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Formulation and Process Validation of Coated Granules of Clarithromycin

Abhishek Gurjar*, and Tara Chand

Regional college of Pharmacy, Jaipur,(Rajasthan)-302022

ABSTRACT

The study is to prepare taste masking and enteric-coated clarithromycin granules by Wurster coating or air suspension coating technology. The basic concept embodied in a Wurster coater (also known as air suspension coater) is to separate the particles from one another in a heated air (gas) stream and spray a coating formulation on the particles while they are suspended.

Keywords: Clarithromycin, Wurster Coating, Coated Granules, Air-suspension Technique, Octagonal Blender, Fluidised Bed.

Correspondence Author*

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INTRODUCTION

The taste masking and enteric-coated clarithromycin granules not only have good taste masking effect, but also have a good release behavior. It is expected to have better clinical application. A rapid, efficient method of applying enteric film coats by a modified Wurster air-suspension technique is described. Enteric film coats describes a composition suitable for oral administration comprising and antibiotic macrolide and a polycarbophil[1-5].

Process Validation

Establishing documented evidence with a high degree of assurance, that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics. It is designed to verify that all established limits of the critical process parameter are valid and that satisfactory products can be produced even under the worst conditions. Prospective Validation was performed on three validation batches after trial batches. A validation protocol was prepared and approved prior to manufacturing batches. Three consecutive batches were taken to perform for the process validation [6-8].

MATERIALS AND METHODS

Materials

Clarithromycin, sucrose, hypromellose, hydroxypropyl cellulose-L, povidone (pvp k30), alginic acid (kelacid, purified water, acetone, hypromellose phthalate, castor oil, colloidal silicon dioxide were procured commercially. All the reagents and solvents were used analytical grade.

FT-IR Study

IR spectra of individual components were measured using FT-IR. The IR spectrum was recorded using a shimadzu FTIR 8201 PC at 282 nm and spectrum depicted. FT-IR spectra of API was interpreted with the BP standard FT-IR spectra of clarithromycin.[9]

Differentianl scanning calorimeter (DSC) and Melting Point

Melting Point was determined by differential scanning calorimetry (DSC) examination and conducted on the APIs. Endothermic peaks were used to study the physical state of the API. DSC data were generated using a mettle Toledo DSC 820. In general, samples were analyzed in a vented, dealed aluminum pan. Because the endothermic peak may vary depending upon the rate of heating and the calibration and precision of the instrument, with the amount of peak variation dependent upon the same, consistent condition heating at 1^0 C. per minute under a nitrogen purge a 40 ml per minute.[9]

Scanning Electron Microscopy (SEM)

The morphology of the CAM particles of each fraction was examined using high resolution SEM (JSM-6700F, JEOL, and Japan) operating at 10 keV. The samples were

mounted on carbon sticky tabs and sputter coated with platinum for 1 min (Cressington Sputter Coater 208HR, UK). [9]

Bulk Density

It is the ratio of total mass of powder to the bulk volume of powder. It is expressed in g/ml and is given by[10]

$$\text{Bulk density (g/mL)} = \frac{\text{weight (g)}}{\text{Unsettled apparent volume (mL)}}$$

Carr's index or % Compressibility

It indicates powder flow properties. One of the ways of measurement of free flowing powder is compressibility as computed from density of a powder. It was calculated by using the formula[10,11]

$$\text{Compressibility Index (CI) (\%)} = \frac{100 \text{ X (Tapped density} - \text{Bulk density}}{\text{Tapped density)}}$$

Tapped Density

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%.
It is expressed in g/ml and is given by.

$$\text{Tapped density (g/mL)} = \frac{\text{weight (g)}}{\text{Final tapped volume(mL)}}$$

Hausner's Ratio

Hausner ratio is an indirect index of ease of powder flow. If the hausner ratio of powder is near to 1.25, indicates better powder flow. It is calculated by the formula

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{bulk density}}$$

Wruster or Fluidised Bed Coating

The basic concept embodied in a Wurster coating (also known as air suspension coater) is to separate the particles from one another in a heated air (gas) stream and spray a coating formulation onto the particles while they are suspended. The fluidised bed is a widely used process in the production of coated granules, having been successfully used for coating solid particles such as pellets, granules and powder. During this process, granules are fluidised by hot air in which the coating solution is applied using a spraying nozzle. The nozzle could be positioned at either the top or bottom of the fluidised bed [12].

