Journal of Pharmacreations

PharmaCreations

ISSN: 2348-6295

Pharmacreations | Vol.7 | Issue 3 | Jul - Sep- 2020

Journal Home page: www.pharmacreations.com

Research article *Open Access*

Preparation and characterization of stable co-crystals of Quercetin with enhanced dissolution profile

R. Sivakumar, U. Ubaidulla, T. Sathish Kumar, Grace Rathnam

Department of Pharmaceutics, C.L.Baid Metha College of Pharmacy, Chennai – 97

Corresponding author: R. Sivakumar

ABSTRACT

Quercetin is a challenging molecule to be delivered orally due to its poor solubility, low hydrophilicity, and minimal absorption in gastrointestinal tract but it has numerous pharmacological activities including antioxidant, anticancer, hepatoprotective etc., Pharmaceutical co-crystals have demonstrated significant promise in their ability to modify the physicochemical and pharmacokinetic properties of drug substances, such as the solubility and dissolution rate, bioavailability, and particle morphology. Aim of the current research was to prepare and characterize the co-crystals of quercetin and to provide useful information for the potential application of co-crystal technology for water-insoluble drugs, especially flavonoid compounds like quercetin. Quercetin cocrystals was prepared successfully and enhanced dissolution rate was observed when compared to pure quercetin.

Keywords: Quercetin, Co-crystals, enhanced dissolution rate

INTRODUCTION

Pharmaco-dynamically, co-crystal former could be a stability molecule (the same applies to salts), and therefore the GRAS rules apply. Pharmaceutical co-crystals area unit crystalline elements created from an API and one or additional co-former or another API [1-8]. Co-crystals are a unit at the moment the foremost dynamically developing cluster of solid pharmaceutical substances.

The advance of crystal engineering has remodeled the pace of analysis in molecular solids. Attaining the specified properties in molecular solids by controlled manipulation of unit interactions holds the key to success during this space of analysis. A co-crystal entails or additional neutral molecules to be control along by weak unit interactions in an exceedingly definite quantitative relation. Since unit interactions guide properties of molecular solids, co-crystal formation is of nice interest to crystal engineers. For that matter, strength and radial asymmetry of weak interactions are unit necessary options to be taken under consideration. Crystal engineering, through supramolecular synthons, permits US to style co-crystals with desired chemistry properties.

Quercetin is a polyphenolic flavonoid with potential chemopreventive activity (Figure 1). Quercetin, ubiquitous in plant food sources and a major bioflavonoid in the human diet, may produce antiproliferative effects resulting from the modulation of either EGFR or estrogen-receptor mediated signal transduction pathways [9-12].

Although the mechanism of action is not fully known, the following effects have been described with this agent in vitro: decreased expression of mutant p53 protein and p21-ras oncogene, induction of cell cycle arrest at the G1 phase and inhibition of heat shock protein synthesis.

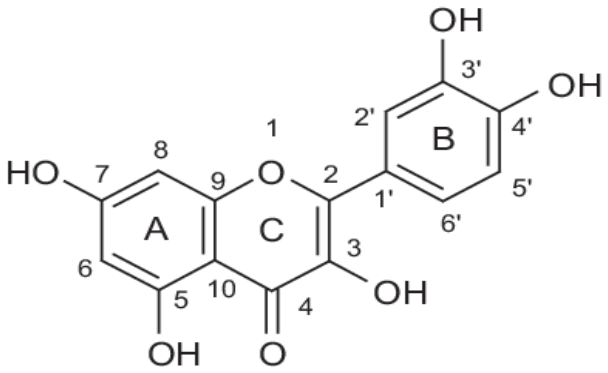

Figure 1: 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one

Quercetin appears as yellow needles or yellow powder and converts to anhydrous form at 203-207°F. Alcoholic solutions taste very bitter. This compound also demonstrates synergy and reversal of the multidrug resistance phenotype, when combined with chemotherapeutic drugs, in vitro. Quercetin also produces anti-inflammatory and anti-allergy effects mediated through the inhibition of the lipoxygenase and cyclooxygenase pathways, thereby preventing the production of pro-inflammatory mediators.

