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OPTIMIZATION AND VALIDATION OF PROCESS FOR FORMULATION AND COATING OF RANITIDINE HYDROCHLORIDE TABLET

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ABSTRACT

Process validation is a requirement of the current Good Manufacturing Practices (cGMP) Regulations for Finished Pharmaceuticals. The FDA defines process validation as the establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristic. In this study, formulation and development of coated tablet containing drug Ranitidine which act as a histamine H_2 receptor antagonist. Film coating was done using hydroxypropylmethylcellulose 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.

Key words: Process validation; Optimization; Ranitidine; film coating

1. 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].

The FDA defines process validation as the establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristic [1].

Assurance of product quality is derived from careful attention to a number of factors including selection of quality parts and materials, adequate product and process design, control of the process, and in process and end-product testing. Due to the complexity of today's medical products, routine end-product testing alone often is not sufficient to assure product quality for several reasons. Some end-product tests have limited sensitivity. In some cases, destructive testing would be required to show that the manufacturing process was adequate, and in other situations end-product testing does not reveal all variations that may occur in the product that may impact on safety and effectiveness [2].

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;

(3) Each step of the manufacturing process must be controlled to maximize the probability that the finished product meets all quality and design specifications.

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

In this study, formulation and development of coated tablet containing drug Ranitidine which act as a histamine H_2 receptor antagonist. Optimization and validation of 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.

2. MATERIAL

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

3. METHOD

3.1 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 [3, 4].

a. Bulk Density

Method

The powder sample under tests was screened through sieve no. 18 and the sample equivalent to 25 g was accurately weighed and filled in 100 ml graduated cylinder and the powder was leveled and the unsettled volume, (V_o) was noted. The bulk density was calculated in g/cm^3 by the formula,

$$Bulk\ density\ (\rho o) = M / V o \qquad (1)$$

Where M is Mass of powder taken and V_o is Apparent unstirred volume.

b. Tapped Density

Method

The powder sample under test was screened through sieve no. 18 and the weight of sample equivalent to 25 g was filled in 100 ml graduated cylinder. The mechanical tapping of the cylinder was carried out using tapped density tester at a nominal rate of 300 drops per minute for 500 times initially and the tapped volume V_o was noted. Tapping was preceded further for an additional tapping 750 times and tapped volume V_b was noted. The difference between two volumes was less than 2%, so V_b was considered as a tapped volume V_f.

The tapped density was calculated in g/cm^3 by the formula,

$$Tapped\ density\ (\rho t) = M / V f \qquad (2)$$

Where M is weight of sample powder and V_f is tapped volume

c. Carr's Index (Compressibility Index)

The bulk density and tapped density were measured and Compressibility index was calculated using the formula,

$$Carr's\ Index = \rho t - \rho o / \rho t\ X\ 100 \quad (3)$$

Where ρt is tapped density and ρo is bulk density.

d. Hausner's Ratio

Tapped density and bulk density were measured and Hausner's Ratio was calculated by using the formula,

$$Hausner's\ Ratio = \rho t / \rho o \quad (4)$$

Where ρt is tapped density and ρo is bulk density

3.2 FTIR spectroscopy of drug and polymers

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

a. Fourier Transfer Infrared spectroscopy of Ranitidine HCl

The potassium bromide disc containing drug was prepared to record the spectrum in the range of 4000 to 400 cm^{-1} by using FTIR spectrophotometer.

b. 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 cm^{-1} by using FTIR spectrophotometer.

c. 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 cm^{-1} by using FTIR spectrophotometer.

d. 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.

3.2 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 µg/ml. From this aliquot, samples were made in the concentration range of 2-20 µg/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 [5, 6].

3.3 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.

3.4 Determination of hygroscopicity of Ranitidine hydrochloride by weight gain method

Ranitidine hydrochloride is a hygroscopic drug and its hygroscpicity 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 (40º C ± 1º C and 75% RH ± 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 [7].

3.5 Formulation of Core Tablets

Core tablets were formulated as per formula given in table no.1.

