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Formulation and Evaluation of Clarithromycin Co-Crystals Tablets Dosage Forms to Enhance the Bioavailability

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Abstract
Clarithromycin is a semi-synthetic macrolide antibiotic which inhibits bacterial protein synthesis by binding to the bacterial 50S ribosomal subunit. In this work BCS Class II drug Clarithromycin is used as a model drug, which is having poor solubility but high permeability. A pharmaceutical co-crystal is a single crystalline solid that incorporates two neutral molecules, one being an active pharmaceutical ingredient (API) and the other a co-crystal former. Co-crystals of Clarithromycin were prepared using co-crystal former (urea), with method of preparation (solvent evaporation). In the present study, Clarithromycin co-crystals tablets were prepared and evaluated in order to improve the dissolution by enhancing the solubility of Clarithromycin using urea co crystals to improve the bioavailability. In this work, the wet granulation method was attempted for formulation of conventional tablets of Clarithromycin. The Clarithromycin tablets are available in 250mg- 500mg, doses in market. Dose of 250mg was selected for the present research work.

Keywords: Clarithromycin, Poor solubility, co-crystal, Tablet, Bioavailability etc.

Introduction
The poor solubility of drug is a major problem which limits the development of highly potent pharmaceutics. The drugs with low solubility lead to low oral bioavailability and erratic absorption which is particularly pertinent to drugs within class II of the Biopharmaceutical Classification System (BCS). BCS Class II drug Clarithromycin is having poor solubility but high permeability [1-4]. Therefore, one of the most challenging tasks in drug development is to improve the drug solubility in order to enhance the bioavailability of these drugs. Several strategies have been employed to overcome these limitations. The approaches to increase the solubility and the available surface area for dissolution are classified as physical and chemical modifications. Clarithromycin, Fig. 1, is a semi-synthetic macrolide antibiotic which inhibits bacterial protein synthesis by binding to the bacterial 50s ribosomal subunit. In this work, the wet granulation method was attempted for formulation and evaluation of conventional tablets of Clarithromycin to improve the bioavailability [5-9].

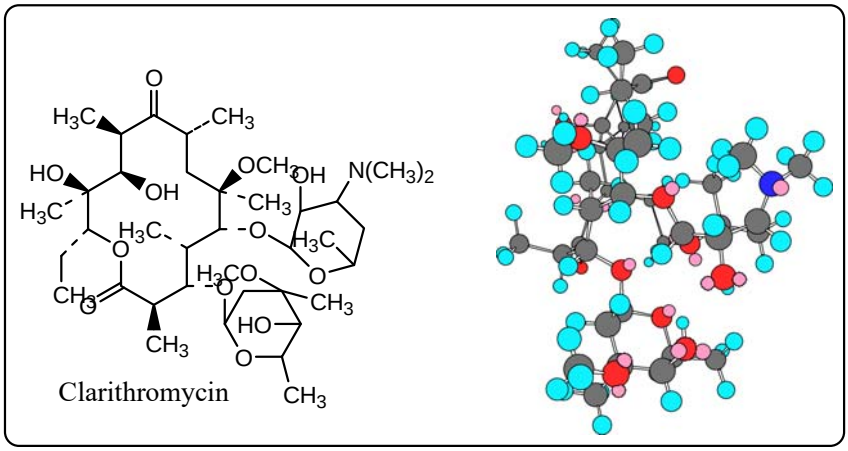


Fig 1: Structure of Clarithromycin

Materials and Methods

Materials

Clarithromycin (Quality Trading Company, New Delhi), Urea (DNS Fine Chemicals and Laboratories, Ltd, Mumbai, Lactose Monohydrate, Magnesium Stearate (Shreenath Chemicals, Mumbai), Methanol, HCl and Acetone (Merck Specialties Pvt. Ltd Mumbai), Hydroxy propyl methyl Cellulose (A.B. Enterprises, Mumbai),. All other reagents and chemicals used were of analytical reagent grade and were used as such without any further purification. Purified water USP was used where ever required.

Methods

Preformulation studies of Clarithromycin pure drug [10-14]

Preformulation studies of Clarithromycin (CLN) pure drug was carried out by determination of Melting point (capillary method), Solubility of CLN in various solvents. Lambda max (λ_{max}) of CLN was determined using phosphate buffer at pH 7.4, scanning between 200-400nm and Calibration curve was prepared. The FT-IR spectra of Clarithromycin, was obtained on Jasco FT/IR-4100 spectrometer, (Japan) over the range 400- 4000cm^{-1}. Dry KBr (50mg) was finely ground in mortar and drug (1-2mg) were subsequently added and gently mixed in order to avoid trituration of the crystals.

Differential Scanning Calorimetry (DSC) analysis was performed using Samples (3-5 mg) were crimped in non-hermetic aluminium pans with lids and scanned from 50 to 300ºC at a heating rate of 10ºC/min under a continuously purged dry nitrogen atmosphere (flow rate 20mL/min). The X-ray diffraction (XRD) pattern of pure drug was recorded applying voltage 35 kV, 20 mA. Micromeretics properties of pure CLN drug was studies by determining of bulk density, Tapped Density, Car's Index, Angle of Repose and Hauser's Ratio. Drug-excipient compatibility was performed using FTIR spectrum studies.

