

## Optimization and Validation of Process for Formulation and Coating of Ranitidine Hydrochloride Tablets

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### Abstract

Process validation is a requirement of the current Good Manufacturing Practices (cGMP) Regulations for Finished Pharmaceuticals. Validation is defined as a documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance criteria. In this study, formulation and development of coated tablet containing drug Ranitidine which act as a histamine H<sub>2</sub> receptor antagonist. Film coating was done using hydroxypropyl methyl cellulose and ethyl cellulose. Infrared spectroscopy was done to evaluate interaction or incompatibility between drug and excipient. Optimization and validation of process for formulation and coating of Ranitidine hydrochloride tablets was done. The objectives of this study were to determine critical process parameters for tablet compression and coating operation, to establish boundary limits for critical process parameters which influence the product, process quality and performance and to evaluate compressed and coated tablets.

**Keywords:** Process validation; Optimization; Ranitidine; Film coating

### Introduction

Process validation is a requirement of the current Good Manufacturing Practices (cGMP) Regulations for Finished Pharmaceuticals, 21 CFR Parts 210 and 211, and of the Good Manufacturing Practice Regulations for Medical Devices, 21 CFR Part 820, and therefore, is applicable to the manufacture of pharmaceuticals and medical devices [1].

Validation is defined as a documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance criteria [1].

The concept of validation was first proposed by two Food and Drug Administration (FDA) officials, Ted Byers and Bud Loftus, in the mid 1970's in order to improve the quality of pharmaceuticals. The first validation activities were focused on the processes involved in making these products, but quickly spread to associated processes including environmental control, media fill, equipment sanitization and purified water production [2,3]. In a guideline, validation is act of demonstrating and documenting that any procedure, process, and activity will consistently lead to the expected results. It includes the qualification of systems and equipment. The goal of the validation is to ensure that quality is built into the system at every step, and not just tested for at the end, as such validation activities will commonly include training on production material and operating procedures, training of people involved and monitoring of the system whilst in production. In general, an entire process is validated and a particular object within that process is verified. The regulations also set out an expectation that the different parts of the production process are well defined and controlled, such that the results of that production will not substantially change over time.

The basic principles of quality assurance have as their goal the production of articles that are fit for their intended use. These principles may be stated as follows:

1. Quality, safety, and effectiveness must be designed and built into the product;
2. Quality cannot be inspected or tested into the finished product;

Process validation is a key element in assuring that these quality assurance goals are met [2,3].

In this study, formulation and development of coated tablet containing drug Ranitidine which act as a histamine H<sub>2</sub> receptor antagonist. Optimization and validation process for formulation and coating of Ranitidine hydrochloride tablets. The objectives of this study were to determine critical process parameters for tablet compression and coating operation, to establish boundary limits for critical process parameters which influence the product, process quality and performance and to evaluate compressed and coated tablets.

### Material

Ranitidine hydrochloride was obtained from Orchev Pharma Pvt Ltd., Gujarat, India. Hydroxypropylmethylcellulose and Ethyl cellulose were obtained from Colorcon Asia Pvt. Ltd., Goa, India.

### Method

#### Physical properties of drug, polymer and excipients

The drug, polymer and all excipients were studied for bulk density, tapped density, compressibility index and Hausner's ratio [4,5].

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**Received** February 05, 2013; **Published** April 05, 2013

**Citation:** Thakre S, Erande KB, Bhople A, Thakre A, Patil S (2013) Optimization and Validation of Process for Formulation and Coating of Ranitidine Hydrochloride Tablets. 2: 658 doi:[10.4172/scientificreports.658](http://dx.doi.org/10.4172/scientificreports.658)

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**Bulk density: Method:** Bulk density was determined by Weight of powder / Volume of powder before tapping.

**Tapped density: Method:** Tapped density was determined by Weight of powder / Volume of powder after tapping

**Carr's index (Compressibility Index):** The percentage compressibility of granules was calculated according to equation given below.

$$\% \text{ compressibility} = (D_o - D_f) / D_o \times 100 \quad (1)$$

Where  $D_f$  is bulk density and  $D_o$  is Tapped density

**Hausner's Ratio:** The Hausner ratio of a microsphere was calculated according to equation given below,

$$\text{Hausner ratio} = D_o / D_f \quad (2)$$

Where  $D_o$  is Tapped density and  $D_f$  is bulk density.

### FTIR spectroscopy of drug and polymers

Fourier Transfer Infrared spectroscopy (FTIR) was done to evaluate the authentication of drug and polymer. It also used to study determine chemical interaction between drug and polymer.

**Fourier transfer infrared spectroscopy of ranitidine HCl:** The drug and excipients were subjected to Fourier Transform Infra Red (FTIR) studies to check drug- excipients interaction using FTIR.

**Fourier transfer infrared spectroscopy of hydroxypropylmethylcellulose:** The potassium bromide disc containing polymer was prepared to record the spectrum in the range of 4000 to 400  $\text{cm}^{-1}$  by using FTIR spectrophotometer.

**Fourier Transfer Infrared spectroscopy of ethyl cellulose:** The potassium bromide disc containing polymer was prepared to record the spectrum in the range of 4000 to 400  $\text{cm}^{-1}$  by using FTIR spectrophotometer.

**FTIR spectroscopy of physical mixture of drug and polymer:** The drug (Ranitidine HCl), Polymers (HPMC and ethyl cellulose) and the physical mixture of the polymer were characterized by FTIR spectra, using KBR pellets. FTIR used to study determine chemical interaction between drug and polymer.