Table No. 1 Ingredients used for tablet formulation

Sr. 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

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.

3.5.1. Process Flow Chart of Tablet Manufacturing

Flow chart for tablet manufacturing was as per shown in Fig. 1.

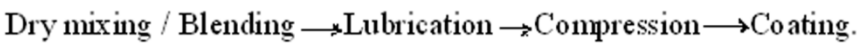


Figure no. 1 Process Flow Chart of Tablet Manufacturing

3.5.2. Critical Process Parameters Considered for Validation

The critical process parameter considered for validation [8] was represented in table no.2.

Table No. 2 Critical process parameters for process validation of tablets

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, Thicknesses, Friability, Weight variation, Disintegration time, Dissolution, Assay

3.5.3. Equipment and process involved during validation

The equipments and process involved during validation was given in table no. 3.

Table No. 3 Equipment and process involved during validation

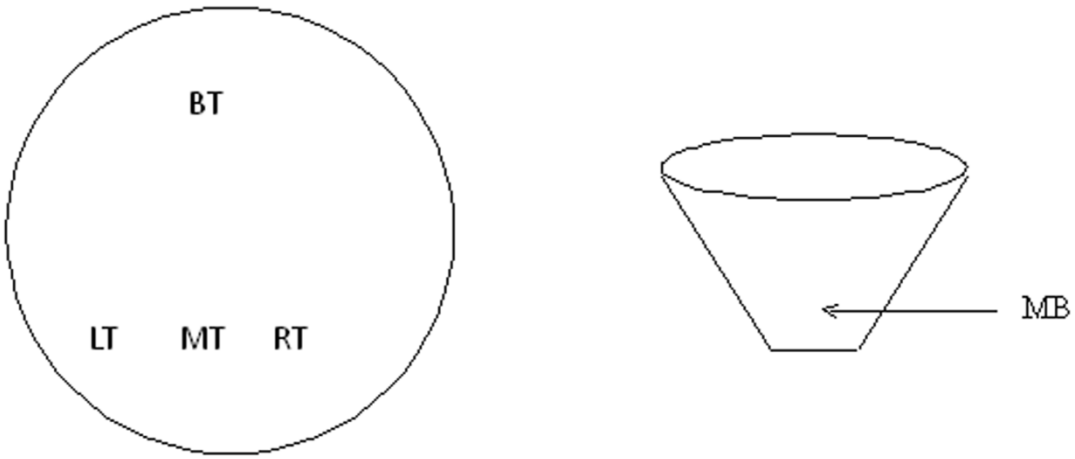
Sr. No.	Equipment	Process Involved
1.	Double cone bender	Dry mixing/ Blending, Lubrication
2.	Compression machine (16 station, C type)	Compression
3.	R & D coater	Coating

A. Dry mixing/ Blending

1. Samples were drawn from different positions of double cone blender as shown in figure no.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.

B. 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 Fig. 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.



NOTE : LT- Left Top, MT- Middle Top, BT- Bottom Top, RT- Right Top, FT- Front Top, MB - Middle Bottom.

Figure No. 2 Different sampling positions in blender

C. 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 no. 4.

Table No. 4 Compressed tablet test parameters

Sr. 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^3
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%

D. 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.

3.5.6 Critical steps validation

A. **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 and angle of repose.

B. 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
- Variables considered for study- Blending time
- Measure response - Assay, Tapped density, Bulk density, Angle of repose.

Acceptance criteria - Free flowing powder blend with no lumps.

C. **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.

D. **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

3.6 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 no. 5.

Table No. 5 Formulation of film coating solution

Sr. 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.

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 [10],

- Batch size - 50 tablets
- Pan size - 8"
- Baffles - 3
- Spray nozzle - 1 mm
- Spray gun - 1
- Atomization pressure - 1.2 kg/cm^2
- Spraying - Continuous
- Tablet bed temperature - 33^0 C ± 2^0
- Pre-warming - 10 to 15 min at slow rpm
- Post drying - 10 to 15 min 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 no. 6.

