Polymorphic Transformation of Ornidazole with Nicotinamide in Solid Dispersion to Enhance Solubility and Dissolution Rate

Gopal Prasad Agrawal1*, Anuj Garg1

1 Institute of Pharmaceutical Research, GLA University, 17 Km Stone, NH-2, Mathura-Delhi Road, P.O. Chaumuhan, Mathura-281406, (U.P.) India

ABSTRACT

The solubility study of Ornidazole with different concentration of Nicotinamide was carried out to construct phase solubility diagram. The solid dispersion was prepared and characterized for its solid-state properties by employing FTIR, DSC and powder XRD techniques. The morphology of prepared solid dispersion was evaluated by using SEM. The dissolution study was also carried out for Ornidazole, PM and SD. Phase solubility diagram indicated an Ap type of relationship for the Ornidazole and Nicotinamide. DSC result indicated the shifting of melting endothermic peak of Ornidazole from 91.2°C to 77.16 °C in SD, which could be attributed to polymorphic transformation of Ornidazole in Form II to Form I in presence of Nicotinamide and also confirmed by FT-IR and XRD studies. Hence, the present study showed the transformation of one polymorphic form of Ornidazole to another low melting point polymorphic form in presence of Nicotinamide lead to significant enhancement of their dissolution rate.

Keywords: Ornidazole, Nicotinamide, Solid dispersion, Polymorphic form, Phase solubility

INTRODUCTION

Ornidazole is a third generation nitroimidazole derivative, a potent antimicrobial drug and used to treat infections caused by protozoa and certain strains of anaerobic bacteria. It is used to treat infections of the stomach, intestine, urinary tract and genital area. This compound is white to pale yellow crystalline powder, freely soluble in methanol, very slightly soluble in ether and slightly

*Corresponding author: Gopal Prasad Agrawal, e-mail: gopalprasad.agrawal@glau.ac.in
Gopal Agrawal ORCID Number: 0000-0003-3714-0165
Anuj Garg ORCID Number: 0000-0003-0442-3863
(Received 22 October 2019, accepted 05 November 2019)
soluble in water. It exhibits low dissolution rate due to which large variation appear in in-vitro dissolution testing and also affect its bioavailability.1,2

The problem of poor aqueous solubility and low dissolution rate of drugs has received extensive considerations and various techniques have been investigated to enhance their dissolution rate and bioavailability. The general methods include particle size reduction (formation of nanocrystals/ micronization etc.), inclusion complexation (using cyclodextrins), micellar solubilization, chemical derivatization (formation of polar prodrugs) and solid dispersion.3,4,5,6,7,8,9 Solid dispersion is one of the most promising approaches to enhance the dissolution rate of drugs having poor aqueous solubility. Solid dispersion can easily be prepared with suitable carriers by different methods and used to devise amorphous or crystalline multicomponent systems. The widely used methods for preparing solid dispersions are fusion, solvent evaporation and fusion-solvent methods.10,11 Some of the first carriers11 employed in their preparations were crystalline carriers such as urea, sugars and Nicotinamide (Vitamin B3). These types of carriers were able to create crystalline or partially crystalline solid molecular dispersions. They are more thermodynamically stable as compared to that of amorphous form. Therefore, solid dispersion offers potential benefit over the amorphous forms with respect to their stability. Previously, solubility of Ornidazole was found to be increased from 0.01g/mL to 0.0368g/mL and 0.0902g/mL in 10% w/v and 20% w/v Nicotinamide aqueous solution, respectively.12 In marketed formulation (suspension), the dose is 125mg/5mL but the reported solubility of Ornidazole in water is 15mg/mL.13 In this study, the solubility of Ornidazole was determined in higher concentration of Nicotinamide (30%w/v) which showed further increase in solubility of Ornidazole. Therefore, the main objective of the present work is to increase the solubility of Ornidazole by formation of solid dispersions with Nicotinamide as a carrier. The solid dispersion was prepared and characterized for their solid-state characteristics by employing differential scanning calorimetry, FT-IR, and powder XRD. Any chemical interaction of Ornidazole with Nicotinamide was also studied by using HPLC. Morphology of solid dispersion was studied by using Scanning Electron Microscope (SEM) to observe the difference from that of pure Ornidazole crystals. The dissolution study was carried out for Ornidazole, physical mixture and solid dispersion to assess the effect of solid dispersion on dissolution rate of Ornidazole.