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Drug Layering

Performed as per conditions tabulated in table 1.

Table No.1 Drug layering

S.No.	Operation	Parameter	Condition
1	Coating	Inlet temp.	30-35^{0}c
		Bed temp.	30-40^{0}c
		Spray rate	160-185g/min
		Blower speed	44-64 rpm
		Peristaltic speed	10-15 rpm
2	Drying	In v.t.d. for 36-42 hrs. Till lod is nmt 30 g	

Enterric Coating

Performed as per conditions tabulated in table 2.

Table No.2 Enteric coating

S.no.	Operation	Parameter	Condition
1	Coating	Inlet temp.	30-35^{0}c
		Bed temp.	30-40^{0}c
		Spray rate	170-190g/min
		Blower speed	44-64 rpm
		Peristaltic speed	10-15 rpm
2	Drying	In v.t.d. for 36-42 hrs. Till lod is nmt 30 g	

RESULTS AND DISCUSSION

FT-IR Study

Figure No.1 FT-IR Spectrum of Clarithromycin BP

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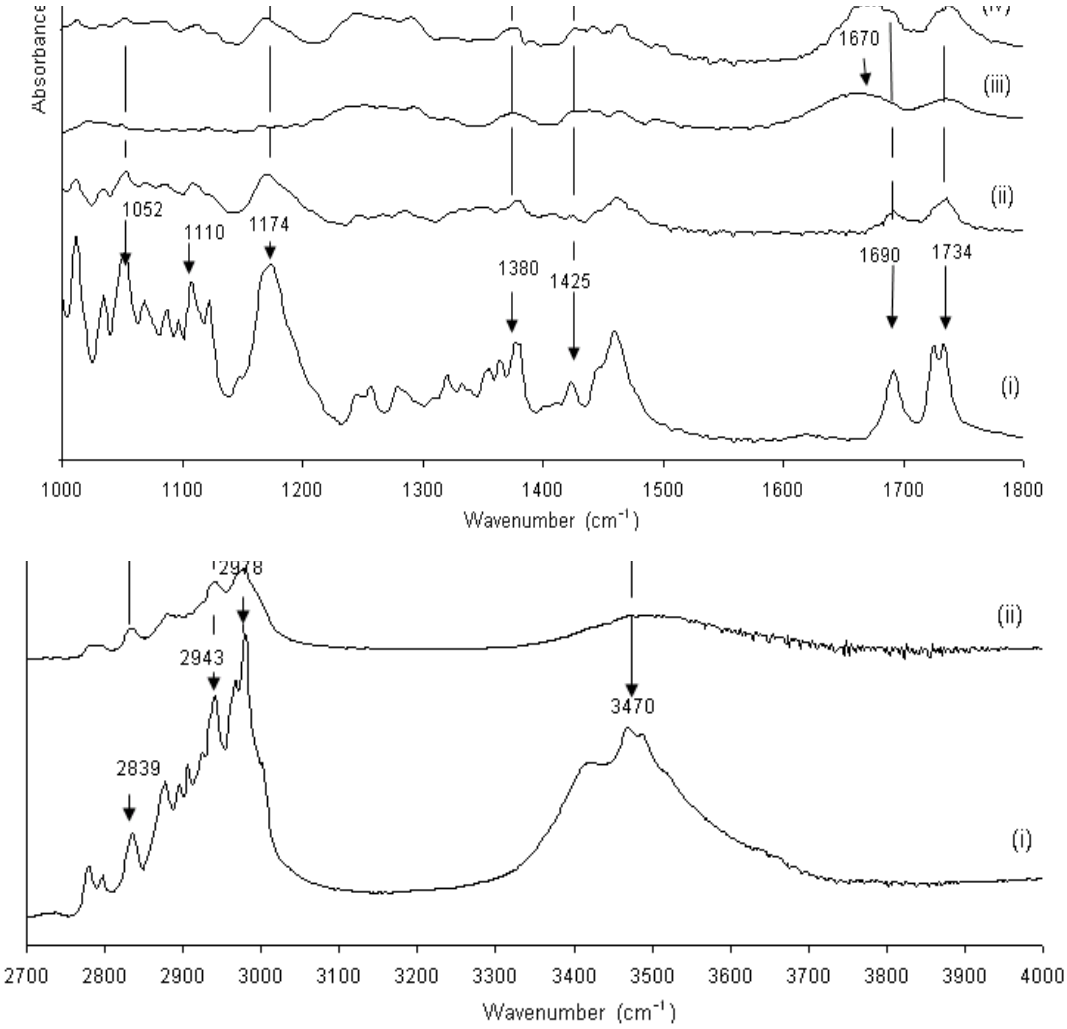

