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Research article

Co-crystal formation of cilnidipine with urea and benzoic acid: an efficient approach to enhance the solubility and dissolution rate

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ABSTRACT

Co-crystallization is the process to enhance the physical properties of the molecule, especially the solubility and dissolution rate. The physical and chemical property improvements through pharmaceutical co-crystals draw closer the fields of crystal engineering and pharmaceutical science. Objective:In this work BCS Class II drug Cilnidipine is used as a model drug, which is having poor solubility but high permeability is incorporated with urea to enhance bioavailability and dissolution rate. Co-crystals are formed by solvent evaporation and solvent drop grinding method with urea and benzoic acid as a co-formers. Methanol is used as a solvent. Differential Scanning Calorimetry (DSC) and Powder X-ray Diffraction (PXRD) and FTIR techniques were employed to support the formation of co-crystals and to find out the optimized ratio of components of co-crystals. All the prepared co-crystals showed high solubility to the parent drug. Based on the formulation development and their results, co- crystals engineering is viable alternative to increase the aqueous solubility of poorly soluble drugs, which ultimately increases dissolution profile and bioavailability.

Keywords: Co-crystallization, Cilnidipine, Urea, Benzoic Acid, Methanol.

INTRODUCTION

Poorly water-soluble drug candidates often emerge from contemporary drug discovery programs, and present formulators with considerable technical challenges. The absorption of such compounds when presented in the crystalline state tothe gastrointestinal tract is typically dissolution rate-limited,and the drugs are typically Biopharmaceutical Classification System (BCS) class II or class IV compounds [1].

Cilnidipine (CLD), a novel dihydropyridine calcium channelblocker, has been reported to exhibit excellent clinicaleffects on cardiovascular diseases. A unique pharmacological property for cilnidipine is that it inhibits both L-type and N-type calcium channels in various types of neurons. Recently, cilnidipine was found to possess much moreunique advantages compared with traditional calcium channel blockers. The drug is practically insoluble in aqueous media and exhibits a low oral bioavailability or limited clinical efficacy [2].

Co-crystal, as a novel research focus, has recently been studied about the design, preparation and some physical properties. However, most of these studies only discussed a small aspect of co-crystals and none of them investigated the possibility of co-crystal production from an industrial interested point of view. A pharmaceutical co-crystal is a single crystalline solid that incorporates two neutral molecules, one being an API and the other a co- crystal former. Addition of co-crystal formers has been employed previously with various category of drugs with solubility and dissolution enhancement by many folds. The present study aims to prepare co-crystals of CLD with urea (UA) and benzoic acid (BA) as co-formers and enhancing the solubility, dissolution rate and ultimately the bioavailability of the drug [3].

MATERIAL AND METHODS

Materials

Cilnidipinewas obtained as a generous gift from Macleods Pharmaceuticals Ltd., Mumbai, India.Urea and Benzoic Acid were obtained from DNS Fine Chemicals and Laboratories (P) Ltd, Mumbai and Ranbaxy Fine Chemicals Limited, New Delhi respectively. Methanol was purchased from Merck Specialities Pvt. Ltd, Mumbai. All other

reagents used were of analytical grade [4].

Method

Preformulation studies of pure CLD: Determination of melting point. Melting point of CLD was determined by capillary method. The capillary tube was closed at one end by fusion and was filled with CLD by repeated tapings. The capillary tube was placed in melting point apparatus. The rise in temperature of thermometer was viewed. The temperature at which the drug starts melting was recorded. The experiment was performed in triplicate and the average value was calculated.

Solubility Studies

Solubility of CLD was determined in distilled water, methanol, ethanol, acetone, 0.1 N HCl and buffer solution (pH 7.4).

Fourier transform infrared (FTIR) spectroscopy.

The FT-IR spectra of CLD was obtained onJasco 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 thecrystals.

Differential Scanning Calorimetry (DSC)

Thermal analysis of the drug was performed on a Shimadzu DSC 60 which was calibrated for temperature and enthalpy using pure Indium. Drug (3-5 mg) was crimped in non-hermetic aluminium pans with lids and scanned from 50 to 300ºC at a heating rate of 10ºC/min under a RTYUIOP [5].

/4*10+2ontinuously purged dry nitrogen atmosphere (flow rate 20mL/min). The instrument was equipped with a refrigerated cooling system.

Powder X-ray diffraction (PXRD)

The X-ray diffraction pattern of pure CLD was obtained using a Bruker D8 advance diffractometer (BRUKER, Germany) equipped with 2.2 KW Cu anode, dermic X-ray tube as source, Lynuxeye detector, beta filter made of Ni filter and sample holder of zero background and PMMA.

