A COMPREHENSIVE REVIEW ON FORMULATION AND EVALUATION OF CILNIDIPINE C0-CRYSTALS WITH DIFFERENT CO-FORMERS TO ENHANCE SOLUBILITY AND DISSOLUTION

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ABSTRACT

The objective of the present study is to improve the solubility of Biopharmaceutical Classification System (BCS) Class-II drug, Cilnidipine by formulating them as solid dispersions and to make controlled released formulations. Solid dispersions of Cilnidipine were prepared by solvent evaporation technique using plasdone K-29/32. Various physical parameters were evaluated for the prepared solid dispersions. The *in vitro* drug release studies were performed for the solid dispersions using phosphate buffer pH 6.8. The solid dispersions which showed maximum drug release were selected for the preparation of oral controlled release formulations. Tablets were prepared using Cilnidipine solid dispersions and varying concentrations of polyethylene oxide (PEO) WSR 303 by direct compression technique. Pre and post-compression parameters were evaluated along with *in vitro* drug release studies. *In vitro* dissolution studies revealed that solid dispersion CP3 containing Cilnidipine and plasdone K-29/32 in 1:3 ratios showed faster drug release. Formulation CPP5 containing CP3 solid dispersion with 25% w/w of PEO WSR 303 showed prolonged drug release up to 12h. The solubility of Cilnidipine was enhanced using plasdone K-29/32 and the drug release was delayed using PEO WSR 303 as polymer.

Key Word: Co-Crystals, Co-Former,Cilnidipine, Maleic acid,Urea,Benzoic Acid,Water bathetc

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 particularly pertinent to drugs within class II of the Biopharmaceutical Classification System (BCS).

❖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

➢**For the physical modification, the techniques include**

❖ *Decreasing particle size (micronization, nanonization)*

❖ Formation of polymorphs/pseudopolymorphs (including solvates)

❖ Preparation of drug dispersions in carriers (eutectic mixtures, non- molecular

Solid dispersions, solid solutions).

❖ Preparation of co-crystals using co-former(Co-crystallization)

➢ **For the chemical modification, the used technique is the synthesis of soluble pro-drugs (**ACE inhibitors -captopril) **and salts**

CO-CRYSTALS:

❖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. Co-crystal former may be an excipient or another drug .

❖Co crystal is *" a stoichiometric multi-component crystal in which all its components are neutral and*

❖Co-crystallization with pharmaceutically acceptable compounds does not affect pharmacological activity of API but can improve physical properties, such as solubility, ygroscopicity, compaction behaviour.

❖The components in a co-crystal exist in a definite stoichiometric ratio (1:1; 1:1.5;1:2;), and assemble via non-covalent interactions such as hydrogen bonds, ionic bonds, π-π or Vander Waals interactions rather than by ion pairing.

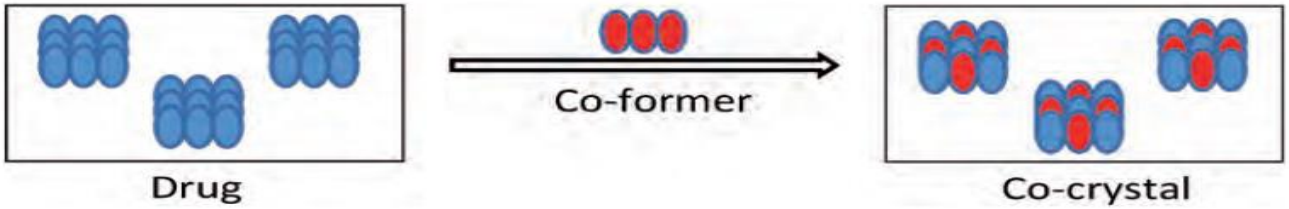


Figure 1. Co-crystal formation

CO-FORMERS

❖Co-crystal former may be an excipient or another drug.

❖It should have at least one functional group from amine, amide, aldehyde, mketone, thio ketone, ether, pyridine, imidazole, indole, pyrrolidine, carboxyl, carbonyl, phenol, sulfone, sulfonyl, mercapto and methyl thio.

❖**Examples**: Maleic Acid, Nicotinamide, Benzoic acid, urea, etc.