Figure No.2 FT-IR Spectrum of Clarithromycin Observed

Table No.3 Characteristic absorptions and functional groups of CAM (BP Specification)

Characteristic absorptions peaks at intensity	Functional groups of CAM	Observed peaks
1052 cm-1, 1110 cm-1, 1174 cm-1	(C-O-C stretch)	1052 cm-1, 1110 cm-1, 1174 cm- 1
1200-1390 cm-1	(CH_2)	1380 cm-1
1425- 1470cm-1	(N-CH_3)	1425 cm-1
1690-1680 cm-1	(ketone, C=O)	1690 cm-1
1734-1745 cm-1	(lactone, C=O)	1734 cm-1
2780-3000 cm-1	(alkane stretching peaks)	2839, 2943, 2970 cm-1
3470-3570 cm-1	(hydrogen bonds between O-H groups)	3470 cm-1

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FT-IR spectra of API was compile with the BP standard FT-IR spectra of clarithromycin. All peak were same in the IR of BP and observed IR of API so the drug was same as CAM mentioned in BP (Figure 2).

All observed IR peaks of CAM were found same in the of BP and so the drug was same as CAM mentioned in BP (Table 3).

Differentianl scanning calorimeter (DSC) and Melting Point

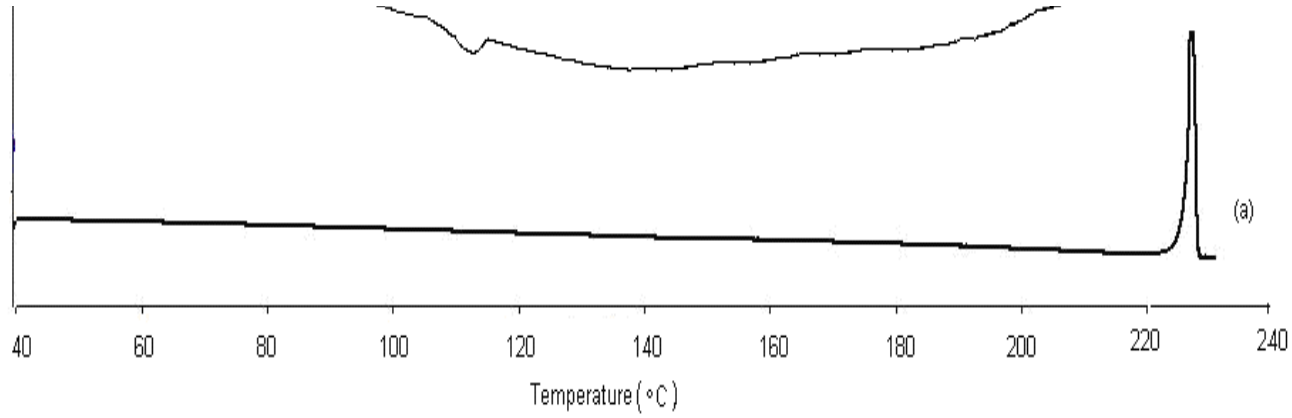

Figure No.3 DSC Thermograms of CAM

Analysis by DSC show characteristic peaks at 226^{0}C which was corresponding to the melting point of CAM(Figure 3).

Scanning Electron Microscopy (SEM)