METHODOLOGY

Ornidazole and Nicotinamide were procured from Yarrow Chem, and Quiligens Fine Chemicals, Mumbai, India. All other chemicals and solvents were used of analytical grade.
Phase Solubility studies

The phase solubility studies were conducted as per the method reported by Higuchi and Connors (1965). Excess of Ornidazole was added separately into 25-mL stoppered conical flasks containing 10 mL of distilled water or aqueous solution (1–30% w/v) of Nicotinamide. The flasks were sealed and agitated on a rotary shaker at ambient temperature (25°C) for 24 h and equilibrated for 2 days. The whole material was centrifuged at 2000 g to separate out the excess drug. The supernatant was filtered through filter paper (Whatman Grade 41). The filtrate was appropriately diluted with methanol and the absorbance was measured at 311 nm [13] by UV spectrophotometer to determine drug concentration using regression equation $y = 0.0419x + 0.0056$. The apparent 1:1 stability constant, $K_s$, was calculated by the equation reported by Garg et al, 2010. 

Preparation of solid dispersions (SDs)

For preparation of solid dispersions, Ornidazole and Nicotinamide (1:2, 1:4 and 1:6 in ratio) were transferred to 200 mL of Erlenmeyer flask. Firstly, Nicotinamide (6.6 g) was transferred with the addition of about 2-3 mL distilled water and kept at 60-65°C temperature to dissolve it. Afterwards, Ornidazole (3.3 g) was added to it in portions and stirred well. The temperature of the whole mixture was allowed to come down. The whole mass was then transferred to watch glass and allowed to dry in an oven maintained at temperature 40°C±5°C. The dried mixture was scraped off. The whole mass was transferred to the pestle mortar to get a powder, again kept in oven for drying. After drying, the powder of solid dispersion was passed through sieve number 100 and kept in desiccators. Finally, the powdered mass was stored in air-tight container. Same procedure was followed to prepare SDs of 1:4 (Ornidazole 2.0 g) and 1:6 (Ornidazole 1.4 g) ratios of Ornidazole and Nicotinamide as a carrier.

Physical mixture (PM)

Only higher Drug: carrier ratio (1:6) was used for preparation of PM. Ornidazole (1.4 g) and Nicotinamide (8.6 g) were accurately weighed and mixed for 10 min using glass pestle and mortar with trituration. Then, powder was passed through sieve number 100. There after the physical mixture was stored in air-tight glass bottles.

Determination of drug content in SD and PM

Solid dispersions (100 mg of each) and PM (100 mg) were accurately weighed and transferred to small beaker and dissolved in small volume of methanol. The content was quantitatively transferred to volumetric flask (100 mL) with the aid
of methanol using Whatman grade 41 filter paper. The volume was made up to the mark with methanol. Further dilutions were made to achieve the concentration in the range of standard calibration curve using methanol as a solvent and the absorbance of this solution was measured at 311 nm. In each case, the experiments were carried out in triplicate and results were summarized in Table 1.

**Table 1.** Drug contents of physical mixtures and Solid dispersions (n = 3)

| Drug: Hydrotrropic Agent | Percent drug content (mean ± S.D.) |
|--------------------------|-----------------------------------|
|                          | PM                                | SD          |
| ONN 1:2                  | -                                 | 33.38±0.074 |
| ONN 1:4                  | -                                 | 20.12±0.082 |
| ONN 1:6                  | 14.18±0.073                       | 14.57±0.076 |

PM - Physical mixture; SD - Solid dispersion; S.D. – Standard deviation; ON – Ornidazole; ONN – Ornidazole Nicotinamide

**FTIR Spectroscopy**

About 1-5 mg of the sample was triturated with approximately 300 mg of dry, finely powdered potassium bromide (IR grade) in a pestle and mortar. The sample was scanned over wave number region of 4000 to 400 cm⁻¹ at resolution of 4 cm⁻¹.