### Standard calibration curve of Ranitidine HCl in distilled water

**Preparation of standard calibration curve in distilled water:** Accurately weighed 100 mg of the pure drug Ranitidine HCl was dissolved in 100 ml of distilled water in a volumetric flask. It was then shaken for 10 min. 10 ml of the stock solution was pipette out to another 100 ml volumetric flask and diluted with water to 100 ml. This gives the working stock solution of 100  $\mu\text{g}/\text{ml}$ . From this aliquot, samples were made in the concentration range of 2-20  $\mu\text{g}/\text{ml}$ . The absorbance of the solution was measured against distilled water as blank, at 313 nm using UV Spectrophotometer. The graph of absorbance v/s concentration was plotted and data were subjected to linear regression analysis [6,7].

### Assay of Ranitidine hydrochloride

Accurately 10 mg of drug was weighed into a 100 ml volumetric flask, dissolved by swirling with 50 ml of water and then solution was made up to the mark with water. Ten ml of the resulting solution was diluted to 100 ml in another volumetric flask, and the absorbance of the final solution is measured at 313 nm against water.

### Determination of hygroscopicity of Ranitidine hydrochloride by weight gain method

Ranitidine hydrochloride is a hygroscopic drug and its hygroscopicity increases in the presence of light causing problems during processing and handling. Hygroscopicity is also of concern in stability related issues. Most popular method for dealing with such stability related problem of Ranitidine hydrochloride is film coating of tablets with suitable polymers.

About 100 mg of Ranitidine hydrochloride was weighed and subjected to accelerated conditions of temperature and humidity ( $40^\circ\text{C} \pm 1^\circ\text{C}$  and  $75\% \text{RH} \pm 3\%$ ) in humidity chamber in presence and absence of light. Increase in weight was recorded after every 2 hours. The study was continued for as long as the sample gained the moisture and discontinued, once the equilibrium was attained [8].

### Formulation of core tablets

Core tablets were formulated as per formula given in table 1.

**Procedure:** All ingredients in the above formula except magnesium stearate were blended for variable time. This powder blend was then lubricated with magnesium stearate and blended again. Finally, this blend was compressed into tablets. During this process, various process variables were optimized for validation.

**Process flow chart of tablet manufacturing:** Flow chart for tablet manufacturing was as per shown in figure 1.

**Critical process parameters considered for validation:** The critical process parameter considered for validation [9] was represented in table 2.

S No	Ingredient	Quantity (mg/tablet)
1	Ranitidine hydrochloride	300
2	Microcrystalline cellulose (Avicel PH-102)	140.27
3	Pregelatinised starch (Starch 1500)	111.11
4	Fumed silica (Aerosil 200)	2.77
5	Magnesium stearate	1.39
	Total	555.54

**Table 1:** Ingredients used for tablet formulation.

Dry mixing / Blending → Lubrication → Compression → Coating.

**Figure 1:** Process Flow Chart of Tablet Manufacturing.

Process Stage	Sampling Frequency	Controlled Parameter	Tests
Dry mixing/ Blending	At end of mixing	Mixing time, speed	Assay, Bulk density, Tapped density, Angle of repose
Lubrication	At end of Blending	Blending time, speed	Assay, Bulk density, Tapped density, Angle of repose
Compression	Start, middle, End	Machine speed, compression force	Appearance, Thickness, Hardness, Friability, Disintegration time, Dissolution, Assay
Coating	At end of coating	Pan rpm, spray rate, pump rpm, spray pattern, nozzle to bed distance, air temperature	Appearance, Thickness, Hardness, Friability, Disintegration time, Dissolution, Assay

**Table 2:** Critical process parameters for process validation of tablets.

**Equipment and process involved during validation:** The equipments and process involved during validation was given in table 3.

#### Dry mixing/ Blending:

1. Samples were drawn from different positions of double cone blender as shown in figure 2.
2. Each sample was collected in butter paper at different intervals from top, middle and bottom.
3. Sample size should be 1 to 3 times of the unit weight.
4. The samples were collected and subjected to analysis for assay, bulk density, tapped density, angle of repose, etc.
5. Acceptance criteria were uniform distribution of drug and other contents.

#### Lubrication/ Blending:

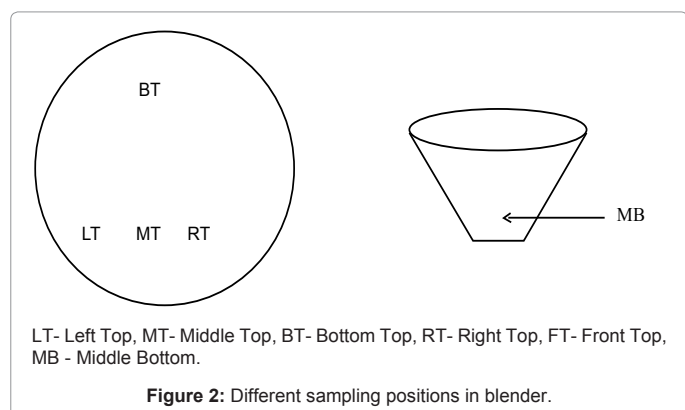
1. Lubricant (magnesium stearate) was added to initial powder blend, till the free flowing powder was produced.
2. Samples were collected from different positions of blender as shown in figure 2.
3. Each sample was collected in butter paper at different interval of time.
4. The samples were subjected for further tests i.e. tapped and bulk density, angle of repose, assay.
5. Acceptance criterion was free flowing powder blend.

#### Compression:

1. The tablets were compressed by varying compression speed and force.
  2. Following tests were performed and the process variables were optimized.
  3. The three optimized batches of tablets were produced and samples were collected at start, middle and bottom of each batch.
- Compressed taste parameters were shown in table 4.

