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Process Validation of Paracetamol tablet as per ICH guidelines

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Abstract

Process validation is an integral part of pharmaceutical manufacturing, ensuring that tablets are consistently produced with quality and efficacy in line with regulatory requirements. The International Council for Harmonization ICH) provides guidelines for the systematic validation of manufacturing processes. This research article presents a comprehensive study on process validation for Paracetamol tablets following the ICH guidelines. The article focuses on various aspects of the validation process, including process design, qualification, and continued process verification, with specific emphasis on Paracetamol tablet manufacturing. Experimental studies were conducted to characterize the critical process parameters and assess their impact on the tablet's quality attributes. The article also discusses the use of statistical analysis techniques for data evaluation and demonstrates the establishment of a robust validation protocol for Paracetamol tablet manufacturing. Through the application of the ICH guidelines, this research contributes to ensuring the consistency and reliability of Paracetamol tablets, enhancing patient safety and meeting regulatory expectations.

Keywords: Process validation, ICH guidelines, Critical process parameters, Critical Process Attribution, Statistical analysis, and validation protocol;

Introduction

The oral route of drug administration is the most important method of administering drugs for systemic effects. At least 90% of all drugs used to provide systemic effect are administered by oral route. 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. (1)

Validation:

Drug development is a difficult process that includes finding new drugs, testing them in labs, studying animals, conducting clinical trials, and registering them with the appropriate authorities. Many regulatory agencies, including the USFDA, also demand that the drug product be tested for its identity, strength, quality, purity, and stability before it can be released for use. This is done to further improve the efficacy and safety of the drug product after approval. A crucial component of quality assurance is validation, which entails systematically examining systems, facilities, and processes to ascertain whether they carry out their intended functions adequately and consistently as specified.

Elements of Validation:

- Design Qualification
- Installation Qualification

- Operational Qualification
- Performance Qualification

Major Phases in Validation:

Phase 1: This is the Pre-validation Qualification Phase which covers all activities relating to product research and development, formulation pilot batch studies, scaleup studies, transfer of technology to commercial scale batches, establishing stability conditions and storage, and handling of in-process and finished dosage forms, equipment qualification, installation qualificationmaster production document, operational qualification and process capacity.

Phase 2: This is the Process Validation Phase. It is designed to verify that all established limits of the critical process parameter are valid and that satisfactory products can be produced even under the worst conditions.

Phase 3: Known as the Validation Maintenance Phase, it requires frequent review of all process related documents, including validation of audit reports, to assure that there have been no changes, deviations, failures and modifications to the production process and that all standard operating procedures (SOPs), including change control procedures, have been followed. At this stage, the validation team comprising of individuals representing all major departments also assures that there have been no changes/deviations that should have resulted in requalification and revalidation. A careful design and validation of systems and process controls can establish a high degree of confidence that all lots or batches produced will meet their intended specifications.

Process Validation:

USFDA defines process validation as "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".

It means that the process when operated under the prescribed conditions will consistently produce a product that meets the present specifications and quality attributes. In brief and simple terms, process validation is ensuring that the process does what it purports to do. [3]

Process Validation activities are described in below steps:

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.

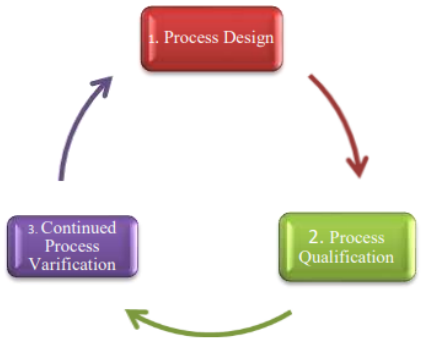


Figure 1: Process validation lifecycle approach between the three stages.