Table No. 6 Coating parameters study

Sr. No.	Variable	Batch		
		I	II	III
1.	Pan speed (rpm)	30	25	20
2.	Air temperature	50^0C	45^0C	35^0C
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

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.

3.7 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 ºC ± 1 ºC 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 [10].

3.8 Stability Study

The stability study of film coated tablets was carried at accelerated condition of 40^0 C ± 2^0 C temperatures and 75% ± 5% relative humidity for a period of three months [11, 12].

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.

4. RESULT AND DISCUSSION

4.1 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. All values of above studies found were in standard limits. Results of above studied represent in table no.7.

Table No. 7 Physical properties of polymers, drug and additives

Ingredients	Parameters			
	Bulk Density*	Tapped density*	% Compressibility*	Hausner Ratio*
Ranitidine HCl	0.406 ± 0.04	0.623 ± 0.033	34.83 ± 0.39	1.03 ±
Microcrystalline cellulose (Avicel PH 102)	0.360 ± 0.001	0.451 ± 0.002	20.18 ± 0.17	0.81 ± 0.33
Pregelatinised starch (Starch 1500)	0.577 ± 0.018	0.876 ± 0.07	34.13 ± 0.019	1.45 ± 0.39

Fumed silica (Aerosil 200)	0.037 ± 0.008	0.066 ± 0.013	43.94 ± 0.055	0.10 ± 0.11
Magnesium stearate	0.159 ± 0.01	0.286 ± 0.02	44.41 ± 0.33	0.45 ± 0.025
Hydroxy propyl methyl cellulose	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)**

4.2 FTIR spectroscopy of drug and polymers

a. **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 (Fig. 3) was established and compare with official standards, it was found that the spectra and value of sample Ranitidine HCl (Table no. 8) was match with official standards.

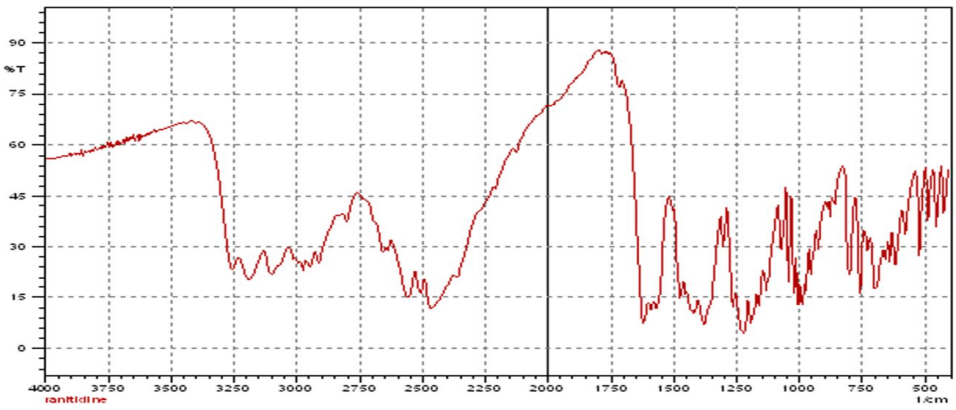


Figure No. 3 FTIR spectra of Ranitidine HCl

Table No. 8 Interpretation of FTIR spectra of Ranitidine HCl

Frequency (cm^{-1})	Assignment
1620.09	-C=N stretching vibration
2636.51 & 2557.43	$-N^{+}H$ bond in tertiary amino group
2995.25	$-CH_3$ group

b. Fourier Transfer Infrared spectroscopy of hydroxypropylmethylcellulose

FTIR study of the drug was done to check authenticity of excipients. In this FTIR spectra of hydroxyproplymethylcellulose (Fig. 4) was established and compare with official standards, it was found that the spectra and value of sample hydroxyproplymethylcellulose (Table no.9) was match with official standards.

