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Original Research Article

DESIGN AND DEVELOPMENT OF CONVENTIONAL TABLETS OF HYDROCHLOROTHIAZIDE AND PROPRANOLOL HYDROCHLORIDE CO-CRYSTALS

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Abstract: Hydrochlorothiazide (HCT) is a class IV drug which has limited solubility and permeability, for overcome this problems co-crystallization method is used. Co-crystallization is the process to enhance the physical properties of drug molecule especially the solubility. HCT belongs to diuretic category and Propranolol Hydrochloride (PPL) belongs to Beta blocker category they are combined for use in tablet formulation. Co-crystallization was used to combine two drugs in single solid phase and thus to achieve new approach for combination therapy. Using the new approach co-crystals of PPL with HCT were prepared. Co-crystallization of two drugs were carried out by using solvent evaporation and solution co-crystallization method. The saturation solubility was done to evaluate the solubility of co-crystals. Dissolution properties were determined and compared with the marketed tablet formulation. The prepared co-crystals has shown several times faster release than marketed tablet and optimized co-crystals were characterized by using DSC, FTIR and SEM.

Keywords: HCT, PPL, Solvent evaporation, Solution co-crystallization, Characterization.

1. Introduction:

Hydrochlorothiazide (HCT) is a diuretic agent, chemically described as a 6-chloro-3,4-dihydro-2H-1, 2, 4-benzothiadiazine-7-sulphonamide 1, 1-dioxide, which is widely used in antihypertensive pharmaceutical preparations, which reduce sodium reabsorption and peripheral vascular resistance. Its molecular formula is $C_7H_8ClN_3O_4S_2$ having molecular weight 297.74 gm/mole. It is insoluble in water, freely soluble in methanol, soluble in diluted ammonia or sodium hydroxide.[1] According to the Biopharmaceutics Classification System (BCS) aqueous solubility and permeability are the most important variables affecting drug bioavailability. HCT is classified as Class IV, where the drugs have low solubility and low permeability characteristics after oral administration.

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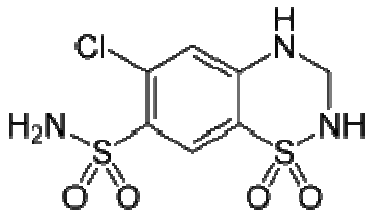

Figure 1. Chemical structure of Hydrochlorothiazide

Propranolol hydrochloride is a sympatholytic non selective β blocker. Sympatholytics are used to treat hypertension, anxiety and panic.[2,3] It is chemically described as RS)-1-[(1-Methyl ethyl amino)-3-(1-naphthyloxy)-2-propan-2-ol]. Its molecular formula is $C_{16}H_{21}NO_2$.HCL having molecular weight 295.81 gm/mole.[4] PPL is highly lipophilic and almost completely absorbed after oral administration. One gram of PPL is soluble in about 20 ml of water or alcohol.

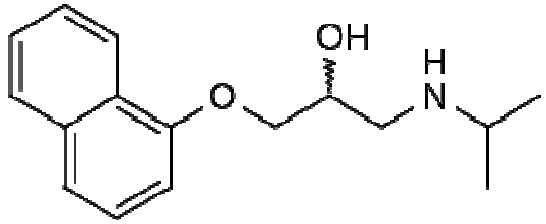

Figure 2. Chemical structure of Propranolol Hydrochloride

The concept of co-crystallization constitutes a selective route to the concerted design of pharmaceutical compounds with desired pharmacokinetic and physical properties. The term "co-crystals" is not easily defined but is most commonly used in order to describe a crystal containing two or more components that form a uniform phase. A more refined definition describes a co-crystal as a "multicomponent crystal that is formed between two compounds that are solids under ambient conditions, at least one component is a neutral API and the co-crystal former is a pharmaceutically acceptable ion or molecule". In early studies, Etter and co-workers proposed several "hydrogen bond rules," including the observations that all good proton donors and acceptors are used in hydrogen bonding, and the best donor typically pairs with the best acceptor in a given crystal structure. The combined use of the hydrogen bond rules with a geometric analysis assisted Etter and co-workers in implementing rational design of co-crystals in the synthesis of many new supramolecular structures.[5,6]

Co-crystal is a crystalline entity formed by two different or more molecular entities where the intermolecular interactions are weak forces like hydrogen bonding and π-π stacking. The concept of modifying the properties of a drug molecule by forming a pharmaceutical co-crystal containing single APIs and a pharmaceutical relevant co-former with improved properties compared with the pure drug crystal has generated immense interest. Physicians prescribe combination therapy frequently to treat and manage a plethora of medical conditions. Multi-API co-crystals, relatively unexplored solid forms of APIs, have potential relevance in the context of combination drugs for pharmaceutical drug development.[7]

The design of co-crystals seem to be straight forward because the donor and acceptor functionalities can be brought together more easily than with single component systems since the partners are more accessible to arrange themselves into an optimal geometry, leading to favorable intermolecular interactions.