Types of Process Validation:

a. **Prospective Validation:** It is establishment of documented evidence of what a system does or what it purports to do based upon a plan. This validation is conducted prior to the distribution of new product.

b. **Retrospective Validation:** It is the establishment of documented evidence of what a system does or what it purports to do based upon the review and analysis of the existing information. This is conducted in a product already distributed based on accumulated data of production, testing and control.

c. **Concurrent Validation:** It is establishment of documented evidence of what a system does or what it purports to do information generated during implemented of the system

d. **Revalidation:** Whenever there are changes in packaging, formulation, equipment or processes which could have impact on product effectiveness or product characteristics, there should be revalidation of the validated process. Conditions that require revalidation studies are: Changes in critical component Change in facility or plant Increase or decrease in batch size Sequential batches that fail to conform product and process specifications. [4]

Critical Process Parameters and Critical Quality Attributes:

Critical process parameters (CPPs) are the key variables that directly influence critical quality attributes (CQAs) of a product. In the process validation of Paracetamol tablets, CPPs may include factors such as blending time, compression force, granulation moisture content, and drying temperature. These parameters have a significant impact on critical attributes like tablet hardness, disintegration time, dissolution rate, and content uniformity. It is crucial to identify and control CPPs within specified limits to ensure consistent product quality. By monitoring and optimizing CPPs, manufacturers can effectively meet the desired CQAs, thereby enhancing the efficacy, safety, and performance of Paracetamol tablets

EXPERIMENTAL WORK

Procedure:

Evaluation of Paracetamol tablet was done for formulation batch as well as for trial batch. The evaluation parameters are enlisted below:

a. Pre-Compression parameters (Angle of repose, bulk density, tapped density, Hausner's ratio)
b. Post-Compression parameters (Weight variation, hardness, friability, Disintegration time)
c. Assay
d. LOD
e. Dissolution, etc.

Instruments used:

S.No.	Instrument Name	Function
1	Analytical Balance	Weighing
2	Hot air Oven	Drying for LOD
3	Bulk density apparatus	Density test of powder
5	UV Visible spectroscopy	Identification and Assay
6	Disintegration apparatus	Disintegration time
7	Dissolution apparatus	Dissolving time
8	Friability apparatus	Friability test
9	Tablet Hardness tester	Hardness Test

Equipment used:

S.No.	Equipment Name	Function
1	Vibro sifter #60	Sifting of raw material
2	Multimill	Milling
3	Rapid Mixer Granulator	Dry mixing and granulation
5	Mechanical stirrer	Stirring
6	Fluid Bed Dryer	Drying
7	Octagonal Blender	Blending
8	Rotary tablet compression	Compression
9	Tablet inspection belt	Inspection

10	Blister Pack machine	Packing of tablets

Drug and Raw material used:

S.No.	Ingredient	Function
1	Paracetamol	API (Antipyretic)
2	Sodium starch glycol	Anti-adherent/ Disintegrant
3	Lactose	Diluent/ Filler
4	Talc	Glidant/ Mineral
5	Magnesium Stearate	Diluent/ Lubricant
6	Corn Starch	Diluent/ Disintegrant/ Binder

RESULTS AND DISCUSSION

Pre-compression parameters:

Batches (Trial)	Angle of Repose (θ)	Bulk density	Tapped density	Hausner's Ratio
1	47.08	0.54	0.72	1.33
2	44.01	0.52	0.71	1.36
3	35.23	0.6	0.80	1.33

Pre-compression parameters for the trial batches

Batches	Angle of Repose (θ)	Bulk density	Tapped density	Hausner's Ratio
1	32.21	0.6	0.82	1.36
2	33	0.6	0.83	1.38
3	31.23	0.6	0.82	1.36

Pre-compression parameters for the Formulation batches

Discussion:

The blend was analyzed 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.

During trial Batch 1 and 2 showed poor flow ability.

Post Compression Parameters:

Batches (Trial)	Weight Variation (Avg SD)	Hardness (kg/cm2)	Friability (%)	Disintegration Time
1	661.2±0.45	8 kg	0.001%	4 min 45 sec
2	655.3±0.50	7.8 kg	0.001%	4 min 4 sec
3	659.2±0.35	5 kg	0.09%	3 min 50 sec

Post-compression parameters for the trial batches

Batches	Weight Variation (Avg SD)	Hardness (kg/cm2)	Friability (%)	Disintegration Time
1	661.2±0.45	4.8 kg	0.83%	3 min 6 sec
2	655.3±0.50	5 kg	0.79%	3 min 14 sec
3	659.2±0.35	4.8 kg	0.81%	3 min 30 sec

Post-compression parameters for the formulation

Discussion:

There was no weight variation during trial batches.

Tablets obtained during the trial of Batch 1 and 2 were too hard because of the starch paste and excess of starch in tablets.