METHODOLOGY

Saturation solubility studies

Saturation solubility was determined by the shake-flask method. Plain Quercetin in excess quantity was placed in glass-stoppered flasks containing 10 ml of distilled water. The samples were placed in a mechanical shaker (technico, Chennai) at 37 °C and 100 rpm until equilibrium was achieved (24 h). The aliquots were filtered through Whatman No. 41 filter paper [13-20]. The filtrates were diluted appropriately in distilled water and assayed spectrophotometrically at 370 nm.

Fabrication of Quercetin co-crystals with chitosan and succinic acid

Quercetin and chitosan is dissolved in acetic acid and add 1% sodium citrate solution gradually to form Quercetin chitosan Co-crystals (Table 1). Quercetin and succinic acid dissolved in acetonitrile to form Quercetin-succinic acid Co-crystals (Table 2).

Table 1. Preparation of QR Co-crystals with Chitosan

Ingredients	F1(1:1)	F2(1:2)
Quercetin	150 mg	150 mg
Chitosan	150 mg	300 mg
Acetic acid	1%	1%
Sodium citrate	2%	2%

Table 2. Preparation of QR Co-crystals with Succinic acid

Ingredients	F1(1:1)	F2(1:2)
Quercetin	150 mg	150 mg
Succinic acid	150 mg	300 mg
Solvent (ml)	10	10

CHARACTERIZATION OF CO-CRYSTALS

FT-IR spectral analysis of Quercetin chitosan co-crystals

Characterization of co-crystals was done by IR spectroscopy (IR), The FTIR spectra were performed on Thermo scientific Nicolet ISF, FTIR spectrometer. FTIR spectra of quercetin-chitosan co-crystals were recorded by potassium bromide (KBr) disc method and scanned at the resolution of 4.0 cm^{-1} over the wave number region 4,000–400 cm^{-1}.

Surface morphology study

The external surface morphology was evaluated by using the SEM (Sem-jeol Jsm-840, nanotechnology lab, Anna University).The Quercetin and co-crystals were mounted directly on the SEM sample stub using the double sided sticking tape and coated with gold film (thickness 200nm) under the pressure low vacuum. The voltage was used is 20KV and the width was 3.5mm.

Differential scanning calorimetry (DSC)

DSC analyses of the samples were performed with a DSC Q20 calorimeter (TA Instruments, USA), which was calibrated for temperature and heat flow accuracy using indium (mp 156.6 °C and ΔH of 25.45 J g−1). The samples (3–5 mg) were placed in sealed non-hermetic aluminium pans and scanned at a heating rate of 10 °C min^{-1} from 30 to 300 °C under a dry nitrogen atmosphere (flow rate of 50 mL min^{-1}). The data were analysed using Universal Analysis 2000 software (TA instruments).

In vitro dissolution study of Quercetin and co crystals

The in vitro release of Quercetin and co-crystals was tested in an USP XXII dissolution apparatus. An equivalent weight of co-crystals containing 40mg of quercetin and co-crystals was placed separately in 900ml of gastric fluid (pH 2.0) maintained at 37 $\pm$ 0.5°C and stirred at 75 rpm. Aliquots of 5ml were collected at regular time intervals, and the same amount of fresh dissolution medium was replaced into a dissolution vessel to maintain the sink condition throughout the experiment. The aliquots were filtered, further diluted suitably and estimated spectrophotometrically at 370 nm.

RESULTS AND DISCUSSION

Solubility study

Solubility study of quercetin was carried out in distilled water. The solubility of quercetin in distilled water was found to be 0.124 mg/ml, which is indicating that the present drug having very poor solubility.

Calibration curve for Quercetin

The calibration curve of Quercetin in distilled water was derived from the concentration and corresponding absorbance (Figure 2). Values of linear regression analysis gave the equation for the line of best fit as y= 0.0401x-0.0178. Linearity was observed in the concentration range between 5 to 25 µg/ml.