2. Materials and Methods

2.1. Materials

Hydrochlorothiazide was received as gift sample from the Okasa Pharma Pvt. Ltd., Satara, Maharashtra, India. Other chemicals and solvents were obtained from different commercial suppliers.

2.2. Preparation of co-crystals

2.2.1. Solvent evaporation method[8,9,10]

Taken 10 ml of Ethanol in a beaker and placed it on magnetic stirrer then added a small amount of benzoic acid in that beaker. After a few minutes, added 1 GM. of propranolol in that beaker and was stirred for 5 minutes after added 1 gm. Of Hydrochlorothiazide in that solution and the resulting mixture was stirred on a

magnetic stirrer for 1 hour at 50 rpm. Ethanol was removed by evaporation at room temperature and co-crystals were obtained.

2.2.2. Solution co-crystallization[9]

Taken 10 ml of Ethanol in a beaker and heated on a water bath at temperature 50 to 55°C. Then added a small amount of benzoic acid in the beaker, then added equimolar ratio (1:1) of HCT-PPL in that beaker until it saturates. The Ethanol was removed by evaporation at room temperature and co-crystals were obtained.

2.3. Methods of characterization of co-crystals[9]

2.3.1. Saturation study

Solubility studies were performed according to the method reported by Higuchi and Connors. Excess of pure drug and prepared co-crystals were added to 10 ml of distilled water taken in stopper conical flasks and shaken for 24 hours in a rotary flask shaker at room temperature. After shaking to achieve equilibrium, appropriate aliquots were withdrawn and filtered through Whatman filter paper no. 41. The filtrate so obtained was analyzed by spectrophotometrically at 271 nm (Lab India).

2.3.2. FTIR Spectroscopy

FTIR spectra of HCT-PPL co-crystals were obtained by Attenuated Total Reflectance (ATR Bruker Alpha). IR spectrum of drug was recorded as potassium bromide pellet at a resolution of 4cm^{-1} over a range 4000-650 cm^{-1}.

2.3.3. Differential Scanning Colorimetry

DSC of HCT-PPL co-crystals done using SDT Q600 V20.9 Build 20 at a heating rate of 10°C/min between 0-300°C under nitrogen flow. Accurately weighted samples were placed in sealed aluminium before heating under nitrogen flow.

2.3.4. Scanning Electron Microscopy

The SEM of HCT-PPL co-crystals were carried out to determine the external morphology. The sample was mounted directly on to the SEM sample holder using double sided adhesive tape images were recorded at the required magnification using SEM (JEOL 5400, Japan).

2.3.5. Dissolution Rate Study

Dissolution was performed according to the Dissolution tester (USP Type II) in 900 ml of 0.1 N Hydrochloric acid at the thermostatically controlled temperature of 37°C ±0.5°C and stirred at 50 rpm. At various time intervals, samples were collected, filtered and analyzed by UV Spectrophotometer (Lab India).

3. Formulation of Conventional tablets

Ingredients	Quantities (mg)
PPL + HCT co-crystals	40+25
Starch	30
Microcrystalline Cellulose	20
Magnesium Stearate	3
Talc	12
	Total=130

4. Results and Discussion

4.1. Melting point determination[11]

Melting point of the drug samples and co-crystals were determined by open capillary method by using melting point apparatus and found to be shown in the table.

