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Design and development of co-crystals of paracetamol and diclofenac and its characterization

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ABSTRACT

Paracetamol is a class III drug which has limited permeability and High solubility, Diclofenac is a class II drug which has High permeability and Low solubility, 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. Paracetamol is analgesic and Diclofenac belongs to anti-inflammatory drug (NSAID). 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 Diclofenac with Paracetamol was prepared. Co-crystallization of two drugs was 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 have shown several times faster release than marketed tablet and optimized co-crystals were characterized by using FTIR, Dissolution study.

Keywords: Paracetamol, Diclofenac, Solvent evaporation, Solution co-crystallization, Characterization.

INTRODUCTION

Paracetamol is a non-opioid analgesic devoid of the major contraindications.[1] It is a derivative of acetaminophen, or paracetamol, with the molecular formula glycine, N, N-diethyl-, 4-(acetyl amino) phenylester. Its molecular formula is C14H20N2O3 having molecular weight 264.325 gm. /mole. It is soluble in Alcohol, Water. Paracetamol is classified as Class III, where the drugs have High solubility and low permeability characteristics after oral administration.

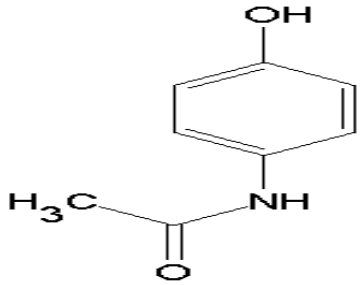

Figure 1. Chemical structure of Paracetamol

Diclofenac is a phenyl acetic acid derivative and non-steroidal anti-inflammatory drug (NSAID). Diclofenac, like other NSAIDs, is often used as first line therapy for acute and chronic pain and inflammation from a variety of causes. It is chemically described as2-{2-[(2, 6-dichlorophenyl) amino] phenyl} acetic acid. Its molecular formula is $C_{14}H_{11}Cl_2NO_2$ having molecular weight 296.149 gm/mole. Which means low solubility and high permeability compound? The pKa of diclofenac is about 3.80 at 25.8°C [2-4]

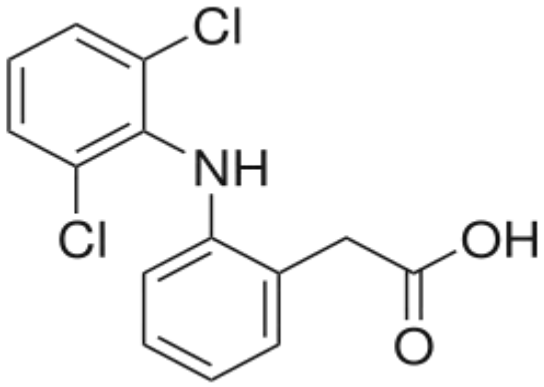

Figure.2 Chemical structure of Diclofenac

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 Etters and co-workers in implementing rational design of co-crystals in the synthesis of many new super molecular 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 seems to be straight forward because donor and acceptor functionalities can be brought together more easily than with single component systems since the partners are more accessible to arrange themselves in to an optimal geometry, leading to favorable intermolecular interactions.

MATERIALS AND METHODS

Materials

Paracetamol was received as gift sample from the S G Marg, Saraf Mansion, Ground Floor, Princess Street, Mumbai, Maharashtra, India. Other chemicals and solvents were obtained from different commercial suppliers.

PREPARATION OF CO-CRYSTALS

Solvent evaporation method

Taken 10 ml of Ethanol in beaker and placed it on magnetic stirrer then added small amount of benzoic acid in that beaker. After few minutes, added 1 gm. of Paracetamol in that beaker and was stirred for 5 minutes after added 1 gm of Diclofenac in that solution and the resulting mixture was stirred on magnetic stirrer for 1 hour at 50 rpm. Ethanol was removed by evaporation at room temperature and co-crystals were obtained. [8-10]

Solution co-crystallization

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

Methods of characterization of co-crystals

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 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 spectro-photometrically at 271 nm (Lab India).

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}.

Dissolution Rate Study

Dissolution were 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).

