INTERNATIONAL JOURNAL OF PHARMACEUTICAL, CHEMICAL AND BIOLOGICAL SCIENCES

Available online at www.ijpcbs.com

Research Article

PROCESS VALIDATION OF BETHANECHOL CHLORIDE TABLET 25 mg

B. Patil Prashant[1], K. More Rupesh[2] and G. Khan Zamir[2]*

[1]Department of Quality Assurance, H. R. Patel Institute of Pharmaceutical Education & Research, Karwand Naka, Shirpur, Dist: Dhule, Maharashtra, India-425 405.

[2]Department of Pharmaceutical Chemistry, H. R. Patel Institute of Pharmaceutical Education & Research, Karwand Naka, Shirpur, Dist: Dhule, Maharashtra, India-425 405.

ABSTRACT

The present study provide a high degree of assurance that a specific process for manufacturing of Bethanechol Chloride Tablet 25 mg will consistently produce a product meeting its predetermined specifications and quality attributes. It mainly involves the steps to be followed to evaluate and qualify the acceptability of manufacturing process of Bethanechol Chloride Tablet 25 mg. The process is limited to the three batches manufactured of specific batch size with specified equipments and control parameters for tablets. It involves All parameters related to the each step were evaluated by respective standard test involved in the manufacturing. Sampling, testing plan and acceptance criteria for each step were monitored. The results were found to be Blend Uniformity results for pre - lubricated blend between 97.3 – 101.8% and for lubricated blend between 94.3 – 101.8 %. Compression assay results between 98 – 103 % were found within acceptable limit. Other test related to compression such as hardness, thickness, disintegration and dissolution for all three batches were found within acceptable limit.

Keywords: Bethanechol Chloride, Blend Uniformity, Assay, Process Validation.

INTRODUCTION

Validation is defined as process of establishing through a documented program, which provides a high degree of assurance that a specific process will consistently produce, a product meeting its pre-determined specifications and quality attributes. The word validation simply means, 'assessment of validity' or 'action of proving effectiveness' a validated manufacturing process is one, which has been proved to do what it purports to or is represented to do. Validation necessarily includes process qualification (the qualification of materials, equipment, system, buildings and personnel).

Process Validation is defined as the collection and evolution of data from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products. It assures Quality, Safety, and efficacy. (According to 2011 United State of Food and Drug Administration (USFDA) guideline).

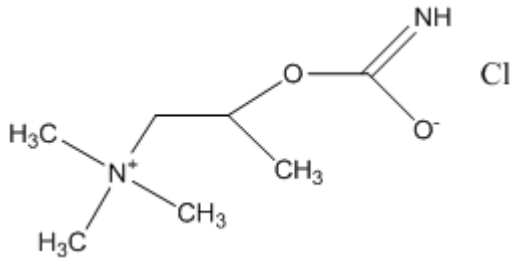
Approaches to Process Validation

Stage 1 – Process Design
Stage 2 – Process Qualification
Stage 3 – Continued Process Verification.

MECHANISM OF ACTION OF BETHANECHOL CHLORIDE

Bethanechol Chloride acts principally by producing the effect of stimulation of the parasympathetic nervous system. It increases the tone of detrusor urine muscle, usually producing a contraction sufficiently strong to initiate maturation and empty the bladder. It stimulates gastric motility, increase gastric tone and after restores impaired rhythmic peristalsis. Stimulation of parasympathetic nervous system releases acetylcholine at the nerve ending. When spontaneous stimulation is reduced and therapeutic intervention is required acetylcholine can be given, but it is rapidly

hydrolyzed by cholinesterase and its effect more prolonged than those of acetylcholine.
Effects on the GI and urinary tracts sometimes appear within 30 minutes after oral administration of Bethanechol Chloride, but more often 90 and 60 minutes are required to rich maximum effectiveness.



Chemical Structure of Bethanechol Chloride

Molecular Formula $C_7H_{17}N_2O_2Cl$
Molecular Weight 196.68 g/mol (With Chloride), 161.22208 g/mol (Without Chloride)
Synonyms 2 [(aminocarbonil) oxy] – *N, N, N*- tri methyl - 1- Propanaminium Chloride

MATERIALS AND METHODS

Prospective process validation was performed on the three batches of Bethanechol Chloride Tablets 25 mg. The three consecutive batches were labeled as Batch A, Batch B, Batch C. The experimental work includes list of raw materials, list of equipment's used, process flow diagram, critical process parameters, standard specification and acceptance criteria & sampling plan as given below. During the manufacturing process samples were collected and sent for analysis to Q.C. department.

List of Equipment and Status Table 1 indicate list of equipments which are used in manufacturing process of Bethanechol Chloride Tablets 25 mg and give the involvement of equipment in which manufacturing stage
Details of Input Raw Material Table 2 indicates row material of which is used in the manufacturing of Bethanechol Chloride tablets 25 mg. with their specification and category.
Sampling and Testing Plan Table 3 indicates the planning for sampling and testing with their manufacturing stage, sample location, sample size, rational and test. **Manufacturing Process flow chart** In which indicates the manufacturing stages (process), equipments, critical process parameters, critical quality attributes.

RESULTS AND DISCUSSION

This report is limited to evaluation of consecutive three batches of Bethanechol Chloride Tablet 25 mg manufactured with batch size of 320.00 kg (1,000,000 Tablets).

Product Details
Label Claim The label claim involve the Product Name as Bethanechol Chloride Tablet USP 25 mg, labeled is each tablet contain Bethanechol Chloride USP 25 mg and Blend size is at blend stage 320.00 kg and Compression stage 320.00 (1,000,000 Tablet)

Batch Details Three manufacturing batches are validated in process validation the batches are labeled as Batch A, Batch B, Batch C at Blend stage, Compression stage and Packing stage. The manufacturing date for all three batches is June 2015 and expiry date is May 2018.

List of Equipment used in Manufacturing Table 4 indicates the lists of equipments are involved in the manufacturing of Bethanechol Chloride Tablets 25 mg. The all equipments are qualified.

