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RESEARCH ARTICLE

Implementation of Quality by Design to the Process Validation with Risk-Based Approach for Quality Assurance of Salbutamol Sulphate Tablets

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ABSTRACT

Quality by Design (QbD) refers to a holistic approach towards drug development. The purpose of research was to implement quality by design to study prospective process validation of 4 mg Salbutamol Sulphate Tablets with risk-based approach. Validation is one of the important steps in achieving and maintaining the quality of the final product. Quality Target Product Profile, Critical Quality Attributes, Critical Process Parameters, Design Space and control strategy are identified with the help of Quality Risk Management. Three initial batches of same size, method, equipment was taken for process validation. The critical parameters involved in sifting, dry mixing, preparation of granulating solution, wet mixing, drying, sizing, lubrication, compression were identified and evaluated. The formulation properties of three initial batches of process validated tablets are compared with the marketed products of Salbutamol Sulphate Tablets (Astahlin tab and Salbetol tab). Results obtained with this process validation data provides high degree of assurance that manufacturing process produces product meeting its predetermined specifications and quality attributes. The output of process validation can be used to increase productivity, its consistent quality and decreasing the need for processing and market complaints.

KEYWORDS

QTPP, CQA, CPP, QRM, Design Space, Control Strategy.

INTRODUCTION

Quality by Design (QbD) is a concept first outlined by well-known quality expert Joseph M. Juran. Juran believed that quality could be planned, to minimize most quality crises and problems in the first place.[1] Continuous improvement of quality of product can be done with the help of QbD as shown in Figure no. 1.

Quality by design implementation targets the following departments within a pharmaceutical company- Management, Procurement, R&D, Manufacturing, Testing, Quality control, Quality assurance, Regulatory, Logistics, Sales, Warehouse/ Supply chain including vendor's facilities, CRO and CMO.[2]

Defination Of Qbd:- A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.[3]

Quality Assurance of Salbutamol Sulphate Tablets

Quality by Design is implemented to maintain the Quality of Salbutamol Sulphate tablets at

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every stage of processing such as formulation development, manufacturing, analysis, packing, batch release. Quality Assurance of Salbutamol Sulphate tablets are directly and indirectly depends upon following parameters;

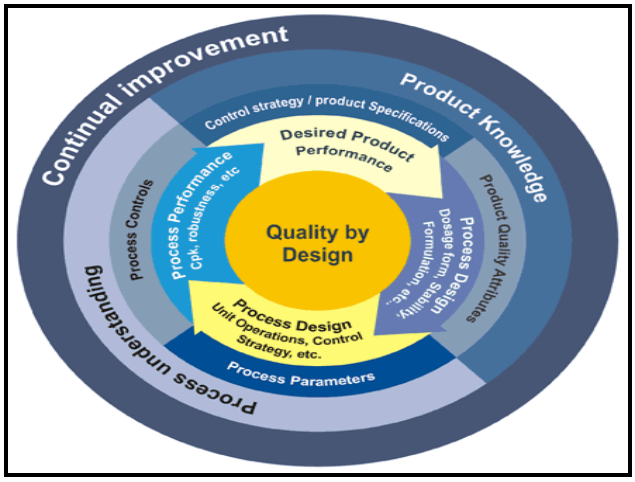

Figure 1: Quality by Design[4]

1. Purified Water System, Analysis and Validation
2. Qualification of Equipments with risk-based approach
3. Analysis of Raw Materials
4. Evaluation of Granules Ready for Compression (GRC) of Salbutamol Sulphate tablets
5. Evaluation of Salbutamol Sulphate tablets
6. Total Bacterial Count Test
7. Process validation of Salbutamol Sulphate tablets with risk-based approach
8. Validation of Analytical method

Water used for Manufacturing, Analysis is purified water from Validated Water System. The frequency of water analysis is every 2 weeks.[5] Equipments used for Manufacturing of Salbutamol Sulphate tablets were qualified with risk-based approach.[6] Raw Materials are analyzed as per specifications in Official Pharmacopoeias[7, 8].

Granules are evaluated for angle of repose, bulk density, tapped density and compressibility index. Tablets are evaluated for weight variation, hardness, friability, disintegration time, dissolution, content uniformity and assay.[9] Total bacterial count test is done for raw materials, finish products and purified water. For Salbutamol Sulphate tablets analytical methods was developed and validated.

