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Original Research Article

OPTIMIZATION AND EVALUATION OF IMMEDIATE RELEASE FILMCOATED TABLET OF MACROLIDE ANTIBIOTICS

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Abstract: The objective of the present study was to formulate, optimize and evaluate clarithromycin immediate release film coated tablet. In this work, selection of excipient Preformulation studies, tablets were formulated by wet granulation method, Pre-compression parameters, Post compression parameters and formulated trial batch was taken for optimization by full factorial design and Optimized batches on the basis of dissolution and stability studies, Optimized batches were coded as OF1, OF2, OF3, OF4, OF5, OF6, OF7, OF8 and OF9. The in vitro dissolution study was performed for all the optimized formulations. Similarity is found in the results of all the optimized formulations and innovator product. Among the entire optimized batches, formulation OF7 has been selected for calculating similarity factor, since it shows better results (i.e., faster disintegration time and rapid drug release) than other optimized batches. Similarity factor was calculated by comparing the in-vitro drug release profile for batch OF7 with the innovator product. The dissimilarity factor f1 value of 5.147 and similarity factor f2 value of 59.658 indicates that the two products were similar in in-vitro drug release. .From this study, it was concluded that optimized clarithromycin tablet (OF7) containing croscarmellose sodium (3.029%) and pregelatinized starch (6.029%) could be manufactured with reproducible characteristics from batch to batch. The finding of the present study has initiated the company to go in for scale up trial. Based on the reproducible results produced from batch to batch the company will decide to launch the product in the future.

Keyword: clarithromycin, immediate release, film coated tablet, factorial design.

Introduction: Immediate release drug delivery systems are based on single or multipleunit reservoir or matrix system, which are designed to provide immediate drug levels in short period of time[1]. Immediate release drug delivery is desirable for drugs having long biological half-life, high bioavailability, lower clearance and lower elimination half-life.Clarithromycin is macrolide antibiotic produced by various strains

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of streptomyces. The mechanism of action of clarithromycin is inhibition of bacterial protein biosynthesis[2]. Clarithromycin is acid stable and it is rapidly absorbed from the gastrointestinal tract after oral administration. The plasma half-life of clarithromycin is 2-3 hours. The usual duration of treatment of clarithromycin is 6 to 14 days. Clarithromycin is economically beneficial than all other macrolide antibiotics. Clarithromycin is rapidly absorbed from the GIT and undergoes first pass metabolism. The bioavailability of the drug is about 55%. The terminal half-life of clarithromycin is reportedly about 3-4 hrs. Compared with erythromycin, clarithromycin possesses greater acid stability, improved pharmacokinetic properties and fewer GIT, rapid gastrointestinal absorption, highly soluble at acidic pH absorption of clarithromycin is unaffected by food. More than half of an oral dose is systematically available as the parent drug and the active 14- hydroxyl metabolite, pharmacokinetics are nonlinear, with plasma concentration increasing in more than proportion to the dosage[3]. First pass metabolism results in the rapid appearance of the active metabolite. 14 Hydroxy clarithromycin and its active metabolite are found in greater concentrations in the tissue and fluids of the respirator, it has higher eradication rate in-vivo to H.pylori. The recommended dosage regimen for these types of infection in adult patients is 250mg to 500mg twice daily for 7-14 days of the immediate- release oral formulation of clarithromycin [4].

Material and Method

Clarithromycin was procured as a gift sample from Cipla Pithampur, Dewa Madhya Pradesh, Croscarmellose other ingredients were of laboratory grade.

Formulation of Clarithromycin Immediate-releaseTablet

The method used in the formulation of clarithromycin IR tablets was wet granulation non-aqueous method. All the batch formulations in these studies are formulated by wet granulation method[5,6].

Table 1: Formulation Trial Batches

S.No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
1	Clarithromycin	500	500	500	500	500	500	500	500
2	Croscarmellose sodium	13.75	1.75	24.75	-	-	-	-	-
3	Sodium starch glycolate	-	-	-	13.75	19.25	24.75	-	-
4	Povidone	-	-	-	-	-	-	13.75	24.75
5	Hydroxy propyl Cellulose	15	20	-	-	-	-	-	-
6	Microcrystalline cellulose PH101	235	229	230	220	-	-	-	-
7	Microcrystalline cellulose PH102	50	48	-	36	251.50	249	199	196
8	Pregelatinised starch	-	-	-	-	-	-	50	50
9	Talc	-	-	8.50	4.25	10.0	8.65	8.65	9.50
10	Magnesium stearate	4	6	4.75	8.5	5	6.35	6.35	7.50
11	Isopropyl Alcohol	-	-	-	q.s	q.s	q.s	q.s	q.s
12	Purified water	q.s	q.s	q.s	-	-	-	-	-

Coating Solutionformula [7,8]: Clarithromycin tablet was coated using the following ingredients mentioned in the Table No.2.