**Differential scanning calorimetry (DSC)**

A large number of solid dispersions have been characterized by DSC studies to assess the possibility of interactions between drugs and water-soluble carriers. Attempts were made to assess the possibility of interaction of hydrotrropic agent (Nicotinamide) with drug (Ornidazole). In order to obtain the DSC thermograph of Ornidazole, solid dispersion and physical mixture, DSC Q 20 (TA Instruments USA) was used. The samples (4 mg) were weighed accurately and sealed in aluminium pans. The sealed pans of both sample and reference were placed in heating cell and heated in range of 25°C-300°C at a rate of 10°C/min with purging of nitrogen.

**Powder X-ray diffraction studies**

The X-ray diffractions (XRD) of the Ornidazole, solid dispersion and physical mixture were studied on X’pert Pro (PANalytical, Netherland) using Ni-filter and CuKα1 radiation with Spinner PW3064. A voltage of 45 kV and 40 mA current were applied with a scintillation counter. The samples were scanned by the XRD instrument in a range of 5° to 80°.
**HPLC analysis**

A High-performance liquid chromatography (HPLC) method was used to determine the chemical incompatibility between drug and hydrotrropic agent. The HPLC system isocratic mode-Cyber lab LC 100 plus (USA) separation module having maximum pressure of 5000 psi, detector—LC-UV 100 Plus, UV detector was used. The mobile phase consists of acetonitrile: water, (50:50 v/v), 0.2% triethylamine, the pH was adjusted to 4 using ortho-phosphoric acid (The mobile phase was filtered using 0.45 μm membrane filters and degassed by ultrasonic vibrations for 30 minutes prior to use). The flow rate was kept at 1 mL min⁻¹. C18 Cosmosil packed column having 4.6 mm internal diameter and 250 mm length. The wavelength was selected at 312 nm. From SD (ratio 1:6), 1µg/mL solution was prepared in methanol and 10µL was injected in HPLC.

**Scanning electron microscopy (SEM)**

SEM analysis was performed to visualize the morphology of the pure crystal of Ornidazole, PM and SD. Sample powder was attached to a aluminum metal sample holder using double-sided adhesive tape and then made electrically conductive by coating with gold in a vacuum. The sample was observed by SEM (JEOL, JSM-6100, Japan) at various magnifications. The analysis was set at voltage was set at 5 kV and the current was 12 mA.

**Dissolution rate studies**

Dissolution rates of pure crystal of Ornidazole, PM (ratio 1:6), and SD (ratio 1:2, 1:4 and 1:6) were studied using USP paddle type dissolution rate test apparatus. Drug (Ornidazole), PM, and SDs equivalent to 100 mg drug were taken in 900 mL of 0.1 M Hydrochloric acid as dissolution medium. The stirring rate of 50 rpm and temperature of 37±0.5°C was maintained throughout the dissolution study. Samples (5 mL) of dissolution medium were withdrawn at predetermined time intervals and replaced with same volume of fresh dissolution medium after each withdrawal. The samples were filtered through Whatman grade 41 filter paper and after suitable dilution with methanol analyzed for drug contents at 311 nm wavelength. The dissolution studies were performed in triplicate. The percentage dissolution efficiency (%DE) is defined as the ratio of area under the dissolution curve up to a definite time (t) to the area of the rectangle for 100% dissolution in that time. It is calculated by the following equation:

\[
DE_T = \frac{\int_{0}^{T} y_t \cdot dt}{\frac{y_{100}}{T}}
\]
where \( y_t \) is the percentage of drug dissolved at any time \( t \), \( y_{100} \) denotes 100% dissolution, and the integral represents the area under dissolution curve between time 0 and \( T \) in minutes. The time \( T \) in this study was 90 min. Dissolution efficiency was calculated for pure drug, PM and SD by using above equation.

**RESULTS AND DISCUSSION**

The phase solubility diagram for Ornidazole as a function of Nicotinamide concentration in water is shown in Figure 1.