Process validation of initial 3 batches of Salbutamol Sulphate tablets with risk-based approach. Three batches having same strength and same batch size. The first batch is taken as optimization batch and remaining two batches are considered as validation batches. Process validation is done for establishing documented evidence that process variables including critical process parameters are under control and that the process consistently produces product meeting its predetermined license specification and its quality attributes. Parameters are evaluated by samples withdrawn at predefined interval as per sampling points.[6]

Quality by Design per Unit Operation

QbD is implemented with the help of many components as shown in Figure no. 2

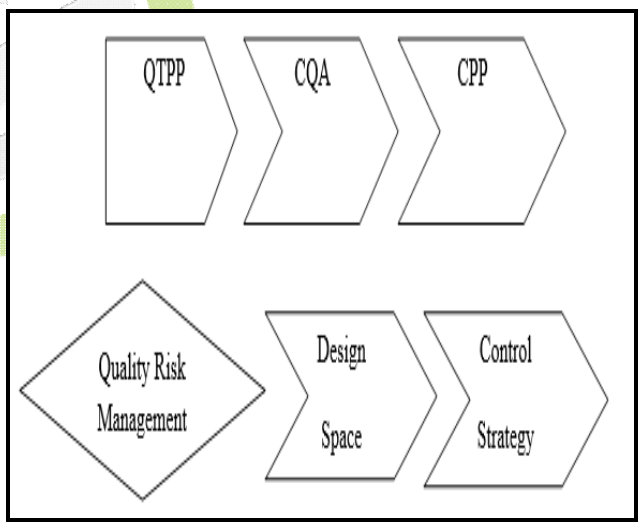

Figure 2: Components of Quality by Design[10]

Quality Target Product Profile (QTPP)

The QTPP is a term that is a natural extension of target product profile (TPP) for product quality. It guides formulation scientists to establish formulation strategies and keep formulation efforts focused and efficient. This is related to identity, assay, dosage form, purity, stability in the label.[11]

A drug product designed, developed and manufactured according to QTPP with specification (such as dissolution/release acceptance criteria) consistent with the desired in vivo performance of the product.

Careful characterization of Critical Quality Attributes and critical process parameters with appropriate biopharmaceutics studies, result in desired in-vivo performance, and thereby, enable linking product, process, and patient (desired therapeutic outcomes).[12]

Table 1: Quality Target Product Profile for Salbutamol Sulphate Tablets

Sr. No	QTPP Element	Target
1.	Dosage form	Tablet
2.	Dosage design	Conventional release tablet
3.	Route of administration	Oral
4.	Dosage strength	4 mg
5.	Container closure system	HDPE bottles
6.	Pharmacokinetics	Conventional release enabling T_{max} in 15-20 minutes or less.
7.	Shelf life	36 onths

Critical Quality Attributes (CQA)

CQA has been defined as "a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality".[13] Identification of CQAs is done through risk assessment as per the ICH guidance Q9.

All Quality Attributes are mentioned in the Table no.2. Out of all Quality Attributes of Mixing, Wet granulation, drying & Compression some Quality Attributes are critical.

Mixing: In this stage, Content Uniformity is Critical Quality Attributes. The uniformity of powder Blend is depends upon the Mixing time & speed of Mixer. Equipment capacity/Load also affects the content Uniformity of powder Blend. The allowed powder blend load is 40 - 70% of working volume. Overloaded mixer causes improper mixing.

Wet Granulation: In this stage, Flow Characteristics is Critical Quality Attributes. Flow Characteristics depends upon the bulk density, tapped density and angle of repose of granules. Granules should be hard enough to avoid breaking or chipping during handling. More fines and semi dry granules affects tapped density & angle of repose and ultimately affects compressibility index of granules.

Drying: In this stage, Moisture content is Critical Quality Attributes. Moisture content of granules is depends upon the inlet and outlet air flow, temperature and volume. Inlet temperature is critical to the drying efficiency of granules.

Compression: In this stage, Hardness is Critical Quality Attributes. Hardness has narrow range. Hardness affects the disintegration and dissolution of tablets. The Hardness is control by adjusting compression force of tablets.

Critical Process Parameters (CPP)

A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.[13]

The first phase is to identify potential CPPs—that is, the specific process parameters that may affect particular CQAs. The evaluation takes into account experimental knowledge as well as practical experience. Some process operation may be difficult or an operating range may be narrow to optimize a variable. Only those parameters with potential CQA or API influence are taken into account for further analysis as CPPs.

All process parameters are mentioned in the Table no.2. Out of all process parameters of Mixing, Wet granulation, Drying & Compression some process parameters are critical.

