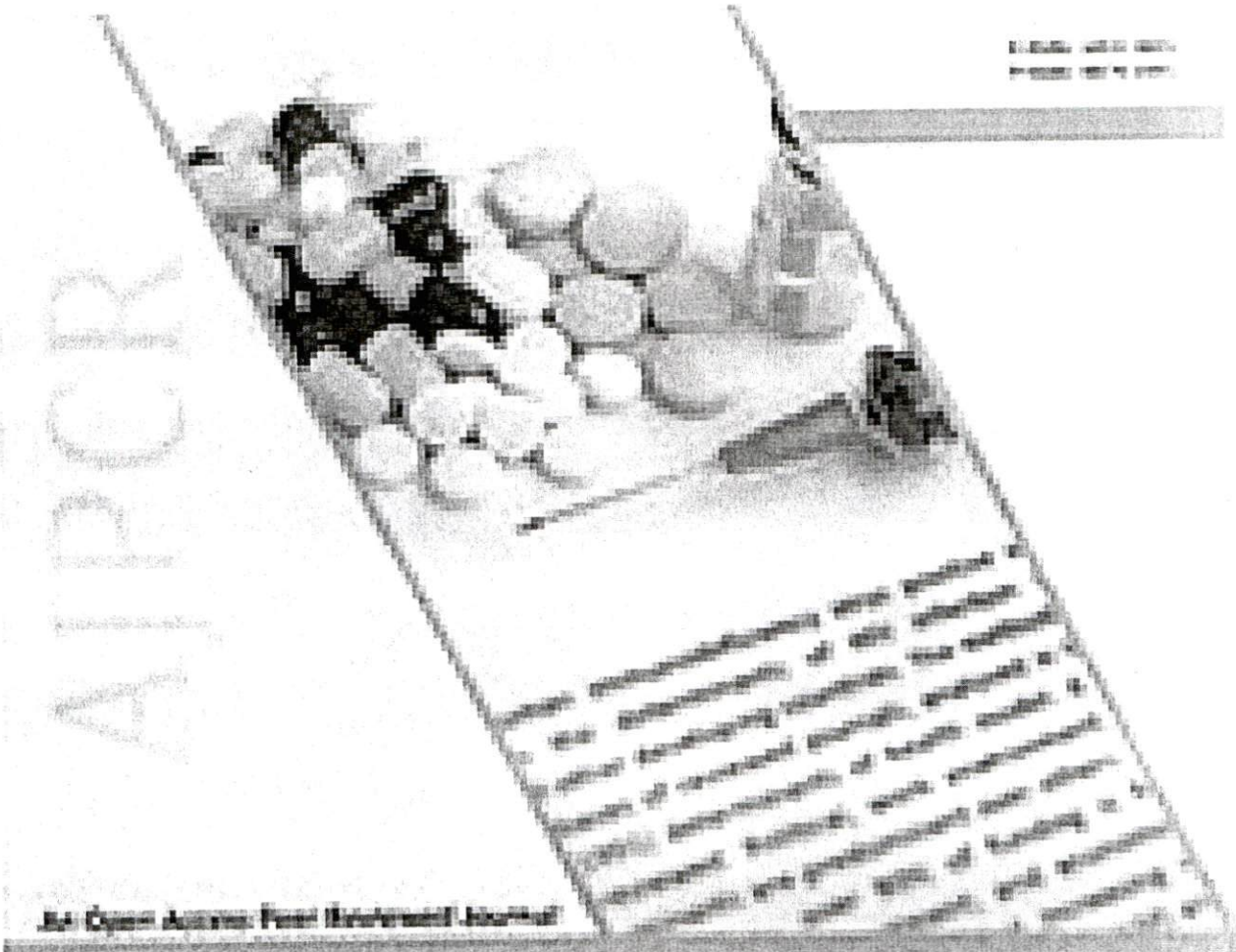

Asian Journal of Pharmaceutical & Clinical Research

Asian Journal of
Pharmaceutical and Clinical Research

E-ISSN: 2455-3891
P-ISSN: 0974-2441

Editorial Board

Editorial Board

AJPCR is committed to have dynamic and potential advisory-editorial board. Those established in the field can directly send their resume. New people are first needed to serve as referee before being considered member of advisory-editorial board. Email your resume to editor@ajpcr.com