S No	Equipment	Process Involved
1	Double cone bender	Dry mixing/ Blending, Lubrication
2	Compression machine (16 station, C type)	Compression
3	R & D coater	Coating

**Table 3:** Equipment and process involved during validation.



**Figure 2:** Different sampling positions in blender.

S No	Test	Number of tablets	Limit
1	Average weight (gm)	20	NLT 0.528 and NMT 0.584
2	Hardness	6	8- 12 kg/cm <sup>3</sup>
3	Friability	20	NMT 1.0%
4	Disintegration time	6	NMT 60 mins
5	Thickness (mm)	6	2.90-4.1
6	Diameter (mm)	6	11.9-12.1
7	Assay	6	NLT 90% and NMT 110%
8	Dissolution	6	NLT 80%

**Table 4:** Compressed tablet test parameters.

#### Coating:

1. Tablets were first coated by varying different process variables of coating and samples were collected and subjected to analysis.
2. The three optimized batches of coating were produced.
3. Tablets were collected at end of coating process and checked for surface defect, friability, disintegration, dissolution and assay.

#### Critical steps validation:

**Dry mixing:** The fixed parameters of dry mixing process during critical step validation were given below,

- Batch size - 250.00 gm
- Batches taken for study - A, B, C
- Variable considered for study - Mixing time
- Acceptance criteria - Mixing end point by assay, bulk density, tapped density

**Lubrication:** The fixed parameters of lubrication process during critical step validation were given below,

- Batch size - 250.00 gm
- Batches taken for study - A, B, C
- Variable considered for study - Blending time
- Measure response - Assay, Tapped density, Bulk density, Angle of repose.
- Acceptance criteria - Free flowing powder blend with no lumps.

**Compression:** The fixed parameters of compression process during critical step validation were given below,

- Type of machine - 16 station single rotary compression machine
- Variables considered for study - Compression force and Machine speed.

**Compression force and machine speed study:** The objective was to study effect of compression force and machine speed on tablet hardness and other physical parameters. Tablets were compressed at 3.5, 4 and 5 tones force and machine speed of 25 and 30 rpm.

**Normal production:** The fixed parameters of normal production process during critical step validation were given below,

- Batch size - 250.00 gm
- Batches taken for study - A, B, C
- Sampling - Initial, Middle, End
- Measure response - Tablet physical parameters, Assay

## Tablet coating

**Film coating:** The film coating was done with hydroxypropylmethylcellulose and ethyl cellulose using solvent Isopropyl alcohol and dichloromethane [10]. The formulation of coating solution was given in table 5.

**Coating parameters study:** Different coating parameters were analyzed to get good coated tablets. The fixed parameters of coating process during critical step validation were given below [11],

Batch size	- 50 tablets
Pan size	- 8"
Baffles	- 3
Spray nozzle	- 1 mm
Spray gun	- 1
Atomization pressure	- 1.2 kg/cm <sup>2</sup>
Spraying	- Continuous
Tablet bed temperature	- 33°C ± 2°C
Pre-warming	- 10 to 15 mins at slow rpm
Post drying	- 10 to 15 mins at slow rpm
Sampling	- At end of coating
Measure response	- Tablet physical parameters, disintegration time, dissolution and assay.

The various variable of coating parameter study for three batches given in table 6.

**Normal film coating Operation:** The fixed parameters of normal film coating process during critical step validation were given below (10),

Batch size	- 50 tablets
Batches taken for study	- A, B, C.

Other parameters were same as that applied to coating parameters study in batch II.

## Determination of hygroscopicity of film coated Ranitidine hydrochloride tablets by weight gain method

The film coated Ranitidine hydrochloride tablet was placed in beaker and subjected to accelerated conditions of temperature and humidity (40°C ± 1°C and 75%RH ± 3%) in humidity chamber in presence and absence of light. Increase in weight was recorded after every 10 days for 3 months [11].

## Stability study

The stability study of film coated tablets was carried at accelerated condition of 40°C ± 2°C temperatures and 75% ± 5% relative humidity for a period of three months [12,13].

**Method:** The twenty tablets from each batch were collected placed in crucible and kept at above specified condition in the stability chamber for a period of three months. After each month tablet sample was analyzed for the physical parameters such as physical appearance, thickness, hardness and *in vitro* drug release.

## Result and Discussion

### Physical properties of drug, polymer and excipients

The drug, polymer and all excipients were studied for bulk density,

S No	Ingredient	Quantity
1	Hydroxypropylmethylcellulose	1.2 kg
2	Ethyl cellulose (7cps)	0.3 kg
3	PEG 6000 (Starch 1500)	0.04 kg
4	Propylene glycol	0.02 kg
5	Sodium lauryl sulphate	0.01 kg
6	Titanium dioxide	0.25 kg
7	Color	0.20 kg
8	Isopropyl alcohol	18 lit.
9	Methylene chloride	30 lit.