Dissolve ethyl cellulose in isopropyl alcohol in a stainless steel vessel and disperse HPMC15 cps to the ethyl cellulosesolution.Add dichloro

methane to ethyl cellulose, HPMC solution and mix well for 10 minutes under mechanicalstirring.Weigh accurately quinoline yellow lake, titanium dioxide and talc. Pass through sieve No.60 and triturate in a mortar. Transfer to above stirred solution and mix well understirring. Add propylene glycol to the above steps and mix well understirring. Load the tablets in coating pan with baffles fixed and sets the parameters according to the suitability of the machine.

Table2: Coating solution formula

S.No.	Ingredients	Uses	Qty/500Tablet (gm)
1	Hydroxy Propyl Methyl Cellulose 15 cps	Film former	7.20
2	Ethyl cellulose	Coating agent	2.40
3	Titanium dioxide	Opacifizer	2.20
4	Talc	Anti-caking agent	1.175
5	Quinoline yellow (lake)	Colour	0.250
6	Ethyl vanillin	Flavour	1.2
7	Propylene glycol	Plasticizer	1.65
8	Dichloro methane	Solvent	144ml
9	Iso propyl alcohol	Solvent	144ml

Optimization Of Trial Batch (Cir8) By Full Factorial Design[9,10]

In order to obtain "best" or an "optimized product" nine different formulations were generated using a 3^2 randomized full factorial. Based on preformulation study the amounts of croscarmellose sodium (X_1) and microcrystalline cellulose PH102 (X_2) were selected as the independent factors, studied at 3 levels each (-1, 0, +1). The percentage drug release (y_1) and disintegration time (y_2) were taken as dependent factors. Experimental trials were performed at all 9 possible combinations of X_1 and X_2. Batches for factorial design are shown in Table No.3

Table 3: Formulation trials as per experimental design

Trial No.	Coded factor levels	
	X_1	X_2
I	-1	-1
II	-1	0
III	-1	1
IV	0	-1
V	0	0
VI	0	1
VII	1	-1
VIII	1	0
XI	1	1

Table 4: Translation of Coded Levels in Actual Units

Coded level	-1	0	1
X_1: CCS (%)	2	3	4
X_2:MCC102 (%)	21	23	25

Formulation Trial Batches For Optimized batches

Table 5: Formula for optimized batches of F8

Ingredients	Formulation Code Qty/Tab (mg)								
	OF1	**OF2**	**OF3**	**OF4**	**OF5**	**OF6**	**OF7**	**OF8**	**OF9**
Clarithromycin	500	500	500	500	500	500	500	500	500
Croscarmellose sodium	17.0	17.0	17.0	17.0	17.0	17.0	17.0	17.0	17.0
Povidone	35.00	35.00	35.00	35.00	35.00	35.00	35.00	35.00	35.00
Croscarmellose sodium	25.25	25.25	25.25	25.50	25.50	25.50	25.75	25.75	25.75
Microcrystalline cellulosePH102	194.5	196.5	198.5	194.5	196.5	198.5	194.5	196.5	198.5
Pregelatinised starch	51.75	49.75	47.75	51.5	49.5	47.50	51.25	49.25	47.25
Talc	9.50	9.50	9.50	9.50	9.50	9.50	9.50	9.50	9.50
Colloidal silicon Dioxide	9.50	9.50	9.50	9.50	9.50	9.50	9.50	9.50	9.50
Magnesium Stearate	7.50	7.50	7.50	7.50	7.50	7.50	7.50	7.50	7.50
Isopropyl Alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
TOTAL	850	850	850	850	850	850	850	850	850

Formulation procedure was repeated as per above trial batch and coated. All the optimized formulations were evaluated for its description, average weight, friability, thickness, hardness, disintegration time, assay anddissolution.

Evaluation of granules of clarithromycin (Pre-compressionparameters)[11]

It is a very important parameter to be measured because it affects the mass of uniformity of the dose. It is usually predicted from flow property, bulk density, tapped density, compressibility index and hausners ratio as per stander Procedure.

Evaluation of tablets[12-14]

Post compression parameters: The formulated film coated tablets were evaluated for the following physicochemical parameters,

Thickness: Thickness mainly depends on die filling, physical properties of material to be compressed under compressional force. There is bound to be a small variation in the thickness of individual tablet in a batch. But it should not be apparent to the unaided eye. The thickness and diameter were measured by using vernier calipers.

Hardness: Tablet requires certain amount of strength or hardness, measured by Monsanto hardness tester. Ten tablets were randomly picked from each formulation and evaluated for hardness during manufacturing and are expressed in kg/cm^2.

Friability: Friability was performed by using friability test apparatus, normally pre-weighed ten tablets were placed in the plastic chamber of friabilator. This was then operated for 100 revolutions. Tablets were dropping from a distance of six inches with each revolution. Tablets are then dusted and reweighed. Loss of less than 1% in weight is considered to be acceptable.

Twenty tablets were selected randomly and weighed individually. Calculate average weight and compare the individual tablet weight to the average. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in Table No.:

20 and none deviates by more than twice the percentage.