Preparation of Co-Crystals and Formulation Development

Co-crystal was prepared using the stoichiometric ratio of CLN: Urea in 1:1, 1:1.5, 1:2, and 1:2.5 respectively by using solvent evaporation technique [15]. The tablets of CLN-co-crystals (250 mg) were prepared using wet granulation method according to the formulae given in Tables 1. All the ingredients except magnesium stearate were weighed and passed through # 40mesh separately and mixed in geometrical order. Granulation was done with distilled water and granules were dried at 55ºC in hot air oven and shifted through # 30mesh. All the lubricant and left amount of glidant were added and mixed for 10 minutes. The blend thus obtained was compressed using 9mm flat round punches into tablets of 360mg on a 6- rotatory tablet machine. [16-18]

Table 1: Formulation design for Clarithromycin: Urea co-crystal Tablets

S. No	Ingredients (mg/Tablet)	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)
1.	Clarithromycin: Urea co crystal	250:20.08 (1:1)	250:30.12 (1:1.5)	250:40.16 (1:2)	250:50.2 (1:2.5)
2.	Lactose monohydrate	65	65	65	65
3.	HPMC	20%	20%	20%	20%
4.	Starch	5%	5%	5%	5%
5.	Magnesium Stearate	10	10	10	10
6.	Talc	10	10	10	10

Evaluation of clarithromycin co-crystals powder (pre-compression parameters) [19-20]

Angle of Repose (Θ)

The angle of repose of powder was determined by the funnel method. The accurately 10 gm weighed powder were taken in a funnel. The height of the funnel was adjust and the powder was allowed to flow through funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation-

$\text{Tan}\,\theta = \frac{h}{r}$, Where θ = angle of repose, h = height of the cone, r = radius of the cone base

Bulk density

A quantity of 10 g of powder from each formulation, previously lightly shaken to break any agglomerates formed was introduced into a 50 ml measuring cylinder. The bulk volume and mass of the powder was determined. The bulk density was calculated using following formula.

$$\text{Bulk density} = \frac{\text{Weight of granules}}{\text{Volume of granules}}$$

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume occupied in the cylinder and the mass of the blend was measured. The tapped density was calculated using the following formula.

$$\text{Tapped density} = \frac{\text{Weight of granules}}{\text{Volume of granules after 100 tapping}}$$

Carr's Index

The simplest way for measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by Carr's index which is calculated as follows.

$$\text{Carr's index (\%)} = \frac{\text{TBD - LBD}}{\text{TBD}} X100$$

Where,

LBD = weight of the powder/volume of the powder

TBD = weight of the powder/tapped volume of the powder

Hausner's ratio

Hausner's ratio value is less than 1.25 indicates good flow and greater than 1.5 indicates poor flow property which was calculated by using following formula-

$$\text{Hausnre's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Evaluation of Clarithromycin Co-Crystals Tablets (Post Compression Parameters) [21-26]

The tablets of every batch after punching were evaluated for in-process and finished product quality control tests i.e. thickness, hardness, friability, weight variation, disintegration time and in- vitro dissolution studies.

***In vitro* dissolution study**

In vitro drug release of all formulations was carried out using USP-type II dissolution apparatus (paddle type). The dissolution medium, 900 ml Phosphate buffer pH 7.4 was placed into the dissolution flask maintaining the temperature at 37 ± 0.50C and speed of 75 rpm for 30mins. 5ml of the Aliquot was taken at intervals of 5min, 10min, 15min, 20min, 25min and 30mins. After collecting the sample, the dissolution medium was replenished with the same volume of fresh medium, and the sample was filtered. 1ml of the filtrate was diluted to 10 ml with phosphate buffer pH7.4 and analyzed using UV spectrophotometer at 207 nm.

Disintegration time

To test for disintegration time, one tablet was placed in each tube and the basket rack was positioned in a 1-L beaker of water at 37 ± 2 °C, such that the tablet remain 2.5cm below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker.

Determination of Drug content

Five Tablets from each formulation batch were weighed and taken in mortar-pestle and crushed to make powder. Quantity of powder equivalent to 250 mg of Clarithromycin was weighed and taken in 100 ml volumetric flask and dissolved in 5 ml of acetone and diluted up to 100ml with Phosphate buffer pH 7.4. It was then shaken vigorously on a Magnetic stirrer for 2 min and filtered into 50 ml volumetric flask up to the mark by using Whatman filter paper. Further appropriate dilutions were made and absorbance was measured at nm 207 nm.

Comparative dissolution Study with marketed product

Comparative study of prepared optimized co-crystal tablet and marketed product was performed in paddle type dissolution apparatus containing 0.1 N Phosphate buffer.

***In-Vitro* Antimicrobial Study**

The batch of Tablets with high solubility and dissolution rate was selected for in-vitro anti- microbial study. To perform the study, agar plates were prepared under sterile condition and 0.2 ml of test organism i.e. staphylococcus aureus was swabbed. Tablet containing drug was selected for both free drug and drug loaded batches was placed in a small well and cut into the agar plates with the help of sterile forceps, the four similar plates were prepared and kept at different time for diffusion. The time period for diffusion was 2, 4, 6, and 8 hrs. After the diffusion period the plates were kept for incubation (37^0C). Each plates was incubated for 18 hrs and zone of inhibition was observed.