Editor-in-Chief

- **Dr. Anurekha Jain**
  Dept. of Pharmaceutical Sciences, Jyoti Mahila Vidyapeeth University, Jaipur, Rajasthan
  Email: anurekhajain@jvwu.ac.in

Associate Editor

- **Dr. Nuray Arı**
  Prof., Department of Pharmacology, Faculty of Pharmacy, Ankara University, 06100 Ankara, Turkey. Email: ari@ankara.edu.tr

- **Dr. Neeraj Upmanyu**
  Prof., Peoples Institute of Pharmacy & Research Center, Bhopal, MP, India. Email: drneerajupmanyu@gmail.com

Assistant Editor

- **Dr. Omotoso Abayomi Ebenezer**
  Prof., Department of Pharmaceutical & Medicinal Chemistry. Faculty of Pharmaceutical Sciences, University of Port Harcourt, Nigeria. Email: abatoseb2001@yahoo.com

- **Dr. Vimal Kumar Jain**
  Principal, ITM School of Pharmacy, ITM Universe, Vadodara & Associate Dean, Pharmacy, GTU, Ahmedabad

Editorial Board Members

Editorial office

Asian Journal of Pharmaceutical and Clinical Research
B-11, In front of Beema Hospital, Nayi Awadi, Mandasaur 458001, MP, India
E-mail:editor@ajpcr.com

Online ISSN: 2455-3891

Print ISSN: 0974-2441

ICV 2018: 121.2

Journal Metrics 2018

Source Normalized Impact per Paper (SNIP): 0.655

Asian Journal of Pharmaceutical and Clinical Research

E-ISSN: 2455-3891
P-ISSN: 0974-2441

CASE STUDY(S)

COUGH AND CHEST PAIN WITH AN UNCOMMON CAUSE

PAYEL TALUKDAR, INDRANI DAS, KALYAN DAS, SUMIT VERMA, MOLOY KANTI MAKHAL MAKHAL

Pages 2-3

View PDF Abstract Download PDF

DICLOFENAC INDUCED ANGIOEDEMA: A CASE REPORT

HARSHAL NUTANRAO PISE, SUDHIR L. PADWAL

Pages 4-5

View PDF Abstract Download PDF

MULTIDRUG-RESISTANT ACINETOBACTER BAUMANNII FROM NOSOCOMIAL URINARY TRACT INFECTION: A CASE REPORT

SREENIVASAN SRIRANGARAJ, LAVANYA SEGAR, ARUNAVA KALI

Pages 6-8

View PDF Abstract Download PDF

WHEN THE Â€ŒRIGHT WAS WRONGÂ€: A CASE OF Â€ŒMISSED NEGLIGENCEÂ€

TANUJ KANCHAN, ALOK ATREYA

Pages 9-10

View PDF Abstract Download PDF

THE COMBINATION THERAPY MODEL OF ANDROGRAPHIS PANICULATA EXTRACT AND CHLOROQUINE ON PLASMODIUM BERGHEI INFECTED MICE

ACHMAD FUAD HAFID

Pages 205-208

View PDF Abstract Download PDF

ENHANCEMENT OF ROSUVASTATIN CALCIUM BIOAVAILABILITY APPLYING NANOCRYSTAL TECHNOLOGY AND IN-VITRO, IN-VIVO EVALUATIONS.

KARTICK PALANI, G.V.PETER CHRISTOPER, SATHESH KUMAR KESAVAN

Pages 88-92

View PDF Abstract Download PDF

SOLUBILITY, DISSOLUTION TEST AND ANTIMALARIAL ACTIVITY OF ARTESUNATE NICOTINAMIDE CO CRYSTAL PREPARED BY SOLVENT EVAPORATION AND SLURRY METHODS

DWI - SETYAWAN, NARENDRA KUSUMA, RETNO SARI

Pages 164-166

View PDF Abstract Download PDF

FOURIER TRANSFORM INFRARED ANALYSIS OF ULVA LACTUCA AND GRACILARIA CORTICATA AND THEIR EFFECT ON ANTIBACTERIAL ACTIVITY

MOHAIDEEN AMEER, DURAISAMY RADHIKA

Pages 209-212

View PDF Abstract Download PDF

TO DETERMINE THE RISK FACTORS ASSOCIATED WITH ECTOPIC PREGNANCY

RAJESH BASNET, NEELAM PRADHAN, LAXMAN BHARATI, NIRAJAN BHATTARAI, BUDDHA BAHADUR BASNET, BIDUR SHARMA

Pages 93-97

View PDF Abstract Download PDF

FLAVONOID FROM METHANOLIC EXTRACT OF LIMONIASTRUM FEEI (GIRARD) BATT (PLUMBAGINACEAE)