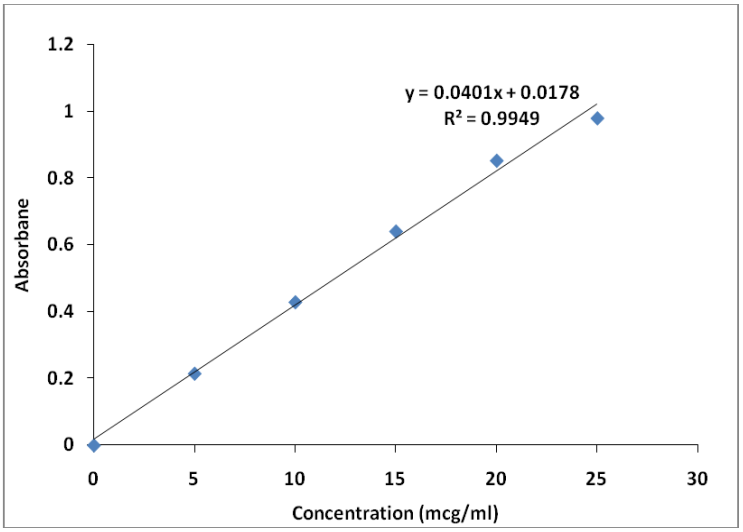

Figure 2. Calibration curve of Quercetin

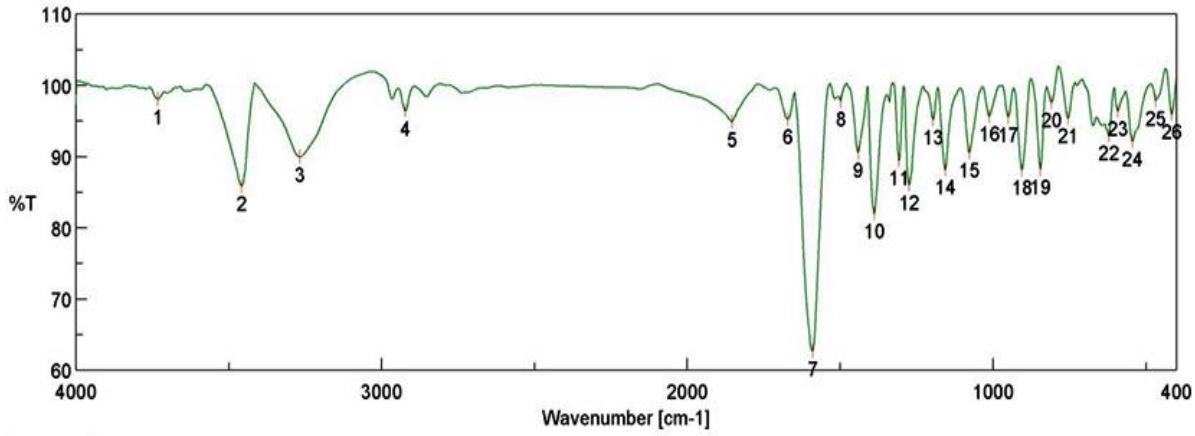

Figure 3. FTIR spectrum of co-crystal of Quercetin with chitosan

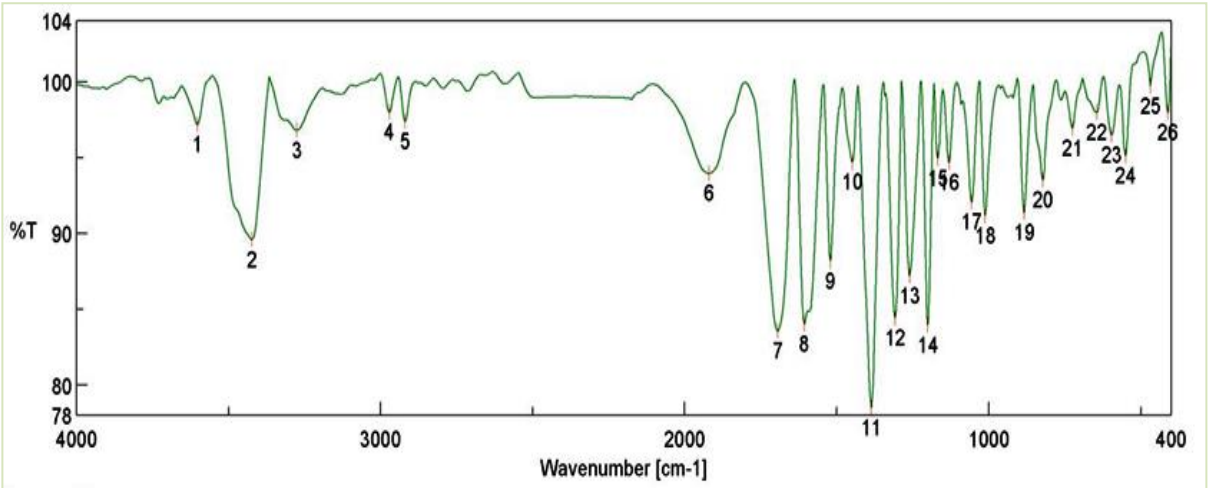

Figure 4. FTIR spectrum of co-crystal of Quercetin with Succinic acid

Drug excipients compatibility study

FTIR spectroscopy was used to study the possible interactions between Quercetin and cocrystals co-former chitosan and succinic acid. There is no significant difference in the FTIR spectra of pure drug and cocrystals. All major peaks of Quercetin were observed at wavenumbers 3436.81 cm-1 (free O–H stretching vibrations); 3358.55 and 2923.56 cm^{-1} (C–H stretching vibrations); and 1693.19 cm^{-1} (stretching vibration of ester and lactone carbonyl functional groups); 1600.63, 1454.06 and 1268.93 etc.., cm^{-1}(C-O stretching of esters and anhydrides) were retained in cocrystals, which clearly indicate that no interaction exists between pure drug and co-former. This indicates that the drug was compatible with the formulation components.

DSC analysis

DSC thermograms are shown in Figure 9, 10, 11 and 12. The DSC curve of pure quercetin exhibits two endothermic responses corresponding to its dehydration temperature (117 °C) and melting point (324 °C). Chitosan has endothermic peak at 120°C. The physical mixture of quercetin and chitosan featured a endotherm at 122.57°C and a broad endothermic event from 300.83°C to 310.34°C. Succinic acid melting point is 184°C . The physical mixture of quercetin and succinic acid featured a melting endotherm at 194.82°C and a broad endothermic event from 265.53°C to 294.95°C. The results were shown in Figure no. 05 and 06.