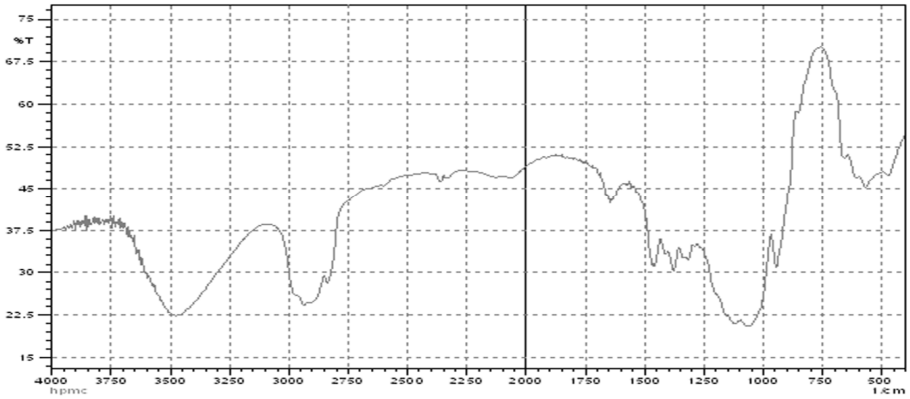


Figure No.4 FTIR spectra of hydroxypropylmethylcellulose

Table No. 9 Interpretation of FTIR spectra of hydroxypropylmethylcellulose

Frequency (cm^{-1})	Assignment
3444.63	-OH stretching vibration for free OH group
1120.56	-OH deformation (primary alcohol)
2935.46 & 2835.16	Aliphatic –CH stretching vibration

c. Fourier Transfer Infrared spectroscopy of ethyl cellulose

The peaks (Fig. 5) and values of frequencies of sample ethyl cellulose (Table no.10) found was match with official standards. So it conclude that sample of ethyl cellulose was authentic one.

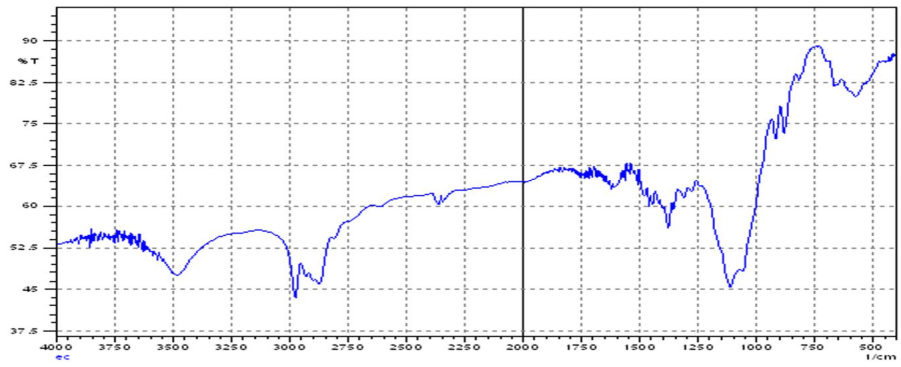


Figure No.5 FTIR spectra of ethyl cellulose

Table No. 10 Interpretation of FTIR spectra of ethyl cellulose

Frequency (cm^{-1})	Assignment
3475.49	OH stretching vibration
1056.92	-C-O stretching vibration
1110.92	-O-C_2H_5 group

d. 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 (Fig. 6). Hence their was no interaction or incompatibility between drug and polymer.

