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Original Article

Co-Crystals Formation of Clarithromycin with Urea: An Efficient Approach to Enhance the Solubility and Dissolution Rate

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ABSTRACT

Objective: Our main aim was to prepare co-crystals of Clarithromycin, which is having poor solubility but high permeability. Thus the main aim is used to enhance the solubility and dissolution rate.

Methods: 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. In this method co-crystal components or co-crystal formers are taken in stoichiometric ratio and solubilize in a common solvent. The resultant solution is allowed to evaporate slowly. This technique works on the principle that, when different molecules of complimentary functional groups afford hydrogen bonds that is more favorable than each of the individual molecular components. In this case, the co-crystal is likely to be thermodynamically favored. In-vitro dissolution studies were carried out in USP apparatus II (paddle) using 900mL phosphate buffer pH 7.4 as dissolution media at 75rpm for 30minutes.

Results: In-vitro dissolution studies of co-crystals it was found that the Pure CLN shows only a release of 75% after 30min whereas, the co-crystals shows a few folds increase (80%) in the dissolution profile. Hence, it is clear that the CLN: Urea co-crystals shows better *in-vitro* drug release than pure drug.

Conclusion: The prepared co-crystals showed improved solubility of CLN and in turn higher dissolution rate than the pure drug indicating co-crystal approach as a novel and valuable means to alter the physical characteristics of an API without chemical modification.

Keywords: Co-crystals, solvent evaporation, Clarithromycin, Urea and Solubility 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. Literature states that about 60% of all drugs coming directly from synthesis are nowadays poorly soluble[1-3]. Clarithromycin (CLN) is a semi-synthetic macrolide antibiotic chemically related to erythromycin and azithromycin (Zithromax). Clarithromycin is a poorly water soluble practically insoluble in water. Drug which has a reported water solubility is 0.33 mg/l. Therefore lots of efforts have been made to increase dissolution of drug[4-6].Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents and solid dispersion.

Co-crystals formation is a good methods for enhance the solubility, bioavailability and dissolution rate's crystal is 'a stoichiometric multi component crystal in which all its components are neutral and solid under ambient conditions when in pure form'.[7-8]**.** Co-crystal is a crystalline structure consisting of two or more components that form a unique structure having specific properties. The physical and chemical property improvements through pharmaceutical co-crystals draw closer the fields of crystal engineering and pharmaceutical sciences[9-10], Figure 1.

Pharmaceutical co-crystals have been described for many drugs such as acetaminophen, aspirin, ibuprofen, flurbiprofen etc. Co-crystals of anti-tubercular drugs with dicarboxylic acids were reported using carboxylic acid-pyridine synthon as a reliable tool[11-13].Our main aim was to prepare co-crystals of Clarithromycin, Clarithromycin is a semisynthetic macrolide antibiotic derived from erythromycin, 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[14-15]. Thus the main aim is used to enhance the solubility, bioavailability and dissolution rate by prepare co-crystals by solvent evaporation method and valuate the physicochemical properties of prepared co-crystals.

MATERIALS AND METHODS

Materials

Clarithromycin (Quality Trading Company, New Delhi), Urea (DNS Fine Chemicals and Laboratories, Ltd, Mumbai) Hydroxypropylmethyl Cellulose (A.B. Enterprises, Mumbai), Lactose Mono-hydrate, Magnesium Stearate (Shreenath Chemicals, Mumbai), Methanol, HCl and Acetone (Merk Specialities Pvt Ltd 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

Preparation of Co-Crystals

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. In this method[16] co-crystal components or co-crystal formers are taken in stoichiometric ratio and solubilize in a common solvent. The resultant solution is allowed to evaporate slowly. This technique works on the principle that, when different molecules of complimentary functional groups afford hydrogen bonds that is more favorable than each of the individual molecular components. In this case, the co-crystal is

likely to be thermodynamically favoured[17-18].