Table 1: Melting point of PPL, HCT and Co-crystal

Sample	Standard Melting Point(°C)	Observed Melting Point (°C)
Propranolol hydrochloride	158-160	161-163
Hydrochlorothiazide	269-271	273-275
Co-crystal	148-149	--

4.2. FTIR analysis

The IR spectra of HCT-PPL are shown in figure. The IR spectroscopy has also been used to assess the interaction between guest and PPL at shifts or changes in absorption spectra. The IR spectrum of HCT showed an absorption band at 3360.00 cm-1, 3263.56 cm-1, 3163.26 cm-1 due to NH stretching, 1597.06 cm-1 stretching of C=C aromatic ring, 1330.88 cm-1 showed C-N stretching and 1371.39 cm-1 showed SO2is stretching.[12,13] The IR spectrum of pure PPL showed an absorption band at 3482.77 cm-1 due to N-H stretching, 3054.68 cm-1 stretching of C=C, 2993.05 cm-1 aldehyde stretching, 3448.87 cm-1 O-H stretching, 1392.46 cm-1 due to isopropyl group and 763.73 cm-1 due to bending of aromatic ring.[14]

From FTIR graph of drug and co-crystal there was shifting of –OH, -NH, C=C aromatic ring, C-N stretching, SO2stretching peaks towards 3356.14 cm-1, 3265.49 cm-1, 1606.70 cm-1, 1332.51 cm-1, 1373.32 cm-1 and also shifting of –NH, C=C stretching peaks towards 3485.64 cm-1, 3057.13 cm-1.

From this, we concluded that co-crystals might have formed.

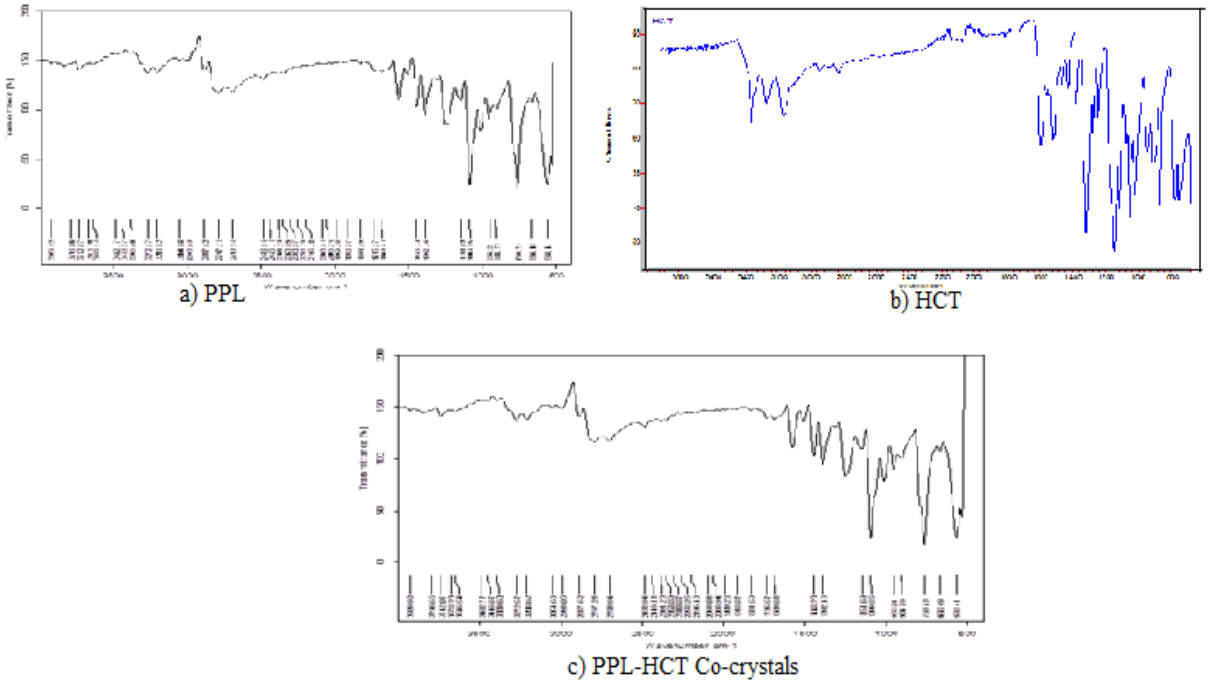

Figure 3. FTIR study of A- HCT, B-propranolol , C- Cocrystals of PPL-HCT

4.3. DSC analysis

DSC thermogram of HCT-PPL co-crystal was recorded by using Differential Scanning Colorimetry with computerized data. HCT, PPL, and Benzoic acid shown a single endothermic peak maxima at 268.12°C, 167.46°C and 122.7°C due to melting of drug.[12,13,15] The thermal behavior of HCT-PPL co-crystal had shown backward shifting of peak at 148.78°C for PPL and backward shifting of peak of HCT at 220.87°C and also backward shifting of peak of benzoic acid at 102.43°C due to melting of co-crystals.