Reference Documents
- Validation Master Plan
- Batch Manufacturing Record
- In process Specification
- Finished Product Specification

Details of Input Materials
Details of Input Material For Batch A, B, C. material name with their specification and issued quantity are shown in **Table 5**

Environmental Conditions
The Environmental condition during manufacturing of Bethanechol Chloride Tablet 25 mg is monitored. The Temperature not more than 25 ^{0}c and relative humidity not more than 30% are maintained throughout the manufacturing process of Bethanechol Chloride Tablet 25 mg.

Critical Process Parameters
The blend manufacturing and compression stage processing steps like sifting, co shifting, blending (pre-lubrication and lubrication), and compression stage with their parameters and specification for all three manufacturing batches mentioned in **Table 6.**

Sifting Stage
Sifting of API and inactive material was carried out as specified in the BMR for all three batches. Sifting of these three batches carried out by using 40# mesh stainless steel sieve. Sieve integrity was checked before and after of sifting is ok. This is also mentioned in **Table 6.**

Blending

The pre – lubrication blending was carried out by using double cone blender for 24 RPM ± 1 and blending time for 15 minutes as per BMR, the samples for blend uniformity were withdrawn from 12 point sampling location of blender which shown in figure 2 and found that the blend uniformity was well within the limit of 90.0 % to 110.0 % of labeled amount of Bethanechol Chloride with RSD not more than 4.5 %. The RSD value for three batches of pre – lubricated blend sequentially was found to be 1.2%, 2.4%, 2.9% which were found to be well within the acceptable limit not mere than 4.5% as shown in the **Table 7.**

Lubrication

The blending was carried out after addition of after addition of lubricant by using double cone blender for 24 RPM ± 1 and blending time for three minutes as per BMR. The samples for blend uniformity were withdrawn from 12 point sampling location of blender which shown in figure 2 and found that the blend uniformity was well within the limit of 90 .0 % to 110.0 % of labeled amount of the Bethanechol Chloride with RSD not more than 4.5 %. The RSD value for three batches of lubricated blend sequentially was found to be 1.8%, 1.4%, 1.3% which was found to be well within the acceptable limit not more than 4.5% as shown in the **Table 8**.

At this stage lubricated blend composite sample also tested for Description and Assay (by HPLC) which also found to be well within the acceptable limit as shown in **Table 9.**

Compression

The compression was carried out as per BMR by using compression machine CADPRESS IV double rotary for all three validation batches, the sample were collected as per protocol and found that all physical parameters and analytical parameters of tablet were well within the limit for all three batches i.e. average weight: 320 mg ± 2.5 %, weight variation: ± 5% of average weight, hardness: 59 N to 118 N, thickness: 3.60 4.30 mm, friability: not more than 1 % w/w, disintegration time: not more than 10 minutes, content uniformity: less than or equal to 15.0, assay: not less than 95.0 % and not more than 105.0 % and all above values were within the limit only. The samples were collected for performing those all parameters at different speed of machine such as minimum speed (1980 tabs./min.), maximum speed (2420 tabs./min) and initial, middle, end (2200 tabs./min.) which shown in **Table 10 to 15.**

Dissolution found within acceptable range. Dissolution profile tabular representation shows in **Table 16, 17 and 18.**

And graphical representation shows in **Figure 3, 4 and 5.** The sample were collected at each time interval of compression and found that all parameters were within limit.

Bottle Packing

The bottle packing of tablet was carried out as per BPR at CVC packing machine, the bottle pack size is 20 tablets in each HDPE container with screw cap. Leak test is performed at this stage the results as mentioned in **Table 19** are satisfactory.

Finished Product analytical results like description, identification by IR, average weight. LOD, dissolution, content uniformity, assay, weight variation, thickness, disintegration time etc are shown in **Table 20.**

CONCLUSION

Three process validation batches of Bethanechol Chloride Tablets 25 mg were manufactured as per approved manufacturing record by using API's and excipients which are from approved vender agencies. The test performed approved process validation protocol and the observations, conclusion made thereafter are concluded below,

Based on the pooled sample results it can be concluded that the sifting procedure as given in batch manufacturing record is sufficient to ensure proper sifting of API's with all dry sifted material in sifter. Sifting of all excipients was done through 40 mesh sieve. Bethanechol Chloride Co-sifted with Anhydrous Lactose through 40 mesh sieve as per procedure given in batch manufacturing record.

Based on the data obtained, it can be concluded that blending for 15 minutes at 24 RPM ± 1 RPM as per BMR**.** Result of blend uniformity and assay for all three validation batches found within limit of acceptance criteria. Average blend uniformity result between 98.6% to 100.4% and percentage RSD between 1.3% to 1.8%.

From the above data it can be calculated that existing compression process is sufficient to produce the compressed tablet meeting all the predetermined specification which are mentioned in the approved process validation protocol.

All the three process validation batches manufacture as per approved batch manufacturing record by using API's and other excipients which are approved from vender qualification program and found to comply with the predetermined acceptance criteria and

found adequate to produce Bethanechol Chloride Tablet USP 25 mg. The bottle packing of Bethanechol Chloride Tablet; the machine configuration and related parameters was found to be satisfactory which meets the predetermined specification and quality attributes.

ACKNOWLEDGEMENT

Authors are thankful to Wockhardt Ltd. Aurangabad, Maharashtra for giving necessary facilities to carry out this work.