Table 2: Quality Attributes and Process Parameters of Salbutamol Sulphate Tablets

Sr. no.	Process	Parameters	Quality Attributes
1.	Mixing	a) Type and geometry of mixer b) Order of addition c) Mixer load level d) Mixing time & speed	a) Uniformity of blend b) Particle Size Distribution c) Bulk/Tapped Density d) Flow Properties
2.	Wet Granulation	a) Impeller speed, configuration and location b) Chopper speed and configuration, and location c) Binder concentration d) Post granulation mix time	a) Blend uniformity b) Flow Characteristics c) Moisture content d) Particle size distribution
3.	Drying	a) Inlet air flow, vol., temperature, dew point b) Product temperature c) Exhaust air temperature and flow d) Filter properties and size e) Total drying time	a) Flow Characteristics b) Bulk/Tapped Density c) Moisture Content d) Residual Solvents
4.	Compression	a) Compression Force b) Hopper design, height, vibration c) Tablet weight and thickness d) Depth of Fill e) Ejection Force	a) Weight Variation b) Hardness and Variation c) Friability d) Content Uniformity e) Assay f) Disintegration g) Dissolution

Mixing: In this stage, Mixing time & speed are Critical Process Parameters. Over mixing results in demixing or separation of materials. Avoid demixing which affects physical property differences such as particle size distributions and density. It is specific to the particular process steps. Mixing time & speed are finally affects drug content uniformity of Salbutamol Sulphate Tablet. Hence Mixing time & speed are Critical Process Parameters.

Wet Granulation: In this stage, binder concentration is Critical Process Parameters. Binder concentration of granulating solution affects the bonding within granules. Bonding in granules should be strong enough to make hard granules which not break during handling. If the binder is to be sprayed, the binder solution is to be dilute enough so that it can be pumped through the spray nozzle.

Drying: In this stage, Inlet air flow, volume, temperature is Critical Process Parameters. Inlet air flow, volume, temperature affects moisture content of granules. The inlet temperature is critical to the drying efficiency of the granulation. Inlet temperature is set high enough to maximize drying without affecting the chemical/physical stability of the granulation. The outlet temperature is an indicator of the granulation temperature. It will increase toward

the inlet temperature as the moisture content of the granulation decreases (evaporization rate).

Compression: In this stage, Compression force is Critical Process Parameters. Compression force affects the hardness of tablets. Disintegration and dissolution of tablets are depends upon the hardness. Compression force of tablets having narrow range hence it is Critical Process Parameters.

Quality Risk Management

A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle.

Effective risk management requires a sufficient understanding of the business, the potential impact of the risk, and ownership of the results of any risk management assessment. Risk assessment must take into account the probability of a negative event in combination with the severity of that event – This principle also serves a useful working definition for risk (i.e., risk represents the combination of the probability and severity of any given event).[13]

In the each stage of Salbutamol Sulphate Tablet Manufacturing, some parameters are critical in the process and quality of tablets. These parameters are having narrow limit range. Hence it is necessary to implement Quality Risk Management in every stage of Salbutamol Sulphate Tablet Manufacturing. [15]

Mixing: In this stage content Uniformity is Critical Quality Attributes and Mixing time & speed are Critical Process Parameters. Dose accuracy and precision of tablets are depends upon these parameters. These are interrelated. If the materials are over mixed, resulting in demixing or segregation of the materials. If planetary mixer is overloaded, it causes improper mixing.

Wet granulation: In this stage Flow Characteristics is Critical Quality Attributes and binder concentration is Critical Process Parameters. If binder concentration is less than limit, then more amount of granulating solution require making granules & it may over wet granules and more time require to dry the granules. If binder concentration is more than limit, then it affects the uniformity of granules.

Drying: In this stage Moisture content is Critical Quality Attributes and Inlet air flow, volume, and temperature is Critical Process Parameters. If Moisture content is more than limit, then it promotes the degradation of tablets, also affects the flow characteristics of granules; hence it is Critical Quality Attributes.

Compression: In this stage Hardness is Critical Quality Attributes and Compression force is Critical Process Parameters. If Hardness is less than limit, then tablets are brittle and may break during handling. If Hardness is more than limit, then it takes more time to release drug content. Hardness affects the disintegration and dissolution of tablets.

Design Space

The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.[13]

During manufacturing process development, it was revealed that blending process, lubricant blending process and compression process give small impact on Drug release quality. These processes were included as a component in the design space because it has been demonstrated that drug product with appropriate quality can be manufactured when applying the controls shown below.

Blending Process

Blending homogeneity is control by evaluation of content uniformity should be within design space of 95.0-105.0% and standard deviation less than 2%. Content uniformity of blend affects the dose accuracy and precision of tablets.

Lubricant Blending Process

The design space of the lubricant blending time will be established after process validation at the commercial scale production. After specified time interval, samples are withdrawn for content uniformity.

Compression Process

Compression pressure 3 to 5 Kg/cm^2 has been demonstrated to produce tablets with appropriate quality; therefore this pressure range was set in the design space. Compression pressure affects hardness of tablets. [14]

Final Product Specification

The final drug product specifications are used to assure safety and efficacy during the shelf-life of Salbutamol Sulphate Tablets as mentioned in the Table no. 3.