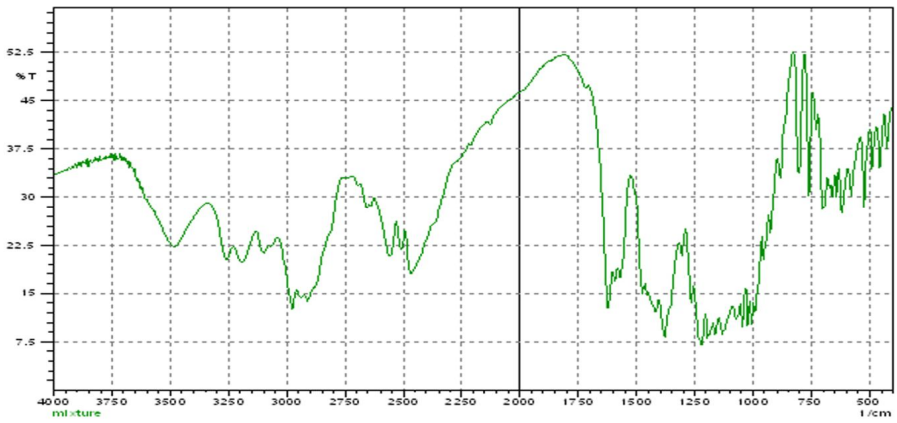


Figure No. 6 FTIR-spectra of drug-polymer mixture

4.3 Standard calibration curve of Ranitidine HCl in distilled water

The standard calibration curve of drug in distilled water is depicted in Fig. 7 and the data is shown in Table no. 11. The concentration of drug on X axis plot against absorption on Y axis, a linear line was developed. The linear line indicates that Ranitidine HCl follows Beer's Lamberts law hence drug sample is authentic one.

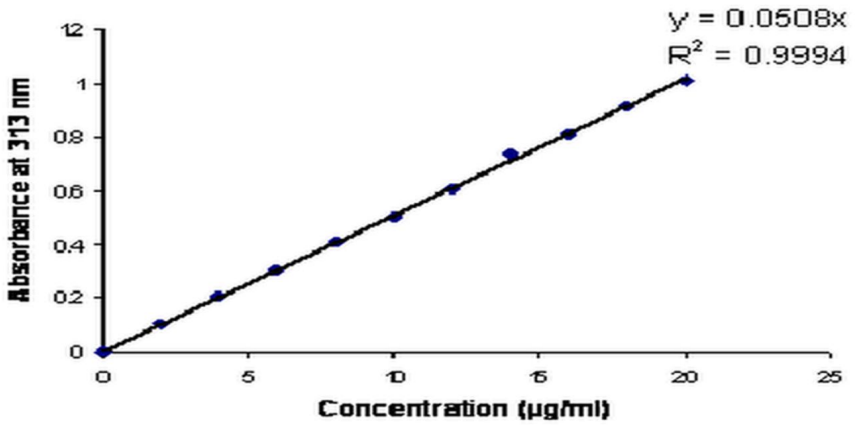


Figure No.7 Standard calibration curve of Ranitidine hydrochloride in distilled water at 313 nm

Table No. 11 Data of standard calibration curve of Ranitidine hydrochloride in 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

4.4 Assay of Ranitidine hydrochloride

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

4.5 Determination of hygroscopicity of Ranitidine hydrochloride by weight gain method

Results of hygroscopicity of Ranitidine hydrochloride were illustrated in table no. 12 and Fig. 8.

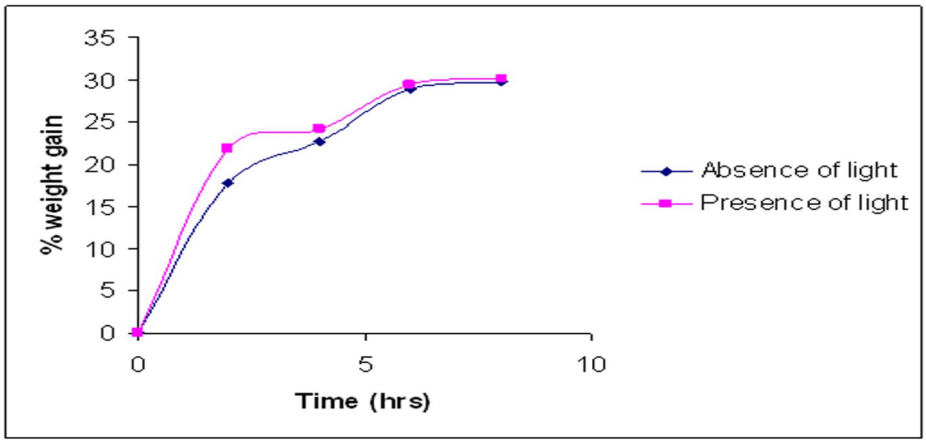


Figure No. 8 Moisture gain behavior of Ranitidine hydrochloride in absence and presence of light

Table No. 12 Moisture gain behavior of Ranitidine hydrochloride in absence and presence of light

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

4.6 Critical steps validation

A. 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 no. 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 min. showed almost same standard deviation as that of 15 min (Table no. 13, 14 & 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 (Table no. 13, 14 & 15). Physical parameters like bulk density, tapped density and angle of repose was done. Observations are noted in table no. 16.