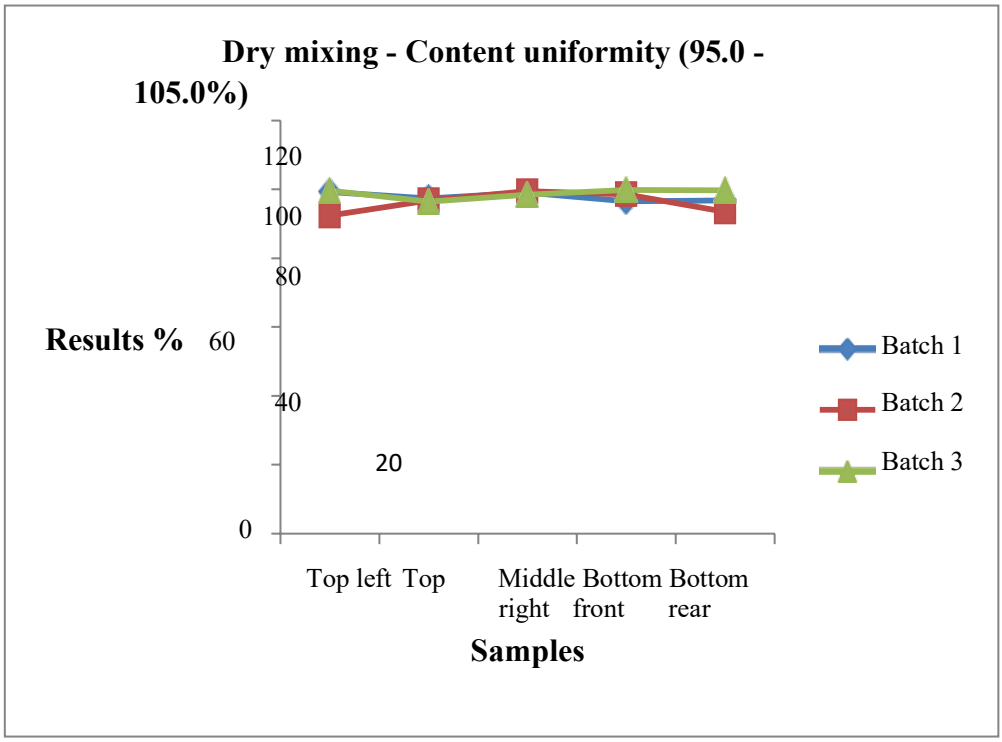
Friability of tablets was less than 1 %.

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

Assay of Paracetamol tablet during dry mixing:

Location	Assay of Paracetamol (%) 5 mins of dry mixing		
	Batch A	Batch B	Batch C
Top left	99.2%	92.3%	99.5%
Top right	97.3%	96.7%	96.4%
Middle	98.9%	99.4%	98.4%
Bottom front	96.5%	98.5%	99.8%
Bottom rear	96.7%	93.4%	99.7%
Mean	97.7%	96.06%	98.7%
SD	1.25	3.11	1.43
%RSD	1.28	3.23	1.45

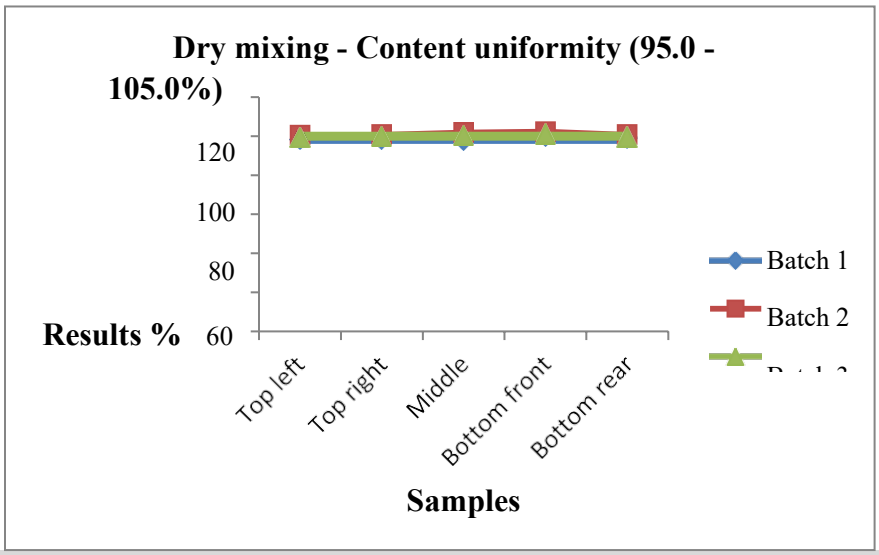
Assay of Paracetamol during Dry mixing for trial batches



