Research Article EMUJPharmSci ISSN 2651-3587 https://dergipark.org.tr/emujpharmsci

EMU Journal of Pharmaceutical Sciences

EMUJPharmSci

Determining the Assay of New Formulation Low Dosage Naltrexone HCl Capsules with a RP-HPLC Method

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Abstract

Naltrexone hydrochloride (NLX HCl) is a medication primarily used in the management of alcohol and opioid dependence. NLX HCl is an opioid antagonist that blocks the effect of opioids by binding to opioid receptors in the brain without activating them. This study aims to determine the assay amount of new formulation low dosage NLX HCl capsules by High-Performance Liquid Chromatography (HPLC). HPLC method is very precise, specific, simple, accurate and sensitive method for assay determination of new formulation NLX HCl (3.0 mg and 4.5 mg). The chromatographic separation was achieved using Eclipse XDB-12 C18 (150 mm x 4.6 mm, 5 µm particle size) column using UV detection at 280 nm. The mobile phase consisted of a variable mixture of Solution A and Solution B with gradient, run at a flow rate of 1.0 mL/min. According to our research, NLX HCl has a retention time of 10.5 minutes. The linearity range was established between 1.1-3.40 mg/mL.

Keywords

Assay, naltrexone hydrochloride, HPLC, formulation.

Article History

Submitted: 05 September 2024 Accepted: 21 November 2024 Published Online: November 2024

Article Info

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Research Article:

Volume: 7 Issue: 2 2024 Pages: 48-54

DOI: 10.54994/emujpharmsci.1544223

INTRODUCTION

Naltrexone belongs to a class of drugs known as opioid antagonists. The chemical name of naltrexone hydrochloride (NLX HCl) is chemically (5α)-17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride (Figure 1). NLX HCl is a medication approved by the Food and Drug Administration (FDA) to treat both alcohol use disorder (AUD) and opioid use disorder. Addiction is a well-known chronic brain condition (Younger et al., 2014). Opioids are a prevalent source of addiction and have been linked to a number of social and medical issues. Naltrexone is becoming a more widely used medication for treating opiate and alcohol addictions.

There are two types of NLX HCl: Full dose and low dose naltrexone (LDN). Full dose naltrexone is available by prescription in several countries in the form of 25 mg or 50 mg oral tablets. For up to 24 hours, a 50 mg tablet efficiently prevents the effects of heroin. LDN that is defined as a daily intake of 1 to 5 mg is a reversible competitive antagonist and acts momentarily inhibiting the brain's opioid receptors. Then, it increases the production of endorphins *via* a positive feedback mechanism. Clinical reports on LDN have indicated potential advantages for a number of illnesses, including multiple sclerosis (Agrawal, 2005), fibromyalgia (Patten et al., 2018), Crohn's disease (Jill et al., 2007), complex-regional pain syndrome (Chopra and Cooper, 2013), Hailey-Hailey disease (Campbell et al., 2018), and cancer (Lia et al., 2018).

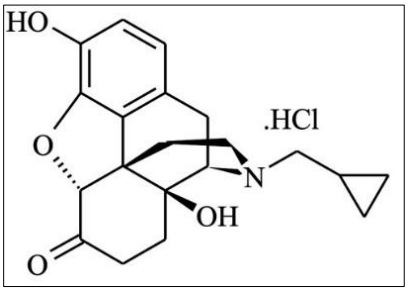


Figure 1: Structural formula of naltrexone hydrochloride.

High-Performance Liquid Chromatography (HPLC) is a sophisticated analytical technique that requires systematic procedure validation and refining for accurate compound separation, identification, and quantification. This study aims to determine the assay amount of new formulation low dosage NLX HCl capsules by HPLC. HPLC method is a very precise, specific, simple, accurate and sensitive method for assay determination of new formulation NLX HCl (3.0 mg and 4.5 mg). The chromatographic separation was achieved using Eclipse XDB-12 C18 (150

mm x 4.6 mm, 5 µm particle size) column using ultraviolet (UV) detection at 280 nm. The mobile phase consisted of a variable mixture of Solution A and Solution B with gradient, run at a flow rate of 1.0 mL/min.