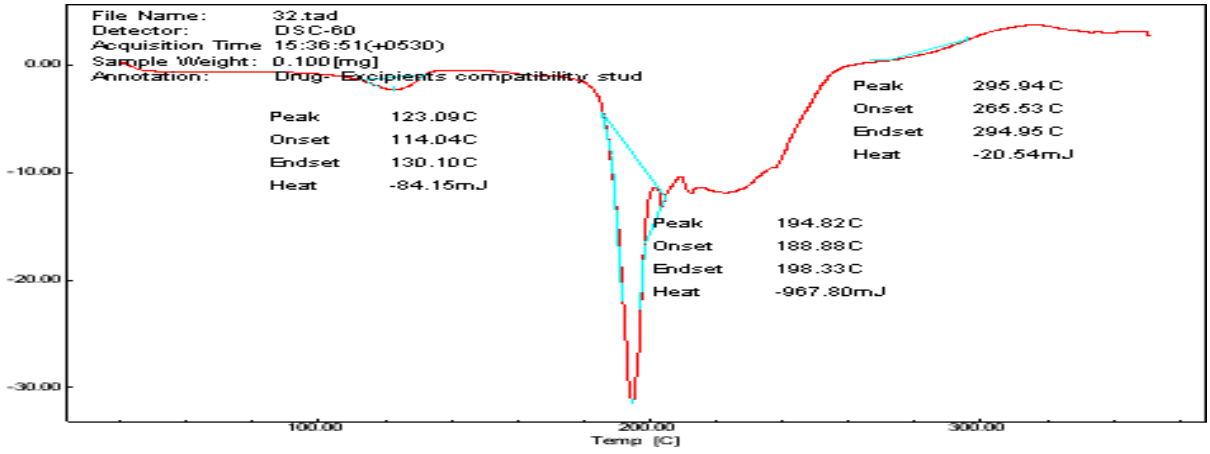

Figure 5. DSC thermogram of mixture of quercetin and Chitosan

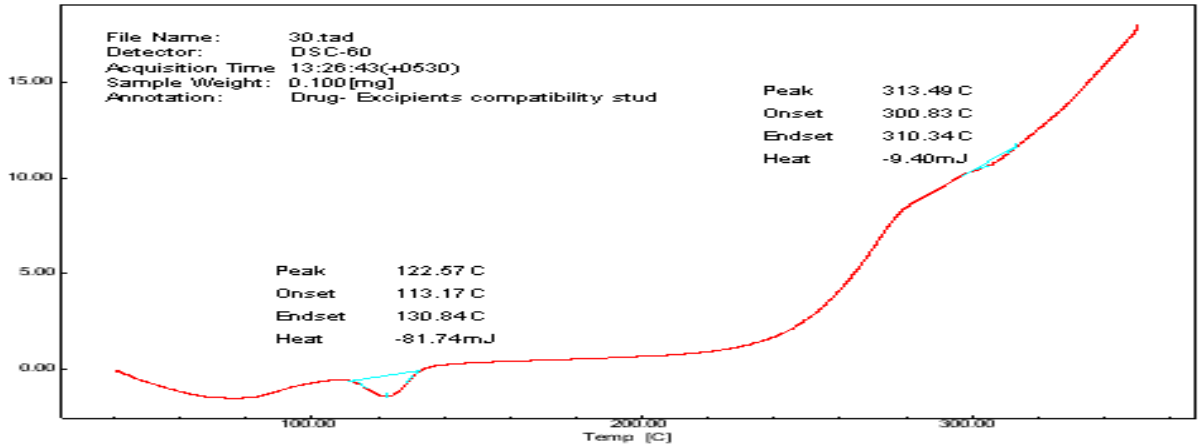

Figure 6. DSC thermogram of mixture of quercetin and Succinic acid

Scanning electron microscopic study

Surface of the all three co-crystals (QR-CH, QR-SA, QR-GA) were characterized by using the SEM analysis. SEM images were analyzed at different magnifications (Figure 7 & 8). The co-crystals were observed smooth surface and crystalline in nature. QR co-crystals were fluffy and possessed a porous and rough surface which enhanced the dissolution rate when compared to that of the pure drug.

