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Kinetic study and mechanism of Niclosamide degradation

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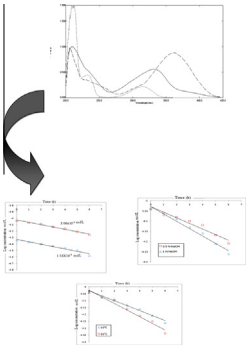
HIGHLIGHTS

- No kinetic spectrophotometric study has been reported for the assay of Niclosamide.
- Kinetic study of Niclosamide as a function of drug concentration, alkaline concentration and temperature has been established.
- Niclosamide followed pseudo-first order with a degradation rate constant (k) of 0.0829 mol/h and half life ($t_{1/2}$) of 8.35 h.
- The overall degradation rate constant as a function of the temperature obeyed Arrhenius equation.

GRAPHICAL ABSTRACT



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ABSTRACT

A spectrophotometric kinetic study of Niclosamide alkaline degradation as a function of drug concentration, alkaline concentration and temperature has been established utilizing double divisor-ratio spectra spectrophotometric method. The developed method allowed determination of Niclosamide in presence of its alkaline degradation products; namely; 2-chloro-4-nitro aniline (DEG I) and 5-chloro salicylic acid (DEG II) with characterization of its degradation mechanism. It was found that degradation kinetic of Niclosamide followed pseudo-first order under the established experimental conditions with a degradation rate constant (k) of 0.0829 mol/h and half life ($t_{1/2}$) of 8.35 h. The overall degradation rate constant as a function of the temperature under the given conditions obeyed Arrhenius equation where the activation energy was calculated to be 3.41 kcal/mol.

Introduction

Niclosamide (Fig. 1), chemically recognized as 5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide [1]. Niclosamide is orally administered anthelmintic drug which is highly effective against cestodes and threadworm. It acts by inhibiting the oxidative phosphorylation in mitochondria and interfering with anaerobic generation of ATP by the tape-worm, as a result tape-worm get partially digested in the intestine [2–4].

After extensive literature survey, few analytical methods have been found for determination of Niclosamide including determination of Niclosamide with Thiabendazole by ΔA spectrophotometric method [5] or in combination with Drotaverine hydrochloride by ΔA, second derivative (ΔD^2) and third derivative (ΔD^3) differential ultraviolet spectrophotometric methods [6], or alone using P-benzoquinone [7]. Also spectrofluorimetric [8], HPLC [9–11], GC [12] and voltammetric [13,14] methods were developed for its determination.

Neither stability investigation of Niclosamide nor possible degradation mechanism has been reported. Niclosamide was subjected to alkaline hydrolysis and the obtained degradation

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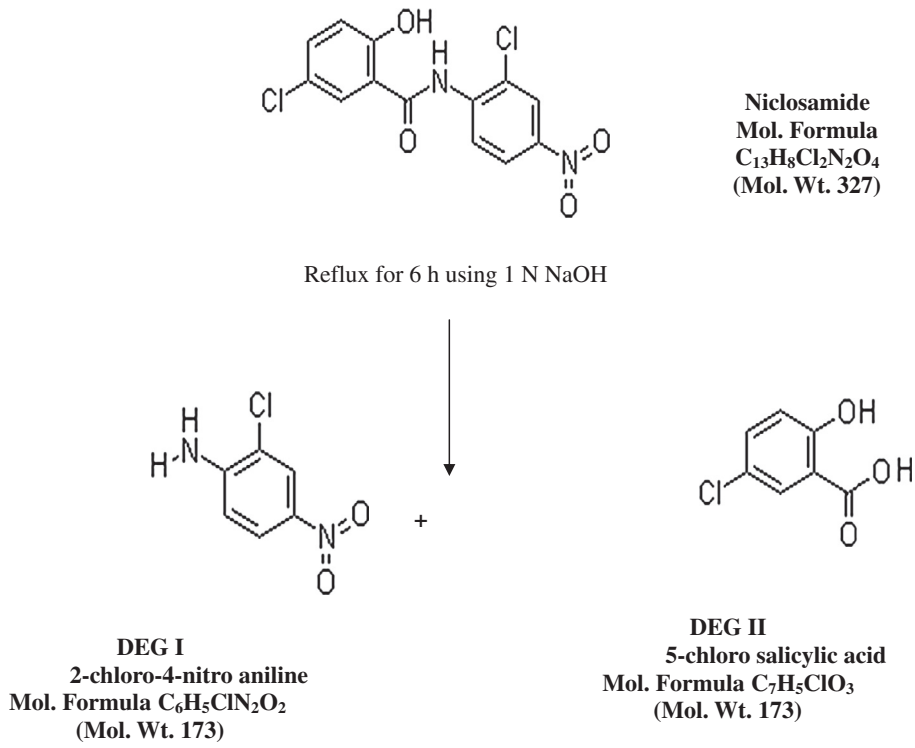