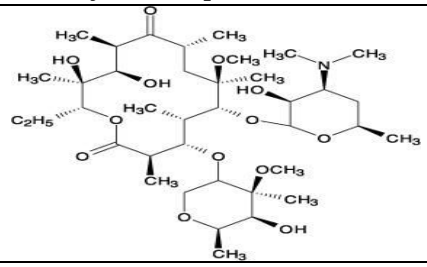
Dissolution: All dissolution was perform as per stander procedure.

Stabilitystudie[15,18]: Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutics and toxicological specifications. The ICH guideline recommends the following storage conditions for stability studies. As per ICH guidelines, the samples for stability analysis must be exposed to an environment of 40˚C±2˚C / 75%RH±5% RH for a period of 6 months. As per the standard protocol the samples must be analyzed at 0, 1, 2, 3 and 6 months'timepoints. Accelerated stability studies were performed for the final tablets. As per ICH guidelines, tablets were packed in Alu-Alu blister and required blisterswereplaced into the stability chamber. The samples were analyzed at 0, 1, 2 and 3 months time points.

Result And Discussion

Preformulationstudies

Table 6: Preformulation of API Raw materialanalysis

S.No	Test	Observation	
1	Description	White to off-white crystalline powder	
2	Chemical nature	Chemical structure	
		Molecular formula	$C_{38}H_{69}NO_{13}$
		Molecular weight	748.95
		IUPAC name	6-O-Methyl erythromycin A
3	Loss on drying	NMT 1.0-1.5%	
4	Solubility	Practically insoluble in water, Soluble in acetone, Slightly soluble in methanol, ethanol and acetonitrile.	
5	Particle size of Distribution	Moderately coarse powder	
6	Hygroscopicity	Non-hygroscopic.	
7	Melting point	217-220^{o}C	
8	pH (1%)	8-9	

Drug-Excipient compatibility studies (Physicalobservation)[19]

The preformulation studies of the excipients were mixed with the drug and kept in different conditions; the observed results are as follows:

Table 7: Compatibility studies of Clarithromycin with excipients

S.No	Drug+Excipient	Parameter	Initial Value of Parameter	Condition				Comments
				1st Month		3rd Month		
				50° C	2-8°C	RT	40°C	
1	Clarithromycin	Color change	No color change	No color change				Compatible

2	Microcrystalline CellulosePH101	Color change	No color change	No color change	Compatible
3	Cross caramellose Sodium	Color change	Nocolor Change	No color change	Compatible
4	Povidone	Color change	No color Change	No color change	Compatible
5	Hydroxy Propyl Cellulose	Color change	No color Change	No color change	Compatible
6	MCCPH112	Color change	No color Change	No color change	Compatible
7	Pregelatinised starch	Color change	No color Change	No color change	Compatible
8	Talc	Color change	No color Change	No color change	Compatible
9	Aerosil	Color change	No color Change	No color change	Compatible
10	Magnesium Stearate	Color change	No color Change	No color change	Compatible

FT-IR studies: The FT-IR spectra of the crude drug samples and the drug-excipient mixtures are as shownbelow.

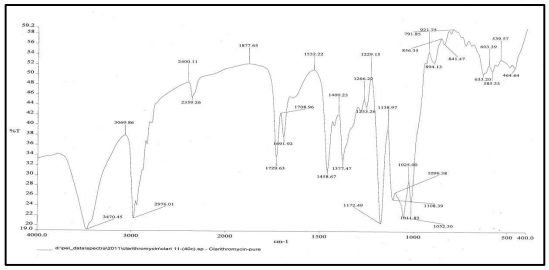


Figure 1: FT-IR spectra of clarithromycin USP- Raw material.

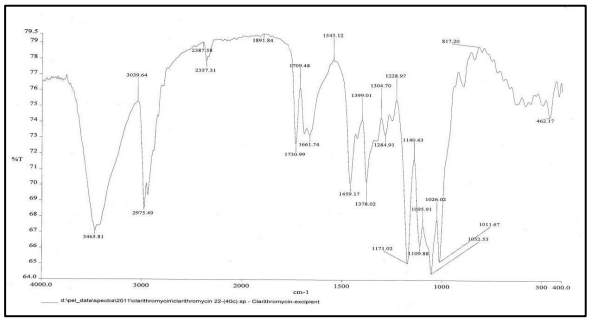


Figure No. 2: FT-IR spectra of clarithromycin and its excipients.

Table8: FTIR spectrum of clarithromycin USP- rawmaterial

Wave Number (cm^{-1})	Functional Group
3470 cm^{-1}	OH stretching
2976 cm^{-1}	CH aliphatic
1729 cm^{-1}	C=O stretching
1458 cm^{-1}	CH_3 bending
1266 cm^{-1}	CH_2 bending
1096 cm^{-1}	C—N stretching
1052 cm^{-1}	C—O stretching

Table 9: FTIR spectrum of clarithromycin + excipients

Wave Number (cm^{-1})	**Functional Group**
3465 cm^{-1}	OH stretching
2975 cm^{-1}	CH aliphatic
1730 cm^{-1}	C=O stretching
1459 cm^{-1}	CH_3 bending
1228 cm^{-1}	CH_2 bending

1026 cm^{-1}	C—N stretching
1011 cm^{-1}	C—O stretching

Inference: Pure Clarithromycin spectra showed sharp characteristic peaks at 3470, 2976, 1729, 1458, 1266, 1096, 1011 cm^{-1}. These peaks are also prominent in the FTIR spectra's of the physical mixtures containing clarithromycin and other excipients in the final formula. This indicates that there is no interaction between the drug and excipients from both physical observation and FT-IRstudies.