RESULTS AND DISCUSSION

Melting point determination

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 table. [11]

Table 1: Melting point of Paracetamol and Diclofenac and Co-crystal

Sample	Standard Melting Point(°C)	Observed Melting Point (°C)
Paracetamol	169 -171	165-168
Diclofenac	156-158	154-157
Co-crystal	-	145-147

FTIR analysis

Compatibility of Paracetamol and Diclofenac with benzoic acid was studied by IR spectral matching approach. The respective spectra are given in figures 3. By comparing the spectra, it was concluded that there was no significant change in

spectral pattern of drug and Co-former, which confirmed the compatibility of Paracetamol and Diclofenac with benzoic acid. The Principal peaks obtained in IR spectra of samples were almost similar to that of pure drug, indicating no interaction between Paracetamol and Diclofenac with the benzoic acid. From this, we concluded that co-crystals might have formed. [12-14]

Physicochemical characterization of co-crystals

The Bulk (BD) and Tapped (TD) densities, Angle of repose, Compressibility index, Hausner's ratio were measured and are shown in 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. [15, 16]

Angle of repose

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

Angle of repose (θ) = $\tan^{-1}$ h/r

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

Bulk density

Density apparatus was used to determine bulk volume.

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

Tapped density

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

Tapped density = Weight of powder / Bulk density.

Hausner's ratio

It was calculated from bulk density and tapped density.

Hausner's ratio = Tapped density / Bulk density.

Compressibility index (%)

It was calculated from bulk and tapped density.

Table 2: Flow properties of co-crystals

Physical Parameters	Value
Angle of Repose	26.21
Bulk Density (gm/ml)	0.32
Tapped Density (gm/ml)	0.33
Hausner's Ratio	1.09
Compressibility Index (%)	10.58

Dissolution rate studies

Dissolution were performed according to the dissolution tester (USP Type 2) in 900 ml of 0.1 N HCL at 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	47.88	26.85
5	52.97	35.32
10	61.77	39.40
15	63.51	49.58
20	66.56	59.77
25	72.00	65.52
30	80.45	68.60
40	88.27	71.35
50	91.69	78.11
60	97.88	83.16