**Table 5:** Formulation of film coating solution.

S No	Variable	Batch		
		I	II	III
1	Pan speed (rpm)	30	25	20
2	Air temperature	50°C	45°C	35°C
3	Spray rate	2.8 ml/min	2.4 ml/min	2.1 ml/min
4	Spray pattern	Narrow	Normal	Broad
5	Nozzle to bed distance (cm)	6.5	6	5.5
6	Pump speed (rpm)	3 – 4	2 – 3	1 – 2

**Table 6:** Coating parameters study.

Ingredients		Parameters		
Ratio*	Bulk Density* (g/cm <sup>3</sup> )	Tapped density*	% Compressibility*	Hausner
Ranitidine HCl	0.406 ± 0.04	0.623 ± 0.033	34.83 ± 0.39	1.03 ± 0.41
Microcrystalline	0.360 ± 0.001	0.451 ± 0.002	20.18 ± 0.17	0.81 ± 0.33
Pregelatinised	0.577 ± 0.018	0.876 ± 0.07	34.13 ± 0.019	1.45 ± 0.39
Fumed silica	0.037 ± 0.008	0.066 ± 0.013	43.94 ± 0.055	0.10 ± 0.11
Magnesium	0.159 ± 0.01	0.286 ± 0.02	44.41 ± 0.33	0.45 ± 0.025
Hydroxy	0.343 ± 0.02	0.554 ± 0.035	38.09 ± 0.021	0.90 ± 0.31
Ethyl cellulose	0.412 ± 0.07	0.589 ± 0.02	30.05 ± 0.20	1.00 ± 0.24

\*Represents mean ± S.D., (n=3)

**Table 7:** Physical properties of polymers, drug and additives.

tapped density, compressibility index and Hausner's ratio. All values of above studies found were in standard limits. Results of above studied represent in table 7.

## FTIR spectroscopy of drug and polymers

**Fourier transfer infrared spectroscopy of Ranitidine HCl:** FTIR study of the drug was done to check authenticity of drug. In this FTIR spectra of Ranitidine HCl (Figure 3) was established and compare with official standards, it was found that the spectra and value of sample Ranitidine HCl (Table 8) was match with official standards.

**Fourier transfer infrared spectroscopy of hydroxypropylmethyl cellulose:** FTIR study of the drug was done to check authenticity of excipients. In this FTIR spectra of hydroxypropylmethylcellulose (Figure 4) was established and compare with official standards, it was found that the spectra and value of sample hydroxypropylmethylcellulose (Table 9) was match with official standards.

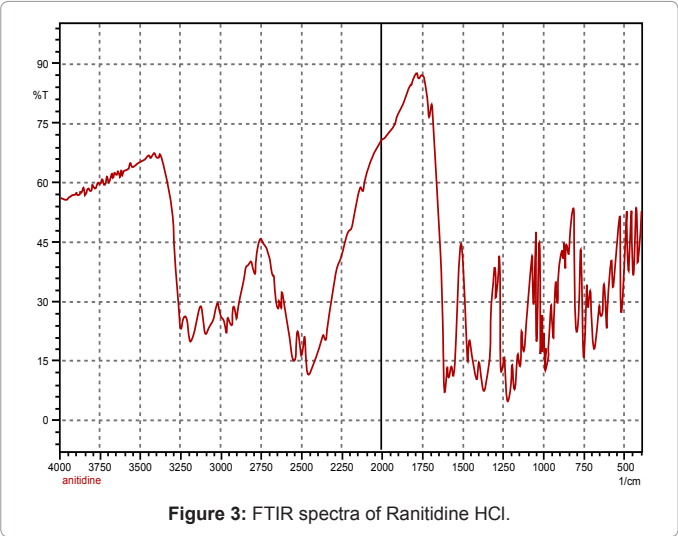
**Fourier transfer infrared spectroscopy of ethyl cellulose:** The peaks (Figure 5) and values of frequencies of sample ethyl cellulose (Table 10) found was match with official standards. So it conclude that sample of ethyl cellulose was authentic one.



**FTIR spectroscopy of physical mixture of drug and polymer:**  
The drug (Ranitidine HCl), Polymers (HPMC and ethyl cellulose) and physical mixture of drug+Polymer were characterized by FTIR spectra, using KBR pellets. This study was done to evaluate any chemical interaction or incompatibility between drugs and excipients. There was no change occur in peak pattern of FTIR spectra of pure drug, pure excipients and physical mixture of drug and polymer (Figure 6). Hence there was no interaction or incompatibility between drug and polymer.

**Standard calibration curve of Ranitidine HCl in distilled water**

The standard calibration curve of drug in distilled water is depicted in figure 7 and the data is shown in table 11. The concentration of drug on X axis plot against absorption on Y axis, a linear line was developed.



Frequency (cm <sup>-1</sup> )	Assignment
1620.09	-C=N stretching vibration
2636.51 & 2557.43	-N <sup>+</sup> H bond in tertiary amino group
2995.25	-CH <sub>3</sub> group

Table 8: Interpretation of FTIR spectra of Ranitidine HCl.

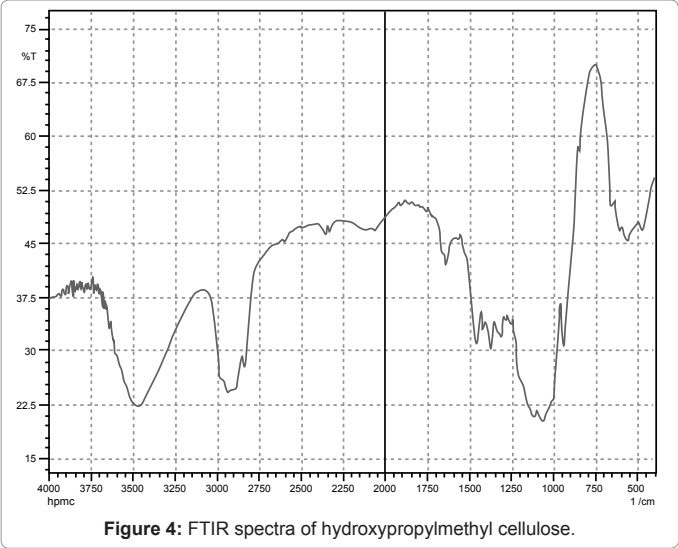


Figure 4: FTIR spectra of hydroxypropylmethyl cellulose.

