Available online on www.ijcpr.com
International Journal of Current Pharmaceutical Review and Research; 7(5); 248-250

ISSN: 0976 822X

Research Article

Enhancement of Solubility and Dissolution Rate of Glibenclamide by Cocrystal Approach with Solvent Drop Grinding Method

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Available Online: 1st October, 2016

ABSTRACT

Solubility is one of the physical properties of active substances that affect drug absorption after dissolved in the gastrointestinal tract. Drugs with a limited aqueous solubility show low bioavaibility and will affect dissolution as a determine rate limiting step in the absorption process of the drug. Glibenclamide is antidiabetic which based on the Biopharmaceutical Classification System (BCS), has low solubility and high permeability which causes low bioavailability. Cocrystallization is the process to enhance the physical properties of drugs, especially the solubility. The research aimed to determine enhancement of solubility and dissolution rate of co-crystal of glibenclamide, and determine the characterization of co-crystal of glibenclamide. The co-crystal of glibenclamide-oxalic acid was made by comparison 1:0, 1:1 and 1:2 with solvent drop grinding method and then were tested for solubility and dissolution rate. After that Co-crystal of glibenclamide-oxalic acid was characterized by X-ray Powder Diffraction (XRPD), Differential Scanning Calorimetry (DSC) and Fourier transform infrared spectroscopy *(*FTIR). The result showed that co-crystal of glibenclamide with oxalic acid could increase solubility and dissolution rate of glibenclamide. Comparison of glibenclamide: oxalic acid 1: 2 showed the highest results of solubility and dissolution test. The results of x-ray diffraction characterization indicated co-crystal formation, the appearance of the new endothermic peak at 99.8-123.9 ^{o}C Differential Scanning Calorimetry (DSC) and changing of spectra between 3367.1-3366.73 cm^{-1} and 2857.99-2931.27 cm^{-1} through Fourier Transform Infrared Spectrophotometry (FT-IR).

Keywords: Glibenclamide, oxalic acid, cocrystal, solvent drop grinding method

INTRODUCTION

The therapeutic effectiveness of active substances depends upon the solubility of drug molecules. Some active substance has poorly soluble drugs and low bioavailability[1,2]. Oral ingestion is ease of administration, cost effectiveness, and flexibility in the design of dosage forms. As a result, many drug companies produce bioequivalent oral drug products. Crystal engineering can improve the solubility and dissolution rate. The Active Pharmaceutical Ingredients crystallize into one or more crystal forms that possess undesirable physical properties and hence there is a need for the development of crystalline form of APIs with desired physicochemical properties[3].

Cocrystal is neutral molecular which are structurally crystalline material containing component present in definite stoichiometric amount. Cocrystallization is a one method with established approaches to physical property optimization of polymorph, hydrate, and salt selection[1,4]. In Pharmaceutical, cocrystal contains an active pharmaceutical ingredient (API) and coformer which may not have pharmacological activity. Coformer generally forms hydrogen bonding with the API. Both the API and Co-former should contain hydrogen donors or accepting group like ether, oxalic acid, fumaric acid etc[1]. Cocrystal methode aims to increase solubilty of the active subtances which poorly soluble drugs.

Glibenclamide is insoluble in water, which leads to poor dissolution rate and subsequent decrease of its gastrointestinal (GI) absorption. Results of several investigations revealed that the absorption of glibenclamide was limited by its dissolution rate[5]. In the Biopharmaceutical Classification System (BCS) Glibenclamide included in class II which has a high permeability but has a low solubility. Therefore, it is important to improve the dissolution rate of glibenclamide, thereby increasing the rate of drug absorption[6,7,8]. The aims this research to prove the solubility and dissolution glibenclamide through cocrystal with oxalic acid using the solvent drop grinding method.

MATERIALS AND METHODS

Glibenclamide (Indofarma), Oxalic Acid (Walargi), potassium bromide, aquadest and methanol (Walargi), Sodium hydrogen phosphate (Merck), Sodium dihydrogen phosphate (Merck), NaOH (Merck).