Water content was set as a component in the design space to control assay, content uniformity, dissolution, and generation of impurities produced from hydrolysis of the API were identified.

Table 3: Design Space for Final Product Specifications

Sr. No.	Process Parameters	Design Space
1.	Average Weight	248 – 252 mg
2.	Disintegration Time	5 – 7 minutes
3.	Hardness	4.0 - 4.5 Kg/cm^2
4.	Thickness	1.80 – 2.20 mm
5.	Drug Content	95.0 – 105.0 %

Control strategy

Control strategy is defined as "a planned set of controls, derived from current product and process understanding that assures process performance and product quality" [18]. The control strategy in the QbD paradigm is established via risk assessment that takes into account the criticality of the CQA and process capability.[13]

The control strategy can include the following elements: procedural controls, in- process controls, lot release testing, process monitoring, characterization, testing, comparability testing and stability testing. It is worth noting that the use of risk assessment in creating the control strategy is unique to the QbD approach. The control strategy for Batch Release is as follows:-

Dissolution- Particle size of drug substance and hardness of tablet affect the dissolution rate. Confirmation of the dissolution rate pattern of tablets.

Content Uniformity- Content Uniformity of tablets is depends on blending homogeneity, ultimately depends on proper mixing.[14]

Packing- Each HDPE bottle contains 50 Salbutamol Sulphate Tablets with appropriately labeled.

MATERIALS AND METHODS

Materials

Salbutamol Sulphate was gifted by Raptakos Brett & Co. Ltd., Mumbai. Microcrystalline Cellulose, Crossmellose Sodium, PVP, Talc and Magnesium Stearate were obtained from S. D. Fine-Chem Limited, Mumbai. All other chemicals and reagents used were obtained from commercial sources and were of analytical grade. Conventional Marketed Products of Salbutamol Sulphate: Brand Name-ASTHALIN tab, Manufacturer- Cipla Labs and Brand Name-SALBETOL tab, Manufacturer-FDC (Proxima)

Methods

Preparation of Tablets

Tablets were prepared by Wet Granulation method**.** All the Ingredients were weighed accurately. Salbutamol Sulphate, Microcrystalline Cellulose, Crossmellose Sodium were passed through 40 # sieve. The sifted materials were mixed in Planetary Mixer at high speed for 15 minutes. Dissolved PVP in iso propyl alcohol (IPA) to prepare clear 5% w/v granulating solution. 5% w/v PVP in IPA solution was added in powder blend & stirred continuously at 80 rpm in Planetary Mixer for 25 minutes. Semi dried granules in air & passed through 10 mesh sieve. Granules was dried in fluidized bed dryer at 40 – 60^{0}C till % Loss on

Drying (LOD) value below 2% w/w. Sifted the dried granules through 20 mesh sieve & collected the fines. Sifted the Magnesium stearate & talc passed through 40 mesh sieve & mixed at high speed for 10 minutes in Planetary Mixer. The tablets were compressed on a 16-station rotary tablet punching machine with 7.0 mm punches plain on both sides. The die cavity adjusted to fill 250 mg tablet weight. The composition of formulations was shown in Table no. 4.

Process Validation with Risk-Based Approach

Dry Mixing stage: - Dry mixing uniformity was evaluated by withdrawn sample at 15 minutes from the sampling points showed in Figure no. 3. Mean and Standard Deviation of samples from each batch was calculated.

Wet Granulation stage:- Wet mixing dough mass consistency was evaluated by studying speed of impeller, time of mixing. Drug uniformity of granules was evaluated by withdrawn sample at 25 minutes. Impeller speed during discharging is noted.

Drying stage:- Granules were dried in fluidized bed dryer at 40 – 60^0C. Drying efficiency of granules was evaluated by %LOD (Loss on Drying), should be less than2% w/w. Representative samples were selected for evaluation of LOD

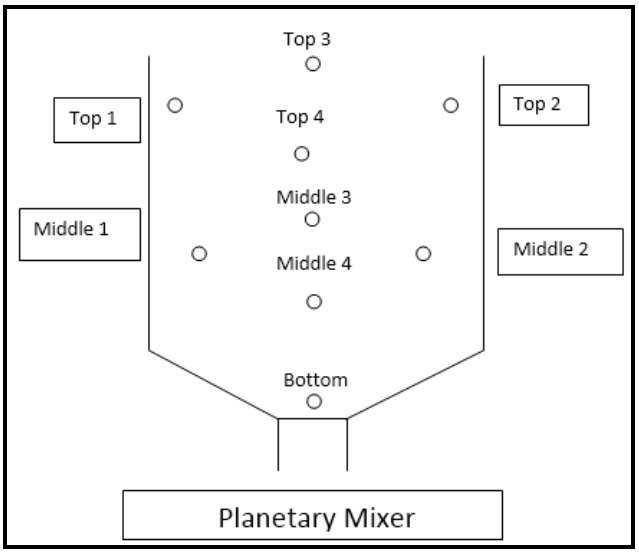

Figure 3: Sampling Pointes

Lubrication stage:- Mixing uniformity was evaluated by withdrawn sample at 10 minutes from the sampling points showed in Figure no.3. Mean and Standard Deviation of samples from each batch was calculated.

