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Research Article

Improvement of Physicochemical and Solubility of Dipyridamole by Cocrystallization Technology

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Abstract

The aim of this study was to develop a pH-independent release formulation of dipyridamole (DP) by the combined use of pH-modifier technology and cocrystal technology tartaric acid (TA) was selected as an appropriate pH-modifier in terms of improving physicochemical properties and dissolution behavior of DP under neutral conditions. Molecular docking method was used to identify the suitable conformer. Upon optimization of the ratio of TA to DP (molar ratio of 1:1, 1:2 and 1:3) was prepared by a solvent assisted grinding method. Scanning electron microscopy images revealed that formation of DP-TA co crystals supported by supported by powder X-ray diffraction and differential scanning calorimetry analyses. Spectroscopic analysis suggested that there might be inter-molecular interaction among DP and TA resulting in pH independent dissolution behavior of drug substance. The study confirmed the selection of proper conformer and exhibited enhanced physicochemical, solubility and stability of the Dipyridamole cocrystals. Hence, based upon results it revealed that cocrystallization helps in improving the physicochemical properties of the API.

Keywords: Dipyridamole, Coformer, Molecular docking, Radar chart, solvent assisted grinding, Cocrystals

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INTRODUCTION

Dipyridamole USP is a platelet inhibitor chemically described as 2,2',2'',2'''-[(4,8- Dipiperidinopyrimido[5,4-d]pyrimidine-2,6-diyl)dinitrilo]-tetraethanol.

Dipyridamole is an odorless yellow crystalline powder, having a bitter taste. It is soluble in dilute acids, methanol and chloroform, and practically insoluble in water. Dipyridamole is BCS class II drug having low solubility and high permeability. It is soluble at low pH but insoluble in high pH (i.e., alkaline pH of small intestine) has a narrow absorption window and is primarily absorbed in the stomach, its oral bioavailability is 37 - 66% & biological half life is also short (40 min). Dipyridamole is highly bound to plasma proteins. It is metabolized in the liver where it is conjugated as a glucuronide and excreted with the bile ¹⁻⁴.

The low water solubility of the active substance is responsible for the risks of low oral bioavailability. In order to enhance the therapeutic efficacy, Dipyridamole needs an alternative drug delivery system. Cocrystals have recently drawn significant attention in the delivery of drugs by enhancing the drug physicochemical properties such as melting point, solubility, dissolution rate, stability and bioavailability without changing their chemical structure ^{5,6}. Cocrystals are compounds with a stoichiometric ratio of drug substance and cocrystal

coformers (CCFs) (1:1, 1:2, 1:3 or vice versa) ⁷. These cocrystals are combined by non-covalent interfaces like hydrogen bonds, Van Der Waals forces and π - π packaging which are robust at room temperature ^{8, 9, 10, 11}. Cocrystal former is a ballast molecule. Identifying and selecting the appropriate conformer continues the most important factor in the effective co-crystal growth ⁷. This technology is explored effectively for the delivery of various drugs such as acyclovir ¹², gliclazide ¹³, piracetam ¹⁴, fexofenadine ¹⁵, furosemide ¹⁶, quercetin ¹⁷, baicalein ¹⁸, myricetin ¹⁹ etc to improve the therapeutic efficacy.

Figure 1: Structure of Dipyridamole

The objective of present paper is to enrich the rate of dissolution, efficacy of Dipyrindamole absorption using solvent assisted grinding method. Literature study shows that there have been few Dipyrindamole formulations reported to date. Dipyrindamole was therefore chosen as the poorly soluble model drug in this work; the solvent assisted grinding method developed Dipyrindamole tartaric acid pH-independent cocrystals. Fourier transform-infrared spectroscopy, Differential scanning calorimetry, scanning electron microscopy and powder X-ray diffraction defined the cocrystals produced and solubility and dissolution studies defined the enhancement of solubility and % drug release.

MATERIALS AND METHODS

Materials:

Dipyrindamole was obtained from Micro Advanced Research Center (Bangalore, India) as a gift sample. Tartaric acid was collected from Poona Chemical Laboratory. Other reagents have been bought from S. D. Fine Limited Chemicals (Mumbai, India).

Methods:

Molecular docking and Selection of cofomers

Molecular docking is effective approach for computer aided structure-based drug discovery. This strategy predicts the probability of binding and orienting one molecule (API) is connected to a second molecule (coformer) to form a new complex¹⁸. The strength of the binding affinity between two

molecules by means of scoring features can be determined^{19, 20}. Based on the literature, seven cofomers were selected for the preparation of the Dipyrindamole cocrystals. The research of molecular docking was carried out on the seven cofomers chosen. Furthermore, the radar chart was used to visually compare the quality docking score of coformer information with an advantage of showing multidimensional information without the use of statistical methods. Tartaric acid was verified among the seven cofomers based on the potential for interaction type, compatibility, and docking score for cocrystals confirmation with Dipyrindamole.