Table No. 13 Assay of samples drawn from different position for batch A

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 No. 14 Assay of samples drawn from different position for batch B

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 No. 15 Assay of samples drawn from different position for batch C

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.	6.60	2.48	1.36	1.35

Table No. 16 Physical parameters study of batches A, B, C

Sr. No.	Parameter	Batch No.		
		A	B	C
1	Bulk density* (g/cm^3)	0.798 ± 0.04	0.821 ±0.037	0.819 ± 0.039
2	Tapped density* (g/cm^3)	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)**

B. 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 low standard deviation in all three batches and samples collected after 15 min, showed almost same standard deviation as that of 10 minutes (Table no. 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 no. 17). Physical parameters like bulk density, tapped density and angle of repose was done. Observations are noted in table no. 18.

Table No. 17 Assay of samples drawn from different positions of blender

Location	Assay (%)								
	A (min.)			B (min.)			C (min.)		
	05	10	15	05	10	15	05	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	1.80	0.98	0.97	1.37	1.09	1.07

Table No. 18 Physical parameters study of lubricated blend of batches A, B, C

Sr. No	Parameter	Batch No.		
		A	B	C
1.	Bulk density* (g/cm^3)	0.617 ± 0.041	0.659 ± 0.034	0.709 ± 0.037
2.	Tapped density* (g/cm^3)	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)**

C. Compression

Observations of effect of compression force and machine speed on tablet are shown in table no. 19.

Table No. 19 Effect of compression force and machine speed on tablets

Sr.	Parameters	Force (Tones)	3.5		4	
		Speed 25 rpm	30 rpm	25 rpm	30 rpm	25 rpm
1.	Hardness (kg/cm^2)		5.91	6.17	7.32	8.14
2.	Thickness (mm)		5.17	4.10	4.41	4.01
3.	Friability (%)		0.95	0.69	0.14	0.10
4.	Disintegration time (min.)		4.20	5.05	6.20	8.45
5.	Dissolution (%)		91.72	90.79	90.14	97.11

D. Normal production

Observation of compressed tablets evaluation of normal production batch A, B and batch C are shown in table No. 20, 21 & 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.

Table No. 20 Compressed tablets evaluation of normal production batch A

Sr. 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 11.676g	10.792	10.697	10.817
3.	Average weight	NLT 0.528 g and NMT 0.584 g	0.540	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^2	8.74	8.91	9.10
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 No. 21 Compressed tablets evaluation of normal production batch B

Sr. 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 11.676g	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 4.10mm	4.01	3.89	4.09
5. Diameter	11.90 mm to 12.10 mm	11.94	12.01	11.99
6. Hardness	8 to 12 kg/cm^2	8.87	8.91	9.17
7. Friability	NMT 1.0%	0.18	0.14	0.17
8. Disintegration time	NMT 60 min	8 min. 40sec.	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 No. 22 Compressed tablets evaluation of normal production batch C

Sr. 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 11.676g	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 4.10mm	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^2	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. 5sec.	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

4.7 Tablet Coating

Film Coating:

Formulation of coating solution given in table no. 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 table no. 24 and 25 respectively.