ADVANTAGES OF CO-CRYSTALS

- ❖ Co-crystals have stable crystalline form no need to make or break covalent bonds.
- ❖ High yield techniques

- ❖ Only solid form designable via crystal engineering and can be produced using solid-state synthesis green technologies
- ❖ No solvent or by-products are formed.etc
- ❖ To enhance the solubility of poorly soluble drug cilnidipine utilizing co-crystallization technique.

❖To investigate different methods and co-formers for preparation of co- crystals.

❖To formulate co-crystals of cilnidipine using different co-formers.

❖To evaluate the physicochemical properties of prepared co-crystals.

- ❖ Stability studies of formulated co-crystals

DRUG PROFILE

CILNIDIPINE

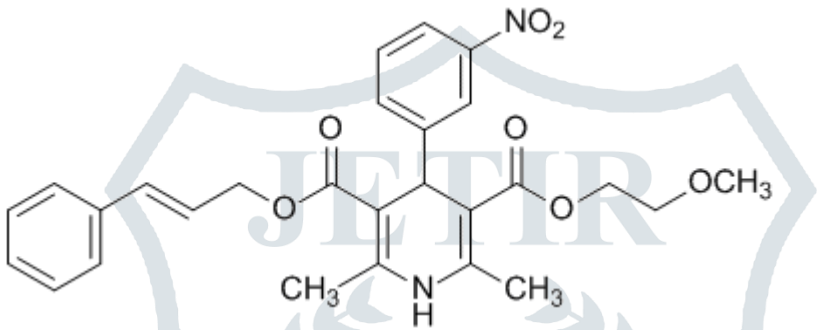
Structure:IUPAC name:3-(E)-3-Phenyl-2-propenyl 5-2-methoxyethyl 2,6-dimethyl-4-(m -nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate

Molecular formula: $C_{27}H_{28}N_2O_7$ Molecular Wt.: 492.52g/mol

Melting point: $110^{o}C$

Description : A light green colour, crystalline powder. **Solubility:** Highly soluble in methanol

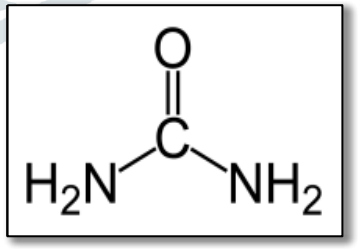
Category: Anti-hypertensive



CO-FORMERS PROFILE:

Urea:

Empirical Formula: CH_4N_2O **Molecular Weight:** 60.06



Melting Point: 132-135^{o}C

Solubility: In water

Description: Solid odourless white crystals or pellets.

Handling Precautions: May irritate eyes.

Storage Temperature: 2-8^{0}C

Benzoic Acid:

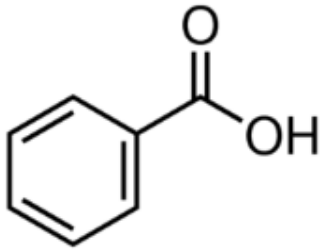
Synonyms: Carboxybenzene; E210, Dracylic acid , Benzenecarboxylic acid. **CAS Number:** 65-85-0

Empirical Formula: $C_7H_6O_2$ **Molecular Weight:** 122.12 g/mol

Functional Category: Anti- fungal abilities. **Description:** Colourless Crystalline Solid. **Handling Precaution:** Irritant.

Melting Point: 122.41^{0}C.

Solubility: In water, methanol, ethanol, acetone

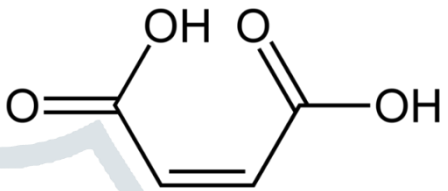


Maleic Acid

Synonyms: D-Malic Acid ,L- Malic Acid ,(S)-Hydroxybutanedioic Acid.

CAS Number: 617-48-1.

Empirical Formula: $C_4H_6O_5$. **Molecular Weight:** 134.09 g/mol.



Description: Colourless Crystalline Solid. **Handling Precaution:** Irritant.

Melting Point: 130^0C. **Solubility:** In Water.

CONCLUSION:

This article Formulation of co-crystals of Cinidipine were prepared using co-crystal former, urea,benzoic acid & maelic acid and method of preparation, solvent evaporation and solvent drop grinding method.

The co-crystals showed improved solubility than the pure drug indicating co-crystal approach as a novel and valuable means to alter the physical characteristics of an API without chemical change.

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