Evaluation Of Precompression Parameters[20]: The prepared clarithromycin granules were evaluated for the following parameters, which includes Bulk density, Tapped density, Compressibity Index, Hausner's ratio and Angle of repose.

Table 10: Pre compression parameters for clarithromycin trial batch

S.No	Formulation Code	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's Index (%)	Hausner's ratio	Angle of repose (o)	Moisture content (%)
1	F1	0.470±0.0010	0.526±0.012	15.10±0.85	1.17±0.15	33.30±0.50	1.25±0.02
2	F2	0.482±0.0005	0.562±0.040	15.62±0.61	1.18±0.02	34.92±0.68	1.04±0.03
3	F3	0.512±0.0015	0.576±0.012	11.32±0.11	1.12±0.03	33.73±0.27	0.93±0.03
4	F4	0.522±0.0015	0.612±0.012	12.91±0.41	1.14±0.04	33.42±0.72	0.85±0.04
5	F5	0.486±0.001	0.563±0.012	13.66±0.05	1.15±0.02	31.42±0.52	0.83±0.02
6	F6	0.533±0.012	0.596±0.012	9.92±0.02	1.10±0.05	31.45±0.34	0.76±0.04
7	F7	0.520±0.02	0.579±0.05	11.36±0.04	1.13±0.03	30.15±0.27	0.86±0.05
8	F8	0.522±0.013	0.596±0.010	10.56±0.10	1.11±0.02	30.01±0.012	0.85±0.02

*All the values are expressed as mean±SD, n=3.

The values of compressibility index, Hausner's ratio and angle of repose of all the batches indicate a good flow property of the granules.

For optimized batches (Uncoatedtablets)

Table 11: Precompression parameters for optimized batch

S.No.	Formulation Code	Bulk Density *(g/cc)	Tapped Density *(g/cc)	Compressibility Index (%)*	Hausner's Ratio*	Angle of Repose* (º)	Moisture content (%)
1	OF1	0.462±0.0015	0.565±0.011	14.94±0.01	1.16±0.01	30.10±0.60	0.82±0.01
2	OF2	0.485±0.005	0.523±0.007	12.08±0.05	1.13±0.04	32.43±0.68	0.85±0.03
3	OF3	0.512±0.0010	0.584±0.015	12.80±0.10	1.12±0.02	32.33±0.27	0.82±0.05
4	OF4	0.530±0.0010	0.610±0.035	14.65±0.02	1.14±0.01	31.20±0.73	0.74±0.01
5	OF5	0.530±0.004	0.594±0.013	10.50±0.02	1.10±0.01	30.24±0.51	0.80±0.05
6	OF6	0.533±0.013	0.625±0.011	11.40±0.03	1.12±0.10	30.33±.34	0.88±0.05
7	OF7	0.576±0.024	0.645±0.062	12.16±0.02	1.13±0.08	34.24±0.29	0.85±0.05
8	OF8	0.574±0.0132	0.660±0.023	13.10±0.01	1.15±0.06	33.21±0.15	0.79±0.02
9	OF9	0.575±0.012	0.650±0.016	12.18±0.01	1.13±0.03	32.50±0.11	0.82±0.01

* All the values are expressed asmean ± SD (n=3).

The values of compressibility index, Hausner's ratio and angle of repose of all the batches indicate an good flow property of granules.

Evaluation FOR Post Compression parameters: Post compression parameters for clarithromycin trial (F1-F8) batch for uncoated tablets.

TableNo12: Post compression parameters for clarithromycin trial batch uncoatedtablets

Formulation code	Average Weight(mg)	Thickness(mm)*	Hardness (kg/cm2)*	Disintegration(min)	Friability (%)	Weight variation (mg)	Assay (%)
F1	846	6.02 ±0.02	9.2±0.67	1.50±0.02	-	840.0±0.06	-
F2	845	5.97±0.03	9.4±0.35	1.43±0.01	-	858.9±0.68	-
F3	850	5.94±0.08	10.2±0.61	1.54±0.02	-	842.73±0.70	-
F4	852	5.98±0.12	10.3±0.5	1.40±0.01	0.2±0.01	840.16±1.19	102.12
F5	852	6.02±0.05	9.4±0.5	1.22±0.02	0.1±0.01	855.93±1.02	102.34
F6	849	6.02±0.187	9.4±0.35	1.26±0.029	0.32±0.03	846.59±1.18	98.01
F7	850	6.05±0.202	9.6±0.612	1.26±0.049	0.27±0.04	845.3±1.47	104.23
F8	851	6.02±0.11	9.4±0.35	1.28±0.02	0.15±0.05	852.03±0.99	102.67

Evaluation of clarithromycin coated tablets of trial batch

Table No. 13: post compression parameters for coatedtablets

S.No.	Formulation code	Average Weight (mg)	Thickness(mm)*	Disintegration (min)	Weight variation (mg)	Assay (%)
1	F4	875	6.12±0.032	2.24±0.019	874.18±1.58	98.88
2	F5	876	6.11±0.052	2.24±0.029	875.93±1.46	98.78
3	F6	877	6.16±0.065	2.23±0.04	876.09±1.34	104.28
4	F7	875	6.12±0.038	2.26±0.057	874.93±1.67	103.76
5	F8	875	6.14±0.035	2.25±0.046	876.03±0.99	104.50

* All the values are expressed asmean ± SD (n=6).