Preparation of Co-crystals

The stoichiometric ratio of CLD: UA were prepared in 1:1, 1:2 respectively by using solvent evaporation technique. Co-crystals of BA were prepared by using solvent drop grinding method.

In solvent evaporation technique, co-crystal formers are taken in stoichiometric ratio and solubilize in a common solvent. The resultant solution is allowed to evaporate slowly. CLD and UA (F1) were added to a reaction vessel. The solid were dissolved in 20 ml of methanol and heated to 70oC for 1 h in water bath. Temperature was decrease in 10oC increments to induce precipitation in a stirrer. Appearance of the co-crystal solid phase was first observed in the range of 60-50ºC. The temperature was further lowered to 30ºC to drive additional precipitation. Following equilibration at 30ºC, solids were isolated using a Buchner funnel. The collected colorless solid was dried in air and kept in desiccator for further characterization.

Solvent drop grinding experiment was performed by combing equimolar ratios of drug and co-formers. CLD (984 mg, 2mmol) and BA (244 mg, 2mmol) were mixed in mortar and 50 ml of solvent (methanol) was added (F2). The mixture was ground by variation of grinding time until completed co-crystallization. After grinding, the products were dried and stored at ambient temperature [6].

Preformulation studies of Co-crystals

Preformulation studies like melting point determination, solubility studies and organoleptic properties (color and odor) of the co-crystals were determined.

Characterization of Co-crystals

Characterizations of the prepared co-crystals were done by DSC, FTIR and PXRD studies.

RESULT AND DISCUSSION

Preformulation Studies of Pure CLD

Determination of melting point

Melting point of CLD was found to be in the range of 107-112ºC, which compiled with IP standards indicating purity of the drug sample.

Solubility Studies

CLD was found to be very slightly soluble in 30% methanol, slightly soluble in 50% methanol and freely soluble in 100 % methanol and acetonitrile.

Fourier transform infrared (FTIR) spectroscopy

Functional group frequencies for CNDshows 3435cm-^{1}(aromatic sec. amine),1297cm-^{1}(C-N stretching), 1527cm-^{1} (N-H bending primary amine), 2840cm-^{1}(-OCH_3methoxy) indicating the purity of drug.

Differential scanning calorimetry (DSC)

DSC was performed to confirm the physical state of the drug. Thermogramof the raw CLD showed a narrow endothermic peak around110.25°C, corresponding to its melting point which impliedits crystalline form.

Powder X-ray diffraction (PXRD)

Sharp peak of the crystalogram indicates that the drug is present as a crystalline form.

Organoleptic characters namely colour, odour, melting pointwere cited in Table 1, solubility of the prepared co-crystals were evaluated and results are reported in Table 2 [7, 8].

Table 1:

Sample	Organoleptic property		Melting point
	Color	Odor	
	Light green	Odorless	107-112ºC
F1	Light green	Odorless	102-106 ºC
F2	Light green	Odorless	100-105 ºC

Table 2:

Solution	Pure CLD	F1	F2
Distilled water	Insoluble	Slightly soluble	Slightly soluble
Phosphate buffer pH 7.4	Sparingly soluble	More than pure drug	More than pure drug
Ethanol (95%)	Slightly soluble	Freely soluble	Freely soluble
Methanol	Freely soluble	Highly soluble	Highly soluble

Acetonitrile	Slightly soluble	Freely soluble	Freely soluble
0.1N NaOH	Poorly soluble	Insoluble	Insoluble
30 % Methanol	Slightly soluble	Slightly soluble	Slightly soluble

Characterizations of co-crystals

Characterizations of the prepared co-crystals were done by FTIR (Fig. 1), PXRD (Fig.2) and DSC studies (Fig. 3) of pure CLD, F1 and F2.

Figure1: FTIR of pure Cilnidipine (a), F1 (b) and F2 (c)