Table 1: List of Equipment and Status

Sr. No.	Equipment	Make	Stages Involved In
1	Weighing balance	Jaypan & AND-FX-200i	All stages
2	Vibratory sifter	Gansons Limited, Ambad Nashik	Sifting of raw materials
3	Rapid Mixer Granulator	Sainath Boilar Pvt. Ltd.	Dry mixing and granulation
4	Double Cone Blender	ADAM Fiberiwerks Pvt. Ltd. Ambad,	Blending
5	Compression machine.	CADPRESS IV	Compression
6	Friability Test Apparatus	ELECTROLAB	To check friability
7	Hardness Tester	ELECTROLAB	To check hardness
8	Dissolution Apparatus	Electrolab 12 Station (USP)	Dissolution Testing
9	Disintegration apparatus	Electrolab (USP)	To check disintegration time
10	Metal Detector	Metal Trap-03	To Detect metal tracks in tablets
11	Tablet Deduster	CIP Machineries	To removing dust on tablet
12	HPLC	Ultimate-3000 THERMOSCINTIFIC	For Blend Uniformity and Content Uniformity

Table 2: Details of Input Raw Material

Ingredients	Specification	Category
Bethanechol Chloride	USP	Active ingredients
Anhydrous Lactose	NF	Diluents
Microcrystalline Cellulose	NF	Emulsifier & Bulking Agent
Sodium Starch Glycolate	NF	Super Disintegrant
Colloidal Silicon Dioxide	NF	
Magnesium Stearate	NF	Lubricant
FD & C Yellow Aluminum Lake	In House	Coloring Agent
D & C Yellow #10 Aluminum Lake	In House	Coloring Agent

*USP- United State Pharmacopeia, NF – National Formulary

Table 3: Sampling and Testing Plan

Stage	Sample Location	Sample Size	Rational	Test
Pre-Lubrication	From Double Cone Blender (Non lubricated blend)	(X to 3X) (318.4mg to 955.2mg) #	Sample shall be collected from 12 different location from blender for blend uniformity	Blend Uniformity (12 samples shall be tested)
Lubrication (Blending)	From Double Cone Blender (Lubricated Blend) After completion of three minutes of blending, draw 12- point samples in triplicate (Refer sampling location diagram ,point 4,3)	(X to 3X) (320.0 mg to 960.0 mg)#		Blend Uniformity (12 sample shall be tested)
	From Blender. One composite samples from different locations (Top, Middle, and Bottom) before unloading	50 gm	Samples shall be collected	1. Description 2. Assay
Compression	1.Minimum speed 2.Maximum Speed 3. At target speed, collect samples from side of machine at initial, middle and end of compression run.	40 tablets for QC# 60 tablets for IPQA from each side	Sample shall be collected as per stage	1. Description 2. Average Wt. 3. Disintegration time 4. Hardness 5. Thickness 6. Friability 7. Weight Variation 8. Content Uniformity 9. Dissolution, 10. Assay
Finished product	One composite sample from all containers after completion of compression	100 Tablets (In duplicate)	Collect one composite sample from all containers	Finished product Analysis and Dissolution profile on 12 units at 5, 10, 15, 30 and 5 minutes

*QC – Quality Control Department, IPQA – In Process Quality Assurance

Table 4: List of Equipment used in Manufacturing

Sr.No.	Equipment	
1	Sifterz	**Batch A Batch B Batch C**
2	Double Cone Blender	
3	Cadmill	
4	Tablet Compression m/c Cadpress- IV /CMB4-35	
5	Tablet Deduster	
6	Metal Detector	

Table 5: Details of Input Material Batch A, B, C

Sr. No	Material Name	Specification	Issued Qty. (Kg)
1	Bethanechol Chloride	USP	25.120
2	Anhydrous lactose (PharmactoseDCL-21)	NF	137.61
3	Anhydrous lactose (PharmactoseDCL-21)	NF	10.00
4	Microcrystalline Cellulose (Avicel PH 101)	NF	136.380
5	Sodium Starch Gycolate (Explotab CLV)	NF	8.00
6	Colloidal Silicon Dioxide (Aerosil 200)	NF	0.400
7	Magnesium Stearate	NF	1.600
8	FD & C Yellow # Aluminum Lake	In House	0.090
9	FD & C Yellow # Aluminum Lake	In House	0.800

*USP- United State Pharmacopeia, NF – National Formulary, Qty. - Quantity

Table 6: Critical Process Parameters at Blend Manufacturing and Compression Stage

Sr. No.	Processing Steps	Parameters to be Study	Specification	Batch A	Batch B	Batch C
1	Sifting	Sieve Used	40#	40#	40#	40#
2	Co-sifting of Bethanechol Chloride USP	Sieve Used	40#	40#	40#	40#
3	Sieve integrity before use	Should be ok	OK	OK	OK	OK
4	Sieve integrity after use	Should be ok	OK	OK	OK	OK
5	Blending (Pre-Lubrication)	Speed of Blender	24 RPM ± 1	24 RPM	24 RPM	24 RPM
		Blending Time	15 minutes	15 minutes	15 minutes	15 minutes
6	Blending (Lubrication)	Speed of Blender	03 minutes	03 minutes	03 minutes	03 minutes
		Blending time	03 minutes	03 minutes	03 minutes	03 minutes
		Yield	98.0 to 100.0 %	99.76 %	99.76 %	99.86 %
7	Compression	Machine Speed	2200 ± 200 Tablets/min's	2200	2200	2200
		Yield	95 to 100 %	96.95	99.93	97.04

*RPM – Rotation Per Minutes

Table 7: Pre Lubrication: - Blend Uniformity

Sr. No.	Location	Acceptance Criteria	Batch A	Batch B	Batch C
1	U1	90.0 % to 110.0 % of labeled amount of Bethanechol Chloride with RSD NMT 4.5 % (Each 320 mg of blend contains 25 mg of Bethanechol Chloride)	97.3	97.2	99.3
2	U2		101	99	101.8
3	U3		100.6	102.2	100.1
4	M1		102.2	97.4	99.9
5	M2		100.9	99.3	95.7
6	M3		101.8	97.9	102
7	M4		101.1	105.2	99.2
8	M5		101.9	97.5	97.5
9	L1		101.6	99.2	98
10	L2		100.9	98.9	100.5
11	L3		101.4	101.2	106.8
12	BO		100.6	98	96.8
Maximum			97.3	97.2	95.7
Minimum			102.2	105.2	106.8
Mean			100.9	99.4	99.8
% RSD			1.2	2.4	2.9