Compression stage:- Set machine at optimum speed (Initial setting at 20 RPM) and compression force. About 200 tablets collected from the compression machine at optimum speed, High Speed and Low speed of machine run. Tablets were evaluated for parameters such as appearance, weight variation, thickness, hardness, DT, friability, drug content. [16]

Table 4: Composition of Formulation of Tablets of Salbutamol Sulphate

No.	Ingredients	Qty/tablet	Qty in Kg/batch	Specifications
1.	Salbutamol Sulphate	4.8 mg	0.480	IP
2.	Microcrystalline Cellulose	227.7 mg	22.77	USP
3.	Crossmellose Sodium	2.5 mg	0.25	USP
4.	5 %w/v PVP in (IPA)	5 mg	0.5	USP
5.	Magnesium stearate	5 mg	0.5	USP
6.	Talc	5 mg	0.5	USP

(4.8 mg of Salbutamol Sulphate equivalent to 4 mg of Salbutamol)

Shelf Life - 36 months

Label Claim- Each tablet contains Salbutamol Sulphate IP equivalent to 4 mg of Salbutamol

***Evaluation of Blend*[9]**

The angle of repose was measured by using fixed funnel method, which indicates the flow ability of the granules. Loose bulk density (LBD) and tapped bulk density (TBD), Compressibility index of the granules were determined by using the following formula:

Angle of repose, Tan θ = h/ r

LBD = height of the powder/volume of packing

TBD = weight of the powder/tapped volume of packing

Compressibility index (CI) = [(TBD-LBD/TBD] x 100

The physical properties of granules were shown in Table 9.

Evaluation of Tablets[9]

Evaluation of prepared tablets and marketed tablets was done as follows:

Thickness: Thickness of the tablets was determined using a vernier caliper.

Weight Variation Test: 20 tablets of each batch prepared tablets and marketed tablets were weighed using an electronic balance and the test was performed according to the official method.

Hardness: The term hardness indicates the ability of tablets to withstand mechanical stress during Packaging, shipment, and handling. Hardness of the tablets was determined by using a Monsanto Hardness testing apparatus.

Friability: Friability of the tablet was checked by using Roche Friabilator. This device subjects tablets to the combined effect of abrasions and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Pre weighed sample of 10 tablets was placed in the Friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed.

Disintegration Test: The test was carried out on 6 tablets using tablet disintegration tester Electro lab, distilled water at 37ºC ± 2ºC was used as a disintegration media. When all six tablets have disintegrated, the time of content release from shell and complete shell residue passed through mess was noted.

Drug Content: 10 Salbutamol Sulphate tablets were taken from batch, crushed & uniformly mixed. Appropriate amount of tablet powder was taken equivalent to one tablet weight of Salbutamol Sulphate tablet. Dissolved in specified volume of distilled water using sonicator to facilitate dissolution. The mixture was filtered through a whatman no. 42. Filter paper and measured spectrophotometrically at λ max 276 nm using UV/VIS Spectrophotometer against distilled water as blank.

Drug Release Studies: *In Vitro* dissolution studies for all batches of the prepared tablets and the marketed tablets of Salbutamol Sulphate was carried out using USP paddle method at 50 rpm in Distilled Water as dissolution media, maintained at 37 ± 0.5º. 5 ml of sample was withdrawn from the dissolution medium at the different time intervals of 5, 10, 15, 20, 25, 30 minutes, filtered through Whattmann filter paper and assayed spectrophotometrically at 276 nm and the drug content was determined from the Standard calibration curve of Salbutamol Sulphate.

RESULTS AND DISCUSSION

As shown in Table 5, Dry Mixing was obtained within the design space of 95.0-105.0%. Mean and Standard Deviation of samples from each batch was calculated. SD was found within design space of less than 2. Consistency of granulating solution was found excellent with 5% w/v concentration. As shown in Table 6, a dough mass consistency was excellent with respect to speed of impeller at 80 RPM and assay. As shown in Table 7, % LOD was obtained within design space of NMT 2%w/w.