![Phase Solubility Diagram](image)

**Figure 1. Phase Solubility Diagram**

The phase solubility diagram clearly indicated that enhancement of solubility for Ornidazole in a linear relationship up to 12.29 mM of Nicotinamide. Further increase in the concentration of Nicotinamide up to 25 mM showed a huge increase in the aqueous solubility of Ornidazole. Hence; phase solubility diagram showed a divergence from linearity, demonstrated an \( A_p \) type of phase solubility diagram. The apparent stability constant was calculated from the linear portion of the phase solubility diagram assuming the formation of 1:1 complex in the linear portion of the phase solubility diagram. The value of apparent stability constant was found to be 5108 M\(^{-1}\). This value of apparent stability constant is adequate to improve the solubility of Ornidazole in presence of Nicotinamide. The solubility of Ornidazole was found to be increased by 11 times at 25 mM of Nicotinamide while only 3 times at 12.3 mM of Nicotinamide. The positive deviation in the solubility of Ornidazole at higher concentration of Nicotinamide was observed which could be attributed to formation of higher order complexes or to the polymorphic transformation of drug. Previous...
ously, solid dispersion of Nicotinamide with flurbiprofen lead to transform the polymorph form of flurbiprofen from high melting polymorph (112°C) to low melting polymorph (97°C) and their solubility phase diagram also indicated Ap type. Thus, it can be hypothesized that high concentration of Nicotinamide induce the transformation of one polymorph to another polymorph.

**Solid State Characterization of Ornidazole Nicotinamide Solid dispersion**

DSC thermogram (Figure 2) of pure Ornidazole showed a single sharp endothermic peak at 91.2°C which corresponds to the melting point of Ornidazole. DSC thermograms of physical mixture and solid dispersion of Ornidazole and Nicotinamide in ratio of 1:6 showed first endothermic peak at 80.26 °C and 77.16°C, respectively (Figure 3a and 3b). Three different polymorphic forms of Ornidazole were reported in literature. The melting point of Form I, Form II and Form III was reported to be in the range of 76-78°C, 89.69°C and 86.9°C, respectively. Hence, the shifting of endothermic peak could be attributed to polymorphic transformation of Ornidazole Form II to Form I in presence of Nicotinamide. Second endotherm peak was observed at 127-128°C which indicated the melting of Nicotinamide (Figure 3c) in physical mixture as well as in solid dispersion. Form I has the lowest melting point, hence expected to provide higher solubility as compared to that of Form II. The A_p type phase solubility diagram for Ornidazole and Nicotinamide was obtained in the present study which could be attributed to this polymorphic transformation in presence of Nicotinamide.

![Figure 2. DSC Thermogram of Ornidazole](image)
Figure 3. DSC Thermograms (a) PM, (b) Solid dispersion and (c) Nicotinamide

The Infra-Red spectra (Figure 4a) of Ornidazole exhibited peaks at 3174 cm$^{-1}$ (O-H str), 3113 & 3089 cm$^{-1}$ (C-H str), 1537 cm$^{-1}$ (asymmetric NO$_2$ str), and 1361 & 1269 cm$^{-1}$ (symmetric NO$_2$ str). The peak at 3174 cm$^{-1}$ was found to be shifted to 3161 cm$^{-1}$ and 3153 cm$^{-1}$ in physical mixture (Figure 4b) and solid dispersion (Figure 4c), respectively indicating the change in O-H stretching of Ornidazole. The asymmetric peak of NO$_2$ at 1537 cm$^{-1}$ was found to be diminished and observed at 1535 cm$^{-1}$ in SD which could be attributed to involvement of oxygen of nitro group of Ornidazole in formation of weak hydrogen bonding with amide group of Nicotinamide. This weak hydrogen bonding between Nicotinamide and Ornidazole lead to change in the spatial arrangement of Ornidazole and transform to polymorph of low melting point as shown by DSC.
The powder XRD pattern for Ornidazole, Physical mixture and solid dispersion of Ornidazole and Nicotinamide were depicted in Figure 5a-c. The diffraction pattern of Ornidazole showed that the solid drug is highly crystalline powder, with sharp diffraction peaks at 2θ of 13.33, 15.88, 20.83, 27.43 and 30.48. Peak at 20.8 showed the 100% relative intensity in pure drug while in physical mixture (Figure 5b) and solid dispersion (Figure 5c), the relative intensity was found to be decreased significantly which indicated change in the crystalline nature of Ornidazole. Similarly, peak at 2θ of 30.48 was disappeared in physical mixture and solid dispersion, hence showed the change in the crystalline nature (i.e transformation of one form to another form or less crystalline form).
of Ornidazole in the presence of Nicotinamide. The characteristic peak of Nicotinamide was found to be at 2θ of 25.8 in physical mixture which is similar to the peak reported in literature. However, the intensity of this characteristic peak was significantly reduced in the solid dispersion. Therefore, indicating the solid-state interaction with Ornidazole during formation of solid dispersion. The results of XRD can be well correlated to that of DSC.