Fig. 1. Degradation pathway of Niclosamide.

products were isolated and characterized for their structures. They are reported as major impurities of Niclosamide namely; 2-chloro-4-nitro aniline (DEG I) and 5-chloro salicylic acid (DEG II) in British pharmacopoia [2] and the European pharmacopoia [15]. Additional results from genotoxic studies in rodents and humans suggest that the drug is absorbed from the gastrointestinal tract, and mutagenic metabolites 5-chlorosalicylic acid and 2-chloro-4-nitroaniline are excreted as the main metabolites [16].

The aim of the recommended work is to liberate double divisor-ratio spectra spectrophotometric method for selective determination of Niclosamide in presence of its degradation products. The proposed method was directed to reveal the degradation kinetic and mechanism of Niclosamide under the specified conditions.

Experimental

Instruments

- A double beam UV–visible spectrophotometer (SHIMADZU, Japan) model UV-1601 PC with quartz cell of 1 cm pathlength, connected to IBM compatible computer. The software was UVPC personal spectroscopy software version 3.7. The spectral band width was 2 nm and wavelength-scanning speed 2800 nm/min.
- UV lamp with short wavelength 254 nm (USA).

Materials

(a) Pure standard

- Niclosamide was kindly supplied from Alexandria Company for pharmaceuticals and chemical industries, Alexandria, Egypt. Its purity was found to be 100.00% according to the reported method [5].

(b) Pharmaceutical formulations

- Yomesan® tablets (Batch No. 1182010) labeled to contain 500 mg of Niclosamide, manufactured by Alexandria Company for pharmaceuticals and chemical industries, Alexandria, Egypt.
- Niclosan® tablets (Batch No. 103021) labeled to contain 500 mg of Niclosamide, manufactured by Misr Company for Pharmaceutical Industry. S.A.E, Egypt.

(c) Chemicals and reagents

- All reagents and chemicals used throughout this work were of analytical grade and were used without further purification.
- Methanol and triethylamine of HPLC grade (CHROMASOLV®, Sigma–Aldrich Chemie Gmbh, Germany).
- Sodium hydroxide (0.5 N and 1 N aqueous solution), HCl (1 N aqueous solution), benzene, ethylacetate (El-Nasr Pharmaceutical Chemicals Co., Abu-Zabaal, Cairo, Egypt).

(d) Degradation of Niclosamide

- 0.5 g of Niclosamide powder was transferred into 50 mL glass stoppered flask, dissolved in 10 mL methanol and completed to the mark with 1 N NaOH solution. The flask was left for 6 h under reflux at 80 °C and complete degradation was followed via TLC using benzene–ethylacetate–methanol–triethylamine (9:1:1:0.1, by volume) as a developing system. After complete degradation, the solution was filtered, the obtained precipitate was washed with water where the collected washing was identified as first degradation product DEG I (2-chloro-4-nitroaniline). Then the filtrate was adjusted to pH = 1.5 using 1 N HCl solution, where the second degradation product DEG II (5-chlorosalicylic acid) precipitated, filtered and then washed with double distilled water. The obtained degradation products were identified by IR and mass spectrometry.