LAID ZIANE, ABDERAHMANE HAMMADI LAZOUNI, ABDELLAH MOUSSAOUI, NOURDDINE HAMIDI, MOHAMMED DJELLOULI, ABDELGHANI BELABBES

Pages 218-219

ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES Knowledge to Innovation

Vol 8, Issue 2, 2015

ISSN - 0974-2441

Research Article

SOLUBILITY, DISSOLUTION TEST AND ANTIMALARIAL ACTIVITY OF ARTESUNATE NICOTINAMIDE CO-CRYSTAL PREPARED BY SOLVENT EVAPORATION AND SLURRY METHODS

DWI SETYAWAN*, NARENDRA KUSUMA WARDHANA, RETNO SARI

Department of Pharmaceutics, Faculty of Pharmacy, Airlangga University Jl. Darmawangsa Dalam Surabaya, Indonesia.
Email: dwisetyawan-90@ff.unair.ac.id

Received: 10 December 2014, Revised and Accepted: 29 December 2014

ABSTRACT

Objective: The aims of this study was to investigate the solubility, dissolution rate and antimalarial activity against *Plasmodium berghei* of artesunate (AR)-nicotinamide co-crystal prepared by solvent evaporation (CoSE) and slurry (CoS) method.

Methods: Co-crystals of AR-nicotinamide prepared by solvent evaporation and slurry methods were tested for solubility, dissolution rate and activity of antimalarial compared to pure AR and physical mixture (PM) of AR and nicotinamide. Solubility test was conducted in distilled water at 37±0.5°C and dissolution test was done in distilled water medium at 37±0.5°C using paddle stirrer. Antimalarial activity test was carried out on female mice infected by *P. berghei* then parasitemia was observed.

Results: The AR solubility of slightly increased from 1236.66±141.42 to 1368.46±49.17 mg/L. Dissolution data at 30 minutes respectively for AR, PM, CoS and CoSE (76.51±14.93; 75.45±18.07; 85.14±12.94 and 123.24±7.68%). The results were antimalarial activity test of *P. berghei* showed that percent inhibition 84.98-89.50%. These data showed no significant differences in antimalarial activity between AR, CoS and CoSE.

Conclusions: Co-crystal AR nicotinamide prepared by solvent evaporation and slurry methods could increase the dissolution rate of AR in distilled water medium compared to pure AR. Co-crystal AR nicotinamide prepared by solvent evaporation was not significant difference as antimalarial activity in *P. berghei* compared to pure AR.

Keywords: Artesunate, Nicotinamide, Co-crystal, Solvent evaporation method, Slurry method, Dissolution rate, Antimalarial activity.

INTRODUCTION

Artesunate (AR), derived from artemisin is an antimalarial drug that has good bioactivity and low toxicity. AR was drug in biopharmaceuticals classification system Class II, means that AR has a low solubility in water and good permeability [1]. Drugs with low water solubility in often show low bioavailability, and dissolution rate is the determining step in the process of drug absorption [2].

Various methods are developed to improve the solubility and dissolution rate of drugs such as the manufacture of solid dispersions, the formation of prodrugs, drug inclusion complex with carrier, modified form of the compound into salt, solvate and co-crystal formation [2].

Co-crystal using crystal engineering principles to design crystalline form of medicine can improve their solubility, bioavailability, stability and other important properties without changing the effectiveness of the drug [3]. Co-crystal formation needs inert conformer with low toxicity such us nicotinamide. Co-crystal had been conducted by several methods such as solvent evaporation, rapid cooling, melting, grinding, and forming slurry [4].

Nicotinamide has demonstrated the ability to increase the solubility of other drugs in the water through chemical or physical modification by forming co-crystal [5]. Nicotinamide is inert co former besides saccharin and acetic acid [6].

Previous study on preparation and characterization AR - nicotinamide co-crystal had been conducted using AR co-crystal formation of nicotinamide as co former by solvent evaporation method and slurry method. Co-crystal of AR - nicotinamide was successfully formed and physicochemical characterization tests had conducted [1].

In this study solubility, dissolution rate and antimalarial activity of co-crystal AR - nicotinamide equimolar ratio of 1:1 by solvent evaporation and slurry methods were examined.