The values of both uncoated and coated parameters in above all batches are in limits

For optimized batches (coated tablets)

Table No.14: Post compression parameters for optimized batches.

S.No.	Formulation Code	Average Weight (mg) *	Thickness (mm)*	Weight variation test* (mg)	Disintegration test* (min)	Assay# (%)
1	OF1	874.54	6.13±0.026	875.10±0.90	3.12±0.04	100.04±0.05
2	OF2	875.20	6.14±0.031	876.56±1.44	3.06±0.06	99.99±0.01
3	OF3	875.08	6.12±0.020	875.03±1.23	3.27±0.04	103.99±0.01

4	OF4	873.78	6.18±0.065	873.75±1.35	2.53±0.023	102.98±0.01
5	OF5	876.05	6.16±0.030	874.03±0.08	2.26±0.018	104.54±0.02
6	OF6	876.32	6.12±0.053	874.0±1.12	2.24±0.01	102.30±0.03
7	OF7	875.12	6.17±0.063	876.05±1.05	2.15±0.02	101.69±0.01
8	OF8	875.10	6.13±0.039	875.89±1.05	2.05±0.04	103.01±0.04
9	OF9	874.20	6.14±0.037	876.55±0.60	1.50±0.05	103.68±0.01

All the values are expressed as* Mean ± SD (n=6); # Mean ± SD (n=3).

The values of optimized coated tablet parameters in above all batches are in limits.

EVALUATION FOR POST COMPRESSIONPARAMETERS

Post compression parameters for clarithromycin trial (F1-F8) batch for uncoated tablets.

Table 15: Post compression parameters for clarithromycin trial batch uncoatedtablets

Formulation code	Average Weight(mg)	Thickness (mm)*	Hardness (kg/cm2)*	Disintegration(min)	Friability (%)	Weight variation (mg)	Assay (%)
F1	848	6.02 ±0.02	9.3±0.67	1.50±0.02	-	850.0±0.06	-
F2	850	5.98±0.03	9.2±0.35	1.42±0.01	-	840.9±0.74	-
F3	852	5.96±0.08	10.0±0.61	1.44±0.02	-	840.73±0.71	-
F4	854	5.98±0.12	10.0±0.5	1.30±0.01	0.2±0.01	840.16±1.19	101.10
F5	850	6.02±0.05	9.6±0.5	1.20±0.02	0.1±0.01	850.93±1.06	100.34
F6	847	6.04±0.187	9.5±0.35	1.26±0.029	0.32±0.02	848.59±1.18	99.01
F7	849	6.05±0.202	9.4±0.612	1.26±0.049	0.27±0.01	850.3±1.47	102.23
F8	852	6.01±0.11	9.5±0.35	1.20±0.02	0.15±0.02	851.03±0.99	105.07

Evaluation of clarithromycin coated tablets of trial batch

Table No. 16: post compression parameters for coatedtablets

S.No.	Formulation code	Average Weight (mg)	Thickness(mm)*	Disintegration (min)	Weight variation (mg)	Assay (%)
1	F4	874	6.16±0.031	2.24±0.019	874.18±1.59	98.87
2	F5	877	6.11±0.053	2.25±0.029	876.93±1.46	98.79
3	F6	877	6.17±0.064	2.25±0.02	876.09±1.35	103.28
4	F7	876	6.13±0.039	2.27±0.057	875.93±1.67	102.76
5	F8	874	6.14±0.037	2.25±0.046	877.03±0.99	104.54

* All the values are expressed asmean ± SD (n=6).

The values of both uncoated and coated parameters in above all batches are in limits.

For optimized batches (coated tablets)

Table No. 17: Post compression parameters for optimized batches.

S.No.	Formulation Code	Average Weight(mg)*	Thickness(mm)*	Weight variation test*(mg)	Disintegration test* (min)	Assay# (%)
1.	OF1	874.54	6.12±0.026	876.10±0.94	3.12±0.04	102.04±0.07
2.	OF2	876.27	6.17±0.031	876.56±1.44	3.06±0.06	99.99±0.02
3.	OF3	875.08	6.12±0.025	876.03±1.23	3.27±0.05	102.99±0.01
4.	OF4	874.79	6.19±0.065	874.75±1.35	2.53±0.02	101.99±0.01
5.	OF5	878.02	6.12±0.031	874.03±0.08	2.20±0.01	104.54±0.05
6.	OF6	876.32	6.12±0.053	874.0±1.12	2.24±0.02	103.30±0.63
7.	OF7	876.15	6.17±0.064	874.06±1.05	2.13±0.02	101.69±0.01
8.	OF8	874.14	6.12±0.039	874.89±1.08	2.08±0.04	103.01±0.04
9.	OF9	875.21	6.15±0.037	876.55±0.64	1.55±0.04	103.68±0.01

All the values are expressed as* Mean ± SD (n=6); # Mean ± SD (n=3).