*U- Upper, M – Middle, L – Lower, B – Bottom, RSD – Relative Standard Deviation, NMT – Not More Than

Table 8: Blending (Lubrication): - Blend Uniformity

Sr. No.	Location	Acceptance Criteria	Batch A	Batch B	Batch C
1	U1	90.0 % to 110.0 % of labeled amount of Bethanechol Chloride with RSD NMT 4.5 % (Each 320 mg of blend contains 25 mg of Bethanechol Chloride)	94.3	101.6	98.1
2	U2		99.1	100.3	99.7
3	U3		97.4	100.2	98
4	M1		98.4	98.4	101.5
5	M2		97.8	97.7	101.8
6	M3		97.4	101	99.9
7	M4		99.2	99.1	98
8	M5		99.5	99.9	99.9
9	L1		100.2	101.6	100.2
10	L2		99.5	102.7	100
11	L3		98.7	100.5	100.5
12	BO		101.5	101.2	100.7
Maximum			94.3	97.7	98.0
Minimum			101.5	102.7	101.8
Mean			98.6	100.4	99.9
% RSD			1.8	1.4	1.3

*U- Upper, M – Middle, L – Lower, B – Bottom, RSD – Relative Standard Deviation, NMT – Not More Than

Table 9: Composite Sample at Lubricated Blend

Test	Acceptance Criteria	Observation (Batch No.)		
		Batch A	Batch B	Batch C
Description	Light Yellow colored free flowing powder	Complies	Complies	Complies
Assay (By HPLC)	Not less than 97.0 % & not more than 105.0 % of the labeled amount of Bethanechol Chloride (Each 320 mg of blend contain 25 mg of Bethanechol Chloride).	100 %	98.9 %	103.6 %

Compression stage: Physical Parameters

Table 10: First Batch: Batch A

Test	Acceptance Criteria	Batch A			
		Minimum Speed (1980 Tabs/min)		Maximum Speed (2420 Tabs/min)	
		LHS	RHS	LHS	RHS
Description	Light Yellow colored oval shaped tablet debossed with W967 on one side and break line on the other side	Complies	Complies	Complies	Complies
Average Weight	320.0 mg ± 2.5 % (312.0 to 328.0 mg)	319.16	319.5	321.6	321.1
Weight variation	± 5 % of Average weight	-0.81 % to 1.06 %	-1.10 % to 0.78 %	0.81 % to 0.75 %	- 1.28 % to 0.91 %
Hardness	59 N to 118 N	Min: 80 Max: 109	Min: 81 Max: 105	Min: 87 Max: 107	Min: 93 Max: 106
Thickness	3.60 to 4.30 mm	Min: 3.95 Max: 3.97	Min: 3.93 Max: 3.97	Min: 3.95 Max: 3.99	Min: 3.96 Max: 4.03
Friability	Not more than 1% w/w	-0.03	-0.13	-0.05	0.05
Disintegration	Not more than 10 minutes	40 sec	46 sec	01 min. 20 sec	01 min 09 sec

Table 10: Continuation

Test	Acceptance Criteria	Batch A (2200 Tabs/min)					
		Initial		Middle		End	
		LHS	RHS	LHS	RHS	LHS	RHS
Description	Light Yellow colored oval shaped tablet debossed with W967 on one side and break line on the other side	Complies	Complies	Complies	Complies	Complies	Complies
Average Weight	320.0 mg ± 2.5 % (312.0 to 328.0 mg)	321.2	320.2	321.1	321.9	320.0	321.1
Weight variation	± 5 % of Average weight	-1.00% to 0.87%	-1.00% to 0.87	-0.97% to 1.53%	-1.83% to 1.58%	-0.94% to 0.94%	-0.97% to 0.90%
Hardness	59 N to 118 N	Min:90 Max:102	Min:92 Max:107	Min:93 Max:107	Min:90 Max:109	Min:93 Max:109	Min:93 Max:110
Thickness	3.60 to 4.30 mm	Min:3.93 Max: 3.99	Min:3.93 Max: 3.99	Min:3.92 Max:3.99	Min:3.92 Max: 3.97	Min: 3.92 Max: 3.99	Min: 3.91 Max: 3.99
Friability	Not more than 1% w/w	0.00	-0.05	-0.05	-0.06	-0.06	-0.03
Disintegration	Not more than 10 minutes	01 min 14 sec	01 min 11 sec	01 min 13 sec	01 min 30 sec	01 min 22 sec	01 min21 sec

*LHS – Left Hand Side, RHS – Right Hand Side, Min. – Minimum, Max. - Maximum

Table 11: Second Batch: Batch B

Test	Acceptance Criteria	Batch B			
		Minimum Speed (1980 Tabs/min)		Maximum Speed (2420 Tabs/min)	
		LHS	RHS	LHS	RHS
Description	Light Yellow colored oval shaped tablet debossed with W967 on one side and break line on the other side	Complies	Complies	Complies	Complies
Average Weight	320.0 mg ± 2.5 % (312.0 to 328.0 mg)	320.1	316.0	318.9	319.9
Weight variation	± 5 % of Average weight	-1.59 % to 1.53 %	-1.27 % to 1.27 %	-1.85 % to 1.60 %	0.91 % to 0.97 %
Hardness	59 N to 118 N	Min: 91 Max:105	Min: 83 Max:112	Min: 90 Max:107	Min: 94 Max:105
Thickness	3.60 to 4.30 mm	Min: 3.98 Max:4.09	Min:3.95 Max:4.05	Min:3.94 Max:4.07	Min: 3.95 Max:4.03
Friability	Not more than 1% w/w	-0.02	0.00	-0.08	-0.02
Disintegration	Not more than 10 minutes	41 sec	39 sec	44 sec	33 sec