Preparation of Glibenclamide cocrystal

Glibenclamide cocrystal was prepared by solvent drops grinding method and taking each component 1:0; 1:1 and 1:2 molar ratio (glibenclamide BM 494 : Oxalic acid BM 126) by different experiment approach.

Determination of solubility

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Table 1: The weight ratio of glibenclamide and oxalic acid

Molar Ratio	(1:0)	(1:1)	(1:2)
Glibenclaimde (gram)	0.494	0.494	0.494
OxalicAcid (gram)	-	0.126	0.252

Table 2: Solubility Studies

Formula	Concentration of glibenclamide (%)
1:0	0.96
1:1	3.50

Table 3: DSC result

Formula	Range of endothermic Peak
1:0	148-1 82.3
1:1	133.5 8-155.4
1:2	99.8-123.9

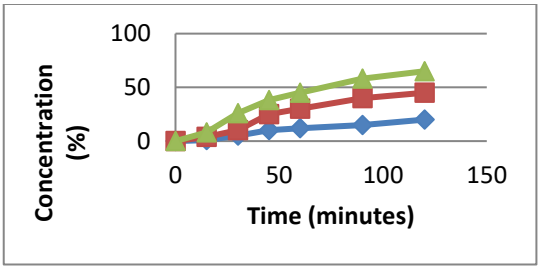

Figure 1: Dissolution Test Result of Glibenclamide (blue), Cocrystal glibenclamide : oxalic acid 1:1 (red) and Cocrystal glibenclamide : oxalic acid 1:2 (green)

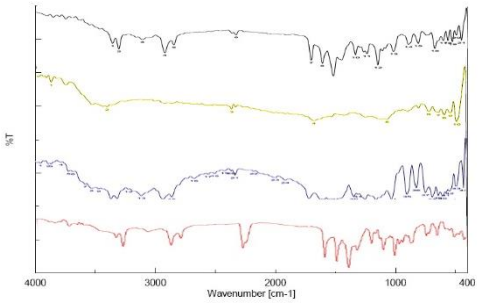

Figure 2: FT-IR Spectrum of glibenclamide (black), oxalic acid (yellow), cocrystal glibenclamide : oxalic acid 1:1 (blue) and cocrystal glibenclamide : oxalic acid 1:2 (red)

50 mg of glibenclamide was placed in Erlenmeyer containing aquadest. These were agitated in mechanical shaker for 24 hours at room temperature. The solution was filtered and the amount of the drug dissolved was analyzed spectrophotometrically at 266 nm[1].

Fourier Transform Infrared Spectroscopy (FTIR)

The compatibility of glibenclamide and oxalic acid was checked by FTIR. The infrared spectra of crystals in KBr pellets were recorded from 400 - 4000 cm^{-1} at room temperature[1,9].

X-ray Powder Diffraction (XRPD)

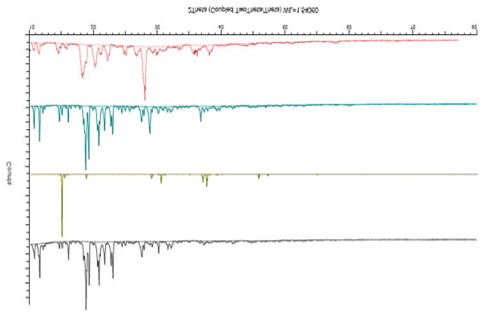

Figure 3: XRPD Spectra of glibenclamide (black), oxalic acid (yellow), cocrystal glibenclamide : oxalic acid 1:1 (blue) and cocrystal glibenclamide : oxalic acid 1:2 (red)

The XRD were undertaken to investigate the crystal nature of glibenclamide, oxalic acid and prepared crystal forms. The Study was carried out by X-ray diffractometer using Cu Kα radiation. The tube operated at 40 KV,40 mA and data were collected over an angular range from 2θ diffraction angle, with scanning mode 0,2° - 0,5° per minutes , and range scanning 2θ = 5° - 60°[9].