Stability Study of Optimized Formulation

The stability study was carried out for optimized formulation as per ICH guidelines. The tablets of the F4 batch were placed in screw capped glass container and stored at 40^0C ± 2^0C (75% ± 5%RH) ICH storage condition. For a period of 4 weeks the samples were further analyzed for physical appearance and the drug content.

Results and Discussion

Melting point of pure Clarithromycin was found to be in the range of 223-225^{0}C. Solubility of Clarithromycin was found to be insoluble in H_2O, slightly soluble in ethanol (95%) and methanol, very slightly soluble in Phosphate buffer pH 7.4, soluble in 0.1 N HCl, freely soluble in Acetone. Lambda max (λmax) of CLN was found at 207 nm. The standard calibration curve was prepared which was found to be linear in the range of 20-100 µg/ml. The regression value was found to be 0.999. Results of FTIR spectrum of clarithromycin is reported in Fig. 2. The DSC curve of Clarithromycin shows a sharp melting endotherm at around 231.64 ºC against the reported melting point of 225 0C using capillary melting method. The onset of melting peak started at 229.77 0C, Fig 3. The XRD spectra of clarithromycin showed characteristics peaks at (2θ values) 8.530, 11.152, 15.199, 17.197, and 18.77, Fig. 4. This data indicated that the drug was in the crystalline and stable form.

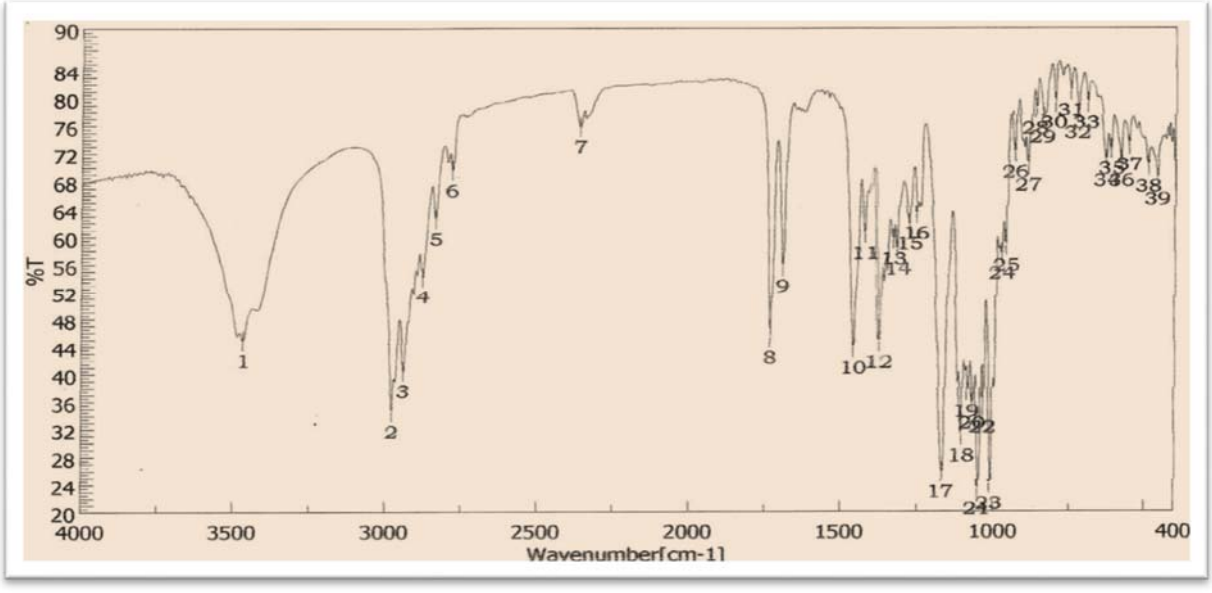


Fig 2: FT-IR spectra of Clarithromycin (Pure Drug)

