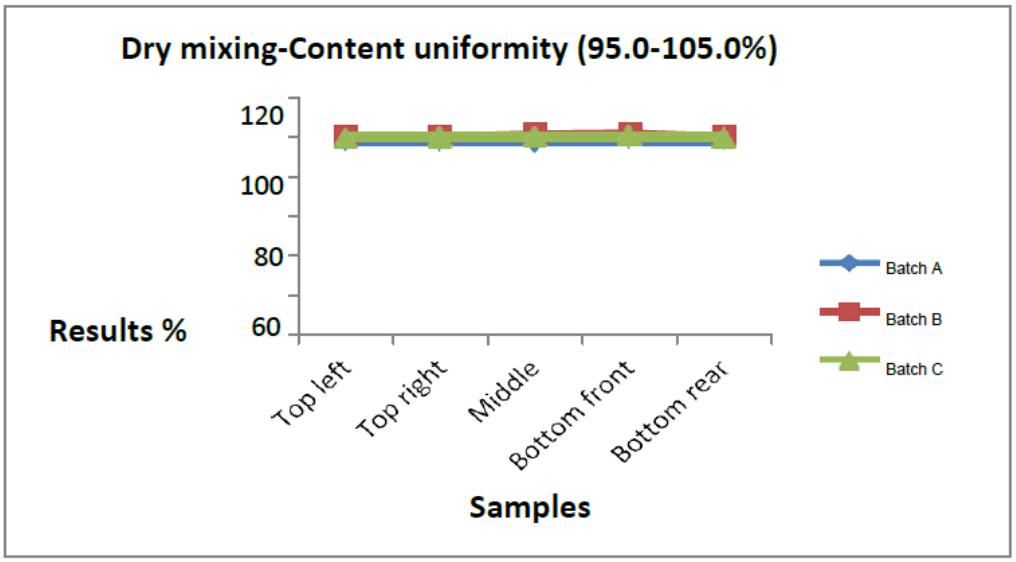
Discussion

Friability of tablets was less than 1 %.So the amount of starch in powder was reduced to achieve a proper hardness of tablet. All Batches showed disintegration time within 5min.

03. Assay of Paracetamol during drying mixing

Table no. 3: Assay of Paracetamol during dry mixing.

Location	Assay of Paracetamol (%) 5 mins of dry mixing		
	Batch A (B232211)	Batch B (B232212)	Batch C (B232301)
Top left	98.3%	100.3%	99.2%
Top right	98.4%	100.6%	99.7%
Middle	97.5%	101.8%	100.2%
Bottom front	99.9%	100.2%	100.8%
Bottom rear	98.9%	100.6%	99.6%
Mean	98.6%	100.7%	99.9%
SD	0.88	0.64	0.61
%RSD	0.89	0.63	0.61



Graph no.1.

Discussion

Dry mixing was done for 5 min at 70 RPM. All the Batches showed good content uniformity.

04. Wet granulation

Table no. 4: Wet granulation.

Batch No.	B232211	B232212	B232301
Addition of Binding agent	5% Starch paste	5% Starch paste	5% Starch paste

05. Drying

Table no. 5: Drying.

Batch no.		B232211	B232212	B232301
Control variables	**Acceptance criteria**			
Inlet temp.	60±5◦C	58◦C	57◦C	58.1◦C
Outlet temp.	55±5◦C	46◦C	47.4◦C	48.6◦C
LOD	NMT 1.0% w/w	0.32%	0.28%	0.35%

06. Sizing or milling of granules

Table no. 6: Sizing and milling of granules.

Batch no.		B232211	B232212	B232301
Control variable	**Acceptance criteria**			
Sieve integrity before milling	**Should not be damaged**	Complies	Complies	Complies
Sieve integrity after milling	**Should not be damaged**	Complies	Complies	Complies

07. Lubrication

Table no. 7: Lubrication.

Pre-lubrication				
Parameters	**Acceptance criteria**	**B232211**	**B232212**	**B232301**
Pre-lubrication time	10min	10min	10min	10min
Pre-lubrication RPM	30 RPM	30	30	30
Lubrication				
Lubrication time	5min	5min	5min	5min
Lubrication RPM	30 RPM	30	30	30

Table no. 8: Pre-lubrication content uniformity for the formulation.