Frequency (cm <sup>-1</sup> )	Assignment
3444.63	-OH stretching vibration for free OH group
1120.56	-OH deformation (primary alcohol)
2935.46 & 2835.16	Aliphatic -CH stretching vibration

Table 9: Interpretation of FTIR spectra of hydroxypropylmethyl cellulose.

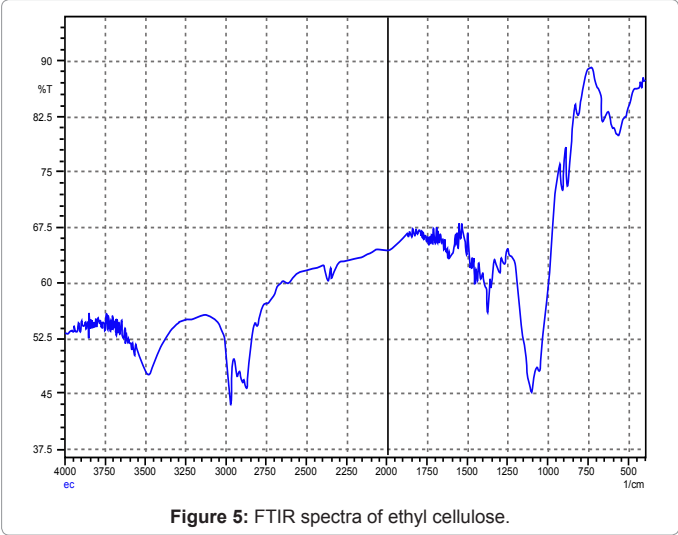


Figure 5: FTIR spectra of ethyl cellulose.

Frequency (cm <sup>-1</sup> )	Assignment
3475.49	OH stretching vibration
1056.92	-C-O stretching vibration
1110.92	-O-C <sub>2</sub> H <sub>5</sub> group

Table 10: Interpretation of FTIR spectra of ethyl cellulose.

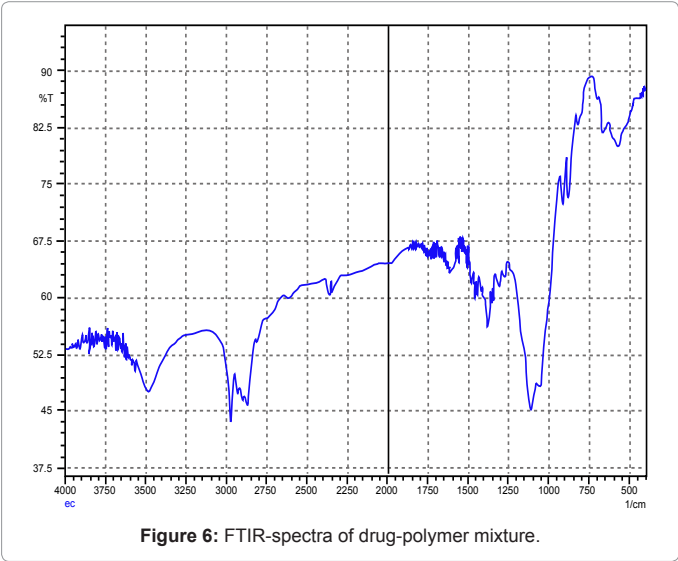


Figure 6: FTIR-spectra of drug-polymer mixture.

The linear line indicates that Ranitidine HCl follows Beer's Lamberts law hence drug sample is authentic one.

**Assay of Ranitidine hydrochloride**

The drug was found to be 99.17% w/w pure.

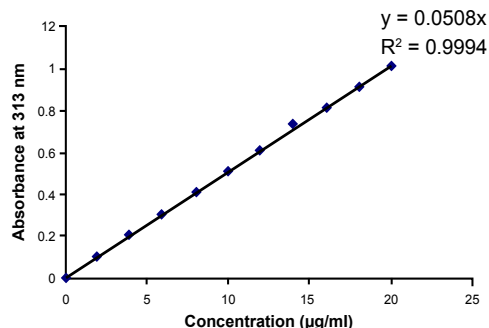
## Determination of hygroscopicity of Ranitidine hydrochloride by weight gain method

Results of hygroscopicity of Ranitidine hydrochloride were illustrated in table 12 and figure 8.

### Critical steps validation

**Dry mixing:** For all the batches, the speed of Double cone blender was kept at 25 rpm and samples were drawn at time interval of 5, 10, 15 and 20 minutes till the uniform distribution of all content was achieved. Samples were drawn from position as shown in figure 1.

The samples collected after 15 min. showed uniform distribution of drug which was confirmed by assay of drug in accordance with very low standard deviation in all three batches and samples collected after 20



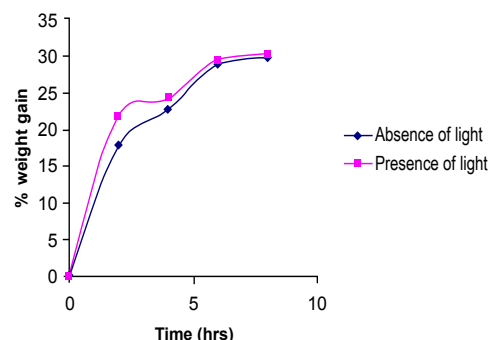
**Figure 7:** Standard calibration curve of Ranitidine hydrochloride in distilled water at 313 nm.