Figure 5. PXRD diffraction pattern of a) Ornidazole, (b) PM and (c) Solid dispersion

HPLC analysis of solid dispersion of Ornidazole was performed and chromatogram was obtained (Figure 6). The Ornidazole peak in the chromatogram was observed as a single peak at 4.14 min. The tailing factor and height equivalent theoretical plate were found to be 1.09 and 9489, respectively. The data observed from the HPLC showed no other peak was merged on the retention time of drug. All the parameters were found within the limit therefore results indicated no chemical incompatibility between Ornidazole and hydrotropic agent (Nicotinamide).
Figure 6. Chromatogram of Ornidazole in Solid dispersion

The photomicrographs of SEM for drug (Ornidazole), PM and SD were obtained as Figure 7a, 7b and 7c respectively. Figure 7a showed rectangular, thick plate like morphology of the drug. In case of PM and SD, Figure 7b–c showed the change in morphology of drug (the rectangular crystals were transformed to some extent in round shape and increase in size). The original morphology of the drug was disappeared in PM and SD. It may assume that hydrotropic agent (Nicotinamide) cover-up the surface of the drug particles but still sharp edge of the particles can be observed, indicating that the crystalline nature of the drug was not completely reduced.
"H-NMR technique has been used as important tool for investigating the group involved in interaction and mechanism of complexation. Ornidazole (Figure 8a), Nicotinamide (Figure 8b), PM (Figure 8c) and solid dispersion of Ornidazole (Figure 8d) [1:6 ratio] were analyzed for "H-NMR. The absence of new peak in the spectra of solid dispersion suggested that the absence of any chemical interaction involving covalent bond. The spectra revealed that under the present condition only changes in chemical shift occurred. Downfield displacements of the protons indicate that they are close to an electronegative atom, like oxygen. The proton of amide moiety (H₅) experienced a pronounced chemical shift variation from 9.16 in pure Nicotinamide to 8.99 ppm in solid dispersion, hence confirmed that hydrogen of amide moiety was involved in the hydrogen bonding with Ornidazole. Results of FT-IR can be well correlated with the results of "H-NMR."
Figure 8. $^1$H-NMR Spectra of a) Ornidazole, (b) Nicotinamide, (c) PM and (d) Solid dispersion

$^{13}$C NMR was also performed for Ornidazole and solid dispersion of Ornidazole with Nicotinamide. In solid dispersion of Ornidazole and Nicotinamide, the characteristic peaks of both Ornidazole and Nicotinamide were observed in spectra.$^{31}$ The $^{13}$C NMR spectra showed no changes in the characteristic peak of Ornidazole and Nicotinamide in solid dispersion hence confirmed the absence of any covalent bonding between them.

The results of dissolution rate studies were shown in Figure 9. Time to release 80% of Ornidazole was calculated from the graph and compared for pure Orni-
Ornidazole, physical mixture and prepared solid dispersions. The $t_{80\%}$ was found to be 30 min for pure Ornidazole. Physical mixture of Ornidazole with Nicotinamide in higher ratio decreased the $t_{80\%}$ from 30 min to 18 min. $t_{80\%}$ for solid dispersion of Ornidazole and Nicotinamide in ratio of 1:2 was found to be 13 min. Upon increasing the ratio of Nicotinamide in solid dispersion (1:4 and 1:6) lead to significant decrease in the $t_{80\%}$ value (8 min and 4 min for 1:4 and 1:6 ratio, respectively).

**Figure 9.** Dissolution profile of pure drug (ON), ONN 1:6 PM, ONN 1:2, ONN 1:4 and ONN 1:6 HSD in 0.1N HCl (n=3)

The percentage dissolution efficiency (%DE) at 30 min was calculated to compare the relative performance of pure drug, PM and solid dispersion. In literature, it was proved to be a better parameter than drug percentage released for comparison as it includes both rate and extent of release. The %DE$_{30}$ of pure Ornidazole, PM and solid dispersion 1:2, 1:4 and 1:6 was found to be 40.95%, 59.82%, 70.39%, 82.17% and 89.71% respectively. The dissolution efficiency of solid dispersion at 30 min was found to be twice as compared to that of pure drug.