MATERIALS AND METHODS

Equipment

The Agilent 1260 Infinity HPLC system was used for this study, which was outfitted with a solvent degasser, quaternary pump, auto sampler, column oven, and diode array detector.

Chemical and reagents

United States Pharmacopeia (USP) Naltrexone RS was obtained from USP Pharmacopeia. Sodium octanesulfonate, sodium acetate, glacial acetic acid and triethylamine were obtained from Sigma Aldrich and they were all reagent grade. HPLC grade methanol was purchased from local vendors. Water was obtained in-house using the Nanopure Diamond water system.

Chromatographic conditions

The assay analysis of new formulation NLX HCl (3.0 mg and 4.5 mg) capsules were done according to USP (USP 32, 2009).

The liquid chromatography is equipped with 280 nm detector and a 3.9 mm x 15 cm column that contains packing L1 and is programmed to provide at a flow rate of about 1 mL per minute a variable mixture of Solution A and Solution B. At the time the sample was injected into the equipment, the percentage of solution A was 100% over the next 35 minutes, the proportion of solution B was increased linearly to 100% and then over the next minute decreasing nearly to 100% of solution A.

Solution A: 1.08 g of sodium octanesulfonate and about 23.8 g of sodium acetate were dissolved in 800 mL of distilled water. Then, 1 mL triethylamine and 200 mL methanol were added into solution and mixed with magnetic stirrer machine. The pH of solution was adjusted to 6.5 ± 0.1 with glacial acetic acid, then filtered and degassed prior to use.

Solution B: 1.08 g of sodium octane sulfonate and about 23.8 g of sodium acetate was dissolved in 400 mL of distilled water, then 1 mL triethylamine and 600 mL methanol added into solution and mixed them with magnetic stirrer machine. The pH of solution was adjusted to 6.5 ± 0.1 with glacial acetic acid, then filter and degas prior to use.

Mobile phase: Use variable mixtures of Solution A and Solution B as directed for chromatographic system.

Procedure

Standard preparation: 22.5 mg of USP naltrexone RS was accurately weighted and added to 10 mL volumetric flask. 1.5 mL of methanol and 0.6 mL of 0.1 N hydrochloric acid was added and dissolved by swirling the flask and diluted with 0.1 M phosphoric acid to volume.

Sample preparation: Not fewer than 20 tablets were transferred into a tared container to determine the average tablet weight. The tablets were ground into a homogeneous mixture. An accurately weighed portion, equivalent to about 250 mg of NLX HCl was transferred to a 100-mL volumetric flask. About 80 mL of 0.1 M phosphoric acid was added and mixed or sonicated for at least 30 minutes. 0.1 M phosphoric acid was used to dilute to volume. The solution was mixed and filtered.

Procedure: Equal volumes (about 20 µL) of the standard preparation and the assay preparation were injected separately into the chromatograph. The chromatograms were recorded and the responses for all the peaks were measured. The quantity, in mg, of $C_{20}H_{23}NO_4 \cdot HCl$ in the portion of NLX HCl was calculated using the formula:

$(377.86/341.41)100C\ (r_U / r_S)$

where, 377.86 and 341.41 are the molecular weights of NLX HCl and naltrexone, respectively; C is the concentration (mg/mL), of USP naltrexone RS in the standard preparation; and r_U and r_S are the peak responses of naltrexone obtained from the assay sample preparation and the standard preparation, respectively.

RESULTS AND DISCUSSION

Linearity

Linear calibration curves of the proposed method were obtained by diluting stock solutions with concentrations of 1.1, 1.68, 2.27, 2.83 and 3.40 mg/mL for NLX. Linearity was evaluated by fitting least-squares regression analysis. The analyses of calibration is shown in Figure 2.