Concentration µg/ml	Absorbance at 313 nm
0	0
2	0.105 ± 0.021
4	0.207 ± 0.004
6	0.306 ± 0.001
8	0.408 ± 0.041
10	0.504 ± 0.023
12	0.604 ± 0.004
14	0.734 ± 0.009
16	0.807 ± 0.019
18	0.912 ± 0.011
20	1.011 ± 0.025

**Table 11:** Data of standard calibration curve of Ranitidine hydrochloride in water at 313 nm.

Time (hrs.)	% Weight gain	
	Absence of light	Presence of light
0	0	0
2	17.8	21.9
4	22.7	24.3
6	28.9	29.4
8	29.7	30.1

**Table 12:** Moisture gain behavior of Ranitidine hydrochloride in absence and presence of light.



**Figure 8:** Moisture gain behavior of Ranitidine hydrochloride in absence and presence of light.

Location	Batch- A (%)			
	05 min.	10 min.	15 min.	20 min.
BT	87.54	97.12	101.91	101.95
LT	99.17	101.9	98.79	99.74
RT	94.71	95.11	100.17	100.35
MT	97.8	98.34	101.09	101.35
FT	102.1	99.12	99.69	98.78
MB	107.38	102.7	100.97	100.55
S.D.	6.72	2.87	1.11	1.12

**Table 13:** Assay of samples drawn from different position for batch A.

Location	Batch- B (%)			
	05 min.	10 min.	15 min.	20 min.
BT	88.01	93.71	100.94	101.02
LT	94.51	102.17	99.01	99.15
RT	102.17	96.97	99.91	100.58
MT	98.97	99.14	101.09	101.21
FT	105.08	101.99	101.97	102.15
MB	107.22	98.97	98.51	98.65
S.D.	7.14	3.19	1.33	1.32

**Table 14:** Assay of samples drawn from different position for batch B.

Location	Batch- C (%)			
	05 min.	10 min.	15 min.	20 min.
BT	89.97	98.91	99.71	99.55
LT	94.91	96.07	98.97	99.15
RT	98.57	101.57	101.91	101.36
MT	102.91	97.01	100.07	98.91
FT	109.15	99.71	101.97	102.1
MB	97.91	102.38	99.02	99.1
S.D.	6.6	2.48	1.36	1.35

**Table 15:** Assay of samples drawn from different position for batch C.

min. showed almost same standard deviation as that of 15 min (Tables 13-15). So, it was observed that uniform blend was formed at mixing time of 15 minutes with blender speed of 25 rpm in all three batches; hence mixing process concluded as validated (Tables 13-15). Physical parameters like bulk density, tapped density and angle of repose was done. Observations are noted in table 16.

**Lubrication:** The lubrication process was carried out with required quantity of lubricant at speed of 25 rpm for 5, 10 and 15 min.

The samples collected after 10 min. showed uniform distribution of drug which was confirmed by assay of drug in accordance with very

S No	Parameter	Batch No.		
		A	B	C
1	Bulk density* ( g/cm <sup>3</sup> )	0.798 ± 0.04	0.821 ± 0.037	0.819 ± 0.039
2	Tapped density* ( g/cm <sup>3</sup> )	0.897 ± 0.037	0.917 ± 0.034	0.914 ± 0.042
3	Angle of repose*	28.19 ± 0.17	29.09 ± 0.07	27.04 ± 0.21

\*Represents mean ± S.D., (n=3)

**Table 16:** Physical parameters study of batches A, B, C.

low standard deviation in all three batches and samples collected after 15 min, showed almost same standard deviation as that of 10 minutes (Table 17). So, it was observed that uniform lubricated blend was formed at lubrication time of 10 min with blender speed of 25 rpm in all three batches; hence lubrication process concluded as validated (Table 17). Physical parameters like bulk density, tapped density and angle of repose was done. Observations are noted in table 18.

**Compression:** Observations of effect of compression force and machine speed on tablet are shown in table 19.

**Normal production:** Observation of compressed tablets evaluation of normal production batch A, B and batch C are shown in tables 20-22 respectively. Sixteen station single rotary compression machine with compression force of 4 tones and machine speed of 30 rpm produced tablets with required specification; hence compression process was concluded as validated.

## Tablet coating

**Film coating:** Formulation of coating solution given in table 23. From above coated batches the batch II showed good tablets with no surface defects and evaluation of batches I, II, III is shown in tables 24 and 25 respectively.

**Normal film coating Operation:** The coating of core tablets was done by applying process parameters considered for batch II. The tablets in pan were pre-heated with hot air and spray gun was started, when tablet bed temperature reaches to 33°C ± 2°C. Coated tablets were evaluated for physical parameters, disintegration time, dissolution time and assay. Observations are shown in table 26. The tablets produced in all three batches meet required specifications; hence tablet coating process was concluded as validated.

## Determination of hygroscopicity of film coated Ranitidine hydrochloride tablets by weight gain method

The result of Determination of hygroscopicity of film coated Ranitidine hydrochloride tablets by weight gain method study was shown in table 27 and figure 9.