The values of optimized coated tablet parameters in above all batches are in limits.

Comparitive Dissolution profile: This comparative dissolution study performed between the formulation OF7 and the innovator product. The formulation OF7 has been selected for comparative dissolution study, since it shows faster disintegration time and rapid drug release compared to all optimized tablets.

Table No. 18: Comparative dissolution profile for OF7 and innovator product.

S.No.	Dissolution time points	Formulation OF7*	Innovator product*	OF7	
				Dissimilarity factors (f1) 0-15	Similarity factor (f2) 50-100
1.	5th min	72.82	80.88	5.144	58.640
2.	10th min	83.90	95.46		
3.	15th min	94.15	97.55		
4.	20th min	98.46	99.34		
5.	30th min	102.10	102.50		

* Mean ± SD (n=6)

The comparative dissolution profile of similarity and dissimilarity profile was studied for formula OF7 and innovator product. The satisfactory resultwas observed.

Discussion: The present study of clarithromycin film coated tablets were developed with a view to deliver the drug immediately. The film coated immediate release tablets were evaluated and the details of results and discussion were given in the followingsections.

Drug Excipient-Compatibility Study: The FT-IR spectrum of clarithromycin raw material was shown in Fig.1. The spectrum of Clarithromycin raw material shows the presence of peaks at 3470 cm-1, 2976cm-11729cm-1,1458cm-1,1266cm-1,1096cm-1and1052cm-

1ofOH,CH, C=O, CH3, CH2, C-N, C—O stretching respectively. The FT-IR spectrum of the combined clarithromycin and excipients was shown in the Fig.2. The spectrum shows the presence of peaks at 3465 cm-1 , 2975 cm-1, 1730 cm-1 , 1459 cm-1 ,1228 cm-1 ,1026 cm-1 and 1011 cm-1of OH, CH, C=O, CH3, CH2, C-N, C—O stretching respectively, indicating there is no interation between the drug and the excipients.

Observation of clarithromycin tablet formulation during inprocess: Initial batches, that is F1 to F3 were formulated with wet granulation by aqueous method with hydroxy propyl cellulose (2.35%) as a binder, MCC PH 101 is used as a diluent. These formulations showed a sticking problem during inprocess compression, which may be due to high moisture content and low amount oflubricants. Therefore, the next trials (F4) were again formulated with non-aqueous granulation with povidone (4.029%) and lubricants like aerosil (0.529%), magnesium stearate (1.0%), talc (0.5%). In this trial, sticking was not observed. But roughness is observed during compression. In the trial F5, in this formulation, MCC PH 101 is replaced by MCC PH 102 (4.23%) andcolloidalsilicondioxide(0.7%)inthegranulation.Inaddition,lubricantsare increased to avoid the sticking problem during compression. Here, all the parameters were foundsatisfactory. In the F6 trial, some amounts of lubricants are increased in both upper and lower granulation parts. All the parameters were found to be satisfactory and this batch tablets were kept for stability studies. During stability studies, dissolution was failed in the 1st month for 40^{o}C ± 2^{o}C/75% ± 5%. Because, while dissolution, the tablet breaks into 2-3 parts and not disintegrated uniformly. The percentage drug release was also less compared to initial month of stability studies. This problem may be due to insufficient disintegrates in theformulation.

In the trial F7, this procedure is also same as trial F5. However, in this formulation, the concentration of MCC PH102 is decreased and pre-gelatinized starch was included in the lubrication part of the formulation for better disintegration during the dissolution. In this, all the parameters were found satisfactory during pre-compression and post-compression. During dissolution of 1st month of stability studies, all the tablets were not disintegrated evenly and divided in to 2 to 3 parts. This may be due to presence of aerosil in the upper granulationpart. In the trial F8, in this formulation, colloidal silicon dioxide was replaced from granulation part to the lubrication part. In addition, increase the lubricants concentration to avoid sticking. In this trial, all the parameters were found satisfactory at initial stages. Therefore, to know the best formula, formulation F8 undergoes the 32 randomized full factorial optimization studies. Based on preformulation studies, the amounts of croscarmellose sodium (X1) and microcrystalline cellulose PH102 (X2) were selected as the independent factors, studied at 3 levels each (-1, 0, +1). The percentage drug release (y1) and disintegration time (y2) were taken as dependent factors.

Optimized batches were coded as OF1, OF2 OF3, OF4, OF5, OF6, OF7, OF8 and OF9. The Precompression and post compression studies was performed for all the optimized batches. Results were found to be similar for all the optimized batches and innovator product. From these studies, OF7 was selected and compared all the evaluation profiles with the innovator product during the period of stability studies.

