THERMAL DECOMPOSITION KINETICS OF SECNIDAZOLE

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***Abstract*:** Secnidazole hemihydrate, an antimicrobial agent was crystallized by gel growth method and the crystal structure was confirmed using single crystal X-ray diffraction method. Non-isothermal thermogravimetric and differential thermal analyses (TGA/DTA) were performed for the determination of thermal decomposition profile. Thermal decomposition kinetics of secnidazole was carried out on the TGA/DTA data using Coats-Redfern (CR) equation. Thermodynamical parameters were also determined and the Arrhenius equation for grown secnidazole crystal was solved and is $k = (8.917x10^{23})\ e^{228671\ /RT}\ mol^{-1}s^{-1}$.

Keywords: Secnidazole, Thermal analysis, Kinetic analysis

1. INTRODUCTION

Secnidazole hemihydrate, (1-(2-Hydroxypropyl)-2-methyl-5-nitroimidazole hemihydrates) a principal derivative of nitroimidazoles is an antimicrobial agent used primarily in the treatment of amoebiasis. It is active against *E histolytica, G lamblia, T vaginalis, Clostridium spp, B fragilis, and Gardnerella spp*. Therapeutic activity of a single dose of secnidazole is practically suitable for the treatment of *urogenital trichomoniasis* (Videau *et al*, 1978). The pharmacodynamics of the drug is by diffusion in to the microorganisms and it is reduced intracellularly by low oxidation-reduction potential ferredoxin which then results in DNA damage **(**Nyvit et al, 1985). The inhibition activity of secnidazole on the corrosion of mild steel was reported (Ebenso EE and Obot IM, 2010) which is a different property other than pharmacological application.

Single crystals serve as the basis for the research to be undertaken on the physical properties of a material. Growth kinetics and decomposition kinetics can be determined precisely using single crystals as there are pure. Thermogravimetric analysis (TGA) is used in pharmaceutical industry to determine physicochemical properties of drugs, polymorphism, and purity. Moreover, the thermal stability, oxidative stability and decomposition kinetics of materials may be determined using TGA. In the recent past, many single crystals particularly of drugs were grown in gel (Ramachandran and Ramukutty, 2012, 2014, 2015 and Ramukutty et al, 2013), as well as in solution (Ramukutty and Ramachandran, 2013, 2014 and Ramukutty et al, 2014) in our laboratory and their decomposition kinetics were also reported (Ramukutty and Ramachandran, 2015,2016,2017). Pharmaceutical properties of secnidazole were discussed in many reports (Patrícia Andréa Bertuol Montovani, 2009, Marcia Marcilio, 2017 and Pentewar, 2015).

In this present work, secnidazole hemihydrate crystals were crystallized by reduction of Solubility method. The grown single crystal's structure was confirmed by using single crystal X-ray diffraction analysis. Thermal analysis was carried out and kinetic parameters were determined from the thermal decomposition data using Coats-Redfern relation.

2. EXPERIMENTAL

2.1 Crystal Growth

Secnidazole was purchased from Abbott Healthcare Pvt.Ltd., and organic solvents from Spectrum Chemical Reagents, Cochin. Silica gel prepared from an aqueous solution of sodium metasilicate ($Na_2SiO_3.5H_2O$) was used as crystal growth medium. Test tubes were used as crystal growth vessels. Crystal growth by reduction of solubility was employed for the crystallization. An aqueous solution of sodium meta-silicate of specific gravity 1.06 g/cm^3 was prepared and the pH of the solution was varied using 5M acetic acid. The pH of the gel was set in the range 3.75 to 6.0. Methanolic solution of secnidazole having concentrations from 0.15 to 0.65M were prepared and served as the reactant. This reactant was placed over the set gel without disturbing the texture of gel. Experiments at different pH of gel and concentration were carried out for getting the best conditions of crystal growth.