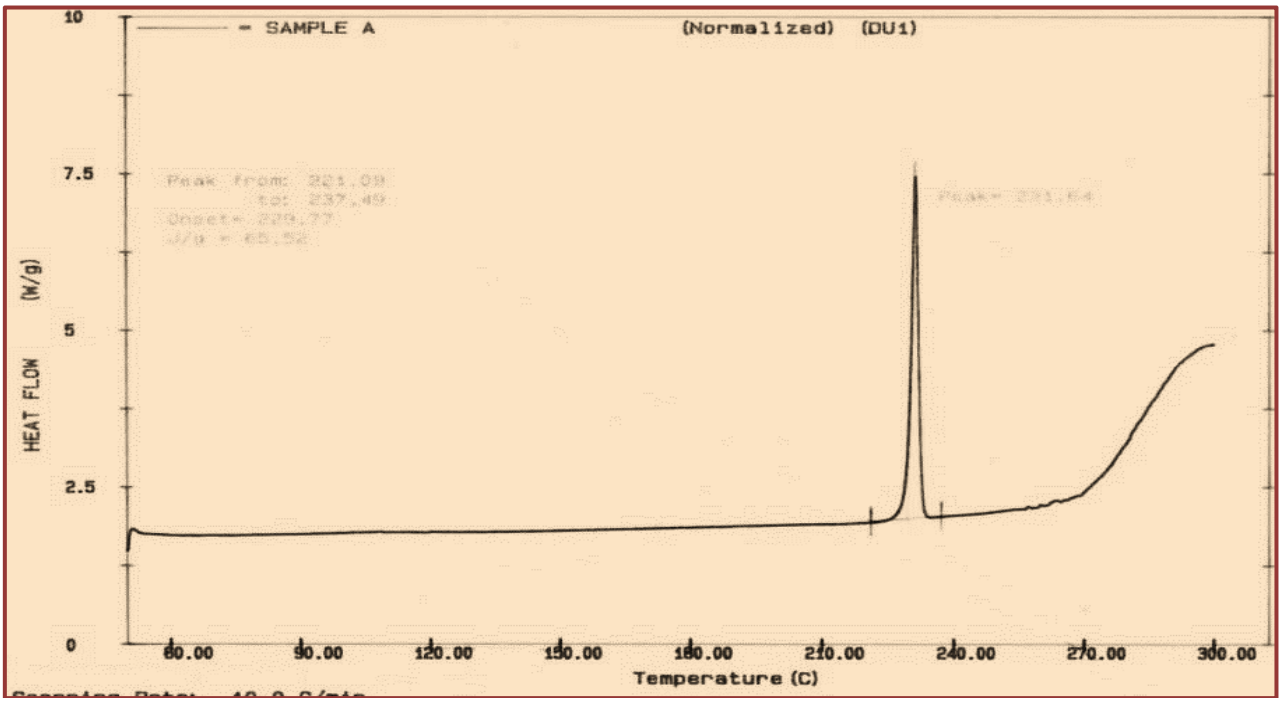


Fig 3: DSC spectra of Clarithromycin (Pure Drug)

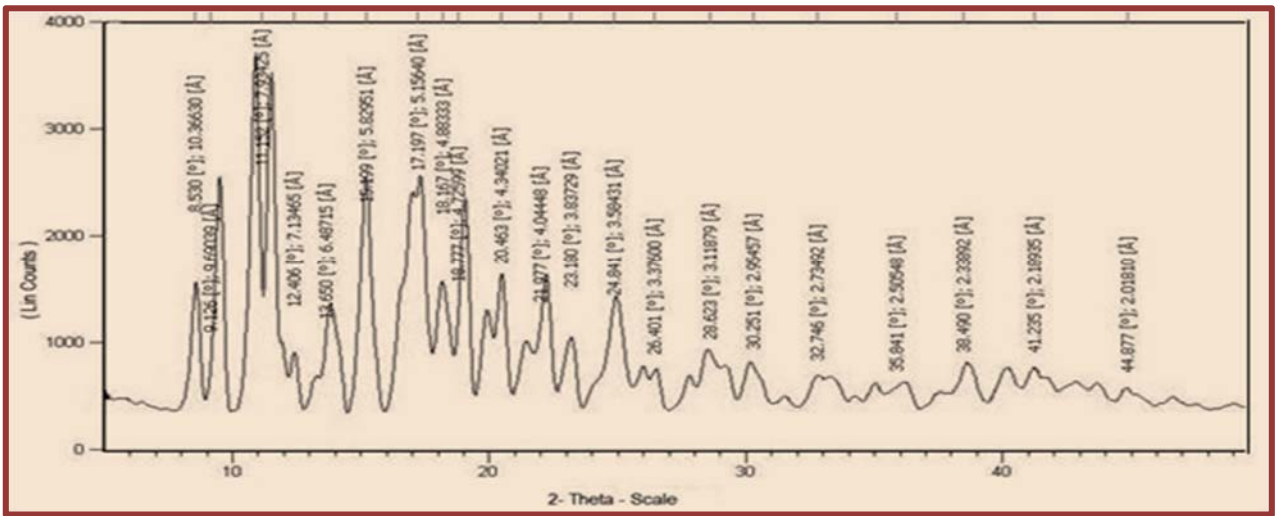


Fig 4: PXRD spectra of Clarithromycin

Results of micrometric studies of Clarithromycin are indicated that, all the values are found to be in range, indicating good flow property of the API, Table 2. FTIR spectra of drug-excipient compatibility are reported in Fig. 5, and the data are reported in Table 3. It was found that Clarithromycin was compatible with the selected excipients used in the formulations as there were neither any extra peaks observed nor any colour change takes place.