As shown in Table 8, Uniformity of mixing in lubrication stage was obtained within design space of 95-105%. Mean & SD was calculated. SD was found within design space of less than 2. As shown in Table 9, average weight was found within design space of 248-252 mg, disintegration time in design space of 5-7 minutes, hardness design space of 4-4.5 Kg/cm^2, thickness in design space of 1.80-2.20mm and

drug content in design space of 95.0-105.0%

Table 5: Dry Mixing Stage

Sr. No.	Sample Location	Content Uniformity (95.0-105.0%) of Salbutamol Sulphate		
	Batch No.	I	II	III
1.	Top 1	97.36	98.64	100.13
2.	Top 2	96.89	97.62	99.89
3.	Top 3	98.87	98.37	101.27
4.	Top 4	98.32	98.19	99.78
5.	Middle 1	98.54	98.94	101.17
6.	Middle 2	98.92	98.16	101.28
7.	Middle 3	97.29	97.67	100.94
8.	Middle 4	97.61	97.69	99.93
9.	Bottom	98.57	98.67	99.79
	Mean	98.04111	98.21666667	100.4644
	SD	0.75869039	0.483166638	0.679045

Table 6: Granulation Stage

Sr. No.	Process Parameters	Batch No.		
		I	II	III
1.	Impeller Speed	80 rpm	80 rpm	80 rpm
2.	Impeller Speed during discharging	Slow Speed	Slow Speed	Slow Speed
3.	Total Granulation Time	20 Min	20 Min	20 Min
4.	% Assay after Granulation	98.59 %	99.26 %	101.39 %

Table 7: Drying Stage

Sr. No	% LOD of Granules of Salbutamol Sulphate			
1.	Batch No.	I	II	III
2.	% LOD NMT 2% w/w	0.982 %	1.219 %	1.186 %

Table 8: Lubrication Stage

Sr. No.	Sample Location	Lubrication Content Uniformity (95.0-105.0%) for Salbutamol Sulphate		
	Batch No.	I	II	III
1.	Top 1	98.57	100.43	99.98
2.	Top 2	99.25	100.13	100.73
3.	Top 3	99.28	99.6	101.83
4.	Top 4	100.93	98.72	101.56
5.	Middle 1	100.16	99.27	102.37
6.	Middle 2	98.58	98.51	102.96
7.	Middle 3	98.42	99.64	102.49
8.	Middle 4	99.46	98.42	100.57
9.	Bottom	100.92	98.92	101.48
	Mean	99.50778	99.29333333	101.552
	SD	0.96737761	0.670919767	0.98267

Table 9: Compression Stage

Sr. No.	Process Parameters	Specifications	Batch No.		
			I	II	III
1.	Appearance	White colored plain tablet	Complies	Complies	Complies
2.	Identification	UV scan of prepared sample	Complies	Complies	Complies
3.	Average Weight	248 – 252 mg	250.78 mg	250.23 mg	250.97 mg
4.	Disintegration Time	5 – 7 min	5min 53sec.	6min 21sec.	6min 07sec.
5.	Hardness	4.0 - 4.5 Kg/cm^2	4.35 Kg/cm^2	4.12 Kg/cm^2	4.41 Kg/cm^2
6.	Thickness	1.80 – 2.20 mm	2.13 mm	2.16 mm	2.24 mm
7.	Dissolution	95.0 – 105.0 %	96.28 %	103.97 %	102.73 %

Table 10: Evaluations of Granules

Sr. No.	Formulation Properties	Batch No.		
		I	II	III
1.	Angle of Repose (^{0})	32.95	33.64	34.64
2.	Bulk Density	0.62	0.59	0.56
3.	Tapped Density	0.69	0.67	0.64
4.	Compressibility index (%)	10.144	11.94	12.5
5.	Flow Property	Good	Good	Good

For each Batch of prepared tablets, Granules of drug and excipients was prepared and evaluated. As shown in Table 10, Angle of Repose was found in range of 31 to 35 while % compressibility index value was ranged in 10 to 13 %. All batches shows good flow ability.

Comparison of formulation properties of prepared tablets with 2 marketed products of Salbutamol Sulphate, Asthalin tab and Salbetol tab, are showed in Table 11. Tablets were prepared by Wet Granulation technique. Hardness, friability, weight variation, assay, uniformity of content, dimensions and disintegration time were found within acceptable limits. In-Vitro studies showed more than 80% of Drug Release within 15 – 20 minutes. Assay of three batches and marketed products of Salbutamol Sulphate Tablets was showed in figure 4-8. Drug release pattern of three batches and marketed products of Salbutamol Sulphate Tablets was showed in figure no. 9.