Solvent assisted grinding method of cocrystallization for Dipyrindamole

Liquid assisted grinding involves the addition of a solvent, typically in a very small amount, to the dry solids prior to the initiation of milling. The solvent has a catalytic role in assisting cocrystal formation and should persist for the duration of the grinding process. More efficient cocrystal formation is suggested for liquid assisted methods than with neat methods.

Dipyrindamole cocrystals synthesis was performed using Liquid assisted grinding technique. Screening of formation of DYP cocrystals was performed by various cofomers in an optimal molar ratio (1:1, 1:2 and 1:3). A mixture of 1:1 Dipyrindamole and tartaric acid (TA) grinding was carried out in mortar and pestle for 30 minutes with the addition of 10 mL ethanol drop wise. And wet crystal was dried in oven and store in desiccator. Crystals were triturated in mortal and pestle and stored at room temperature^{21, 22}.

Figure 2: Preparation of DYP –TA Cocrystals by Solvent assisted grinding method

Characterization of DEM cocrystals

Differential scanning calorimetry (DSC)

A differential calorimeter scanning (DSC7020 thermal analysis system HITACHI) was used for thermal analysis of DYP, DYP cocrystals samples. Powder samples of approximately 2.0 mg were placed in aluminum open crucibles and heated at a rate of 10°C/ min up to 400°C.

Fourier transform-infrared spectroscopy (FT -IR)

FT-IR spectra were registered on a Nicolet iS10 spectrophotometer from 4,000 cm^{-1} to 500 cm^{-1} (Thermo Fisher Scientific, Madison, USA). With 40 scans per spectrum at a resolution of 0.4 cm^{-1} , DYP cocrystals were obtained and analyzed using the DTGS KBr detector.

Powder X-ray diffraction (PXRD)

DYP, DYP cocrystals XRD patterns were achieved using Shimadzu XRD-6000X system at ambient temperature (Shimadzu, Japan). Samples with Ni-filtered Cu-K (α) radiations were irradiated at a voltage of 40.0 kV and a

current of 40.0 mA. The scanning rate ranged from 3° to 50° over a diffraction angle of 2°/min.

Invitro dissolution study

The dissolution studies were performed in a dissolution apparatus Electrolab, Navi Mumbai using the paddle method in 900 mL of pH 1.2 and 6.8 phosphate buffer at 75 rpm maintained at 37±0.5°C. The dissolution medium was added an amount equal to 75 mg of cocrystals and the samples were withdrawn at appropriate intervals. The samples were filtered through Whitman filter paper No. 41, diluted, and spectrophotometrically analyzed at 282 nm.

RESULTS AND DISCUSSION

Dipyrindamole structure consists of two aromatic rings (pyrimido and pyridine), four hydroxyl groups, eight aromatic nitrogen atoms. Dipyrindamole molecule has four hydrogen bond donors as well as twelve hydrogen bond acceptors due to aromatic nitrogen (N) in pyrimidine ring, pyrimidine ring and hydroxy groups and significant conformational flexibility; hence it is possible to form co-

crystals with certain co-formers ²³. Depending on the ability of interaction, hydrogen bond, docking score and compatibility, tartaric acid was selected as coformer for preparation of Dipyridamole cocrystals (Figure 2). The details are summarized in the below Table 1. Figure 3 represents visual comparison of docking score in form of Radar chart. There are several axes in a radar chart where the information can be plotted. Every axis is one category. The information is displayed on the axis as points. It is possible to join the points belonging to a one data series. A point near the center of an axis shows a reduced value and vice versa. Through the visual comparison from Radar charts and docking score from molecular modeling, tartaric acid showed the lowest score. Van Der Waals and the electrostatic energy define the interaction between the API and coformer. Higher docking results in the potential for

repulsion. In contrast, reduced docking score relates to reduced potential.