Table 2: Flow characteristics of CLN Pure powdered

Sr. No.	Parameters	Observations	Specifications
1.	Angle of repose	350	31-35*; Good flow*
2.	Bulk density	0.500 g/ml	-
3.	Tapped density	0.615 g/ml	-
4.	Carr's index	17.73 %	*12-18; Good flow*
5.	Hausner's ratio	1.26	*1.25-1.5; Good flow*

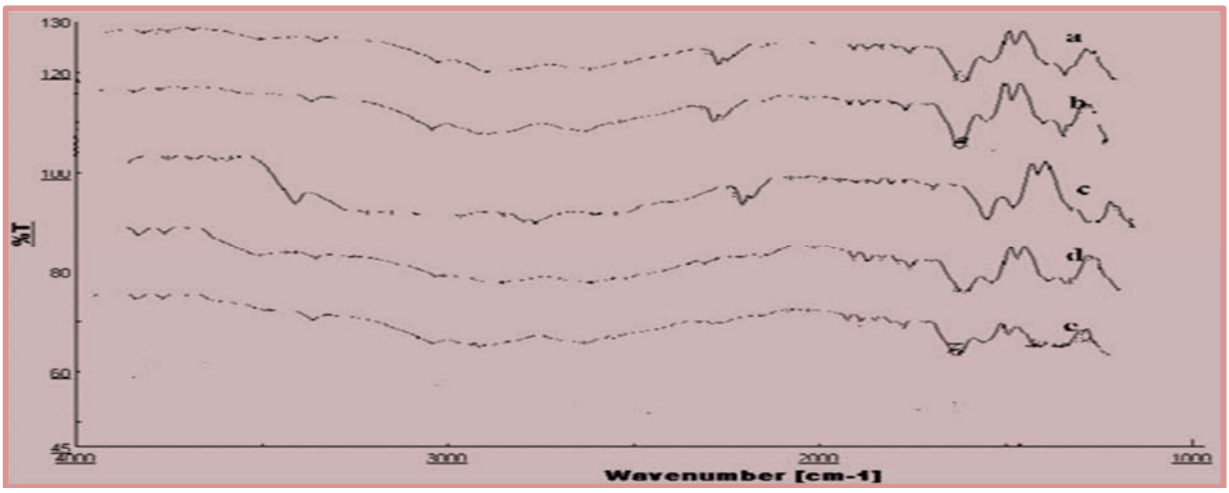


Fig 5: FT-IR spectra of Physical mixture of CLN: Urea co-crystal and excipients

(a) Clarithromycin : Urea co-crystal + starch,
(b) Clarithromycin: Urea co-crystal + Talc
(c) Clarithromycin: Urea co-crystal + HPMC
(d) Clarithromycin: Urea co-crystal+ Lactose,
(e) Clarithromycin: Urea co-crystal+ magnesium stearate

Table 3: Drug-excipient (CLR: UREA co-crystal) compatibility study at 40±2ºC/75±5% RH

Sr. No.	Drug: co-crystal + Excipient (1:1)	Physical Evaluation	Chemical Evaluation	Inference
1.	Physical mixture of CLR:UREA and Starch	No colour change	No change in FT-IR Spectra	Compatible
2.	Physical mixture of CLR:UREA an Talc	No colour change	No change in FT-IR Spectra	Compatible
3.	Physical mixture of CLR:UREA and HPMC	No colour change	No change in FT-IR Spectra	Compatible
4.	Physical mixture of CLR:UREA and Lactose	No colour change	No change in FT-IR Spectra	Compatible
5.	Physical mixture of CLR :UREA and Magnesium stearate	No colour change	No change in FT-IR Spectra	Compatible

Results of Precompression parameters include bulk density, tapped density, angle of repose, Hauser's ratio and compressibility index are reported in Table 4 and it was found that all the observations were within the prescribed limits of IP.

Table 4: Pre compression parameters of formulated CLN: UREA co-crystal granules

Sr. No.	Parameters	F1	F2	F3	F4
1.	Bulk density(g/ml)	0.505	0.512	0.515	0.523
2.	Tapped density(g/ml)	0.610	0.630	0.612	0.621
3.	Hausner's ratio	1.22	1.11	1.18	1.18
4.	Compressibility index	18.03	16.33	15.84	15.78
5.	Angle of repose(º)	30.96	33.02	31.38	29.68

The bulk density of all the formulations was found to be in the range of 0.505- 0.523g/ml, tapped density was in between 0.610-0.621g/ml, and angle of repose lies in range of 29.68º-30.96º, Hausner's ratio was found to be 1.18-1.22 and compressibility index was in between 15.78-18.03 indicating good flow property of tablet granules. Results of Post-compression parameters such as hardness, weight variation, thickness, friability, and drug content. are reported in table 5.

Table 5: Evaluation of CLN: Urea co-crystal tablets (n=3)

Sr. No.	Batch	Hardness (kg/cm2)	Friability (%)	Thickness (mm)	Weight Variation (mg)	Disintegration time (min.)	% Drug content
1.	F1	5.0	0.481	2.95±0.01	360.39±0.15	15.90	80
2.	F2	5.50	0.466	3.00±0.02	360.97±0.04	16.20	80.4
3.	F3	5.50	0.524	2.70±0.04	360.4±.075	16.00	78.8
4.	F4	4.50	0.582	2.98±0.01	360.65±0.27	15.60	80.8