Hence, the present study showed that the transformation of polymorphic form of Ornidazole to another low melting point polymorphic form of Ornidazole in presence of Nicotinamide lead to significant enhancement of their dissolution rate.

The solubility phase diagram showed a significant linear increase in the aqueous solubility of Ornidazole with increasing concentration of Nicotinamide upto
12.3 mM while a non-linear increase in the solubility at higher concentration of Nicotinamide was observed. The solubility of Ornidazole was found to be increased by 11 times at 25 mM Nicotinamide. The study concluded polymorphic transformation of Ornidazole in the presence of higher amount of Nicotinamide as confirmed by the results of DSC, FTIR and P-XRD studies. The solid dispersion of Ornidazole with Nicotinamide can be used for enhancing the dissolution rate which in turn decreases the variability in bioavailability. Further, this solid dispersion could also be utilized to prepare a “Dry Syrup” for pediatric use. In future, dry syrup of Ornidazole will be prepared by using solid dispersion with Nicotinamide.

DECLARATION OF INTERESTS
Authors declare no conflict of interest.

ACKNOWLEDGEMENT
The authors are very much grateful to SAIF, Punjab University, Chandigarh for providing the facilities to carry out the SEM and XRD studies in their lab.
REFERENCES

1. Singh, P.; Mittal, R.; Sharma, G. C.; Singh, S.; Singh, A. Profiles of Drug Substances, Excipients and Related Methodology: Ornidazole: Comprehensive Profile. New Delhi, 2003; p 123-184.

2. Hizarcıolu, S. Y.; Zeynep, A.Y.; Özyazıcı, M. Bioavailability file: Ornidazole. Fabad J. Pharm. Sci., 2004, 29, 133-144.

3. Maheshwari, R. K.; Indurkhya, A. Formulation and Evaluation of Aceclofenac Injection Made by Mixed Hydrotropic Solubilization Technique. Iran. J. Pharm. Res., 2010, 9, 233-242.

4. Marjan, D.; Simin, D.; Azadeh, H.; Masoud, F. A. Potential of Liposomes for Enhancement of Oral Drug Absorption. Curr. Drug Deliv., 2017, 14, 289-303.

5. Rao, M. R.; Babrekar, L. S. Liposomal Drug Delivery for Solubility and Bioavailability Enhancement of Efavirenz. Ind. J. Pharm. Sci., 2018, 80, 1115-1124.

6. Bhanu, P. S.; Malay, K. D. Nanosuspension for enhancement of oral bioavailability of felodipine. Appl. Nanosci., 2014, 4, 189-197.

7. Li, Q.; Chen, F.; Liu, Y.; Yu, S.; Gai, X.; Ye, M.; Yang, X.; Pan, W. A novel albumin wrapped nanosuspension of meloxicam to improve inflammation-targeting effects. Int. J. Nanomedicine, 2018, 13, 4711-4725.

8. Garg, A.; Bhalala, K.; Tomar, D. S. In-situ single pass intestinal permeability and pharmacokinetic study of developed Lumefantrine loaded solid lipid nanoparticles. Int. J. Pharm., 2017, 516, 120-130.

9. Rao, M. G.; Suneetha, R.; Sudhakara, P.; Reddy, S.; Ravi, T.K. Preparation and evaluation of solid dispersions of naproxen. Indian J. Pharm. Sci., 2005, 67, 26-29.

10. Chiou, W.L.; Riegelman, S. Pharmaceutical applications of solid dispersion systems. J. Pharm. Sci., 1971, 60, 1281-1302.

11. Dhirendra, K.; Lewis, S.; Udupa, N.; Atin, K. Solid Dispersions: A Review. Pak. J. Pharm. Sci., 2009, 22, 234-246.

12. Agrawal, G. P.; Maheshwari, R. K.; Mishra, P. Preparation of solid dispersions of Ornidazole using mixed hydrotropic solubilization technique and their characterization. Int. J. Green Pharm., 2017, 11, S715-720.

13. Drugbank. 2019. Marketed Formulations. [accessed 13/03/2019]. https://www.drugbank.ca/drugs/DB13026.

14. Agrawal, S.; Pancholi, S. S.; Jain, N. K.; Agrawal, G.P. Hydrotropic solubilization of Nimesulide for parenteral administration. Int. J. Pharm., 2004, 274, 149-155.