Differential Scanning Calorimetric (DSC) Analysis

DSC analysis is a thermoanalytical technique used to identify the difference in the amount of heat required to increase the temperature of a sample and reference. The samples were analyzed by Differential Scanning Calorimeter (model STA PT1600) over the range of 30-200°C at the rate of 10 °C per minute [3].

Dissolution Test

The studies used 900 ml of a buffer phosphate with a pH of 8, and USP apparatus 2 with an agitation rate of 75 rpm. The sample was measured every 15 minutes up to 120 minutes and was analyzed spectrophotometrically at 266 nm[10,11].

RESULT AND DISCUSSION

Solvent drop grinding has been witnessing a great progress in cocrystal formation via grinding method over the past few years[12]. Solvent as catalyst cocrystal formation, and sholud be lost in the final cocrystal product[13]. Glibenclamide cocrystal was prepared by taking each component 1:0; 1:1 and 1:2 molar ratio with solven drops grinding method.

The Table 1 showed that the highest concentration in the ratio 1: 2. The standard of glibenclamide showed percentage drug dissolved in the amount of 0,96%, while the co-crystal glibenclamide showed the percentage of g in the ratio 1: 1 was 3,50 %, and the ratio of 1: 2 was 6,45 %. The result showed that the co-crystal of glibenclamide increase the solubility compared to standard. This is due to hydrogen bonds would lead to an increase in solubility[14]. As solubility data are complementary of dissolution, if cocrystal solubility is increased in comparison to standard, intrinsic dissolution is also improved for cocrystals in comparison to standard[12].

The fig 1 showed that co-crystal glibenclamide increased the dissolution rate of glibenclamide in comparison to pure glibenclamide. This was indicated by the results of the dissolution at minute 60, the co-crystal of ratio 1: 2

showed 50%, the co-crystal ratio of 1: 1 showed 30% and glibenclaimde standard showed 12%.

The differences in some peaks region, a shift in N-H stretch (3366.73 cm^{-1}), C-H stretch (2857.99 cm^{-1}) and O-H stretch (3120.26 cm^{-1}) were observed. In fig 2, there is no new peak of functional groups. This was indicated that there were not a chemical reaction or not formed new functional groups in cocrystal glibenclaimde-oxalic acid[15,16].

The formation of physical interaction between two materials can be estimated by using analysis thermal, in which case change in the crystalline form it will changes to Thermodynamic of a solid[8]. Differential Scanning Calorimetry (DSC) of glibenclamide standard showed an endothermic peak at 148-182.3°C. To co-crystal glibenclamide with ratio 1:1 showed an endothermic peak at 133.58-155.4 °C. While co-crystal glibenclaimde with ration 1:2 showed an endothermic peak at 99.8-123.9° C. This indicated that the formation of physical interaction between glibenclamide and oxalic acid was occurred[3,8].

XRPD Analysis was conducted to investigate the lattice structure and solid phase of gilbenclamide-oxalic acid. The Fig. 3 showed that difference intensity of the peak at co-crystal glibenclamide with ratio 1:1 from 18 472 to 15 643. Additionally, formed a new peak at 2θ = 30-40 ^oC with intensity peak 3306. This indicated that there has been an increase in size, change in crystal form or the addition of a crystal lattice[1,3].

CONCLUSION

Co-crystal of glibenclamide with oxalic acid could increase solubility and dissolution rate of glibenclamide. Comparison of glibenclamide: oxalic acid 1: 2 showed the highest results of solubility and dissolution test. The results of x-ray diffraction characterization indicated co-crystal formation, the appearance of new endothermic peak at 99.8-123.9 ^oC Differential Scanning Calorimetry (DSC) and changing of spectra between 3367.1-3366.73 cm^{-1} and 2857.99-2931.27 cm^{-1} through Fourier transform infrared spectrophotometry (FT-IR).