Evaluation of blend materials of clarithromycin tablets: The angle of repose of formulation blends of clarithromycin F1 to F8 were in the range of 30.14±0.29° to 34.93±0.68°. The bulk density, tapped density, Carr's index, hausners ratio were found in the range of 0.472 to 0.534g/cc, 0.55 to 0.61g/cc, 10 –15.33g/cc and 1.11-1.18 respectively. It reveals that all the formulation blends were having good flow characteristics and flow rates.

The results of granule evaluation were given in Table 10.Tablet characteristics of clarithromycin uncoated IR tablets:

The tablets of different formulation were subjected to various evaluation tests such as thickness, hardness, friability and drug content. All the formulations of clarithromycin showed uniform thickness. The hardness and percentage friability of all batches (F4 to F8) of clarithromycin ranged from 9.5 – 10.0 kg / cm2 and 0.1 – 0.3 % respectively. The disintegration of all batches (F4 to F8) of clarithromycin is found in limits 1.22-1.54. The drug content of clarithromycin uncoated tablets was found to be uniform among all the formulations which ranges from 99.01% –104.67%. The evaluation results of clarithromycin uncoated IR tablet were given in Table No. 28

Tablet characteristics of clarithromycin coated IR tablet:

The tablets of different formulation were subjected to various evaluation tests such as thickness, disintegration and drug content. All the formulations of clarithromycin showed uniform thickness. The disintegration time of all batches (F4 to F8) of clarithromycin is found within limits 2.24-2.27. The drug content of clarithromycin coated tablets was found to be uniform among all the formulations, which ranges from 98.87% – 104.54%. The evaluation results of clarithromycin IR tablet were given in Table No. 16.

Tablet characteristics of clarithromycin optimized coated IR tablet: The tablets of different formulation were subjected to various evaluation tests such as thickness, disintegration and drug content. The disintegration of all batches (OF1 to OF9) of clarithromycin are found within limits 2.08-3.06 min The drug content of clarithromycin coated tablets was found to be uniform among all the formulations which ranges from 99.99% – 104.54%. The evaluation results of clarithromycin IR tablet were given in Table 14.

In-vitro drug release study from F4 to F8

The in vitro drug release of all the formulations of clarithromycin from F4 to F8 at 5th, 10th, 15th, 20th and 30th minutes was found to be in the range of 68.55-69.19%, 81.57-85.31%, 91.23-96.27%, 92.67-98.36%, and 96.34-101.15% respectively. Among all the formulations, F8 were found to be the best (F8-Clarithromycin-500mg, CCS-17 mg, povidone - 35mg, CCS (L) - 25.50mg, MCC102-196mg, pregelatinized starch (L)- 50mg, talc - 9.50 mg, aerosil l-9.50 %, magnesium stereate-7.50mg) since its release was satisfactory i.e., 69.19%,85.31%, 96.27%,98.36%, 101.15% at 5th,10th,15th,20th,30th minute. Comparison of clarithromycin IR tablets (OF7) with innovator product Table 18, gives the comparison of in-vitro dissolution profile of clarithromycin IR batch (OF7) with the innovator product. The drug release of clarithromycin IR tablet was found to be 70.83%, 84.96%, 95.45%, 98.46%, and 101.62% at 5th, 10th, 15th, 20th, 30th min respectively. The drug release of innovator product was found to be 80.88%, 95.46%,97.55%,99.34% and 102.56% at 5th,10th,15th,20th ,30th minute respectively for clarithromycin . In Table No:33, the formulation OF7 shows the dissimilarity factor f1 and similarity factor f2 values are within the specified limits (i.e., 5.147 and 59.658) when compared with the innovator product. Hence, formulation OF7 was selected for stability studies.

Stability Studies

The clarithromycin immediate release tablets (OF7) was kept on stability at 40° C/ 75 % RH and the three month accelerated condition results were found to be satisfactory. The stability study data's were depicted in the Table19.

Table19: Stability studies for assay of OF7.

Assay (%)	Storage condition 40˚C ± 2˚C / 75% RH ± 5% RH			
	Initial	**1st month**	**2nd month**	**3rd month**
OF7	101.10	102.25	99.74	96.75
Innovator	98.34	98.45	97.62	96.40

Conclusion: The objective of the present study was to formulate, optimize and evaluate clarithromycin immediate release film coated tablet. Literatures regarding, clarithromycin tablet dosage form preparation, excipients selection, manufacturing method, etc., has been collected and reviewed. In this work among the entire optimized batches, formulation OF7 has been selected for calculating similarity factor, since it shows better results (i.e., faster disintegration time and rapid drug release) than other optimized batches. Similarity factor was calculated by comparing the in-vitro drug release profile for batch OF7 with the innovator product. The dissimilarity factor f1 value of 5.147 and similarity factor f2 value of 59.658 indicates that the two products were similar in in-vitro drugrelease.The tablets of OF7 optimized batch was subjected to accelerated stability studies as per ICH guidelines. Theresults of stability studies showed that there were no significant changes in the physical and chemical parametersstudied. From this study, it was concluded that optimized clarithromycin tablet (OF7) containing croscarmellose sodium (3.029%) and pregelatinized starch (6.029%) could be manufactured with reproducible characteristics from batch to batch.