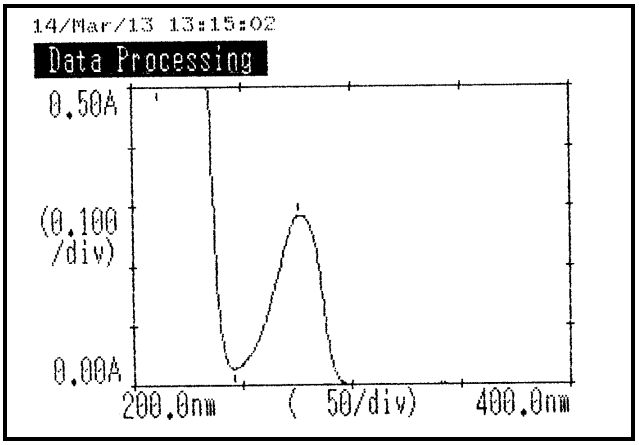

Figure 4: UV Graph of Batch No. 1 of Salbutamol Sulphate Tablets

Table 11: Evaluations of Tablets

Sr. No	Formulation Properties	Batch No.			Asthalin tab	Salbetol tab
		I	II	III		
1.	Weight Variation	Complies	Complies	Complies	Complies	Complies
2.	Identification	Complies	Complies	Complies	Complies	Complies
3.	Diameter (mm)	7.00 ± 0.5	7.00 ± 0.5	7.00 ± 0.5	8.60 ±0.5	8.30 ±0.5
4.	Thickness (mm)	2.00 ± 0.5	2.00 ± 0.5	2.00 ± 0.5	3.00 ± 0.5	2.40 ± 0.5
5.	Average Weight (mg)	250 ± 0.5	250 ± 0.5	250 ± 0.5	224 ± 0.5	171 ± 0.5
6.	Hardness (Kg/cm^2)	4.35 ± 0.26	4.12 ± 0.21	4.41 ± 0.22	4.16 ± 0.31	4.5 ± 0.5
7.	Friability	0.624 ± 0.5	0.541 ± 0.5	0.615 ± 0.5	0.597 ± 0.5	0.458 ± 0.5
8.	Disintegration Time (Minutes)	6 ± 0.26	6 ± 0.21	6 ± 0.12	5 ± 0.22	2 ± 0.43
9.	Drug Release (%)	100.9 ± 1.4	102.4 ± 1.8	101.9 ± 2.1	99.87 ± 1.6	100.64 ± 1.7
10.	Content Uniformity (%)	100.6 ± 1.6	101.4 ± 1.5	101.5 ± 2.3	100.87 ± 2.2	101.19 ± 1.4
11.	Assay (%)	98.74 ± 0.5	99.13 ± 0.5	100.11 ± 0.5	99.64 ± 0.5	99.10 ± 0.5