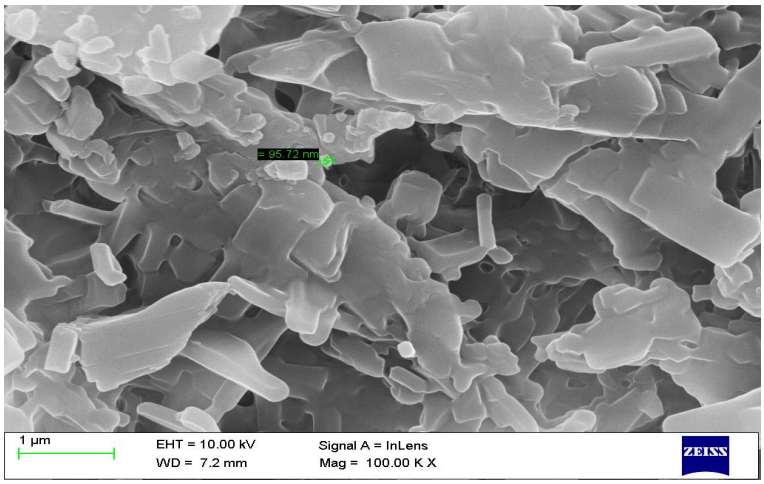

Figure 7. SEM of Co-crystal of Quercetin with Chitosan

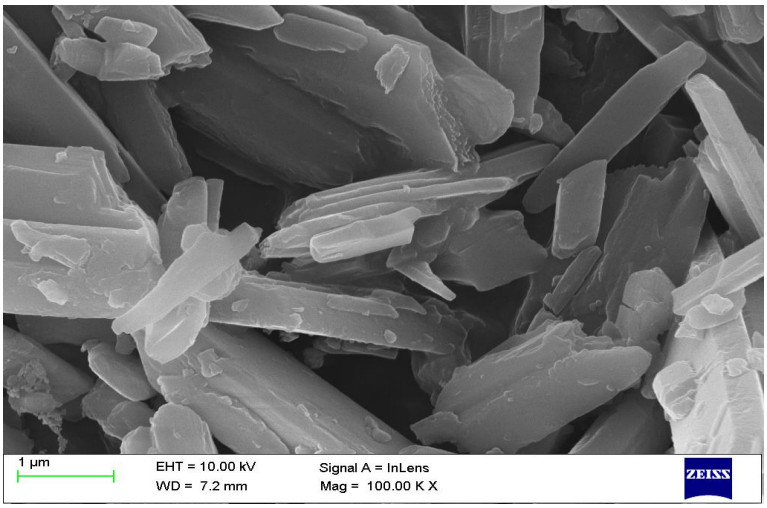

Figure 8. SEM of Co-crystal of Quercetin with Succinic acid

In vitro release study of co-crystals

All the formulations (F1- F6) of prepared co-crystals of Quercetin were subjected to *in-vitro* release studies. These studies were carried out using USP dissolution apparatus type-II in distilled water for 2hrs. The formulations were prepared with Chitosan (F1, F2) and Succinic acid (F3, F4) and Glutaric acid (F5, F6) with different ratios (1:1, 1:2) of drug and co-former (Figure 9 and 10).