Table 11: Continuation

Test	Acceptance Criteria	Batch B (2200 Tabs/min)					
		Initial		Middle		End	
		LHS	RHS	LHS	RHS	LHS	RHS
Description	Light Yellow colored oval shaped tablet debossed with W967 on one side and break line on the other side	Complies	Complies	Complies	Complies	Complies	Complies
Average Weight	320.0 mg ± 2.5 % (312.0 to 328.0 mg)	321.7	322.2	322.7	318.7	321.5	323.1
Weight variation	± 5 % of Average weight	-2.39 % to 1.65 %	-1.30 % to 1.49	-1.15 % to 1.64 %	-1.16 %to 1.04 %	-1.40 % to 2.02 %	-1.27 % to 1.52 %
Hardness	59 N to 118 N	Min:96 Max:102	Min:92 Max:104	Min:96 Max:108	Min:97 Max:104	Min:95 Max:107	Min:95 Max:110
Thickness	3.60 to 4.30 mm	Min:90 Max: 102	Min:92 Max: 107	Min:93 Max:107	Min:90 Max: 109	Min: 93 Max: 109	Min: 93 Max: 110
Friability	Not more than 1% w/w	-0.12	-0.14	-0.09	-0.08	-0.06	-0.09
Disintegration	Not more than 10 minutes	49 sec	56 sec	1 min 19 sec	01 min 10 sec	01 min 13 sec	01 min 16 sec

*LHS – Left Hand Side, RHS – Right Hand Side, Min. – Minimum, Max. - Maximum

Table 12: Third Batch: Batch C

Test	Acceptance Criteria	Batch C			
		Minimum Speed (1980 Tabs/min)		Maximum Speed (2420 Tabs/min)	
		LHS	RHS	LHS	RHS
Description	Light Yellow colored oval shaped tablet debossed with W967 on one side and break line on the other side	Complies	Complies	Complies	Complies
Average Weight	320.0 mg ± 2.5 % (312.0 to 328.0 mg)	318.9	319.2	322.0	317.8
Weight variation	± 5 % of Average weight	-1.23 % to 1.29	-1.94 % to 1.19 %	-1.93 % to 1.55 %	-1.51 % to 1.64 %
Hardness	59 N to 118 N	Min:89 Max:99	Min:86 Max:104	Min:96 Max:101	Min:96 Max:102
Thickness	3.60 to 4.30 mm	Min:3.97 Max:4.07	Min:3.98 Max:4.07	Min: 3.98 Max:4.05	Min: 4.05 Max:4.08
Friability	Not more than 1% w/w	0.02	-0.03	-0.03	-0.05
Disintegration	Not more than 10 minutes	01 min 10 sec	01 min 21 sec	01 min 21 sec	01 min 10 sec

Table 12: Continuation

Test	Acceptance Criteria	Batch C (2200 Tabs/min)					
		Initial		Middle		End	
		LHS	RHS	LHS	RHS	LHS	RHS
Description	Light Yellow colored oval shaped tablet debossed with W967 on one side and break line on the other side	Complies	Complies	Complies	Complies	Complies	Complies
Average Weight	320.0 mg ± 2.5 % (312.0 to 328.0 mg)	316.3	316.8	320.5	321.3	322.3	323.1
Weight variation	± 5 % of Average weight	-1.36 % to 1.49 %	-2.78 % to 1.33 %	-0.78 % to 1.40 %	-0.72 % to 0.84 %	-2.58 % to 2.39 %	-0.99 % to 0.59 %
Hardness	59 N to 118 N	Min:95 Max:109	Min:96 Max:111	Min:95 Max:109	Min:93 Max:109	Min:95 Max:109	Min:96 Max:109
Thickness	3.60 to 4.30 mm	Min:4.00 Max: 4.09	Min:3.99 Max: 4.09	Min:3.99 Max:4.08	Min:4.00 Max:4.09	Min:3.98 Max: 4.07	Min:3.98 Max: 4.07
Friability	Not more than 1% w/w	-0.06	-0.03	-0.05	-0.03	-0.13	-0.14
Disintegration	Not more than 10 minutes	59 sec	01 min 03 sec	01 min 08 sec	59 sec	01 min 08 sec	01 min 13 sec

*LHS – Left Hand Side, RHS – Right Hand Side, Min. – Minimum, Max. - Maximum

Compression Stage: Analytical Results

Table 13: First Batch

Test	Acceptance Criteria	Batch A				
		Min Speed	Max Speed	Initial	Middle	End
Uniformity of Dosage units (by content uniformity) maximum allowed acceptance value	Less than or equal to 15.0	7.0	2.4	4.3	2.5	4.0
Assay (by HPLC)	Not less than 95.0 % and not more than 105.0 % of the labeled amount of Bethanechol Chloride ($C_7H_{17}N_2O_2Cl$)	98.4	99.1	98.3	99.8	99.2

Dissolution Test

Limit: Not less than 80 % (Q) of the labeled amount of Bethanechol Chloride ($C_7H_{17}N_2O_2Cl$) is dissolved in 30 min					
	Min Speed	**Max Speed**	**Initial**	**Middle**	**End**
Min	95	98	96	99	100
Max	98	100	100	102	101
Avg.	97	99	98	101	101

*HPLC – High Performance Liquid Chromatography, Min. – Minimum, Max. Maximum, Avg. – Average, Q - Quantity

Table 14: Second Batch

Test	Acceptance Criteria	Batch B				
		Min Speed	Max Speed	Initial	Middle	End
Uniformity of Dosage units (by content uniformity) maximum allowed acceptance value, L1	Less than or equal to 15.0	4.3	4.1	2.7	3.4	3.2
Assay (by HPLC)	Not less than 95.0 % and not more than 105.0 % of the labeled amount of Bethanechol Chloride ($C_7H_{17}N_2O_2Cl$)	98.2	98.4	98.9	99.8	100.4

Dissolution Test

Limit: Not less than 80 % (Q) of the labeled amount of Bethanechol Chloride ($C_7H_{17}N_2O_2Cl$) is dissolved in 30 min