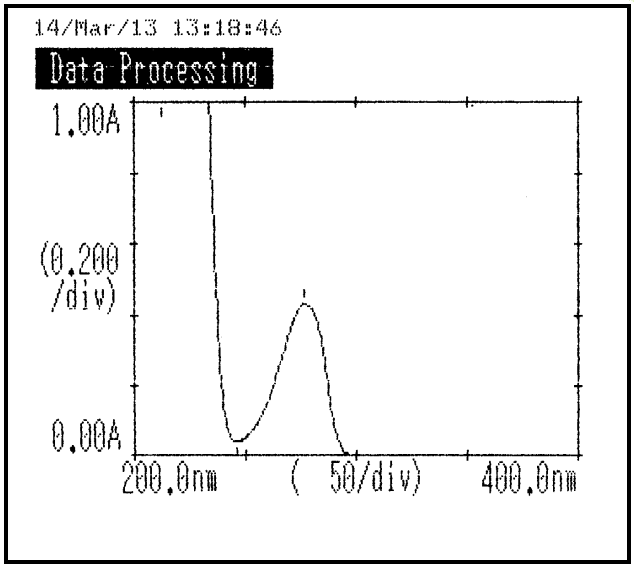

Figure 5: UV Graph of Batch No. 2 of Salbutamol Sulphate Tablets

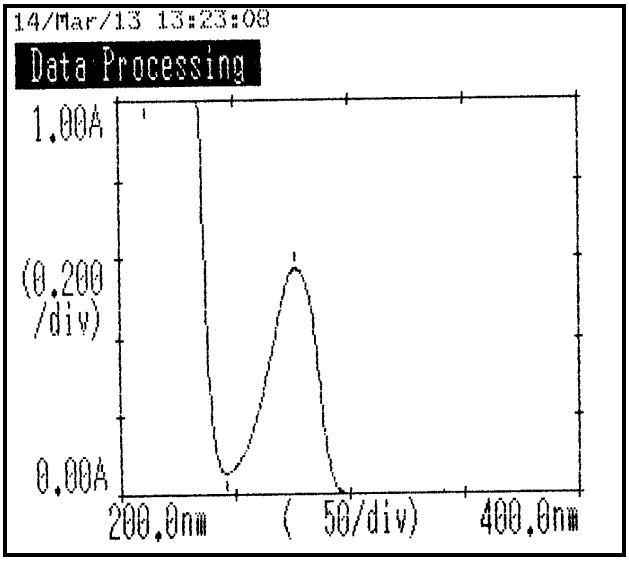

Figure 6: UV Graph of Batch No. 3 of Salbutamol Sulphate Tablets

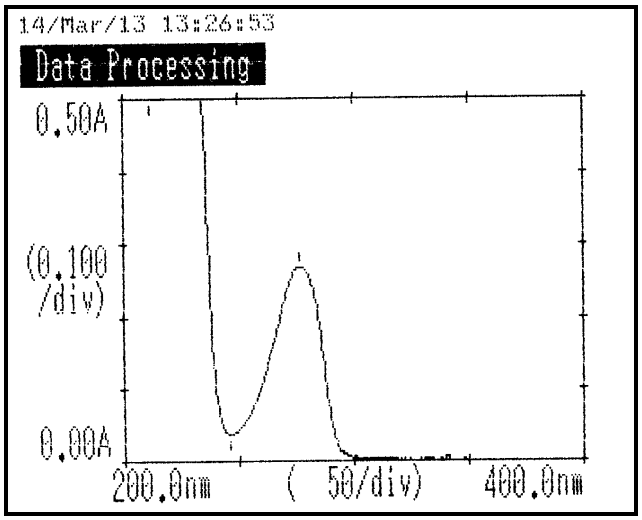

Figure 7: UV Graph of Asthalin tablets

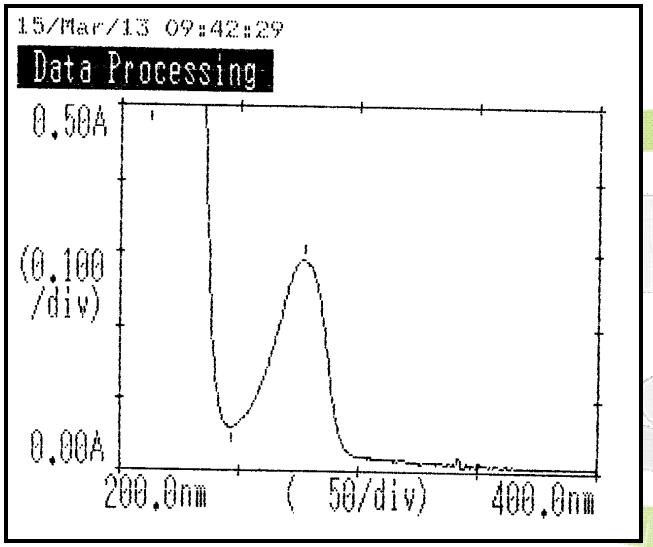

Figure 8: UV Graph of Salbetol tablets

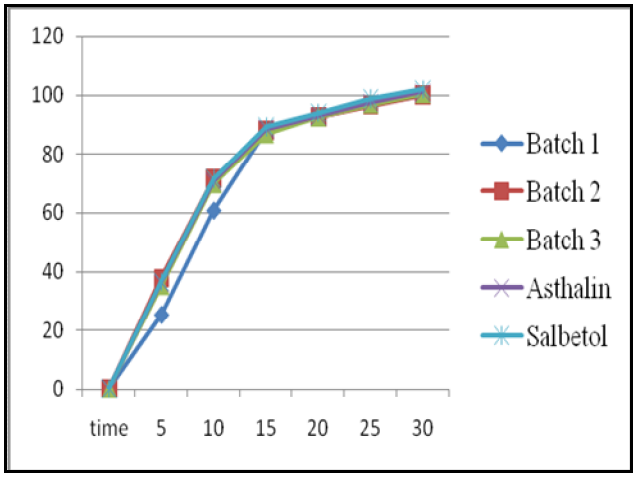

Figure 9: Dissolution Study of prepared tablets and Marketed tablets

CONCLUSION

The Salbutamol Sulphate Tablets was successfully formulated and results are reproducible. Uniformity of dry mixing was excellent because SD found within the specification (NMT 2). Dough mass was formed satisfactory within 10 min wet mixing. Drying time 30 min is suitable for achieving LOD less than 2.0% w/w. Lubrication stage uniformity was achieved with 10 min because SD found within specification (NMT 2) and flow properties was satistisfactoty. Compression machines optimum speed (80 rpm) was satisfactory for effective compression.

The prepared tablets are meeting specifications as mentioned in the QTPP. The CQA and CPP are identified and evaluated with help of QRM. The CQA and CPP are controllable and within the design space. Control strategy was developed and evaluated for dissolution, content uniformity and packing of quality properties of Salbutamol Sulphate Tablets. Therefore based on results produces the batches with no significant deviation and process effectively produces product with predefined reproducible quality standards.

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