The data revealed that percentage dissolution rate was comparatively enhanced in case of all the co-crystals. More than 54% drug release in 30 min was observed in case of all the co-crystals. Whereas, only 40% drug release was observed in case of QR at the end of 120 min.

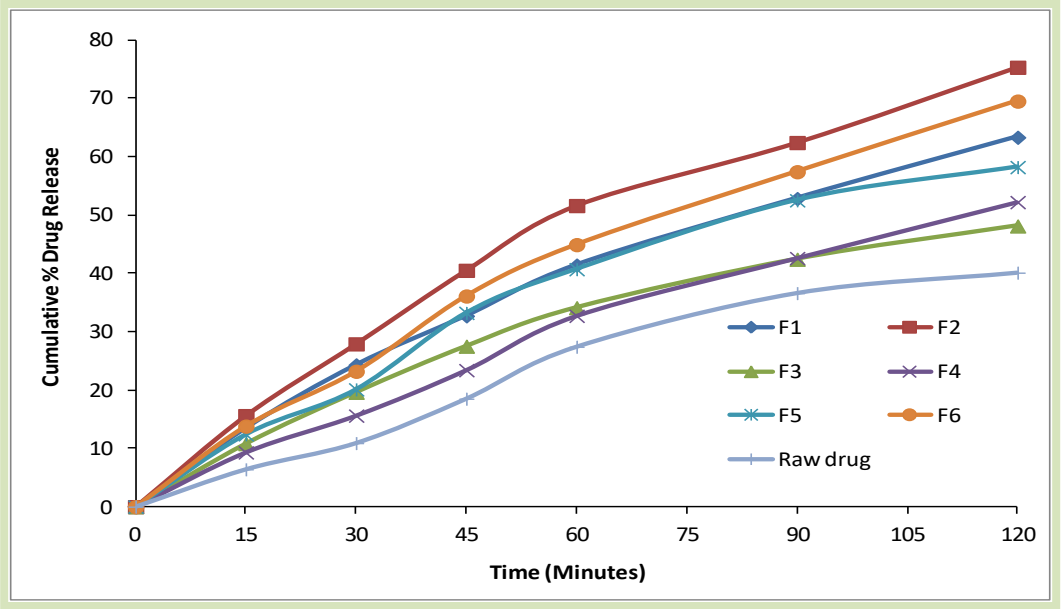

Figure 09. In vitro dissolution profile of co-crystals and raw drug

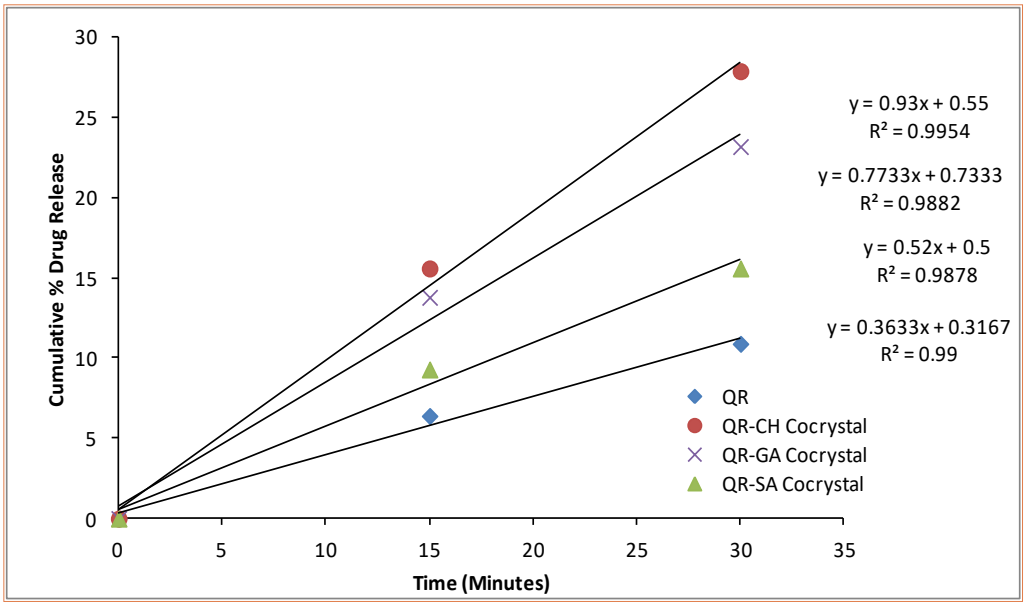

Figure 10. *Invitro* Dissolution Parameters

CONCLUSION

In this contemporary novel approach, it has been demonstrated a beneficial and successful application of the crystal engineering approach to achieve enhanced solubility of this poorly water soluble herbal drug by the cocrystal of quercetin with chitosan, Succinic acid and glutaric acid. For pharmaceutical industries, generation of an API with higher solubility, dissolution, and bioavailability offers great advantage in terms of its commercialization. Availability of more soluble alternatives of drugs also helps to overcome the arduous and lengthy process to apply various approaches to increase their solubility. The current investigation was based on the development of co-crystal of quercitin that could provide precompression properties, enhanced dissolution, and stability.

REFERENCES

[1]. Nair RH, Sarah JN, Adivaraha J, Swarbreek, editors. Co-crystals: design, properties and formulation mechanism, in Encyclopedia of Pharmaceutical Technology. New York: Informa Healthcare; 3(1), 2007, 615.

[2]. Sekhon BS, pharmaceutical co-crystals-a review, Ars pharma, 50, 2009, 99-117.

[3]. Paul EL, Tung HH, Midler M. Organic crystallization processes. Powder Technol. 150, 2005, 133–43.

[4]. Koji S, Noriyuki T, Ryusuke T, Yoshiki H, Katsuhide T. Dissolution improvement and the mechanism of the improvement from co crystallization of poorly water-soluble compounds. Pharm Res. 23, 2006, 1144–56.