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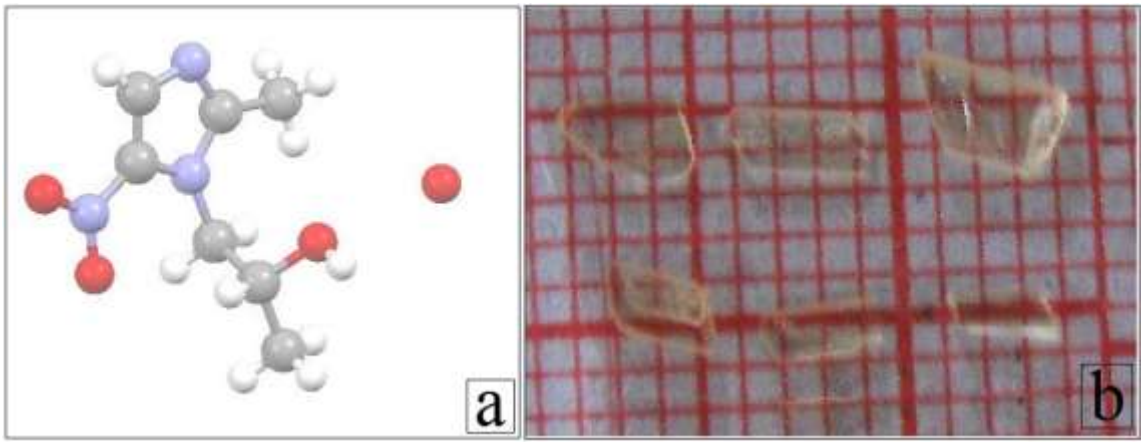

Fig. 1 (a) molecular structure of secnidazole (b) Secnidzole crystals

3. RESSULTS AND DISCUSSION

3.1 Crystal Growth

Crystal growth of secnidazole in silica gel took place below the pH 5.5 and the most suitable pH range was 4.5-5.0. This was identified from the number of crystals obtained, their transparency and size. Transparent, needle shaped crystals ($3 \times 2 \times 0.6$ mm^3) were crystallized over the gel medium for the reactant concentarion 0.27 M.

3.2 Single crystal X-ray diffraction analysis

Enraf-Nonius CAD-4 Diffractometer was used to obtain the accurate cell parameters of the grown secnidazole single crystals at room temperature with MoKα served as a source of radiation. By using continuous least-squares refinement of the setting angles of 346 reflections, lattice dimensions and angles were obtained. The unit cell parameters were determined from the collected X-ray data. Lattice parameters of monoclinic form of secnidazole hemihydrate crystals are: a = 6.6741Å, b = 12.155Å, c = 12.409Å and the space group is $P2_1/c$ with four molecules per unit cell (Z=4). These values agree well with the reported values in the literature (Soni Mishra et al, 2009).

3.3. Thermal analysis

Thermogravimetric analysis (TGA) and differential thermal analysis (DTA) was carried out simultaneously and Differential scanning calorimetric (DSC) analysis was also performed as well for the grown crystals in the temperature range of 40°C to 350°C under a constant heating rate of 10°C/min using Perkin Elmer Diamond thermal analyzer. The TGA/DTA and DSC characteristics are presented in Fig. 2 & 3.

The TGA of secnidazole shows dips around 60°C and a sharp endotherm at 223°C. These variations were analyzed in the DSC. The DSC characteristics (Fig. 3) showed the two endothermic peaks centered at 78.92°C and 234°C and the former is attributed to the melting point of the title compound. A close match for melting point is also noted in literature (www.chemicalland21.com). The additional endothermic peak around 234°C is attributed to the boiling point and sufficient references for this are scarce in literature.

Kinetic parameters

Kinetic parameters for the non isothermal thermo analytical rate measurement were done by the Coats– Redfern (CR) equation. Activation energy (E) and the order of reaction (n) were determined from CR eqn.

$$\log\left[\frac{1-(1-\alpha)^{1-n}}{T^2(1-n)}\right] = \log\left[\frac{AR}{\beta E}\left(1-\frac{2R\bar{T}}{E}\right)\right] - \left[\frac{E}{2.303RT}\right] \qquad (1)$$

The above eqn. vanishes at n = 1. It is valid for all values except n = 1. α is the fraction of the substance decomposed at time t. α can be calculated using the equation (2).

$$\alpha = \frac{m_o - m_t}{m_o - m_f} \qquad (2)$$

where m_t is mass at a given time, m_o & m_f are initial and final masses respectively, A the Frequency factor and R is Gas constant.