As there are slightly shifting of peaks are observed, we might be concluded that there is a formation of HCT-PPL co-crystal.

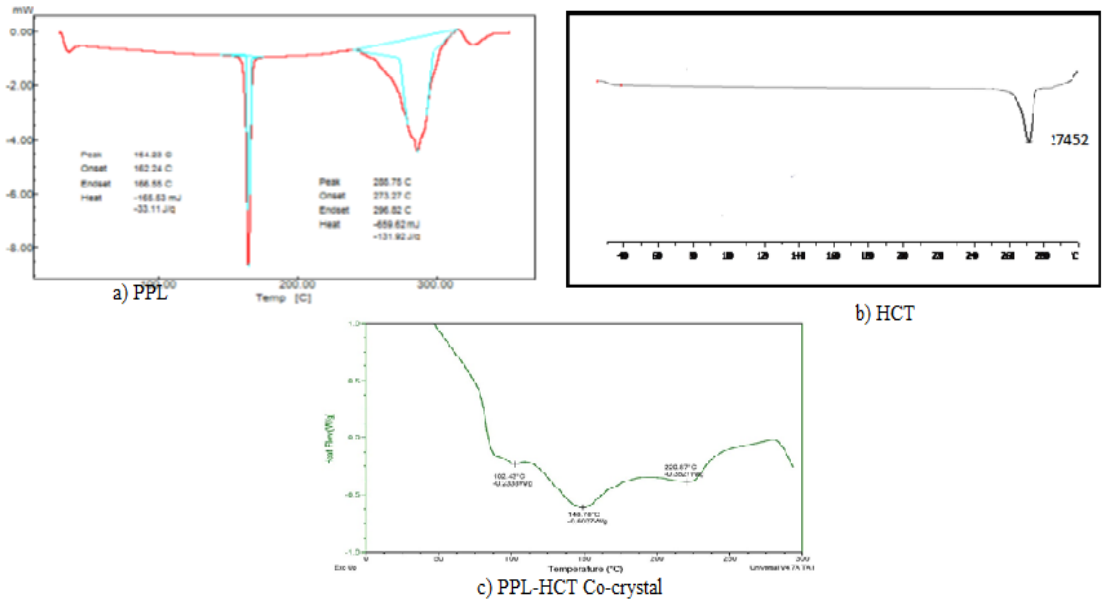

Figure 4. DSC of HCT, PPL & Cocrystals of PPL-HCT

4.4. SEM analysis

The scanning electron microscopy performed for HCT, PPL, and co-crystals of HCT-PPL. SEM was used to determine the surface morphology of the drug and co-crystal. HCT showed stone shaped crystals.[12,13] PPL showed smooth surface morphology.

SEM of HCT-PPL co-crystal indicated needle shaped crystals. From above SEM images we might be concluded that there is a change in surface morphology and the formation of HCT-PPL co-crystals.

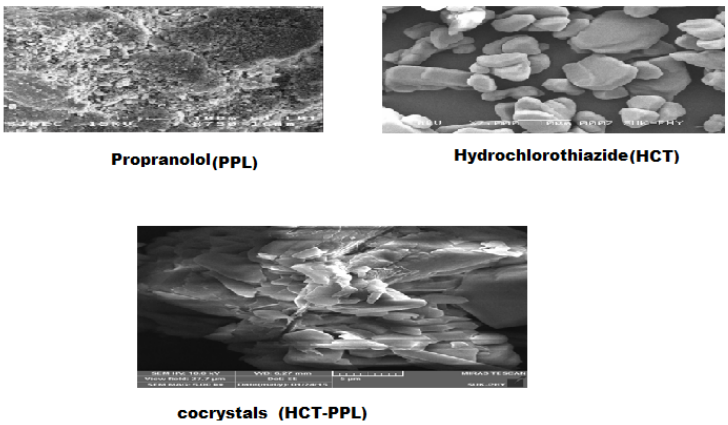

Figure 5. SEM of HCT, PPL,& Cocrystals of PPL-HCT

4.5. Physicochemical characterization of co-crystals[16]

The Bulk (BD) and Tapped (TD) densities, Angle of repose, Compressibility index, Hausner's ratio were measured and are shown in the table. From the values of compressibility index, Hausner's ratio and Angle of repose it was concluded that co-crystals prepared by above methods showed good flow properties and compressibility.