Assay of content during dry Mixing for Trial Batch

Location	Assay of Paracetamol (%) 5 mins of dry mixing		
	Batch A	Batch B	Batch C
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

Assay of Paracetamol during Dry mixing for Formulation



Assay of content during dry Mixing for Formulation Batch

Discussion:

Dry mixing was done for 5 min at 70 RPM.

All the Batches showed good content uniformity.

Wet Granulation and Drying for LOD:

Batch No.	1	2	3
Addition of Binding agent	5% Starch paste	5% Starch paste	5% Starch paste

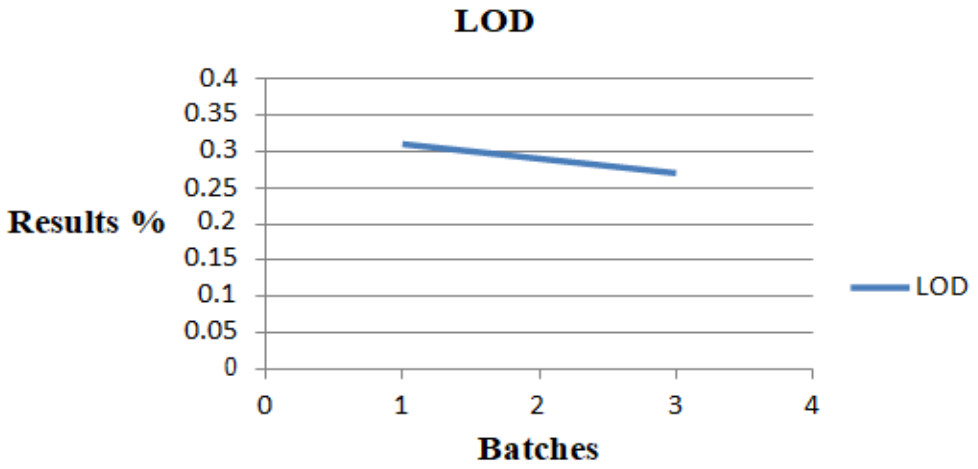
Wet granulation

Batch no.		1	2	3
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

Drying (Equipment name – Fluidized bed dryer)

Batch (Trial)	1	2	3
LOD (NMT 1.0% w/w)	0.31%	0.29%	0.27%

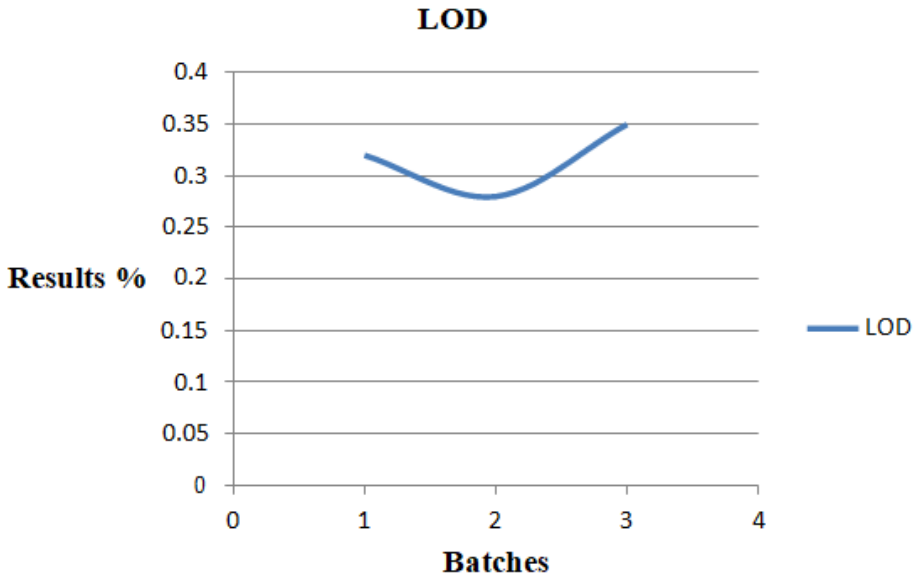
LOD for Trial Batches



LOD for Trial Batches

Batch no.	1	2	3
LOD (NMT 1.0% w/w)	0.32%	0.28%	0.35%

LOD for Formulation Batches



LOD of Formulation Batches

Sizing and Milling of Granules:

Batch no.		**1**	**2**	**3**
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

Sizing and milling of granules (Equipment name – Multi mill)

Lubrication:

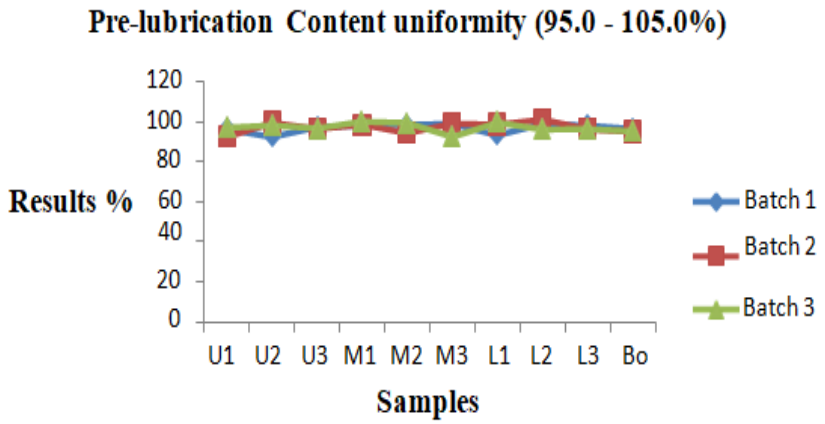
Pre-lubrication				
Parameters	**Acceptance criteria**	**1**	**2**	**3**
Pre-lubrication time	10min	10min	10min	10min
Pre-lubrication RPM	30 RPM	30	30	30
Lubrication				
Lubrication time	5min	5min	5min	5min
Lubrication RPM	30 RPM	30	30	30

Lubrication (Equipment name – Octagonal blender)

Pre-Lubrication Trial Batches:

Sample location	**Pre-lubrication (Trial) -Content of Uniformity (95.0 – 105.0%)**		
Batch no.	**1**	**2**	**3**
U1 (Upper left rear)	96.5%	92.5%	97.2%
U2 (Upper centre front)	92.6%	99.7%	98.3%
U3 (Upper right rear)	97.6%	96.6%	96.8%
M1(Middle left centre)	98.4%	98.7%	100.2%
M2(Middle centre)	98.7%	94.5%	99.4%
M3 (Middle right centre)	99.2%	99.3%	92.5%
L1(Lower left front)	93.5%	99.8%	99.7%
L2 (Lower centre rear)	99.1%	101.2%	96.3%
L3 (Lower right front)	98.3%	96.5%	96.5%
BO (Bottom centre)	96.6%	95.2%	95.4%
Mean	97.05%	97.4%	97.23%
SD	2.31	2.77	1.85
%RSD (NMT 5.0%)	2.38	2.85	1.91

Pre-lubrication content uniformity for trial batches

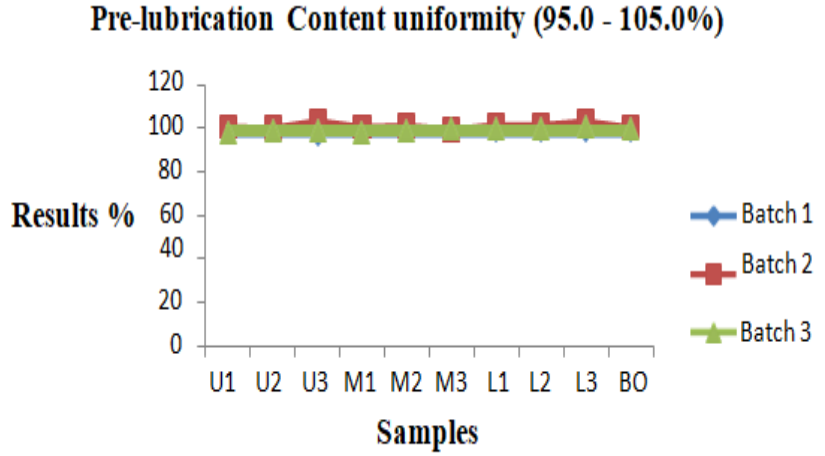


Pre-Lubrication Content Uniformity for Trial Batch

Pre-Lubrication Formulation Batches:

Sample location	Pre-lubrication -Content of Uniformity (95.0 – 105.0%)		
Batch no.	**1**	**2**	**3**
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

Pre-lubrication content uniformity for the formulation

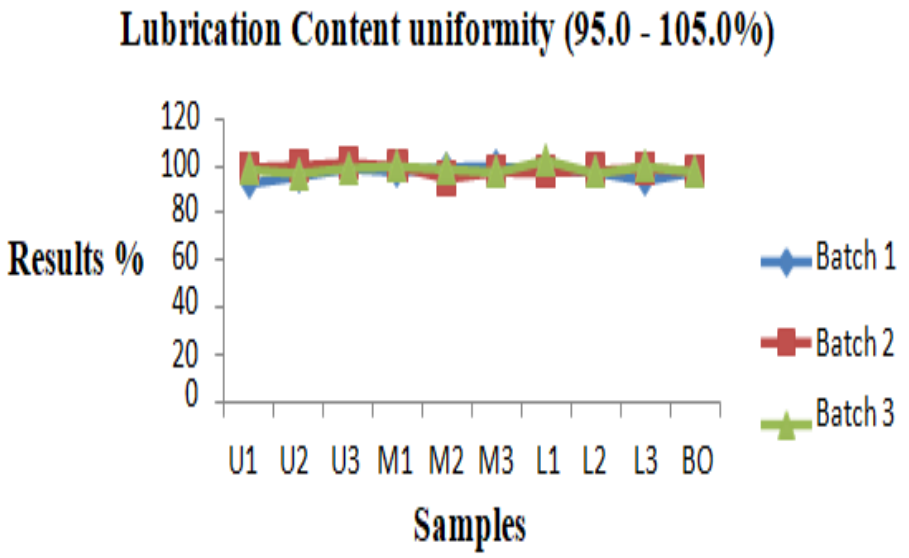


Pre-Lubrication Content Uniformity for Formulation Batch

Lubrication Trial Batches:

Sample location	Lubrication (Trial) -Content of Uniformity (95.0 – 105.0%)		
Batch no.	**1**	**2**	**3**
U1 (Upper left rear)	92.4%	99.2%	98.4%
U2 (Upper centre front)	95.3%	99.9%	96.7%
U3 (Upper right rear)	98.7%	101.2%	99.1%
M1(Middle left centre)	97.4%	99.8%	99.8%
M2(Middle centre)	99.2%	94.6%	98.6%
M3 (Middle right centre)	99.6%	97.5%	97.2%
L1(Lower left front)	98.1%	97.2%	102.2%
L2 (Lower centre rear)	97.3%	98.1%	96.8%
L3 (Lower right front)	93.5%	98.7%	99.8%
BO (Bottom centre)	97.4%	97.6%	97.4%
Mean	96.8%	98.3%	98.6%
SD	2.41	1.83	1.22
%RSD (NMT 5.0%)	2.49	1.86	1.23