	Min Speed	Max Speed	Initial	Middle	End
Min	96	91	96	95	96
Max	98	98	101	102	101
Avg.	97	95	99	99	98

*HPLC – High Performance Liquid Chromatography, Min. – Minimum, Max. Maximum, Avg. – Average, Q – Quantity

Table 15: Third batch

Test	Acceptance Criteria	Batch C				
		Min Speed	Max Speed	Initial	Middle	End
Uniformity of Dosage units (by content uniformity) maximum allowed acceptance value, L1	Less than or equal to 15.0	4.4	3.5	4.1	3.7	6.1
Assay (by HPLC)	Not less than 95.0 % and not more than 105.0 % of the labeled amount of Bethanechol Chloride ($C_7H_{17}N_2O_2Cl$)	100.0	99.2	99.2	102.7	102.3

Dissolution Test

Limit: Not less than 80 % (Q) of the labeled amount of Bethanechol Chloride ($C_7H_{17}N_2O_2Cl$) is dissolved in 30 min

	Min Speed	Max Speed	Initial	Middle	End
Min	94	98	98	98	97
Max	98	100	101	100	102
Avg.	96	99	100	99	100

*HPLC – High Performance Liquid Chromatography, Min. – Minimum, Max. Maximum, Avg. - Average
Remark: Analytical results for Uniformity of dosage unit, assay and dissolution found meeting with acceptance criteria for all three batches.

Dissolution Profile

Table 16: Dissolution Profile of First Validation Batches

1	2	3	4	5	6	7	8	9	10	11	12	Min	Max	Avg.
5 minutes														
60	52	63	56	61	53	58	56	85	62	57	64	**52**	**85**	**69**
10 minutes														
96	93	95	90	97	96	95	95	90	98	95	99	**90**	**99**	**95**
15 minutes														
97	96	95	93	97	96	95	97	97	96	100	96	**93**	**100**	**97**
30 minutes														
98	95	96	94	98	97	95	97	97	96	100	96	**94**	**100**	**97**
45 minutes														
97	95	96	94	96	96	94	95	98	95	100	96	**94**	**100**	**97**

*Min. – Minimum, Max. – Maximum, Avg. - Average

Table 17: Dissolution Profile of Second Validation Batches

1	2	3	4	5	6	7	8	9	10	11	12	Min	Max	Avg.
5 minutes														
59	53	64	60	62	54	59	57	84	63	58	65	**53**	**84**	**62**
10 minutes														
96	94	94	89	98	97	94	95	91	97	96	99	**89**	**99**	**95**
15 minutes														
96	95	96	92	96	97	96	96	97	96	100	97	**92**	**100**	**96**
30 minutes														
97	95	96	93	98	96	95	96	96	97	100	97	**93**	**100**	**96**
45 minutes														
96	95	97	95	96	97	94	96	99	96	100	97	**94**	**100**	**97**

*Min. – Minimum, Max. – Maximum, Avg. - Average

Table 18: Dissolution Profile of Third Validation Batches

1	2	3	4	5	6	7	8	9	10	11	12	Min	Max	Avg.
5 minutes														
58	54	66	59	63	53	60	58	86	63	59	67	**53**	**86**	**62**
10 minutes														
98	93	95	90	99	96	95	96	93	96	97	100	**93**	**100**	**96**
15 minutes														
95	94	95	91	95	96	97	97	96	95	99	96	**94**	**99**	**96**
30 minutes														
97	95	96	94	96	95	96	97	96	95	97	96	**94**	**97**	**95**
45 minutes														
97	96	98	96	97	98	95	97	98	95	99	98	**95**	**99**	**97**

*Min. – Minimum, Max. – Maximum, Avg. - Average

Packing Stage

Table 19: Results for Leak Test

Sr. No.	No. of Bottles	Results for Batch A, B, C
1	1	Passes the test Complies
2	1	
3	1	
4	1	
5	1	
6	1	

Table 20: Finish Product Analytical Results:

Test	Acceptance Criteria	Batch A	Batch B	Batch C
Description	Light Yellow colored, oval shaped tablet debossed with W967 on one side and break line on the other side	Complies	Complies	Complies
Identification 1-By IR absorption	IR absorption spectrum of sample in a mineral oil, exhibits maxima at the same wavelengths as that of a similar preparation of USP Bethanechol Chloride RS	Complies	Complies	Complies
2-By Chloline Test	An emerald- green color produced, which almost entirely fades in 5 to 10 minutes, distinct from choline chloride where color does not fade	Complies	Complies	Complies
Average Weight	320.0 mg ± 2.5 % (Between 312.0 mg and 328.0 mg)	321.6	323.1	326.5
Loss on Drying	Not more than 3 % w/w	1.6	1.5	1.6
Dissolution	Not less than 80 % (Q) of the labeled amount of Bethanechol Chloride ($C_7H_{17}N_2O_2Cl$) is dissolved in 30 minutes	Min: 97% Max: 99% Average:98%	Min: 95% Max: 101% Average:98%	Min: 95% Max: 99% Average:97%
Uniformity of dosage unit (By content uniformity) maximum acceptance value,L1	Less than or equal to 15.0	1.5	4.4	4.8
Assay	Not less than 95.0 % and not more than 105.0 % of the labeled amount of Bethanechol Chloride ($C_7H_{17}N_2O_2Cl$)	98.6	97.7	100.1
Weight Variation	+- 5% of average weight	-0.90 to +0.65	-0.89 to +0.98	-1.12 to +1.10
Thickness	Between 3.6 to 4.0 mm	3.88	3.89	3.89
Disintegration Time	Not mere than 10 minutes	4 minutes	4 minutes	4 minutes
Related Compounds				
2 – Hyderoxypropyltrimenthyl Ammonium chloride	Not more than 1.0%	Not Detected	Not Detected	Not Detected
Any other impurity	Not more than 0.2%	Not Detected	Not Detected	Not Detected
Sum of all impurity	Not more than 1.5%	Not Detected	Not Detected	Not Detected
Residual Solvents (Other, class I,II, and III Solvents)	As per USP General chapter <467>	Complies as per option I	Complies as per option I	Complies as per option I