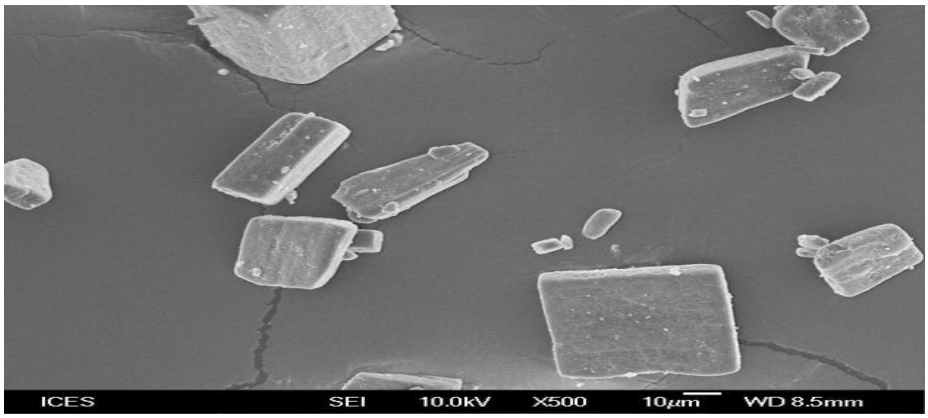

Figure No.4 SEM Images of CAM

The SEM image of CAM powder was represent that the powder's surface texture was crystalline in nature by visual inspection of SEM image (Figure 4).

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Flow Properties

Table No.4 Flow property of CAM

S.No.	Properties	Observation		
		Batch 2176364	Batch 2176365	Batch 2176366
1	Bulk Density	0.38 g/cm3	0.39 g/cm3	0.39 g/cm3
2	Tapped Density	0.51 g/cm3	0.51 g/cm3	0.50 g/cm3
3	Compressibility Index	23.52%	23.51%	23.52%
4	Hausner's Ratio	1.30	1.32	1.30

The bulk density, tapped density, carr's index and hausner's ratio had been determined powder show the poor flow property according to standard limit of carr's index (table 4).

PROCESS VALIDATION OF CLARITHROMYCIN COATED GRANULES

Table No.5 Manufacturing Process Parameters Protocol (Reference)

S.No.	Process Steps Detail		Control variable / Process parameter	Measured Response	Acceptance criteria	Routine sampling and or testing for validation purpose
1	Raw material quantity verification		Balance accuracy			No sampling Recommended
2	Drug layering					No sampling Recommended
	(i)	Coating	Sieve no.	Individual assay	100	
			Inlet temp.		30-55°C	
			Bed temp.		30-40 °C	
			Spray rate		160-185 g/min	
			Lower speed		44-64	
			Peristaltic speed		10-15 rpm	
	(ii)	Drying	Drying time	LOD	In VTD for 36-42 hrs till LOD % w/w is NMT 3.0	
3	Enteric coating					No sampling Recommended
	(i)	Coating	Sieve no.	Individual assay	100	
			Inlet temp.		30-55°C	
			Bed temp.		30-40 °C	
			Spray rate		170-190 g/min	
			Lower speed		44-64	
			Peristaltic speed		10-15 rpm	
	(ii)	Drying	Drying time	LOD	In VTD for 36-42 hrs till LOD % w/w is NMT 3.0	

4	Blending	All materials shall be blended in Octagonal Blender. ● Blender time			● Blend uniformity samples to be collected from 10 different location of the blender and subsequently analysed for API assay as per sampling plan. ● Blend sample to be submitted for analysis as per in process specification.

Process steps detail

Raw material quantity verification

Table No.6 Raw material quantity

Ingredients	Quantity Taken
Drug	52Kg
Diluent	104Kg
Binder	7.3Kg
Coating Polymer	13.6Kg
Enteric Coating Polymer	13.6Kg
Plasticizer	8.5Kg
Glidant	1.4Kg
Disintegrant	6.2Kg
Suspending agent	1.4Kg

Drug layering

Purified water 21.480 kg was taken in a clean stainless steel, equipped with mechanical stirrer. Coating agent 13.6Kg kg was taken, passed through # 100 sieves & added in selected equipment with stirring and stir continuously. under stirring and continue stirring for 45 minutes. The coating suspension was passed through colloid mill at zero clearance. The coating suspension 13.6 kg was transferred to the tank of Wruster Coating machine. The gun was assembled and the size of nozzle used was recorded i.e. size of nozzle = 1.5 mm. Core weighed raw materials was loaded in the Wruster coating machine.