## Stability study

The stability study of film coated tablets was carried at accelerated condition of 40°C ± 2°C temperatures and 75% ± 5% relative humidity for a period of three months. The results of stability studies after each

Location	Assay (%)								
	A (min.)			B (min.)			C (min.)		
	5	10	15	5	10	15	5	10	15
BT	102.02	98.64	98.71	99.76	99.25	99.14	98.17	100.02	100.35
LT	98.99	99.35	100.24	97.91	98.19	98.65	99.02	99.97	99.91
RT	99.76	100.41	99.27	101.91	99.77	100.26	102.11	101.91	101.44
MT	101.97	101.59	101.35	98.01	100.91	100.88	100.02	100.71	100.05
FT	100.01	100.69	100.71	100.15	100.62	101.08	99.72	99.09	98.7
MB	97.69	99.45	98.91	97.06	99.91	99.55	98.91	98.99	98.7
S.D.	1.69	1.07	1.06	1.8	0.98	0.97	1.37	1.09	1.07

**Table 17:** Assay of samples drawn from different positions of blender.

S No	Parameter	Batch No.		
		A	B	C
1	Bulk density* ( g/cm <sup>3</sup> )	0.617 ± 0.041	0.659 ± 0.034	0.709 ± 0.037
2	Tapped density* ( g/cm <sup>3</sup> )	0.791 ± 0.029	0.807 ± 0.037	0.835 ± 0.035
3	Angle of repose*	26.45 ± 0.21	28.01 ± 0.20	25.94 ± 0.49

\*Represents mean ± S.D., (n=3)

**Table 18:** Physical parameters study of lubricated blend of batches A, B, C.

S No	Parameters	Force (Tones)	3.5		4		5	
		Speed	25 rpm	30 rpm	25 rpm	30 rpm	25 rpm	30 rpm
1	Hardness (kg/cm <sup>2</sup> )		5.91	6.17	7.32	8.14	10.14	11.42
2	Thickness (mm)		5.17	4.1	4.41	4.01	3.99	3.71
3	Friability (%)		0.95	0.69	0.14	0.1	0.13	0.08
4	Disintegration time (min.)		4.2	5.05	6.2	8.45	14.05	15.2
5	Dissolution (%)		91.72	90.79	90.14	97.11	71.72	79.97

**Table 19:** Effect of compression force and machine speed on tablets.

S No	Physical Parameter	Limit	Batch A		
			Initial	Middle	End
1	Appearance	Plane tablet with no surface defects	Complies	Complies	Complies
2	Weight of 20 tablets	NLT 10.564 g and NMT 11.676 g	10.792	10.697	10.817
3	Average weight	NLT 0.528 g and NMT 0.584 g	0.54	0.535	0.541
4	Thickness	2.90 mm to 4.10mm	3.99	3.79	3.87
5	Diameter	11.90 mm to 12.10 mm	11.97	12.08	11.99
6	Hardness	8 to 12 kg/cm <sup>2</sup>	8.74	8.91	9.1
7	Friability	NMT 1.0%	0.13	0.11	0.09
8	Disintegration Time	NMT 60 mins	9 min 12 Sec	9 min 45 Sec	10 min 45 Sec
9	Assay	NLT 90% and NMT 110%	97.99	98.41	98.07
10	Dissolution Test	NLT 80%	91.62	90.99	91.09

**Table 20:** Compressed tablets evaluation of normal production batch A.

S No	Physical Parameter	Limit	Batch B		
			Initial	Middle	End
1	Appearance	Plane tablet with no surface defects	Complies	Complies	Complies
2	Weight of 20 tablets	NLT 10.564 g and NMT 11.676 g	10.599	10.697	10.717
3	Average weight	NLT 0.528 g and NMT 0.584 g	0.528	0.535	0.536
4	Thickness	2.90 mm to 4.10 mm	4.01	3.89	4.09
5	Diameter	11.90 mm to 12.10 mm	0.18	12.01	11.99
6	Hardness	8 to 12 kg/cm <sup>2</sup>	8.87	8.91	9.17
7	Friability	NMT 1.0%	0.18	12.01	11.99
8	Disintegration Time	NMT 60 mins	8 min 40 Sec	8 min 55 Sec	9 min 10 Sec
9	Assay	NLT 90% and NMT 110%	96.91	98.76	97.02
10	Dissolution Test	NLT 80%	89.71	90.19	91.07

**Table 21:** Compressed tablets evaluation of normal production batch B.

S No	Physical Parameter	Limit	Batch C		
			Initial	Middle	End
1	Appearance	Plane tablet with no surface defects	Complies	Complies	Complies
2	Weight of 20 tablets	NLT 10.564 g and NMT 11.676 g	10.694	10.797	10.591
3	Average weight	NLT 0.528 g and NMT 0.584 g	0.535	0.534	0.530
4	Thickness	2.90 mm to 4.10 mm	3.87	3.99	3.89
5	Diameter	11.90 mm to 12.10 mm	11.98	11.92	12.09
6	Hardness	8 to 12 kg/cm <sup>2</sup>	8.99	9.41	9.17
7	Friability	NMT 1.0%	0.14	0.11	0.15
8	Disintegration Time	NMT 60 mins	9 min 5 Sec	9 min 55 Sec	9 min 15 Sec
9	Assay	NLT 90% and NMT 110%	100.91	98.96	99.02
10	Dissolution Test	NLT 80%	91.71	91.49	92.01

**Table 22:** Compressed tablets evaluation of normal production batch C.

month were collected and was analyzed statistically and found no statistical significant differences in any of the parameter after 1, 2, 3 months when compared to control zero month. Observations are shown in table 28.

## Conclusion

The present investigation was carried out to check the application

or utility of the different reported critical process parameters of tablet compression and coating in producing uniformity in the production batches. Three batches i.e. A, B, C was considered as a representative for production batches. The process parameters chosen for validation programme were blending process parameters, lubrication process parameters, compression process parameters and coating process parameters. The parameters chosen for validation programme were



S No	Ingredient	Quantity
1	Hydroxypropylmethylcellulose	1.2 kg
2	Ethyl cellulose (7cps)	0.3 kg
3	PEG 6000 (Starch 1500)	0.04 kg
4	Propylene glycol	0.02 kg
5	Sodium lauryl sulphate	0.01 kg
6	Titanium dioxide	0.25 kg
7	Color	0.20 kg
8	Isopropyl alcohol	18 lit.
9	Methylene chloride	30 lit.