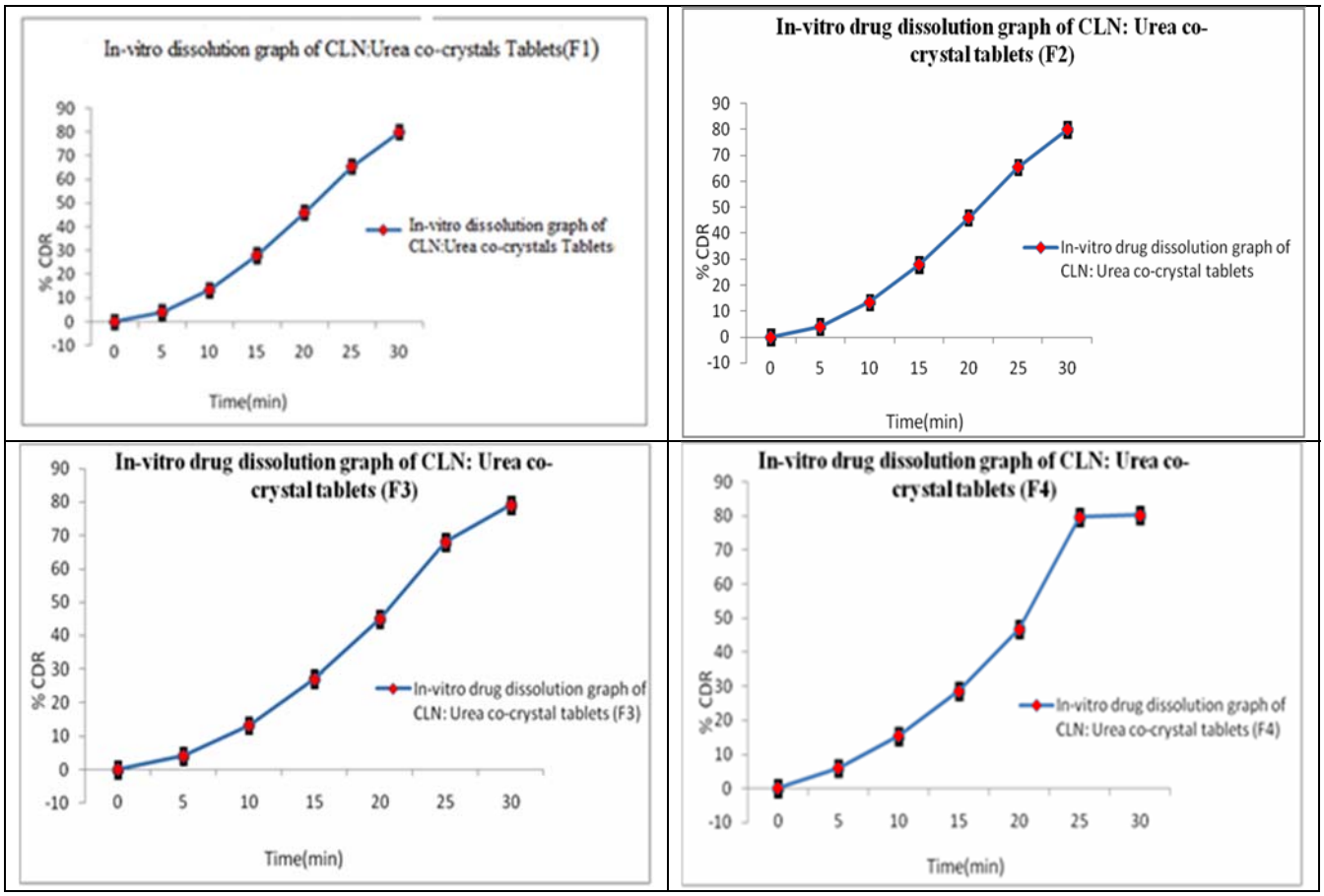


Fig 6: Drug release profile for CLN: Urea co-crystal Tablets (F1-F4)

Table 6: Comparative *in-vitro* drug dissolution data for CLN: Urea co-crystal Tablets

Sr. No	Time (min.)	% Cumulative drug released				
		F1± S.D.	F2± S.D.	F3± S.D.	F4± S.D.	S.E. (F1-F4)
1.	0	0	0	0	0	0
2.	5	4.01±0.01	4.01±0.05	4.01±0.01	5.90±0.01	0.472
3.	10	13.45±0.01	13.45±0.03	13.25±0.01	15.40±0.02	0.50
4.	15	28.00±0	28.00±0	27.02±0.02	28.46±0.01	0.30
5.	20	46.01±0.01	46.01±0.01	45.01±0.01	46.68±0.01	0.34
6.	25	65.51±0.01	65.51±0.04	68.01±0.01	79.70±0	3.3
7.	30	80.01±0.01	80.01±0.01	79.10±0.01	80.23±0.01	0.25

All the formulations showed more than 79% of drug release in 30 min. The formulations F4 shows more drug release (80 % drug release) than formulations F1, F2 and F3, Table 6. A comparison of optimized formulation (F4) was made with marketed Tablets and it was found that the formulated Clarithromycin: Urea co-crystal tablets are comparable with the marketed tablets. The comparison of *in-vitro* drug release of optimized formulation (F4) and marketed tablets was reported in Fig. 7 and Table 7 respectively.