Table No. 23 Preparation of film coating solution

Sr. 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 No. 24 Coating parameters study

Sr. No.	Variable	Batch		
		I	II	III
1.	Pan speed (rpm)	30	25	20
2.	Air temperature	50^0C	45^0C	35^0C
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 No. 25 Evaluation of coated tablets of batches I, II, III

Sr. No.	Physical Parameter	Limit	Batch		
			I	II	III
1.	Appearance	Colored film coated tablet with no surface defects	Not complicated	Complies	Not complies
2.	Weight of 20 tablets	NLT 10.98 g and NMT 12.14g	12.41	11.48	10.61
3.	Average weight	NLT 0.549 g and NMT 0.607 g	0.621	0.574	0.531
4.	Thickness	2.90 mm to 4.10mm	5.09	3.99	3.17
5.	Diameter	11.90 mm to 12.10 mm	12.04	11.99	12.08
6.	Hardness	8 to 12 kg/cm^2	10.97	9.41	8.19
7.	Friability	NMT 1.0%	0	0	0
8.	Disintegration time	NMT 60 mins.	15 min 45sec.	12 min 5 sec.	10 min 55 sec.
9.	Dissolution Test	NLT 80%	79.71	91.49	82.01

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 33^0C ± 2^0C. Coated tablets were evaluated for physical parameters, disintegration time, dissolution time and assay. Observations are shown in table no. 26. The tablets produced in all three batches meet required specifications; hence tablet coating process was concluded as validated.

Table No. 26 Evaluation of coated tablets of batch A, B, C

Sr. No.	Physical Parameter	Limit	Batch		
			A	B	C
1.	Appearance	Colored film coated tablet with no surface defects	Complies	Complies	Complies
2.	Weight of 20 tablets	NLT 10.98 g and NMT 12.14g	11.1	11.68	11.4
3.	Average weight	NLT 0.549 g and NMT 0.607 g	0.555	0.584	0.570
4.	Thickness	2.90 mm to 4.10mm	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^2	9.97	9.41	9.17
7.	Friability	NMT 1.0%	0	0	0
8.	Disintegration time	NMT 60 mins	12 min. 15sec.	11 min. 45 sec.	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

4.8 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 no. 27 and figure no. 9.

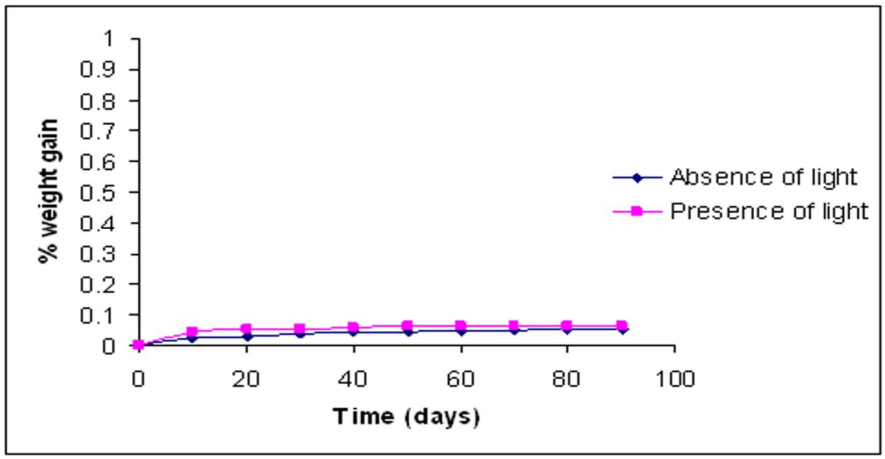


Figure No. 9 Moisture gain behavior of film coated Ranitidine hydrochloride tablets in absence and presence of light

Table No. 27 Moisture gain behavior of film coated Ranitidine hydrochloride tablets in absence and presence of light

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

4.9 Stability Study

The stability study of film coated tablets was carried at accelerated condition of 40^0 C ± 2^0 C temperatures and 75% ± 5% relative humidity for a period of three months. The results of stability studies after each 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 No. 28.

Table No. 28 Stability study of film coated tablets

Sr.No	Parameter	40^0 C ± 2^0 C and 75% ± 5% RH			
		Zero month	One month	Two month	Three month
	Physical appearance	colored tablets with no surface defect	No Change	No Change	No Change
	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)**

5. 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 relevant indicators of a controlled process and shown in Table No. 1. The Figure no. 6 shows the process flow chart for tablet process. The critical process 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 leaded 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.

6. REFERENCES

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