*IR – Infra Red, USP – United State Pharmacopeia, RS – Related Substance

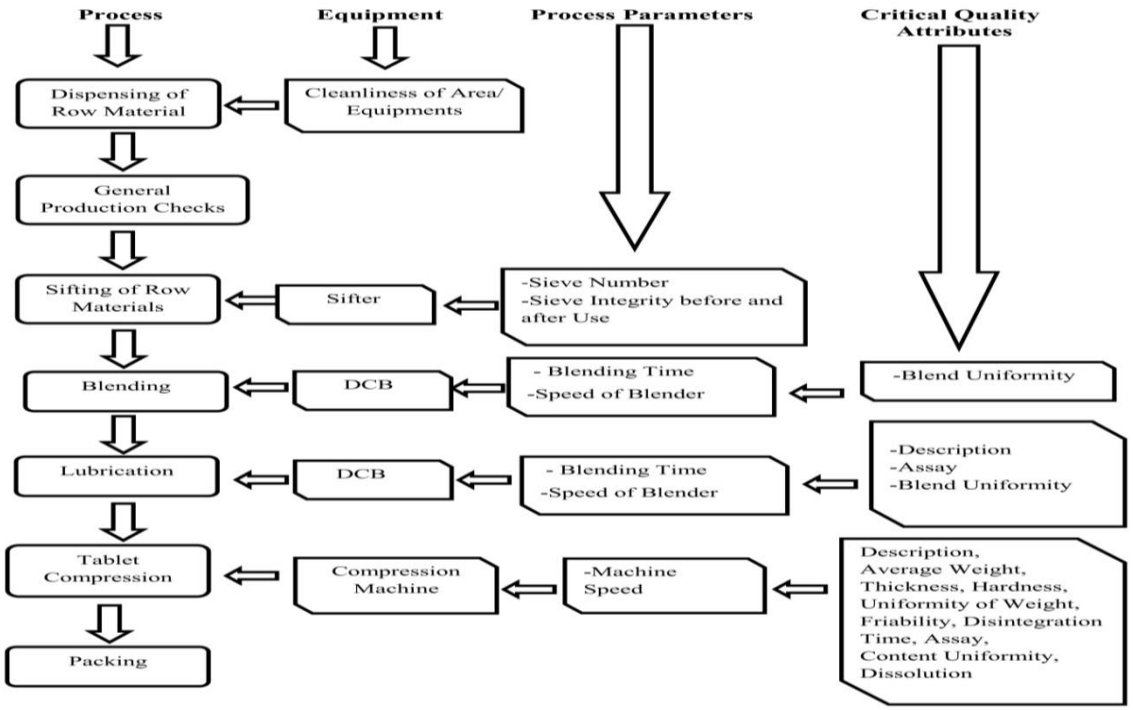


Fig. 1: Manufacturing Process of Bethanechol Chloride Tablet

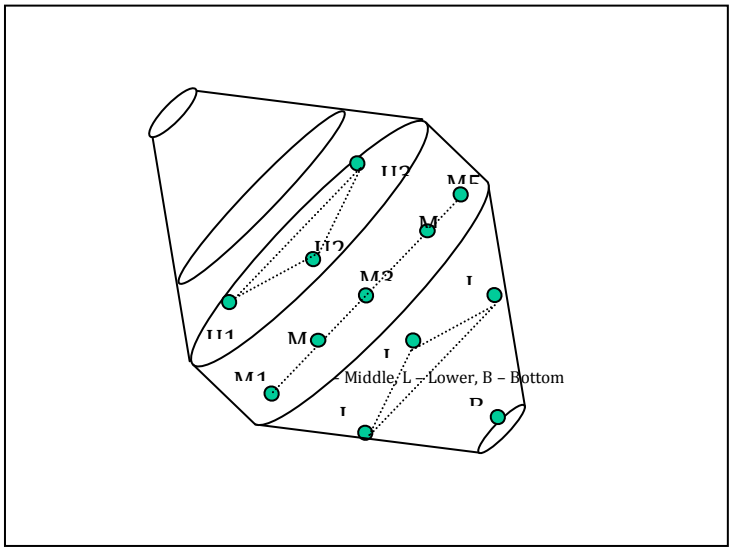


Fig. 2: Sampling Location in Double Cone Blender

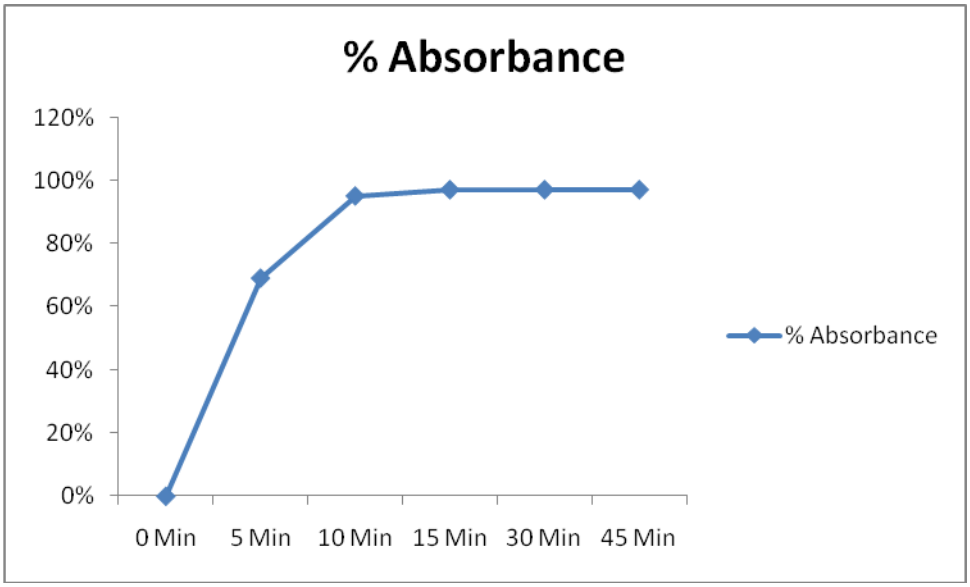


Fig. 3: Dissolution Profile Graph of First Validation Batch

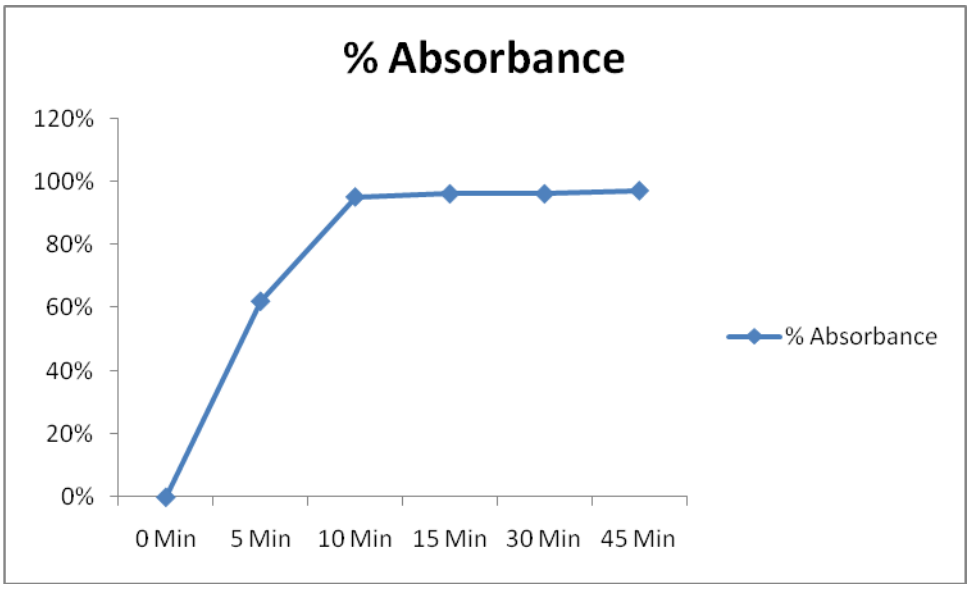


Fig. 4: Dissolution Profile Graph of Second Validation Batch

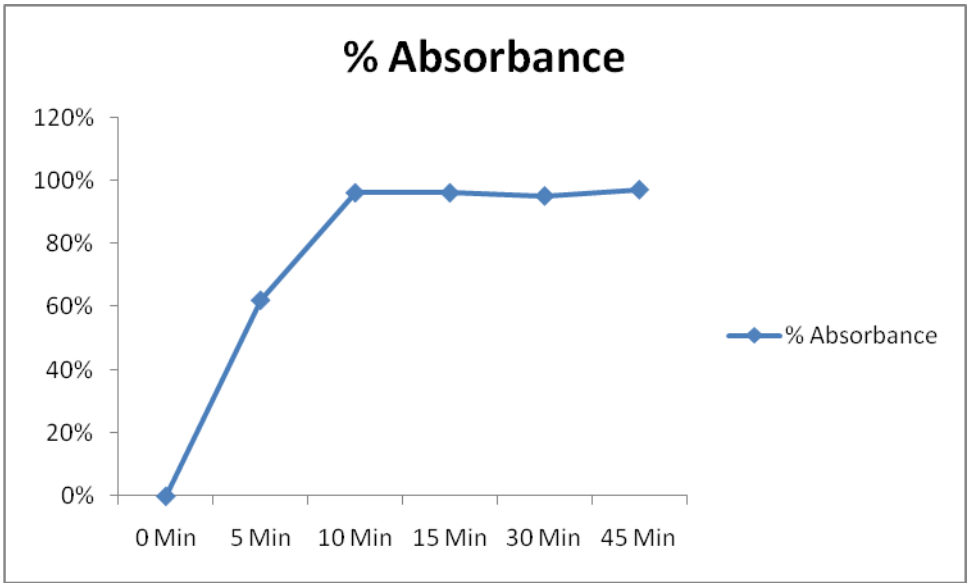


Fig. 5: Dissolution Profile Graph of Third Validation Batch

REFERENCES

1. Manohar A. Potdar. Pharmaceutical Quality Assurance, Nirali Prakashan , Second Edition Dec. 2007:8.1
2. Agalloco J. Validation: an unconventional review and reinvention. PDA Jour of Pharma Sci and Tech. 1995; 49 (4):175-9.
3. Kevis KE. Sterile Products in: Lachman L, Lieberman HA, Kanig JL,(Editors) The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publication House, Mumbai, 1987: 673
4. Food and Drug Administration's Guidance for Industry Process Validation: General Principles and Practices January 2011 Revision I: 8-14
5. Standard Operating Procedure for Process Validation of Wockhardt Limited, L1, Chikalthana, Aurangabad: 15
6. Loftus BT. Regulatory Basis Process Validation, In: Barry IR, Nash RA. Editors, Pharmaceutical Process Validation, Marcel Dekker; 2nd Edition, 1993: 1-7
7. Kour G. Process Validation of Metered Dose Inhaler, Inter. Jour of Res Pharm. 2012;3(3):55-59.
8. Vinod J. Process Validation of Atrovastatine Tablet 1 mg, Indo American Jour of Pharma Res. 2013; 3(12):1438-1450.
9. Sharma A. Process Validation of Solid Dosage Forms, Inter Jour of research in Pharma and Sci. 2013;3(2):12-30 .
10. Bahl A and Bahl BS. A Textbook of Organic Chemistry, Multicolour Edition, S. Chand and Company Ltd., New Delhi: 2006;59-83.
11. The Merck Index, An Encyclopedia of Chemicals, Drugs and Biologicals, Published By Merck Research Laboratories, Devision of Merck and Co., Inc. White House Station NJ. Twelfth Edition: 1232.