REFERENCES

1. Vinesha, V. et al. Enhancement of Solubility of Tadalafil by Co Crystal Approach. *International Research Journal of Pharmacy* . 2013; 4(4):218–23.
2. Zaini, E, Halim A, Soewandhi SN, Setyawan D. Peningkatan Kelarutan Trimetoprim melalui Metode Ko-kristalisasi dengan Nikotinamida. Jurnal Farmasi Indonesia. 2011; *5*(4), 205-212.
3. Pathak, Chirag D., Ketan T. Savjani, Anuradha K. Gajjar, and Jignasa K. Savjani. An Efficient Approach to Enhance Solubility. International Journal of Pharmacy and Pharmaceutical Sciences. 2013. 5(4). 25-121.
4. Jasud, S., Shubhangi Warad, Solunke Rahul, Ganesh Jagdale, Shilpa Zinjad., Cocrystal: A Novel Approach For Bioavailability Enhancement. World Journal Of Pharmacy And Pharmaceutical Sciences. 2013. Volume 2, Issue 6, 4682-4697.
5. Dastmalchi, Siavoush et al. Enhancing Dissolution, Serum Concentrations and Hypoglycemic Effect of Glibenclamide Using Solvent Deposition Technique. Journal of pharmacy & pharmaceutical sciences, 2005; 8 (2): 175–81.
6. Bethlehem. 2011. Biopharmaceutical Classification System and Formulation Development. *Technical Brief 2011 Volume 9.*
7. Salman, E. 2007. Profil Disolusi Tablet Dispersi Padat Glibenklamid-PEG 6000 dengan Bahan Pengisi Avicel PH 102 dan Emcompress. *Direktorat Jenderal Perguruan Tinggi Departemen Pendidikan Nasional.*
8. Dash, Vikash, Kesari, Asha. Role of Biopharmaceutical Classification System In Drug Development Program. Journal of Current Pharmaceutical, 2011; 5 (1): 28-31.
9. Putra, DO. Nugrahani Ilma, Slamet Ibrahim, Uekusa Hidehiro. Pembentukan Padatan Semi Kristalin dan Ko-kristal Parasetamol. *Jurnal Matematika dan Sains*. 2012; 17 (2) : 83-88
10. Gianotto, E., A., S. Dissolution Test for Glibenclamide Tablets. *Quim, Nova*, 2007. 30(5): 1218-1221.
11. Löbenberg, R., J. Krämer, V. P. Shah, G. L. Amidon, and J. B. Dressman. Dissolution Testing as a Prognostic Tool for Oral Drug Absorption: Dissolution Behavior of Glibenclamide. Pharmaceutical research. 2000; 17(4):439–44.
12. Yadav S., Prakash Chandra Gupta, Nisha Sharma,Jitendra Kumar. Cocrystals: An Alternative Approach To Modify Physicochemical Properties Of Drugs. International Journal Of Pharmaceutical, Chemical And Biological Sciences. 2015, 5(2),427-436
13. Zang S., Physical Properties and Crystallization of Theophylline Co- crystals. Thesis. 2010. School of Chemical Science and Engineering. Royal Institute of Technology
14. Qiao Ning, Mingzhong Li, Schlidwein, W., Trappit, G. . Pharmaceutical Cocrystals: An Overview. *International Journal of Pharmaceutics*, 2011; 419: 1-11.
15. Gozali, D., Husein H. Bahti, Sundani N. Soewandhi, Marline Abdassah. Pembentukan Kokristal Antara Kalsium Atorvastatin dengan Isonikotinamid dan Karakterisasinya. Jurnal Sains Materi Indonesia. 2013. No.: 395/D/2012. 103-110
16. Kurniawansyah, I.S., Abdassah, M., Sharon, G. Relationship between Temperature on Sterility of Reusable instruments in Hospital's CSSD. 2015. 33(2). No. 45. Pages 215-219.

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