Clarithromycin and Urea were added to a reaction vessel. The solid were dissolved in 20 ml of acetone and 10 ml of methanol and heated to 70°C for 1 hour in water bath. Temperature was decrease in 10°C increments to induce precipitation in a stirrer, unseeded system.

Appearance of the co-crystal solid phase was first observed in the range of 60–50ºC. The temperature was further lowered to 30^{0}C to drive additional precipitation. Following equilibration at 30^{0}C, solids were isolated using a Buchner funnel. The collected colorless solid was dried in air and kept in desiccator for further characterization[19].

Characterization of Co-crystals

Characterization[20-21]of Co-Crystals carried out using Differential Scanning Calorimetry (DSC), in which we have used Shimadzu DSC 60 which was calibrated for temperature and enthalpy using pure Indium. 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 instrument was equipped with a refrigerated cooling system**.**

Also characterized using Fourier Transform Infrared Spectroscopy (FTIR) in which spectra of Clarithromycin, co-formers and their co-crystals were obtained on Jasco V-530 FTIR-4100 spectrometer (Japan) over the range 400- 4000cm^{-1}.

The X-ray diffraction pattern of pure Clarithromycin and co-crystals were obtained using a Bruker D8 Advance diffractometer (BRUKER, Germany) equipped with 2.2 KW Cu Anode, Dermic X-ray tube as source, Lynux Eye Detector, Beta Filter made of Ni Filter and Sample Holder of Zero Background and PMMA. The diffractograms were recorded under following conditions: voltage 35 kV, 20 mA, angular range 5, divergence slit 10, and receiving slit 0.15 mm. and using Digital Microscopy we have found the Image of co-crystal were taken at 40Xmagnification using Labomed Digi2 digital microscope, Figure 5. Solubility ofco-crystals was studies in different solvent were carried out in purified water.

In-vitro dissolution studies[22-23]were carried out in USP apparatus II (paddle) using 900mL phosphate buffer pH 7.4 as dissolution media at 75rpm for 30minutes.The % Cumulative Drug Dissolved (CDD) was determined for each time interval (5, 10,15,20,25 and 30min) using UV spectrophotometric method and plotted against time.

RESULTS AND DISCUSSION

The DSC thermogram of pure Clarithromycin shows a melting endotherm at 231.64^{0}C however the DSC scan of Clarithromycin: Urea co-crystal by solvent evaporation method shows a broad exothermic peak at 135.66^{0}C followed by a sharp melting peak at 139.37^{0}C. DSC thermogram of Clarithromycin, and Urea co-crystal are reported in figure 2.

FTIR indicate the kind of interactions occurring between API and co-former. From the FTIR spectra of Clarithromycin: Urea co-crystals the N-H stretching (3436.32 cm^{-1}), C-H Stretching (2939 cm^{-1}), O-H stretching (3600.3 cm^{-1}) confirms formation of inter-molecular H bond. Spectra is reported in figure 3.

XRPD patterns of Clarithromycin: Urea co-crystals shows sharp characteristic peaks indicating formation of new phases. From the above results, it is clear that there is transformation in the crystalline lattices of Clarithromycin: co-formers and co-crystals have been formed[24-25]. The XRPD patterns

of Clarithromycin, Urea co-crystals are reported in figure 4.

Co-crystalsofallfourformulationswerefoundtobe highlysolubleinmethanol,freelysoluble inethanol(95%) and solubility of co-crystals in distilled water and phosphate buffer pH 7.4 is more than that of puredrug. In-vitro dissolution studies of co-crystals it was found that the Pure CLN shows only a release of 75% after 30min whereas, the co-crystals shows a few folds increase (80%) in the dissolution profile. Hence, it is clear that the CLN: Urea co-crystals shows better *in-vitro* drug release than pure drug. The *in-vitro* drug release[26-27] data are reported in Tables 1and Figure 6. From the above discussion it is clear that the co-crystals having Urea as co-former are better candidates for drug release than the Pure Clarithromycin.