$\log\left[\frac{1-(1-\alpha)^{1-n}}{T^2(1-n)}\right]$ versus $1/T$ of eqn. for different values of n was plotted and the suitable value of n is chosen from the best linear response. The obtained best fit (n = 1.25) is depicted in Fig. 3. The activation energy and frequency factor are determined from the slope and the intercepts of graph. From the graph, activation energy and frequency factor are calculated as 228.671 KJ/mol and 8.917×10^{23}. Hence the Arrhenius equation for grown secnidazole crystal is $k = (8.917 \times 10^{23})\, e^{228671/RT}\ mol^{-1}s^{-1}$.

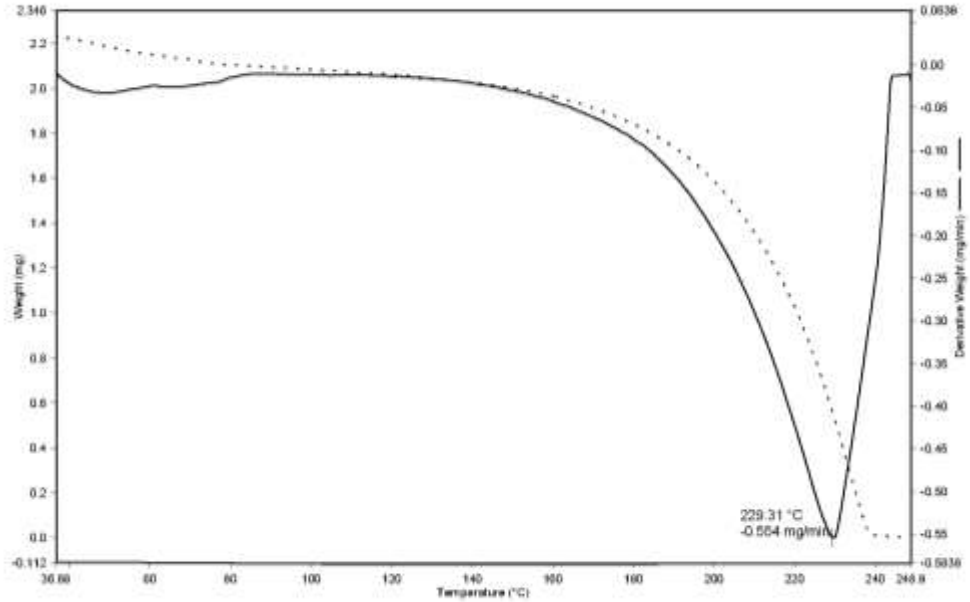

Fig.2 Thermal decomposition charteristics of secnidazole crystals

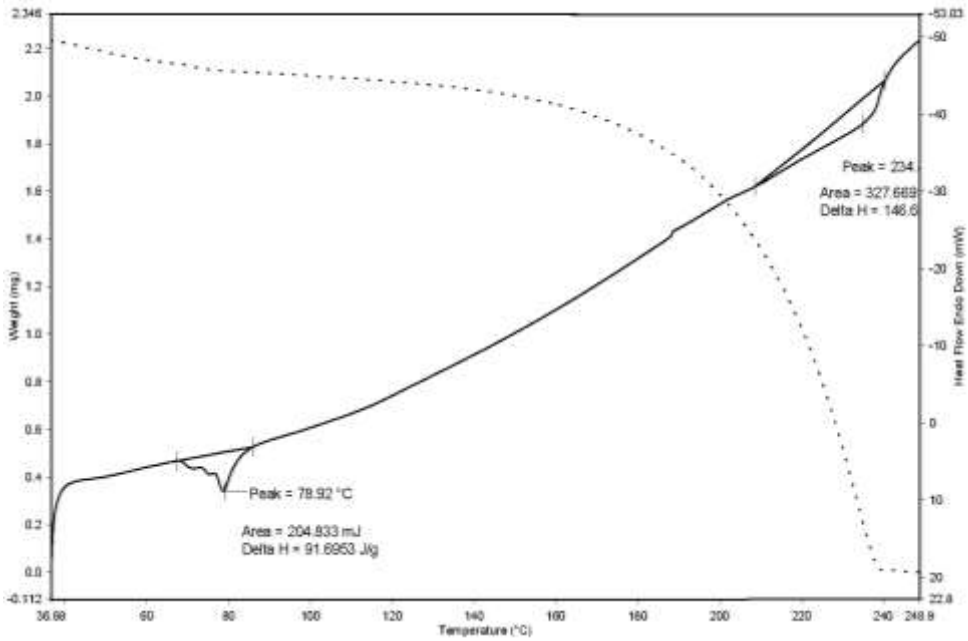

Fig. 3 DSC characteristics of secnidazole crystals

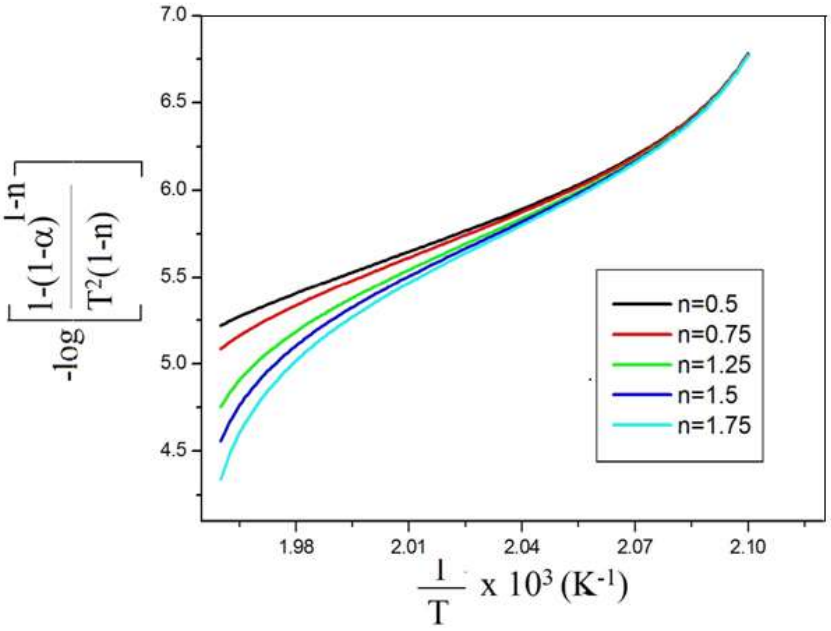

Fig.3 A plot of Coats – Redfern relation for secnidazole

3.2.2 Thermodynamic parameters

The Thermodynamic parameters, entropy of activation (ΔS), enthalpy of activation (ΔH) and Gibbs free energy (ΔG) of secnidazole crystal were calculated using equations

$$A = (kT/h)\, e^{(\Delta S/R)} \quad (4)$$

where h and k are Planck's constant and Boltzmann constant respectively.

$$\Delta H = E - RT \quad (5)$$

$$\Delta G = \Delta H - T\Delta S \quad (6)$$

The calculated values of ΔS, ΔH and ΔG are 209.40 J/Kmol, 224.571 KJ/mol and 121.301 KJ/mol respectively. The positive value of ΔG suggests that the reaction involved in decomposition is not a spontaneous reaction.

4. CONCLUSIONS

Single crystals of secnidazole hemihydrate were crystallized by reduction of solubility method in gel. Monoclinic form of the crystal was confirmed using single crystal X–ray diffraction method. The kinetic parameters of secnidazole were calculated by CR method. Arrhenius equation for secnidazole hemihydrate can also be obtained. Thermodynamic parameter shows that the decomposition reaction of grown secnidazole hemihydrates crystals undergoes non- spontaneous reaction process.