Sample location	Pre-lubrication-Content of Uniformity (95.0–105.0%)		
Batch no.	**B232211**	**B232212**	**B232301**
U1(Upper left rear)	97.7%	100.4%	97.7%
U2(Upper centre front)	99.9%	100.0%	98.3%
U3(Upper right rear)	97.2%	103.2%	98.5%
M1(Middle left centre)	97.7%	100.3%	97.7%
M2(Middle centre)	99.7%	101.0%	98.9%
M3(Middle right centre)	99.9%	99.2%	99.9%
L1(Lower left front)	98.4%	101.3%	99.2%
L2(Lower centre rear)	98.6%	101.2%	99.9%
L3(Lower right front)	98.6%	102.9%	100.0%
BO(Bottom centre)	98.3%	100.2%	99.7%
Mean	98.6%	100.9%	99.2%
SD	0.97	1.251	1.207
%RSD (NMT 5.0%)	0.97	1.25	1.20

Table no. 9: Lubrication content uniformity for formulation.

Sample location	Lubrication –Content of Uniformity (95.0–105.0%)		
Batch no.	**B232211**	**B232212**	**B232301**
U1(Upper left rear)	98.6%	98.4%	98.2%
U2(Upper centre front)	98.4%	102.0%	97.5%
U3(Upper right rear)	100.6%	100.0%	98.1%
M1(Middle left centre)	97.6%	101.8%	97.5%
M2(Middle centre)	100.4%	99.8%	97.7%
M3(Middle right centre)	97.6%	98.5%	98.4%
L1(Lower left front)	99.1%	98.6%	98.6%
L2(Lower centre rear)	100.0%	99.4%	98.2%
L3(Lower right front)	95.9%	97.6%	97.0%
BO(Bottom centre)	100.7%	98.9%	99.8%
Mean	98.8%	99.5%	98.1%
SD	1.578	1.448	0.770
%RSD (NMT 5.0%)	1.59	1.45	0.78

8. Compression Data

Parameters	Batches			Acceptance criteria
	B232211	B232212	B232301	
Description	White coloured round and uncoated Tablets free from loose dust.	White coloured round and uncoated Tablets free from loose dust.	White coloured round and uncoated tablets free from loose dust.	White coloured round and uncoated tablets free from loose dust.
Hardness	4.8 kg	5 kg	4.8 kg	NLT 4kg
Thickness	3.8mm	3.8mm	3.8mm	3.9 mm
Friability	0.83%	0.79%	0.81%	NMT 1%
Diameter	13mm	13mm	13mm	13 mm
Disintegration time	3 min 6 sec	3 min 14 sec	3 min 30 sec	NMT 15 min
Assay	99.5%	100.5%	99.7%	Should be 90-110% of the label claim.
Weight variation	Complies	Complies	Complies	NMT 2 tablets differ by +5% & None differs by +10% from average weight.
Dissolution	99.4%	100.2%	94.2%	NLT 80% of Labeled amount of Paracetamol
Description	White coloured round and uncoated Tablets free from loose dust.	White coloured round and uncoated Tablets free from loose dust.	White coloured round and uncoated tablets free from loose dust.	White coloured round and uncoated tablets free from loose dust.
Hardness	4.8 kg	5 kg	4.8 kg	NLT 4kg
Thickness	3.8mm	3.8mm	3.8mm	3.9 mm
Friability	0.83%	0.79%	0.81%	NMT 1%
Diameter	13mm	13mm	13mm	13 mm
Disintegration time	3 min 6 sec	3 min 14 sec	3 min 30 sec	NMT 15 min
Assay	99.5%	100.5%	99.7%	Should be 90-110% of the label claim.
Weight variation	Complies	Complies	Complies	NMT 2 tablets differ by +5% & None differs by +10% from average weight.
Dissolution	99.4%	100.2%	94.2%	NLT 80% of Labeled amount of Paracetamol

CONCLUSION

The overall data of the three batches (Batch No. B232211, B232212 and B232301) at each of the stages for the specified parameters, it is concluded that with process validation for the Paracetamol tablet produces the batches with no significant deviation and reported documented evidence that process can effectively produce a product with all required characteristics and uniformity in final dosage form, from batches to batches.

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