METHODS

Materials

AR was purchased from Ancalima Lifesciences Ltd., India, Batch No. AS/M-001/07-08. Nicotinamide was purchased from Western Drug Ltd, India, Batch No. 11-12/NMD[P]/B/093. *Plasmodium berghei* strain ANKA from Molecular Biology Department, Eijkman Jakarta, Indonesia, female mice of Balb-C strain were obtained from Animal Laboratory, Faculty of Pharmacy, Gadjah Mada University, Indonesia.

Methods

Formation of co-crystals by solvent evaporation (CoSE) method

AR and nicotinamide (equimolar) carefully were weighed as much as 3.15 g and 1.0 g respectively and dissolved in methanol separately. AR dissolved in approximately 140 mL of methanol to form a clear solution. Nicotinamide was dissolved in approximately 15 mL of methanol. Then the two solutions were mixed and stirred while. Equimolar solution of the two components evaporated at room temperature for 48 hrs. Solids co-crystal was stored in vacuum desiccators and was sieved using mesh No. 100.

Formation of co-crystals by slurry (CoS) method

AR and nicotinamide were weighed equimolar (1:1) as 3.15 g and 1.0 g respectively. Both are mixed homogeneously in a mortar. 15 mL of water was added to the mixture and then mixed homogeneously for 5 minutes. Co-crystal formed was dried at 40°C for 48 hrs. Solids co-crystal was stored in vacuum desiccators, and then sieved using mesh No. 100.

Determination of AR phase solubility

A total of 2.0 g co-crystal powder samples were weighed and put in beaker containing 50 mL of distilled water. The sample was placed and shaked in water bath at 25±1°C at 100 rpm. After 3 hrs the sample solution was taken then filtered with Whatman filter paper and diluted appropriately. AR concentration was determined by simultaneous spectrophotometric method.

Dissolution test of AR - nicotinamide co-crystal

AR - nicotinamide co-crystal was weighed equivalent to 50 mg of AR. Dissolution test was performed using ERWEKA DT 700 LH (Germany) with a paddle stirrer at 50 rpm in 900 ml at 37±0.5°C. Samples were taken at time interval 5, 10, 15, 20, and 30 minutes and 8.0 mL then filtered with Whatman filter paper 0.45 µm and analyzed by spectrofotometric.

Antimalarial activity test

$$\%\text{growth}=\frac{P(d1-d0)+P(d2-d1)+P(d3-d2)+....+P(d6-d5)}{6}$$

Antimalarial activity test was carried out on *P. berghei* infected female mice. Four treatment groups were CoSE, CoS, AR and CMC Na as a control. Parasitemia was observed after orally administration of samples. Infected mice were divided into 4 groups where 6 animals/ group. From the calculated percent blood smear parasitemia. Percent parasitemia calculated by the number of infected erythrocyte cell per 5000 erythrocytes. Percent of parasitemia growth was calculated by following equation:

Where:

$P(d_x-d_{x-1})$ = % parasitemia day (x) subtracted % parasitemia day (X−1)

RESULTS AND DISCUSSION

Solubility of AR

Solubility of AR, physical mixture (PM) of artesunat-nicotinamide, AR -nicotinamide CoS method and AR - nicotinamide CoSE method was determined in distilled water at 37±0.5°C at the saturated solubility of AR. The result of saturated solubility test of AR showed in Fig. 1.

From one-way ANOVA statistical analysis, it was known that saturated solubility of AR of significance value more than 0.05. There is no significant difference from the 30; 60; 120; 180 minutes.

From solubility test, it was known that the solubility of AR in a PM slightly increased affected by solubility of nicotinamide is so that AR easier wetted. Solubility of AR in co-crystal enhanced due to the hydrogen bonding between AR and nicotinamide and co-former solubility properties [7]. Solubility profiles of samples are shown in Fig. 2. Nicotinamide is soluble in water so when AR - nicotinamide bonds, solubility of AR will also increased. Increasing solubility of AR can also be seen from the decreasing of melting point co-crystal. Thermal analysis by differential thermal analysis, melting point of AR is 142.2°C, nicotinamide is 133.3°C and melting point of co-crystal is 98.4°C. Decreasing of melting point indicated decrease in the energy of the crystal lattice, resulting more soluble co-crystal [8].