Table 23: Preparation of film coating solution.

S No	Variable	Batch		
		I	II	III
1	Pan speed (rpm)	30	25	20
2	Air temperature	50°C	45°C	35°C
3	Spray rate	2.8 ml/min	2.4 ml/min	2.1 ml/min
4	Spray pattern	Narrow	Normal	Broad
5	Nozzle to bed distance (cm)	6.5	6	5.5
6	Pump speed (rpm)	3 – 4	2 – 3	1 – 2

Table 24: Coating parameters study.

S No	Physical Parameter	Limit	Batch		
			I	II	III
1	Appearance	Plane tablet with no surface defects	11.1	11.68	11.4
2	Weight of 20 tablets	NLT 10.564 g and NMT 11.676g	0.555	0.584	0.57
3	Average weight	NLT 0.528 g and NMT 0.584 g	4.09	3.99	4.05
4	Thickness	2.90 mm to 4.10mm	12.04	11.99	12.08
5	Diameter	11.90 mm to 12.10 mm	9.97	9.41	9.17
6	Hardness	8 to 12 kg/cm <sup>2</sup>	0	0	0
7	Friability	NMT 1.0%	12 min. 45 sec.	11 min. 15sec.	10 min. 55 sec.
8	Disintegration Time	NMT 60 mins	90.71	91.49	92.01
9	Assay	NLT 90% and NMT 110%	79.71	91.49	82.01
10	Dissolution Test	NLT 80%	11.1	11.68	11.4

Table 25: Evaluation of coated tablets of batches I, II, III.

S No	Physical Parameter	Limit	Batch		
			A	B	C
1	Appearance	Plane tablet with no surface defects	Complies	Complies	Complies
2	Weight of 20 tablets	NLT 10.564 g and NMT 11.676g	11.1	11.68	11.4
3	Average weight	NLT 0.528 g and NMT 0.584 g	0.555	0.584	0.57
4	Thickness	2.90 mm to 4.10 mm	4.09	3.99	4.05
5	Diameter	11.90 mm to 12.10 mm	12.04	11.99	12.08
6	Hardness	8 to 12 kg/cm <sup>2</sup>	9.97	9.41	9.17
7	Friability	NMT 1.0%	0	0	0
8	Disintegration Time	NMT 60 mins	12 min. 45 sec.	11 min. 15sec.	10 min. 55 sec.
9	Assay	NLT 90% and NMT 110%	99.91	98.96	99.02
10	Dissolution Test	NLT 80%	90.71	91.49	92.01

Table 26: Evaluation of coated tablets of batch A, B, C.

relevant indicators of a controlled process and shown in table 1. Figure 6 shows the process flow chart for tablet process. The critical process

Time (Days)	% Weight gain	
	Absence of light	Presence of light
0	0	0
10	0.025	0.045
20	0.031	0.052
30	0.04	0.0534
40	0.044	0.0567
50	0.054	0.062
60	0.056	0.0639
70	0.057	0.0641
80	0.058	0.0645
90	0.058	0.0645

Table 27: Moisture gain behavior of film coated Ranitidine hydrochloride tablets in absence and presence of light.

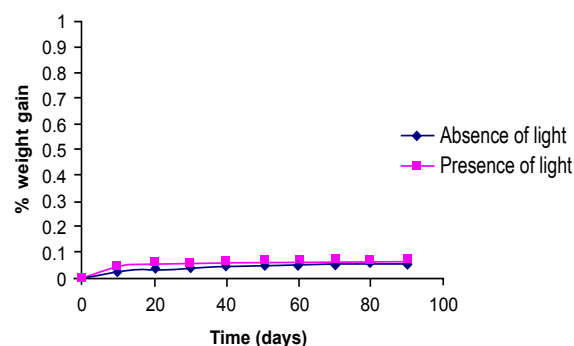


Figure 9: Moisture gain behavior of film coated Ranitidine hydrochloride tablets in absence and presence of light.

S No	Parameter	40°C ± 2°C and 75% ± 5% RH			
		Zero month	One month	Two month	Three month
1	Physical appearance	colored tablets with no surface defect	No Change	No Change	No Change
2	Thickness* (mm)	3.99 ± 0.14	3.99 ± 0.15	3.99 ± 0.19	3.99 ± 0.21
3	Diameter* (mm)	12.06 ± 0.20	12.06 ± 0.11	12.06 ± 0.19	12.06 ± 0.21
4	Drug content* (% w/w)	99.69 ± 0.45	99.58 ± 0.78	99.07 ± 0.82	98.91 ± 0.91

\* Represents mean ± S.D., (n = 3)

Table 28: Stability study of film coated tablets.

parameters were analyzed to establish limits to these attributes which will lead to uniformity in dosage form.

From the study it can be concluded that the critical process parameters considered for study were relevant indicators of a controlled process. List of processes and testing criteria ensured that by scientific means, the product can be manufactured in a manner to ensure uniformity within a lot, consistency between lots within defined limits. The critical process parameters were analyzed to establish limits to these attributes which led to uniformity in dosage form. So these numerical ranges can be used for routine production of Ranitidine hydrochloride tablets to get constantly a good product with all required characteristics and uniformity in final dosage form from batches to batches. The process validation done in this study also helps in creating necessary documentation to support a stepwise evaluation of a pharmaceutical process.

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