CONCLUSION

The prepared co-crystals showed improved solubility and in turn higher dissolution rate than the pure drug indicating co-crystal approach as a novel and valuable means to alter the physical characteristics of an API without chemical modification. DSC and FTIR studies results indicated that no interaction of drug with the carriers and conversion of crystalline form to amorphous form of drug results in improvement of solubility. Based on the results, formulation F4 of Clarithromycin: urea co-crystal was found to be more suitable, Figure 6.Solvent evaporation technique was successfully employed to enhance the aqueous solubility of CLN.

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Table 1. *In-vitro* drug release data for CLN: UREA co-crystal

Time (min)	Mean %Cumulative drug release				
	Pure Drug	CLN: UREA co-crystal			
		F1	F2	F3	F4
0	0	0	0	0	0
5	19.54	20.00	20.22	20.36	21.02
10	31.62	32.66	32.72	32.81	32.99
15	41.06	43.68	43.79	43.89	43.90
20	54.06	56.61	56.72	56.82	57.01
25	67.23	69.96	70.12	70.64	71.24
30	75.45	80.02	80.41	80.86	80.96

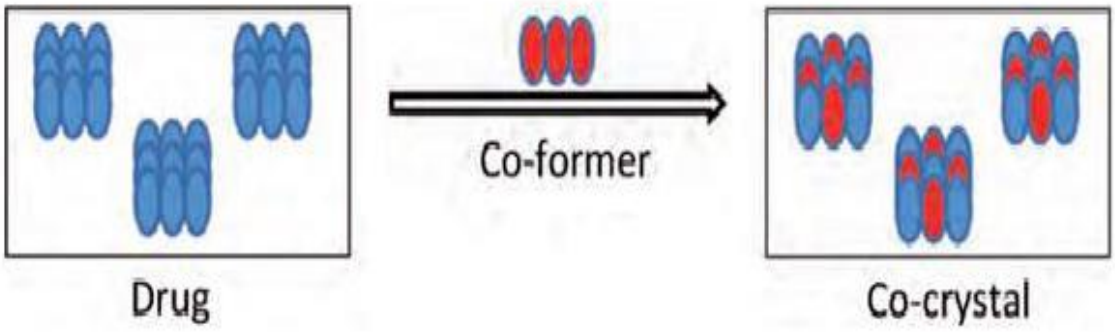

Figure 1. Co crystal composition

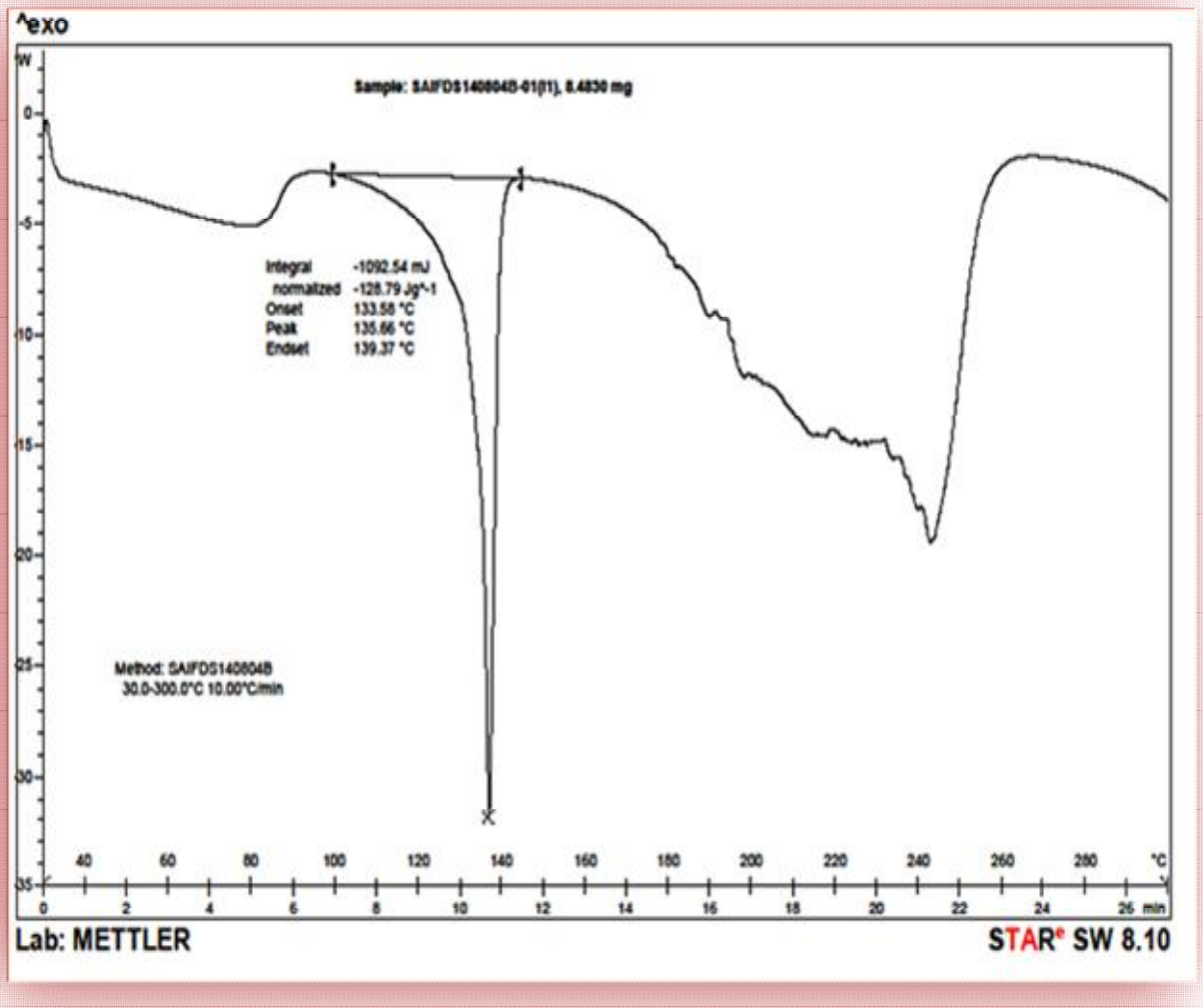

Figure 2. DSC curves of CLR: Urea co-crystal