15. Garg, A.; Gupta, B.; Prakash, R.; Singh, S. Preparation and Characterization of Hydroxypropyl-β- Cyclodextrin (Hp-β-CD) Inclusion Complex of Eugenol: Differential Pulse Voltammetry and 1HNMR. Chem. Pharm. Bull., 2010, 58, 1313-1319.

16. Maheshwari, R. K.; Jagwani, Y. Mixed Hydrotropy: Novel Science of Solubility Enhancement. Indian J. Pharm. Sci., 2011, 73, 179-183.

17. Allen, L. V. J.; Povovich, N. G.; Ansel, H. C. Ansel’s pharmaceutical dosage forms and drug delivery systems, 8th ed. Philadelphia: Lippincott Williams & Wilkins: Baltimore, 2008; p 194.
Ornidazole in Tablet Dosage form by Zero Order UV Spectroscopy. *Int. J. Pharm. Pharm. Sci.*, 2016, 8, 249-254.

19. Pignatello, R.; Ferro, M.; Guidi, G. D.; Vandelli, M. A.; Guccione, S.; Geppi, M.; Forte, C.; Puglisi, G. Preparation, characterisation and photosensitivity studies of solid dispersions of Difunisal and Eudragit RS100 and RL100. *Int. J. Pharm.*, 2001, 218, 27-42.

20. Zerrouk, N.; Mennini, N.; Maestrelli, F.; Chemtob, C.; Mura, P. Comparison of the effect of chitosan and polyvinylpyrrolidone on dissolution properties and analgesic effect of naproxen. *Eur. J. Pharm. Biopharm.*, 2004, 57, 93-109.

21. Drooge, D. J. V.; Hinrichs, W. L. J.; Frijlink, H. W. Anomalous dissolution behaviour of tablets prepared from sugar glass-based solid dispersions. *J. Control. Release.*, 2004, 97, 441-452.

22. Khattab, F. I.; Ramadan, N. K.; Hegazy, M. A.; Ghoniem, N. S. Stability-Indicating Methods for the Determination of Ornidazole in The Presence of its Degradate According to ICH Guidelines. *Pharmaceut. Anal. Acta.*, 2012, 3, 1-8.

23. Hou, P.; Ni, J.; Cao, S.; Lei, H.; Cai, Z.; Zhang, T.; Yu, F.; Tan, Q. Preparation and Evaluation of Solid Dispersions of A New Antitumor Compound Based on Early-Stage Preparation Discovery Concept. *AAPS Pharm. Sci. Tech.*, 2013, 14, 629–638.

24. Abdul-Fattah, A. M.; Bhargava, H. N. Preparation and in vitro evaluation of solid dispersions of halofantrine. *Int. J. Pharm.*, 2002, 235, 17-35.

25. Khan, K. A. The concept of dissolution efficiency. *J. Pharm. Pharma-col.*, 1975, 27, 48–49.

26. Higuchi, T.; Connors, K. A. Advances in Analytical Chemistry and Instrumentation. Phase solubility techniques. Willey-Inter science, New York, 1965; p 117-212.

27. Rasool, A. A.; Hussain, A. A.; Dittert, L. W. Solubility enhancement of some water-insoluble drugs in the presence of nicotinamide and related compounds. *J. Pharm. Sci.*, 1991, 80, 387-393.

28. Varma, M. M.; Pandit, J. K. Dissolution, Solubility, XRD, and DSC Studies on Flurbiprofen-Nicotinamide Solid Dispersions. *Drug. Dev. Ind. Pharm.*, 2005, 31, 417–423.

29. Sirenius, I.; Krogerus, V. E.; Leppanen, T. Dissolution rate of p-aminobenzoates from solid xylitol dispersions. *J. Pharm. Sci.*, 1979, 68, 791-792.

30. Zhen, W.; Chaofu, Y.; Fangye, Z.; Chengli, L.; Hongli, D. inventor; Xi’an Wanlong Pharmaceutical Co., Ltd, assignee. 2014 Oct 15. Ornidazole crystal compound. Chinese Patent CN103073501B.

31. Moety, E. M. A.; Tariq, M.; Al-Badr, A. A. Profiles of Drug Substances, Excipients and Related Methodology: Nicotinamide. Elsevier. New Delhi, 2003; p 492-493.