Figure 2: Hydrogen bonding of Dipyridamole- tartaric acid cocrystals

Figure 3: Application of radar chart to evaluate the cofomers

Table 1: Molecular modeling of Cofomers

Sr No.	Name	Structure	Docking score	Hydrogen bonding
01	Adipic acid		-1.04	Hydrogen bonding possible
02	Malic acid		-1.80	Hydrogen bonding possible
03	Succinic acid		0.00	No bonding
04	Nicotinamide		0.00	No bonding
05	Sodium acetate		-1.46	No hydrogen bond.
06	Benzoic acid		-1.48	No hydrogen bond.
07	Tartaric acid		-4.135	Hydrogen bonding possible

Solvent assisted gridding using ethanol as a solvent and tartaric acid as a coformer resulted in adequate Dipyridamole cocrystal formation. Preliminary cocrystal

formation evaluation was performed by comparing pure drug and cocrystals.

Differential scanning calorimetry (DSC)

An endothermic peak at 156°C represented the melting point of pure drug. Significant difference in the melting point (156 °C) of cocrystals was observed compared to pure drug

(163°C), sharp endothermic peaks appear at lower temperatures in comparison to the sharp endothermic peaks at higher temperatures of the individual components in Figure 4. This could suggest interaction between the components, and formation of co-crystallization.

Figure 4: Differential scanning Calorimetry of a) Dipyridamole and b) Dipyridamole cocrystals

Fourier transform-infrared spectroscopy (FT-IR)

The FTIR showed shifts and changes in the intensity of the peaks in the DYP and DYP co-crystals, as shown in Figure 9.4. Hydrogen bonding in the co-crystals was identified by decreasing the intensity of the O-H peak. A decrease in the N-H stretching and bending frequency indicates that hydrogen

is involved in hydrogen bonding. The degree of decrease in frequency and the relative broadening of the band can determine the magnitude of hydrogen bonding. The role of the degree and strength of the hydrogen bond is to reduce the frequency. Significant modifications in the area of covalent bond between C-C and amine (N-H) stretch have shown the formation of new hydrogen ^{24, 25}.

Figure 5: FTIR graph of a) Dipyridamole and b) Dipyridamole cocrystals

Powder X-ray diffraction (PXRD)

X-ray diffractograms of DYP showed an intense peak at 2 to 20° signifying the crystalline nature of the drug. DYP cocrystals showed no intense drug peaks were observed at 2θ of 20° indicating existence of the amorphous phase (Figure 6). In the case of Dipyridamole cocrystals, however,

there were no intensive drug peaks at 2θ of 20° showing the presence of the amorphous stage. Decreased intensities and fewer peaks may be due to changes in crystal habit or amorphous form. Reduced crystalline characteristics may result in enhanced dissolution of Dipyridamole compared to pure drug ²⁶.

Figure 6: XRD spectra of a) Dipyridamole and b) Dipyridamole cocrystals

In vitro drug release

As reported in literature, Dipyridamole solubility depends on pH. It is highly soluble in acidic media and poorly soluble in alkaline media. Dipyridamole is also susceptible to acid and undergoes degradation. Hence, Dipyridamole cocrystals were developed by improving the physicochemical properties. The dissolution experiment was performed on Dipyridamole and Dipyridamole cocrystals at pH 1.2 and pH 6.8 to verify the pH independent solubility and release of drugs. The Dipyridamole and Dipyridamole cocrystals dissolution profile is depicted in Figure 8 and 9. The Dipyridamole dissolution profile shows that API has a good rate of dissolution in acidic pH (29.03%) as compared to

alkaline pH (48.1%) % at 30 minutes respectively. The complete quantity of Dipyridamole dissolved in 45 min was 62% in acid pH and 32 % in alkaline pH. However, Dipyridamole cocrystals dissolution rate led in a substantial rise as function of pH independent drug release. The quantity of Dipyridamole released from cocrystals in the first 30 minutes was 58.58% and the dissolved quantity was 67.5% at pH 1.2. In the first 30 minutes, the amount of substance dissolved 82.8% drug release in 30 minutes and 96.48 percent drug release at 45 minutes in pH 6.8 (Figure 8 & Figure 9). In addition, higher dissolution of Dipyridamole cocrystals can be ascribed to changes in the crystalline pattern, size and shape of cocrystals that escort to increased cocrystal solubility in dissolution media^{16,24, 27, 32-37}.

Figure 8: Invitro dissolution profile for Dipyridamole and DP-TA cocrystals at pH 1.2

Figure 9: Invitro dissolution profile for Dipyridamole and DP-TA cocrystals at pH 6.8

CONCLUSION:

In the present work prepared Dipyridamole cocrystals exhibited excellent physicochemical properties (solubility and dissolution) properties when compared to pure drugs. From the conducted study, we can conclude that cocrystals with tartaric acid prepared by technique of solvent assisted gridding techniques showed an improvement in the solubility and pH independent drug release, rate of dissolution and stability compared to pure drug.

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