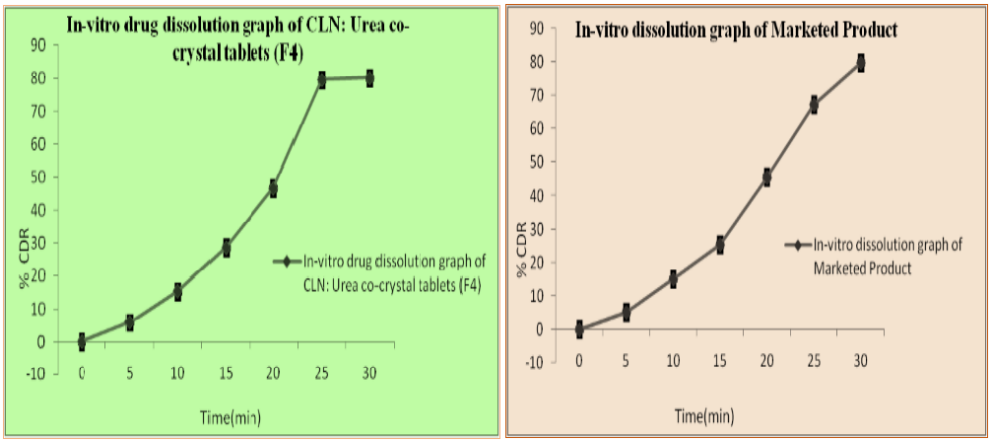


Fig 7: Comparative *in-vitro* drug dissolution profiles for Optimized formulation (F4) and Marketed product

Table 7: *In-vitro* drug release for Optimized formulation (F4) and Marketed product

Sr. No.	Time (min)	% Cumulative drug dissolved		
		F4 ±S.D.	Marketed Product ± S.D.	S.E. between F4 and Marketed Product
1.	0	0	0	0
2.	5	5.90± 0.01	5.21±0.03	0.33
3.	10	15.40± 0.02	15.16 ± 0.01	0.11
4.	15	28.46± 0.01	25.45 ± 0.01	1.49
5.	20	46.68± 0.01	45.57 ± 0.01	0.55
6.	25	79.70± 0	67.34 ± 0.03	1.17
7.	30	80.23± 0.01	79.86 ± 0	0.18

The *in vitro* antimicrobial studies revealed that the optimized formulation F4 was fast released as compared to marketed drug. The drug from co-crystal was released at a fast rate, so that more inhibition activities has been observed as compared to that of marketed drug. Results are reported in table 8 and Fig. 8 and 9. For one month stability shows that all parameters of formulation including physical appearance, dissolution profile and assay shows no significant, So it indicates that the optimized formulation (**F4**) is stable, Table 9.

Table 8: *In-vitro* antimicrobial activity study

Sr. no.	Time (hrs.)	Inhibition zones for F4 (cm)	Inhibition zones Marketed drug (cm)
1	2	1.4	0.8
2	4	2.7	1.0
3	6	3.6	1.4
4	8	4.0	2.1

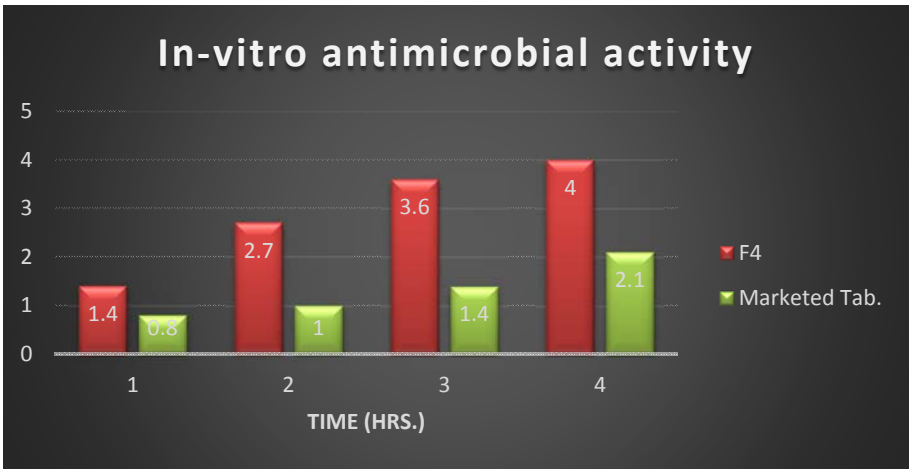
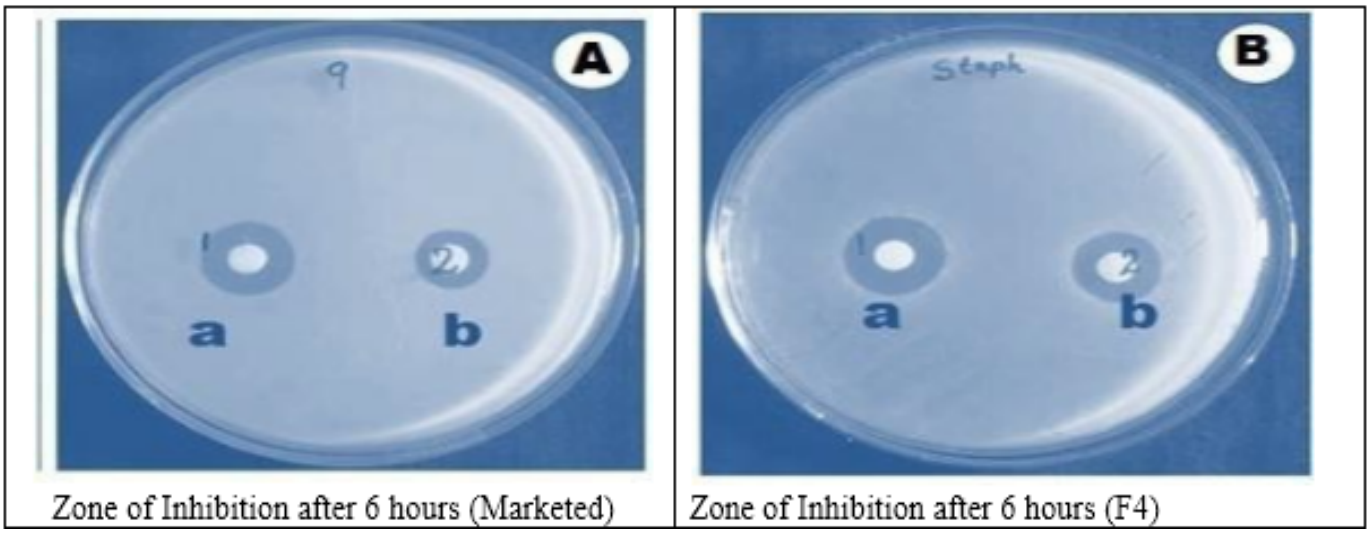