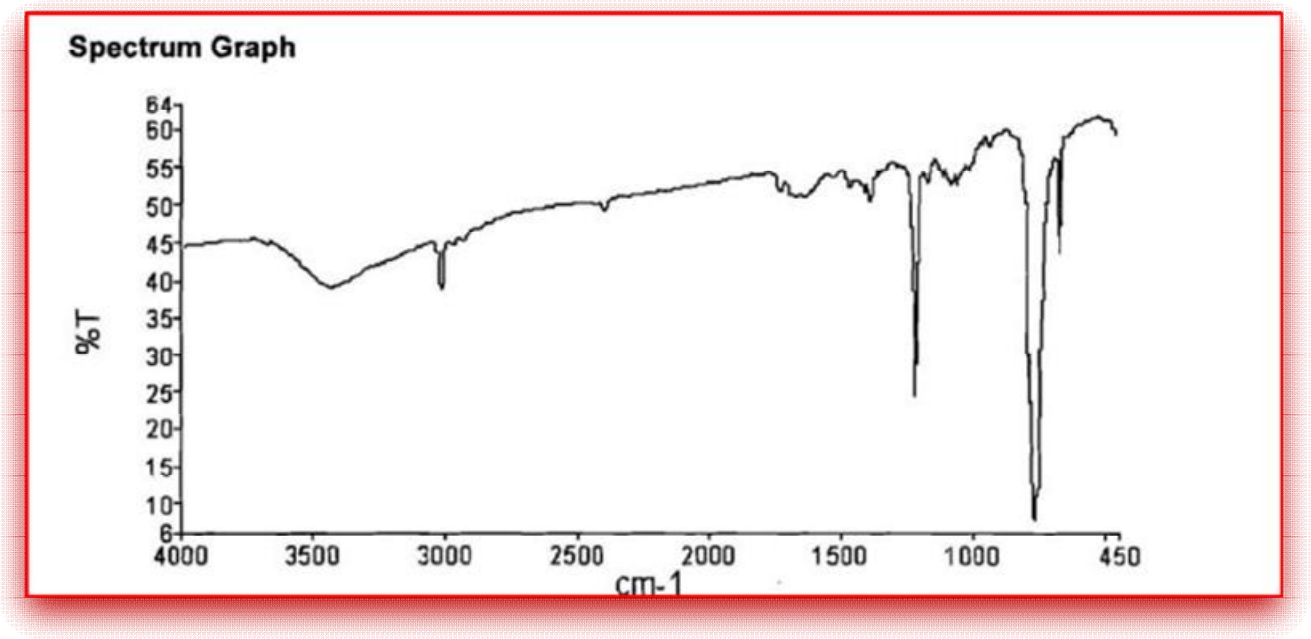

Figure 3. FT-IR spectra's of CLR: Urea co-crystals

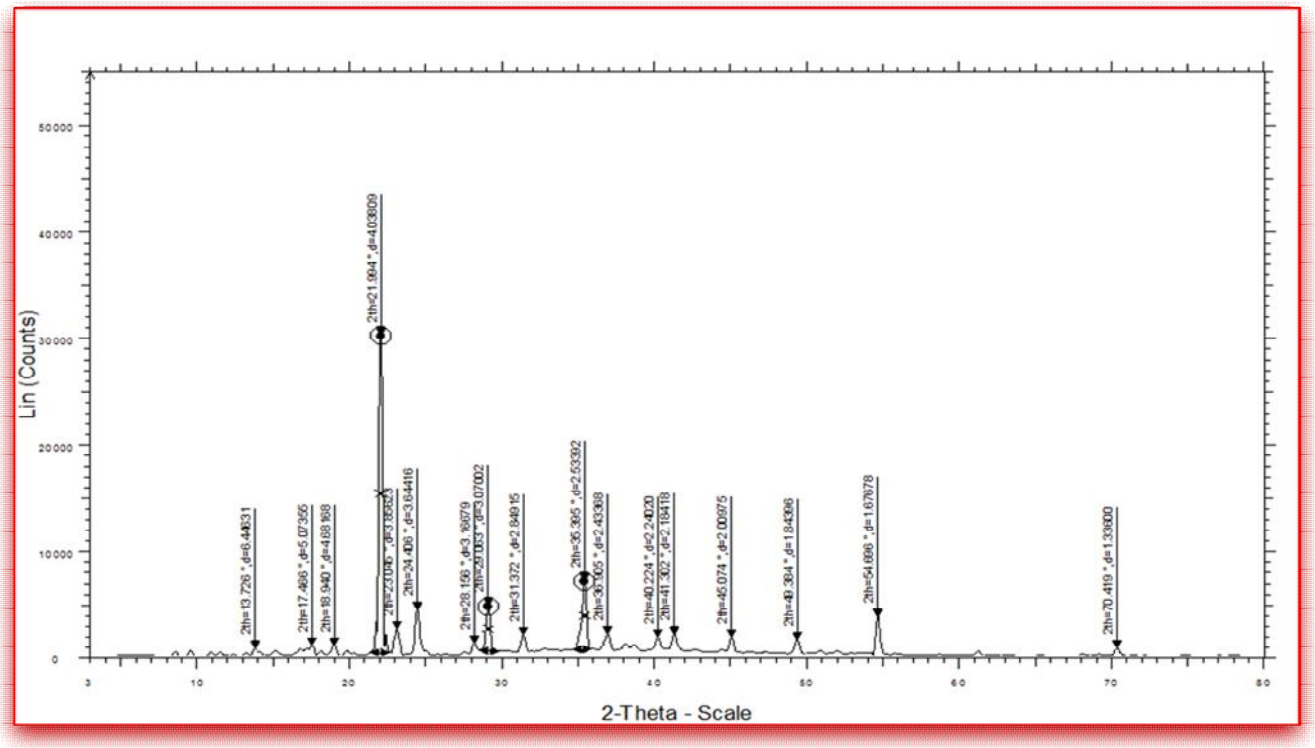

Figure 4. Powder X-ray diffraction patterns of Clarithromycin Urea Co-crystal

Figure 5. Photo micrograph of Clarithromycin: Urea co-crystal

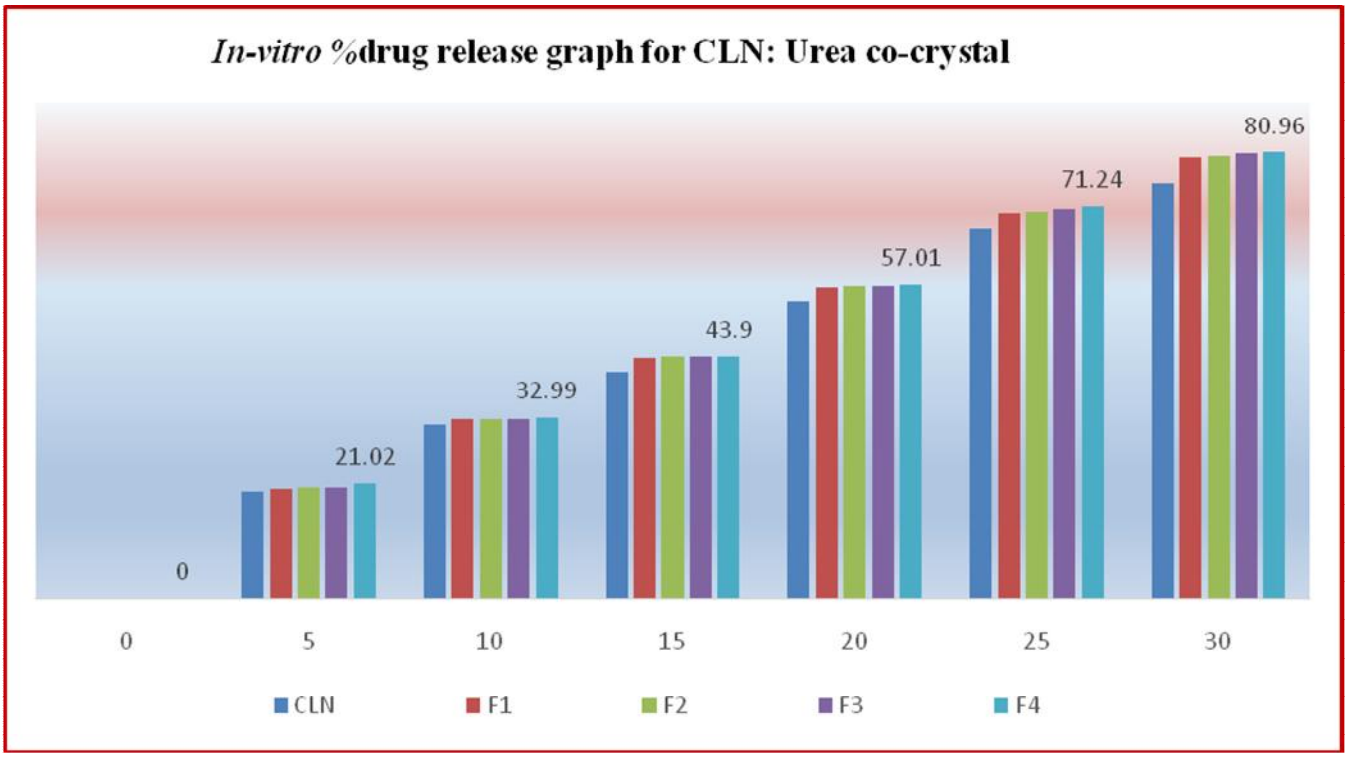

Figure 6. *In-vitro %*drug release with time graph for CLN: Urea co-crystal (F1-F4)