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REFERENCES

[1] Ebenso EE and Obot IM. 2010. Inhibitive Properties, Thermodynamic characterization and Quantum Chemical Studies of Secnidazole on Mild Steel Corrosion in Acidic Medium. International Journal of Electrochemical Science, 5:2012-2035.
[2] Marcia Marcilio, Alexia Lorenzi Raiser, Ligia Paula Fumagalli and Denia Mendes De Sousa Valladao. 2017. Determination and Validation of secnidazole in tablets by Uv spectrophotometric. Bioscience Journal, 33: 1351-1361.
[3] Nyvit J and Sohnel O, Matuchova M and Broul M. 1985. The Kinetics of Industrial crystallization, Elsevier, Amsterdam.
[4] Patrícia Andréa Bertuol Montovani, Ana Maria Pugens Pinto, Mauricio Bedim dos Santos, Daiane Loss Vieira, Anelise Weich do Prado and Josélia Larger Manfio. 2009. Bioavailability of two oral formulas of secnidazole in healthy volunteers. Brazilian Journal of Pharmaceutical Sciences, 45: 687-692.

[5] Pentewar RS, Nishat Kazi1 , Moin Attar, Sugave BK, Rohit Bharti and Gajanan Pulgamwar. Gas powered controlled drug delivery system of Secnidazole for spatial and temporal contro. Der Pharmacia Sinica. 2015; 6: 47-58.
[6] Ramachandran E and Ramukutty S. 2014. Growth, morphology, spectral and thermal studies of gel grown diclofenac acid crystals. Journal of Crystal Growth, 389: 78-82.
[7] Ramachandran E, Ramukutty S and Jeyasudha R. 2013. Thermal kinetics of gel grown diclofenac drug crystals. Thermal energy and power engineering, 2: 44-46.
[8] Ramchandran E and Ramukutty S. 2014. Influence of polymers on the crystal growth of metformin hydrochloride. Research and Reviews: Journals of Pharmaceutics and Nanotechnology, 2: 9-16.
[9] Ramchandran E and Ramukutty S. 2015. Kinetic analysis of the thermal decomposition of tinidazole crystals. International Journal of Solid State Materials, 1: 1-4.
[10] Ramukutty S and Ramachandran E. 2016. Mechanical studies and thermal kinetics of Paracetamol crystals. International Journal of Solid State Materials, 2: 46-50.
[11] Ramukutty S and Ramachandran E. 2012. Growth, Spectral and Thermal studies of ibuprofen crystals. Crystal Research and Technology, 47: 31-38.
[12] Ramukutty S and Ramachandran E. 2012. Mechanical and thermal studies on gel grown racemic ibuprofen crystals. World Journal of Science and Technology, 2: 36-38.
[13] Ramukutty S and Ramachandran E. 2015. Growth, structural, spectral and thermal studies of etoricoxib hemihydrate crystals. International Journal of Solid State Materials, 1: 14-21.
[14] Ramukutty S and Ramachandran E. 2017. Thermal decomposition kinetics of ursodeoxycholic acid crystals. Journal of Crystallization Process and Technology, **7**: 85-90.
[15] Ramukutty S, Jeyasudha R and Ramachandran E. 2013. Mechanical and thermal studies of metronidazole crystals. Indian Journal of Physics, 87: 1001-1004.
[16] Ramukutty S, Jeyasudha R and Ramachandran E. 2014. Mechanical and thermal kinetic parameters of metformin hydrochloride crystals. Research and Reviews: Journal of Pharmacy and Pharmaceutical Sciences, 3: 36-40.
[17] Soni Mishra, Deepika Chaturvedi, Poonam Tandon, Gupta VP, Ayala AP and Honorato SB and Siesler HW. 2009. Molecular Structure and Vibrational Spectroscopic Investigation of Secnidazole Using Density Functional Theory. Journal of Physical Chemistry, 113: 273–281.
[18] Videau D, Niel G, Siboulet A and Catalan F. 1978. Secnidazole - A 5- nitroimidazole derivative with a long half-life. British Journal Venereal Diseases, 54(2): 77-80.
[19] www.chemicalland21.com