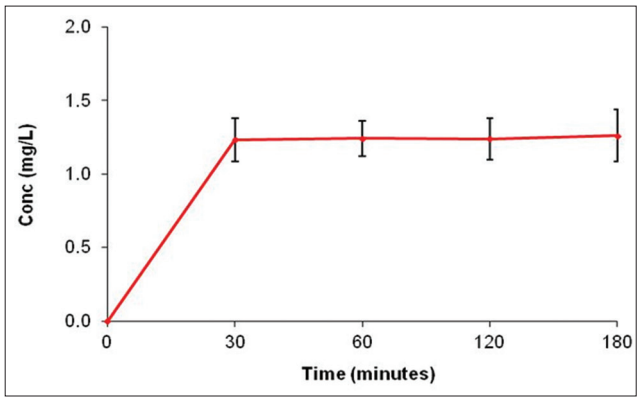

Fig. 1: Saturated solubility of artesunate in distilled water medium at 37±0.5°C

Statistical analysis of solubility one-way ANOVA showed significance difference more than 0.05 that otherwise there is no significant difference of each group.

Dissolution test

The results of the dissolution test of AR, PM, CoS and CoSE can be seen in Fig. 3.

Fig. 3 can be seen that co-crystal of AR - nicotinamide prepared by both methods had higher dissolution rate than pure AR and the PM. CoSE gave fastest dissolution rate.

From efficiency dissolution (ED_{30}), it was known that the dissolution rate AR from CoSE, CoS were increased compared to pure AR (Table 1). Dissolution rate increased due to the increased solubility of AR. The result can be explained by Noyes and Whitney equation. Concentration of a saturated solution of the compound at the temperature of the experiment is proportional to the rate of dissolution [9].

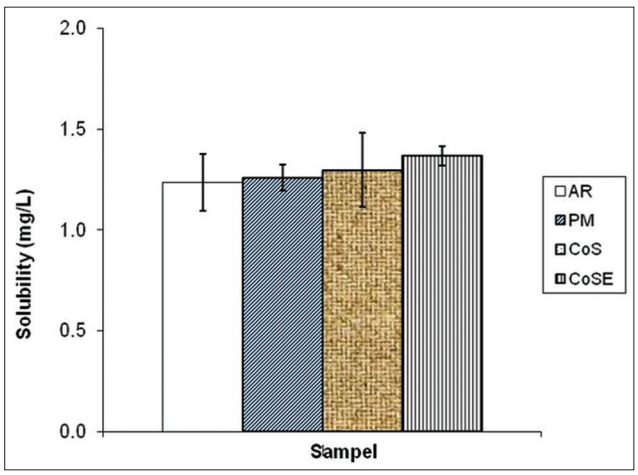

Fig. 2: Solubility of artesunate, physical mixture, co-crystal slurry and solvent evaporation methods

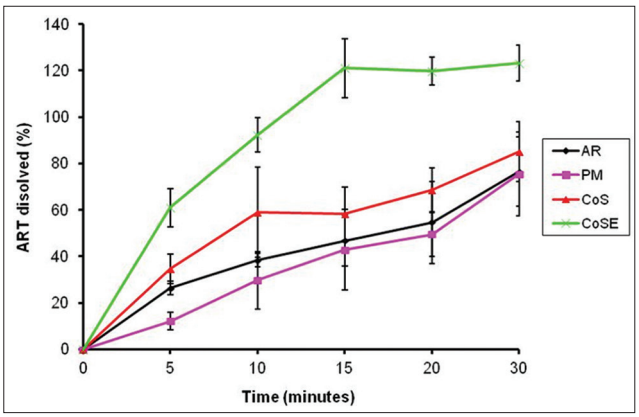

Fig. 3: Dissolution profile of artesunate, physical mixture, co-crystal slurry and co-crystal solvent evaporation in distilled water medium at 37±0.5°C

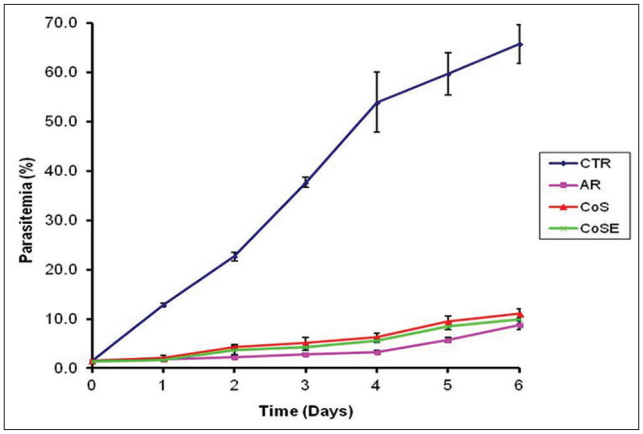

Fig. 4: Curve growth parasitemia of mice infected with Plasmodium berghei

Table 1: ED of AR in 30 minutes

Replicate	AR	PM	CoS	CoSE
1	42.71	29.75	39.52	75.26
2	33.84	36.30	44.72	78.93
3	25.71	19.88	45.63	73.74
Average of ED_{30} (%)	34.09	28.65	43.29	75.98
SD	8.51	8.27	3.30	2.66