[5]. Magali BH, Matthew LP, Lisa AS, Sherry LM, Vetter A, Hector G. Performance comparison of a co-crystal of carbamazepine with marketed product. Eur J Pharm Biopharm. 67, 2007, 112–9.

[6]. Bhatt PM, Azim Y, Thakur TS, Desiraju GR. Cocrystals of the anti-HIV drugs lamivudine and zidovudine. Cryst Growth Des 9(2), 2009, 951-7. DOI: 10.1021/cg8007359.

[7]. Skorepova E, Husak M, Cejka J, Zamostny P, Kratochvil B. Increasing dissolution of trospium chloride by co-crystallization with urea. J Cryst Growth 399, 2014, 19-26. DOI.org/10.1016/j.jcrysgro.2014.04.018.

[8]. Aher NS, Shinkar DM, Saudagar RB. Pharmaceutical cocrystallization: A review. J Adv Pharm Educ Res 4, 2014, 388-96. DOI.org/10.1016/j.ijpharm.2018.06.024.

[9]. Yadav AV, Shete AS, Dabke AP, Kulkarni PV, Sakhare SS. Cocrystals: A novel approach to modify physicochemical properties of active pharmaceutical ingredients. Indian J Pharm Sci 71(4), 2019, 359-70. DOI: 10.4103/0250-474X.57283.

[10]. Vaghela P, Tank HM, Jalpa P. Cocrystals: A novel approach to improve the physicochemical and mechanical properties. Indo Am J Pharm Res 4(10), 2014, 5055-65.

[11]. Mutalik S, Prambil A, Krishnan M, Achuta NU. Enhancement of dissolution rate and bioavailability of aceclofenac: A chitosan based solvent change approach. Int J Pharm 350, 2008. DOI.org/10.1016/j.ijpharm.2007.09.006.

[12]. Sugandha K, Kaity S, Mukherjee S, Isaac J, Ghosh A. Solubility enhancement of ezetimibe by cocrystal engineering technique. Cryst Growth Des 14, 2014, 4475-86 DOI: 10.1021/cg500560w.

[13]. Nehm SJ, Rodriguez-Spong B, Rodríguez-Hornedo N. Phase solubility diagrams of cocrystals are explained by solubility product and solution complexation. Cryst Growth Des 6, 2006, 592-600. DOI: 10.1021/cg0503346.