Lubrication content uniformity for trial batches

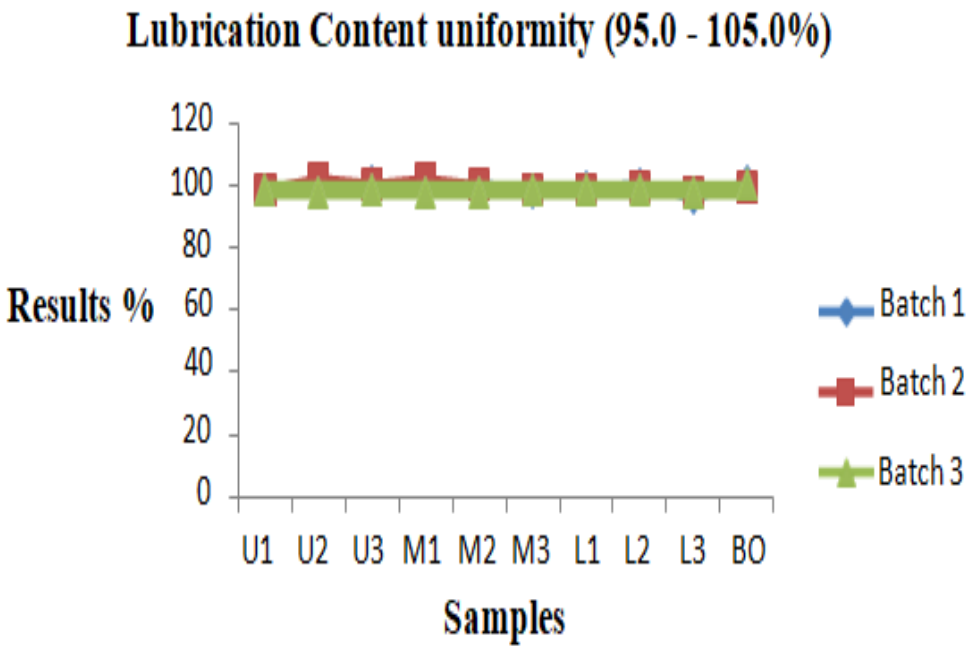


Lubrication Content Uniformity for Trial Batch

Lubrication Formulation Batches:

Sample location	Lubrication -Content of Uniformity (95.0 – 105.0%)		
Batch no.	**1**	**2**	**3**
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

Lubrication content uniformity for formulation



Lubrication Content Uniformity for Formulation Batch

COMPRESSION DATA:

Parameters	Batches			Acceptance criteria
	Batch A	Batch B	Batch C	
Description	White colored round and uncoated tablets free from loose dust.	White colored round and uncoated tablets free from loose dust.	White colored round and uncoated tablets free from loose dust.	White colored round and uncoated tablets free from loose dust.
Hardness	4.8 kg	5 kg	4.8 kg	NLT 4 kg
Thickness	3.8mm	3.8mm	3.8mm	3.9mm
Friability	0.83%	0.79%	0.81%	NMT 1%
Diameter	13mm	13mm	13mm	13mm
Disintegration time	3 min 6 sec	3 min 14 sec	3 min 30 sec	NMT 15 min
Assay (By UV)	99.5%	100.5%	99.7%	Should be 90-110% 0f label clam.
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 labelled amount of Paracetamol in the tablets is dissolved in 30 Minutes.

Compression data

Conclusion

The overall data of the three batches (Batch No. 1, 2 and 3) 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.

Future Scope:

The future of process validation for tablets holds promising advancements driven by technology and regulatory expectations. Automation and data-driven approaches will play a vital role in ensuring real-time monitoring and control of critical process parameters. Process analytical technology (PAT), continuous manufacturing, and quality by design (QbD) principles will further optimize process validation by enabling faster and more efficient manufacturing processes while maintaining product quality. Additionally, the incorporation of artificial intelligence (AI) and machine learning algorithms will enhance data analysis and prediction capabilities. The integration of advanced technologies and a science-based approach will streamline process validation, leading to improved efficiency, reduced costs, and enhanced patient safety.

References

1. Lodaya, Mayur P. 2011. “Oral Solid Dosage Forms.” In Martin’s Physical Pharmacy and Pharmaceutical Sciences: Physical Chemical

and Biopharmaceutical Principles in the Pharmaceutical Sciences: Sixth Edition.
2. Boqué, Ricard, Alicia Maroto, Jordi Riu, and F. Xavier Rius. 2002. "Validation of Analytical Methods." Grasas y Aceites.
3. Kruve, Anneli et al. 2015. "Tutorial Review on Validation of Liquid Chromatography-Mass Spectrometry Methods: Part I." Analytica Chimica Acta.
4. Manadas, Rui, Maria Eugénia Pina, and Francisco Veiga. 2002. "A Dissolução in Vitro Na Previsão Da Absorção Oral de Fármacos Em Formas Farmacêuticas de Liberação Modificada." Revista Brasileira de Ciencias Farmaceuticas/Brazilian Journal of Pharmaceutical Sciences.
5. Aleem, H. et al. 2003. "Pharmaceutical Process Validation: An Overview." Proceedings of the Institution of Mechanical Engineers, Part E: Journal of Process Mechanical Engineering.
6. Liu, Junjie, Yongli Yu, Liu Zhang, and Chenglong Nie. 2011. "An Overview of Conceptual Model for Simulation and Its Validation." In Procedia Engineering.