4.5.1. Angle of repose

It was determined by the fixed funnel method and was calculated by using the formula.

Angle of repose (ɵ) = $\tan^{-1}$ h/r

Where h – height of the cone and r – diameter of the cone.

4.5.2. Bulk density

Density apparatus was used to determine the bulk volume.

Bulk density = Mass of the powder (w) / Bulk volume (Vb).

4.5.3. Tapped density

The tapped density apparatus was set to 100 taps per minute.

Tapped density = Weight of powder / Bulk density.

4.5.4. Hausner's ratio

It was calculated from bulk density and tapped density.

Hausner's ratio = Tapped density / Bulk density.

4.5.5. Compressibility index (%)

It was calculated from bulk and tapped density.

Table 2: Flow properties of co-crystals

Physical Parameters	Value
Angle of Repose	25.50
Bulk Density (gm/ml)	0.31
Tapped Density (gm/ml)	0.35
Hausner's Ratio	1.11
Compressibility Index (%)	10.53

4.5.6. Post Compressional Evaluation[17]

Parameters	Observation
Weight variation	129.1
% Friability (%)	1.14
Hardness (kg/cm2)	4.3
Thickness (mm)	84

4.5.7. Dissolution rate studies

Dissolution was performed according to the dissolution tester (USP Type 2) in 900 ml of 0.1 N HCL at a thermostatically controlled temperature of 37°C ± 0.5 °C and stirred at 50 rpm. At fixed time intervals, samples were collected, filtered and analyzed by UV spectrophotometer (Lab India) at wavelength 271 nm.

Table 3 : % DR of Co-crystal and Marketed tablet

Time (min)	Co-crystal tablet	Marketed tablet
2	48.88	27.82
5	52.95	35.32
10	61.77	39.39
15	64.51	49.58
20	66.56	59.77
25	72.00	64.52
30	79.45	68.60
40	88.27	71.32
50	91.69	78.11
60	101.88	82.16

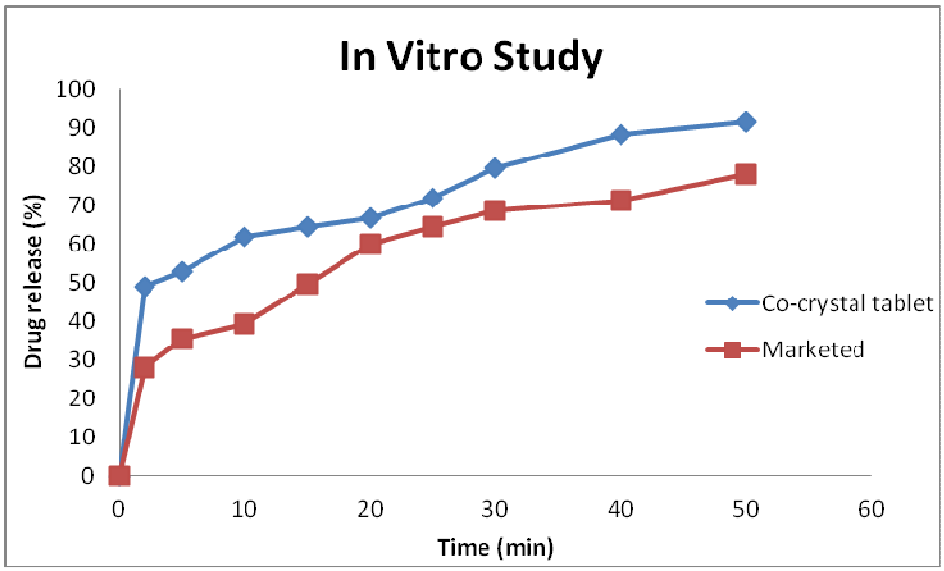

Figure 6: **Comparative dissolution profile**

5. Conclusion

Co-crystals of HCT-PPL was successfully formed using solvent evaporation and solution co-crystallization methods. This can be proved through their characterization using FTIR, DSC and SEM. The study successfully demonstrates that co-crystals has shown increased solubility, flow properties and compressibility. The In Vitro dissolution of HCT-PPL co-crystal tablet was comparatively higher than pure drug and marketed formulation which reflect improvement in solubility.

6. Acknowledgement

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