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Table No.7 Coating parameters

S.No.	Operation	Parameter	Target	Range	Batch 2176364	Batch 2176365	Batch 2176366
1	Coating	Inlet temp.	32^{0}C	30-35^{0}C	32^{0}C	32^{0}C	32^{0}C
		Bed temp.	36^{0}C	30-40^{0}C	36^{0}C	36^{0}C	36^{0}C
		Outlet temperature	To be recorded	To be recorded	35^{0}C	35^{0}C	35^{0}C
		Spray rate	173 g/min	160-185g/min	174 g/min	173 g/min	173 g/min
		Blower speed	58 RPM	44-64 RPM	58 RPM	57 RPM	58 RPM
		Peristaltic speed	14 RPM	10-15 RPM	13 RPM	14 RPM	14 RPM
2	Drying	Time	In V.T.D. for 36-42 hrs. till LOD is NMT 30 g				

Before proceeding drug layering, area clearance has been taken from the quality assurance department. Checklist of cleaning was verified. During the above procedure all the specified parameters were observed in every 30 minutes.

Enteric Coating

Acetone 21.480 kg was taken in a clean stainless steel, equipped with mechanical stirrer.Enteric coating agent 13.6Kg kg, Plasticizer 8.5Kg was taken, passed through # 100 sieves & added in selected equipment with stirring and stir continuously. under stirring and continue stirring for 45 minutes.The coating suspension was passed through colloid mill at zero clearance. The coating suspension 13.6 kg was transferred to the tank of Wruster coating machine. The gun was assembled and the size of nozzle used was recorded i.e. Size of nozzle = 1.5 mm. Core drug layered granules was loaded in the Wruster coating machine.Coating parameters calculated & recorded (Table 8).

Table No.8 Enteric coating

S.No.	Operation	Parameter	Target	Range	Batch 2176364	Batch 2176365	Batch 2176366
1	Coating	Inlet temp.	32^{0}C	30-35^{0}C	32^{0}C	32^{0}C	32^{0}C
		Bed temp.	36^{0}C	30-40^{0}C	36^{0}C	36^{0}C	36^{0}C
		Outlet temperature	To be recorded	To be recorded	35^{0}C	35^{0}C	35^{0}C
		Spray rate	180g/min	170-190g/min	180g/min	180g/min	181g/min
		Blower speed	58 RPM	44-64 RPM	58 RPM	59 RPM	58 RPM
		Peristaltic speed	14 RPM	10-15 RPM	14 RPM	14 RPM	13 RPM
2	Drying	Time	In V.T.D. for 36-42 hrs. till LOD is NMT 30 g				

Before proceeding enteric coating, area clearance has been taken from the quality assurance department. Checklist of cleaning was verified. During the above procedure all the specified parameters were observed in every 30 minutes.

Blending

The blending of granules was done in octagonal blender. The material to be blended was loaded in octagonal blender and blend it for 5 minutes. In-process quality assurance department was informed for sampling of Blend. Samples were collected after blending as per sampling plan taken by Quality Assurance and sent to quality control lab for testing.[13] The obtained results are tabulated in table 9.

Table No.9 Blend uniformity analysis results Clarithromycin coated granules

Batch No		Drug % release											
		U1	U2	U3	M1	M2	M3	L1	L2	L3	BC	Avg.	%RSD
2176364	Mg	4.89	4.78	4.27	4.79	4.92	5.13	4.76	4.79	4.8	4.91	4.85	2.4
	%	97.8	95.7	94.5	95.9	98.4	102.7	95.3	95.9	96.1	98.3	97.1	2.4
2176365	Mg	9.66	9.75	9.85	9.99	9.92	9.82	9.69	9.8	9.78	9.81	9.81	0.9
	%	96.6	97.5	98.5	99.9	99.2	98.2	96.9	98	97.8	98.1	98.1	0.9
2176366	Mg	0.67	9.78	9.85	9.78	10.05	10.15	10.2	9.85	9.67	9.98	9.89	1.8
	%	6.7	97.8	98.5	97.8	100	101.5	102	98.5	96.7	99.8	98.9	1.8

Acceptance criteria: All individual value should be within ±10 % (absolute) of mean of results. Mean of 10 individual should be within the range of 92.5-107.5%. The relative standard deviation should be NMT 5.0 %.The results of all tests were found to be reproducible and satisfactory within limits for both blending step at given blender load (table 9). Hence the blending steps were validated at given parameters.

CONCLUSION

In the production batch the all critical in-process parameters and finished product parameters like preformulation study like, identification of drug (FTIR, DSC, and SEM), in process manufacturing control parameter, Batch production record, evaluation of coating's parameter and all process validation parameters (Raw material quantity verification, drug layering, enteric coating, blending) were found to be in their prescribed limits. Hence the manufacturing process of clarithromycin coated granules stands optimised and validated.

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