[14]. Bysouth SR, Bis JA, Igo D. Cocrystallization via planetary milling: enhancing throughput of solid state screening methods. Int J Pharm 411, 2011, 169-71. DOI.org/10.1016/j.ijpharm.2011.03.037.

[15]. Mukaida M, Watanabe Y, Sugano K, Terada. Identification and physicochemical characterization of caffeine-citric acid cocrystal polymorphs. Eur J Pharm Sci 79, 2015, 61-6. DOI: 10.1016/j.ejps.2015.09.002.

[16]. Shan N, Toda F, Jones W. Mechanochemistry and cocrystal formation: effect of solvent on reaction kinetics. Chem Commun 2002, 2372-73. DOI:10.1039/B207369M.

[17]. Cuadra IA, Cabanas A, Cheda JAR, Martinez-Casado FJ, Pando C. Pharmaceutical cocrystals of the anti-inflammatory drug diflunisal and nicotinamide obtained using supercritical CO2 as an antisolvent. J CO2 Util 13, 2016, 29-37. DOI.org/10.1016/j.jcou.2015.11.006.

[18]. Mutalik S, Prambil A, Krishnan M, Achuta NU. Enhancement of dissolution rate and bioavailability of aceclofenac: A chitosan based solvent change approach. Int J Pharm. 350, 2008, 279–90. DOI: 10.1016/j.ijpharm.2007.09.006.

[19]. Aakeroy CB, Salmon DJ, Smith MM, Desper J. Cyanophenyloximes: reliable and versatile for hydrogen bond directed supramolecular synthesis of cocrystals. DOI: 10.1021/cg0600492.

[20]. Qiao N, Li M, Schlindwein W, Malek N, Davies A, Trappitt G. Pharmaceutical cocrystals: An overview. Int J Pharm 419, 2011, 1-11. DOI.org/10.1016/j.ijpharm.2011.07.037.

[21]. Lin HL, Hsu PC, Lin SY. Theophylline-citric acid co-crystals easily induced by DSC-FTIR microspectroscopy or different storage conditions. Asian J Pharm Sci 8, 2013, 19-27. DOI.org/10.1016/j.ajps.2013.07.003.

[22]. Wu TK, Lin SY, Lin HL, Huang YT. Simultaneous DSC-FTIR microspectroscopy used to screen and detect the cocrystal formation in real time. Bioorg Med Chem Lett 21, 2011, 3148-51. DOI.org/10.1016/j.bmcl.2011.03.001.

[23]. Lu E, Rodriguez-Hornedo N, Suryanarayanan R. A rapid thermal method for cocrystal screening. Cryst Eng Comm 10, 2008, 665-68. DOI**:**10.1039/B801713C.

[24]. Yamashita H, Hirakura Y, Yuda M, Terada K. Coformer screening using thermal analysis based on binary phase diagram. Pharm Res 31, 2014, 1946-57. DOI: 10.1007/s11095-014-1296-4

[25]. Steed JW. The role of cocrystals in pharmaceutical design. Trends Pharmacol Sci 34(3), 2013, 185-93. DOI.org/10.1016/j.tips.2012.12.003.

[26]. Basavoju S, Bostrom D, Velaga SP. Indomethacin-Saccharin cocrystal: Design, synthesis and preliminary pharmaceutical characterization. Pharm Res 25(3), 2008, 530-41. DOI: 10.1007/s11095-007-9394-1.

[27]. Jiang L, Huang Y, Zhang Q, He H, Xu Y, Mei X. Preparation and solid state characterization of dapsone drug-drug cocrystals. Cryst Growth Des 14, 2014, 4562-73. DOI**:** 10.1021/cg500668a.

[28]. Parrott EPJ, Zeitler JA, Friscic T, Pepper M, Jones W, Day GM, Testing the sensitivity of terahertz spectrocopy to changes in molecular and supramolecular structure: a study of structurally similar cocrystal. Cryst Growth Des 9, 2009, 1452-60. DOI**:** 10.1021/cg8008893

[29]. Vogt FG, Clawson JS, Strohmeier M, Edwards AJ, Pham TN, Watson SA. Solid state NMR analysis of organic cocrystals and complexes. Cryst Growth Des 9, 2009, 921-37. DOI**:** 10.1021/cg8007014.