In Vitro Study

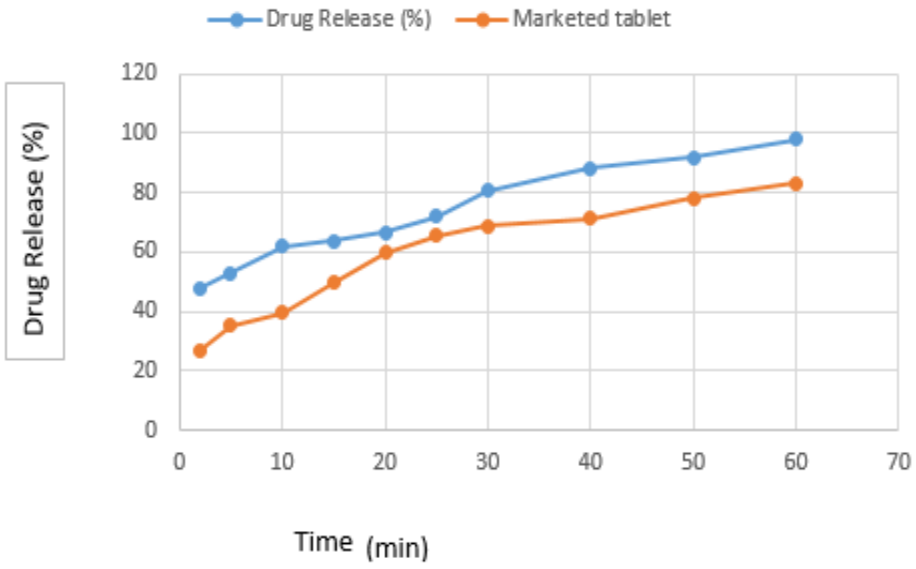

Figure 3: Comparative dissolution profile

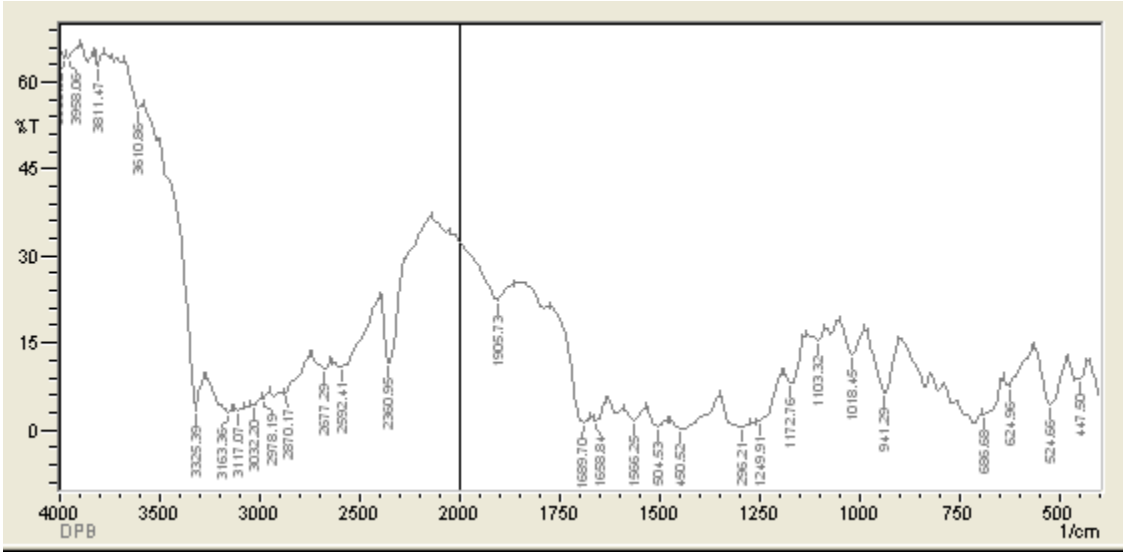

Figure 4: FTIR Graph of Paracetamol and Diclofenac.

Compatibility of Paracetamol and Diclofenac with benzoic acid was studied by IR spectral matching approach. The respective spectra are given in figures (4). By comparing the spectra, it was concluded that there was no significant change in spectral pattern of drug and conformer, which confirmed the compatibility of Paracetamol and Diclofenac with the benzoic acid. The Principal peaks obtained in IR spectra of samples were almost similar to that of pure drug, indicating no interaction between Paracetamol and Diclofenac with the benzoic acid.

CONCLUSION

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

REFERENCES

[1]. K. D. Tripathi; Essentials of Medical Pharmacology, 6, 136-140.
[2]. John M. Beale, Jr. John H. Block. Wilson and Gisvold's textbook of Organic Medicinal and Pharmaceutical Chemistry, 12, 550-554.
[3]. Blagden N; Crystal Engineering of APIs to Improve Solubility and Dissolution Rates. Advanced Delivery Reviews, 59(7), 2007, 617-630.
[4]. Fleischman S. G.; Crystal Growth and Design, 3(6), 2003, 909-919.
[5]. Bhupinder Singh Sekhon; DARU Journal of Pharmaceutical Sciences, 20, 2012, 45.
[6]. Chirag D. Pathak; International Journal of Pharmacy and Pharmaceutical Sciences, 5(4), 414-419.
[7]. Narendra Chandel; International Journal of Pharmacy and Life Sciences, 2(8), 2011, 1020-1028.
[8]. Dwi Setyawan, Asian Journal of Pharmaceutical and Clinical Research, 7(1), 2014.
[9]. Zalte Amar Gangadhar; World Journal of Pharmaceutical Research, 3(4), 1392-1402.
[10]. Pires M. A. Pharmaceutical Composition of Hydrochlorothiazide β-Cyclodextrin: Preparation by Three Different Methods; Physicochemical Characterization and in Vivi Diuretic Activity Evaluation; Molecules, 2011, 4482-4499.
[11]. Patil J. S.; International Journal of Pharmacy and Pharmaceutical Sciences, 2(1), 2010, 71-81.
[12]. Guru Sharan; International Journal of Pharmacy and Pharmaceutical Sciences, 2(2), 2010, 21-31.
[13]. Shivanand Pandey; Scholars Research Library, 2(11), 2010, 75-86.
[14]. H. N. More, A. A. Hajare; Practical Physical Pharmacy; Career Publication, 2, 126-129.
[15]. Madhavi Bhandwalkar, Omkar Bhandwalkar, Pallavi Dhekale et al. Design and development of conventional tablet of hydrochlorothiazide and propranolol hydrochlorides-crystals, Jour. Hormo, Res. Pharm, 4(2), 2015, 173-180.
[16]. Omkar S. Bhandwalkar, Madhavi U. Bhandwalkar, Pallavi Dhekale, Design And Development Of Fast Dissolving Tablets Of Hydrochlorothiazide And Atenolol Co-Crystals, IJPSR, 6(10), 2015, 4368-74.