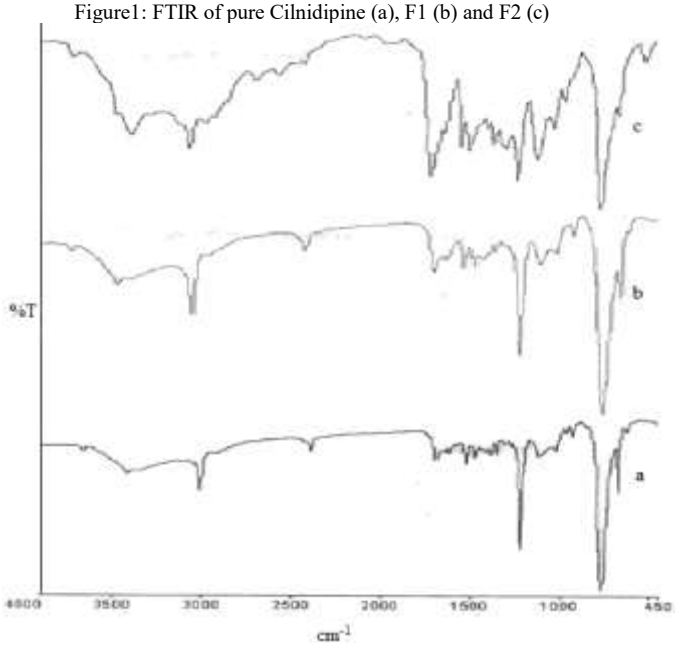


Figure 2: PXRD of pure Cilnidipine (a), F1 (b) and F2 (c)

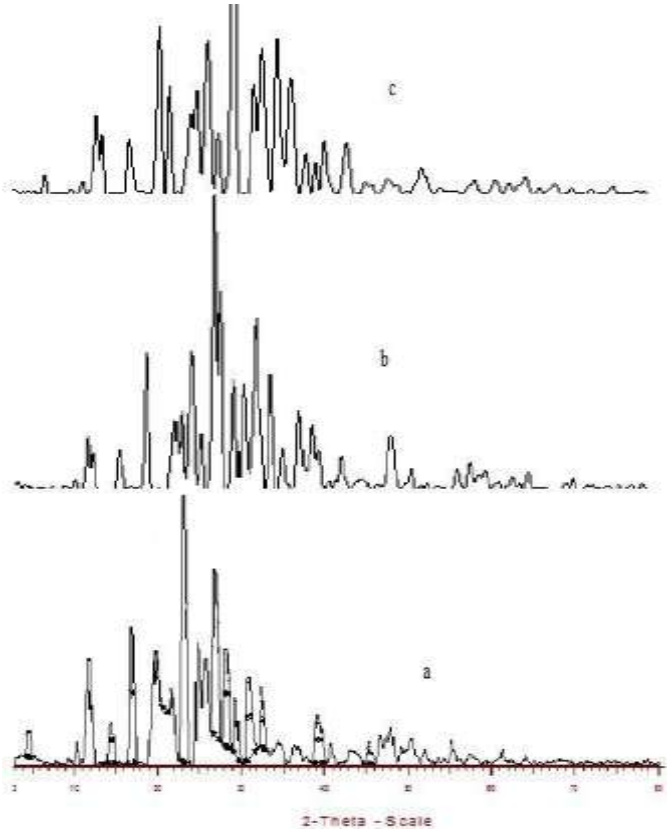
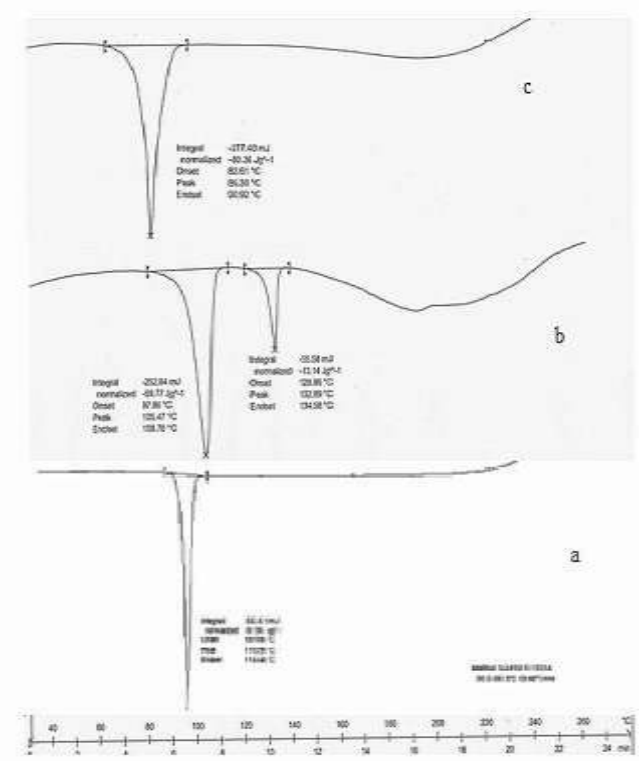


Figure 3: DSC of pure Cilnidipine (a), F1 (b) and F2 (c)



CONCLUSION

Co-crystals of Cilnidipine (F1 and F2) were prepared using co-crystal former; urea and benzoic acid using solvent evaporation and solvent drop grinding method. The prepared co-crystals showed improved solubility in 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. Formulation F1 of Cilnidipine: urea co-crystal and solvent evaporation method was found to be more suitable.This in turn may be responsible for achieving higher oral bioavailability and better therapeutic effect.

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