Fig 8: *In-vitro* antimicrobial activity F4 and Marketed Tab.



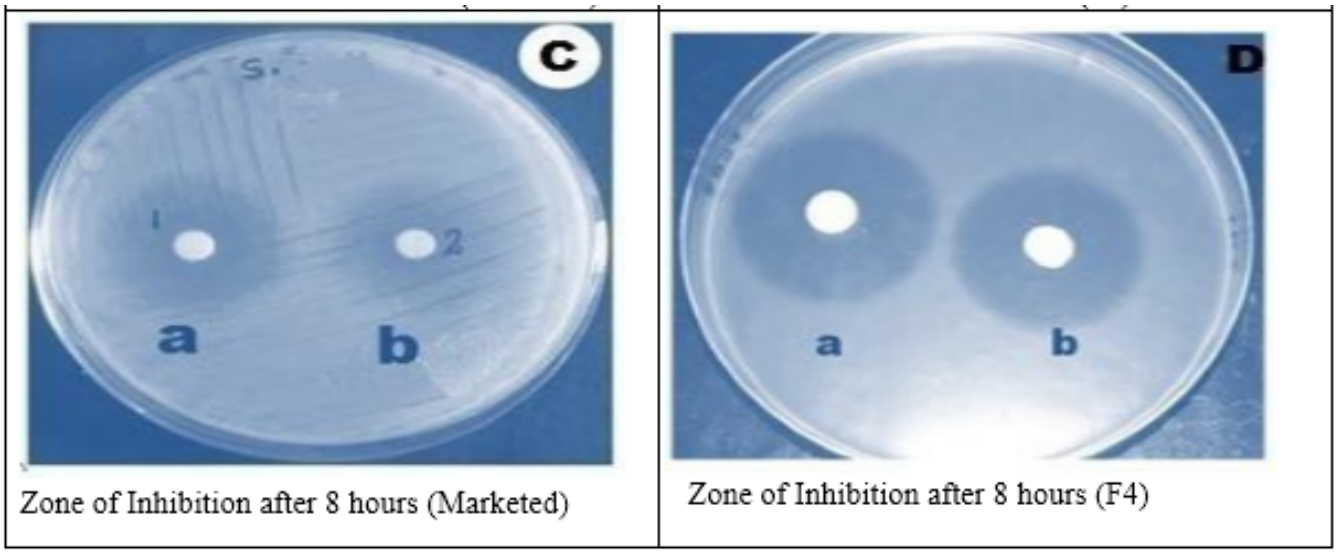


Fig 9: Zone of Inhibition (cm) of F4 and Marketed Drug

Table 9: Stability Study result of optimized formulation (F4)

Condition	Physical Appearance	Dissolution (In 30 min)	(%) Assay
Initial 40°C/75% RH (HDPE)	White	80.23	100
1 month 40°C/75% RH (HDPE)	White	79.56	99.16

Conclusions

The prepared CLN-co-crystals Tablet showed improved solubility and in turn higher dissolution rate than the marketed drug, indicating co-crystal approach as a novel and valuable means to alter the physical characteristics of an API without chemical modification. Based on the results, formulation F4 of Clarithromycin: urea co-crystal Tablet was found to be more suitable. The *in-vitro* drug release of optimized formulation was 80.23% in 30 min with an average hardness of 4.5kg/cm2 and also compared with marketed tablets of Clarithromycin. From the findings, it may be concluded that the formulated tablets of Clarithromycin co-crystals showed improved solubility characteristics and *in-vitro* drug release profile as compared to Marketed Tab. This in turn may be responsible for achieving higher oral bioavailability and better therapeutic effect.

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