AR: Artesunate, PM: Physical mixture, CoS: Co-crystal slurry, CoSE: Co-crystal solvent evaporation, SD: Standard deviation, ED: Efficiency dissolution

Table 2: Results of HSD test of ED_{30} with α=0.05

	AR	PM	CoS	CoSE
AR		-	+	-
PM	-		+	-
CoS	+	+		+
CoSE	-	-	+	

+: Significant difference, -: No significant difference, ED: Efficiency dissolution, AR: Artesunate, PM: Physical mixture, CoS: Co-crystal slurry, CoSE: Co-crystal solvent evaporation, HSD: Honestly significant difference

From statistical analysis one-way ANOVA, ED_{30} of AR, PM, CoS and CoSE significant difference for each treatment group at least one group. Furthermore honestly significant difference (HSD) test to determine which treatment group at these differences. The results of HSD test of ED_{30} with α=0.05 is shown in Table 2.

Antimalarial activity test

Tests carried out on female mice infected. The results of antimalarial activity test showed that percent of *P. berghei* inhibition ranged between 84.98% and 89.50%. These data showed no significant differences in antimalarial activity test between AR, CoS and CoSE as shown in Fig. 4. This is due to the amount of soluble AR were not significantly different, although the dissolution co-crystal AR (CoS and CoSE) faster than pure AR.

CONCLUSIONS

Co-crystal AR nicotinamide prepared by solvent evaporation and slurry methods showed increased of dissolution rate in distilled water medium compared by pure AR. Co-crystal AR nicotinamide prepared by solvent evaporation no significant difference as antimalarial activity in *P. berghei* compared with pure AR.

ACKNOWLEDGMENTS

We would like to thank of Ministry of Research and Higher Education Indonesia for funding the research grant through BOPTN of Airlangga University 2014.

REFERENCES

1. Setyawan D, Sari R, Yusuf H, Primaharinastiti R. Preparation and characterization of artesunate-nicotinamide co-crystal by solvent evaporation and slurry method. Asian J Pharm Clin Res 2014;7(1):62-5.
2. Zaini E, Halim A, Soewandhi SN, Setyawan D. Dissolution rate enhancement of trimethoprim by co-crystallization with nicotinamide. J Farmasi Indonesia 2011;5(4):205-12.
3. Chadha R, Saini A, Arora P, Bhandari S. Pharmaceutical cocrystals: A novel approach for oral bioavailability enhancement of drugs. Crit Rev Ther Drug Carrier Syst 2012;29(3):183-218.
4. Chandramouli Y, Gandhimathi R, Yasmeen BR, Vikram A, Dan Mahitha B, Imroz SM. Review on cocrystal as an approach with newer implications in pharmaceutical field India. Int J Med Anal 2012;2(2):91-100.
5. Montaseri H, Jamali F, Rogers JA, Micetich RG, Daneshtalab M. The Effect of temperature, PH, and different solubilizing agents on stability of taxol. Iran J Pharm Sci 2004;1(1):43-51.
6. Mohanachandran PS, Sindhumol PG, Kiran TS. Enhancement of solubility and dissolution rate: An overview. Int J Compr Pharm 2010;4(11):1-10.
7. Huang N, RodríguezHornedo N. Engineering cocrystal solubility, stability, and phmax by micellar solubilization. J Pharm Sci 2011;100(12):5219-34.
8. Aitipamula S, Banerjee R, Bansal AK, Biradha K, Cheney ML, Choudhury AR, *et al*. Polymorphs, salts, and cocrystals: What's in a name? Cryst Growth Des 2012;12(5):2147-52.
9. Qiao N, Li M, Schlindwein W, Malek N, Davies A, Trappitt G. Pharmaceutical cocrystals: An overview. Int J Pharm 2011;419(1):1-11.