Reference:

1. B. Rasmitha Reddy, B.Venkateswara Reddy, K.Navaneetha. Formulation and evaluation of Dasatinib immediate release tablets, World Journal of Pharmacy and Pharmaceutical Sciences 2014; 3(3): 1113-1123.
2. Kamath AV, Wang J, Lee FY, Marathe PH. Preclinical pharmacokinetics and in vitro metabolism of dasatinib (BMS354825): a potent oral multi-targeted kinase inhibitor against SRC and BCR-ABL. Cancer Chemother Pharmacol 2008; 61(3):365- 76.
3. Sai Madhav Reddy K, Laxmidhar Sahoo, Kamalakar Reddy G, Vamsi Krishna L., 'Formulation and evaluation of immediate release tablets of Linezolid.' Int. J. Pharm and Bio Arch 2011; 2 (4): 1230-1235.
4. Malthi kodithyala et al. Formulation and Evaluation of dasatinib floating microsphers, IJIPSR 2014; 2(9):2086-2105.
5. Rakesh P. Patel and Nitish Thakker. Studies in development of dasatinib nanoformulations, European Journal of Pharmaceutical and Medical Research 2016; 3(7):423-432.
6. Chinmaya keshari sahoo, Muvvala sudhakar, Satyabrata bhanja, Uttam Prasad Panigrahy, Kanhucharan Panda. Development and evaluation of immediate release tablets of dasatinib using sodium starch glycolate as super disintegrant. Innoriginal International Journal of Sciences 2017; 4(1):4-7.
7. Abdel Naser Zaid, Salam Natour, Aiman Qaddomi and Abeer Abu Ghoush. Formulation and in vitro and in vivo evaluation of filmcoated montelukast

sodium tablets using Opadry® yellow 20A82938 on an industrial scale, Drug Des Devel Ther 2013; 7: 83–91.
8. Jain A, Gupta DMK, Sharma V. Formulations and evaluation of film coated immediate release tablets of piracetam. Journal of Biomedical and Pharmaceutical Research 24 Jan.2018;7(1)205-215.
9. Chinmaya keshari sahoo and D. Venkataramana. Formulation and Evaluation of Immediate release Tablets of Dasatinib using Croscarmelose sodium. Research Journal of Pharmacy and Technology 2017; 10(3):833-838.
10. A.K. Das, S. Bhanja, N. Srilakshmi. Formulation and evaluation of quetiapine immediate release film coated tablets, Asian Journal of Pharmaceutical and Clinical Research 2013; 6(3):107-112.
11. Monica RP Rao, Visha KG, Girish SS., „Preparation and Evaluation of an immediate release tablet of metoclopramide Hcl using simplex centroid Mixture design.‟ Int. J. pharmtech Res, 2010; 2(2): 1105-1111
12. Bhowmik, D., Chiranjib. B, Chandira, R.M. and Kumar, K.P. Emerging trends of disintegrants used in formulationof solid dosage from. Der Pharmacia let, 2010; 2: 495-504.
13. Maroni A, Moutaharrik S, Zema L, Gazzaniga A. Enteric coatings for colonic drug delivery: State of the art. Exp Opin Drug Deliv. 2017;14:1027-1029.
14. Liu F, Moreno P, Basit AW. A novel double-coating approach for improved pH-triggered delivery to the ileo-colonic region of the gastrointestinal tract. Eur J Pharm Biopharm. 2010;74:311-315.
15. Roy P, Shahiwala A. Multiparticulate formulation approach to pulsatile drug delivery: Current perspectives. J Control Rel. 2009;134:74-80.
16. Gambhire M. S., Bhalekar M. R., Gambhire V. M.,“Statistical optimization of dithranol-loaded solid lipid nanoparticles using factorial design”, Braz. J. Pharm. Sci., 2011,47(3), 503-11.
17. Pandey A. K., Rawat PK.,Tyagi.C.K., Shah S. K. Formulation And Evaluation Of Mouth Dissolving Tablet Of Prochlorperzine Maleate, International Journal of Pharmaceutics & Drug Analysis 2018:6 (1); 13-21.
18. SHAH S.K. , TYAGI C,K., JHADE D.N., PANDEY P, Oral Control Release Microparticulate Drug Delivery Study Of Aceclofenac Using Natural Polymer., Asian J Pharm Clin Res, Vol 9, Issue 3, 2016, 229-235.
19. Brahmaiah B., Sasikanth K., Nama S., Suresh P., Patan A., “Formulation and dissolution study of valsartan immediate release tablets” Int. J. Inno. Drug Disc., 2013, 3(1), 33-38
20. Rai V.K., Pathak N., Bhaskar R., “Optimisation of immediate release tablets of reloxifene hydrochloride by wet granulation method”, Int. J. Pharm. Sci. Drug Res., 2009, 1(1), 51-54.