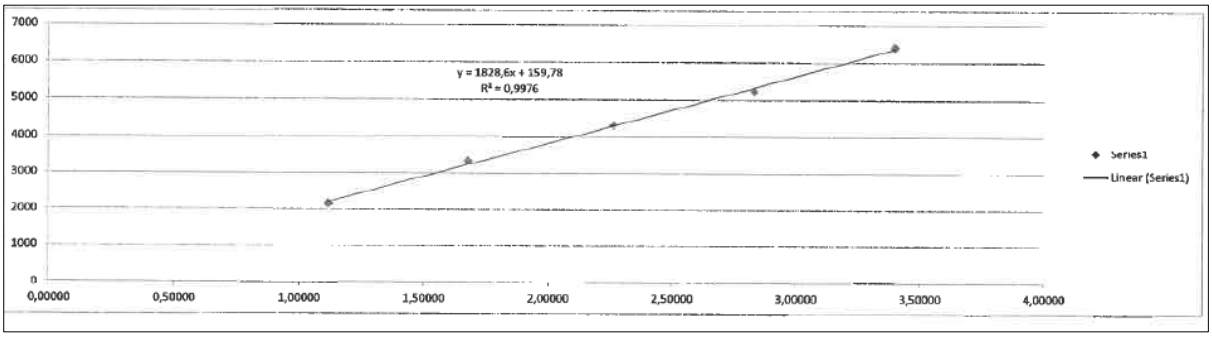


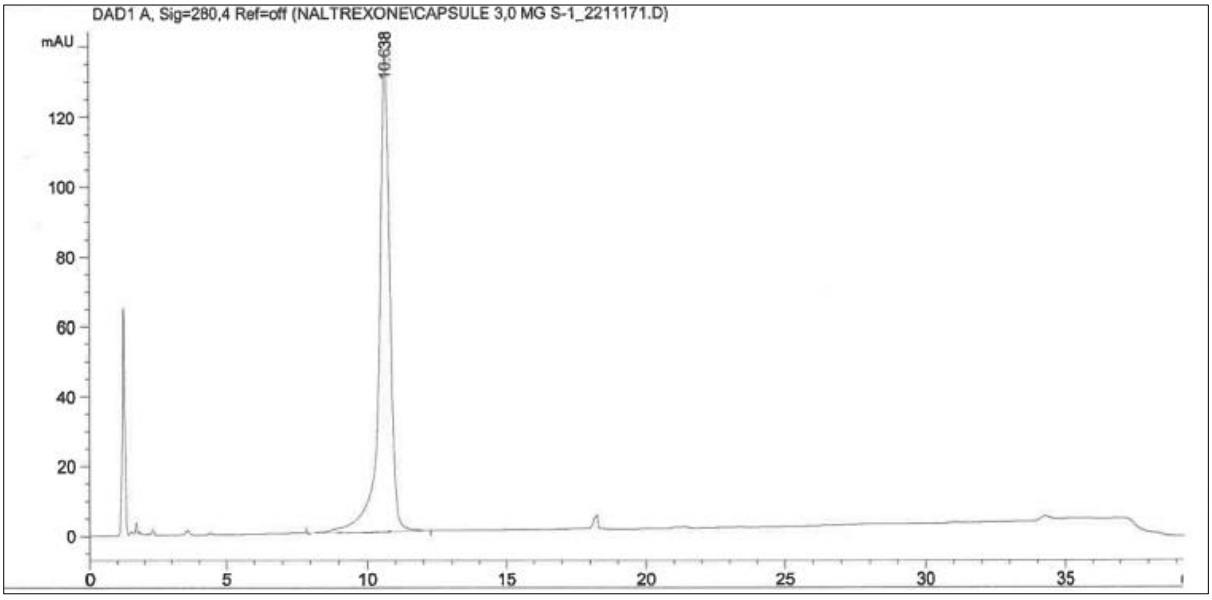
Figure 2: Calibration curve of NLX.

Assay analysis of NLX HCl 3.0 mg and 4.5 mg capsules

In a previous study, forced degradation studies of new formulation containing naltrexone were conducted (Yaghoubnezhadzanganeh and Burgaz, 2019). In this study, the assay analysis of new formulated NLX HCl 3.0 mg and 4.5 mg capsules (2 samples of each one) were conducted and results have been evaluated. The sample solutions have been prepared according to USP method (sample preparation) and measured by HPLC (Table 1). The chromatograms are shown in Figure 3.

Table 1: The assay results of NLX HCl 3.0 mg and 4.5 mg capsules.

Type of the solution	Concentration (mg/mL)	Average Area	Assay
Standard of naltrexone	2.30	3634	
Capsule containing 3 mg naltrexone	2.20	3558	% 93.03
Capsule containing 4.5 mg naltrexone	2.35	3859	% 93.97



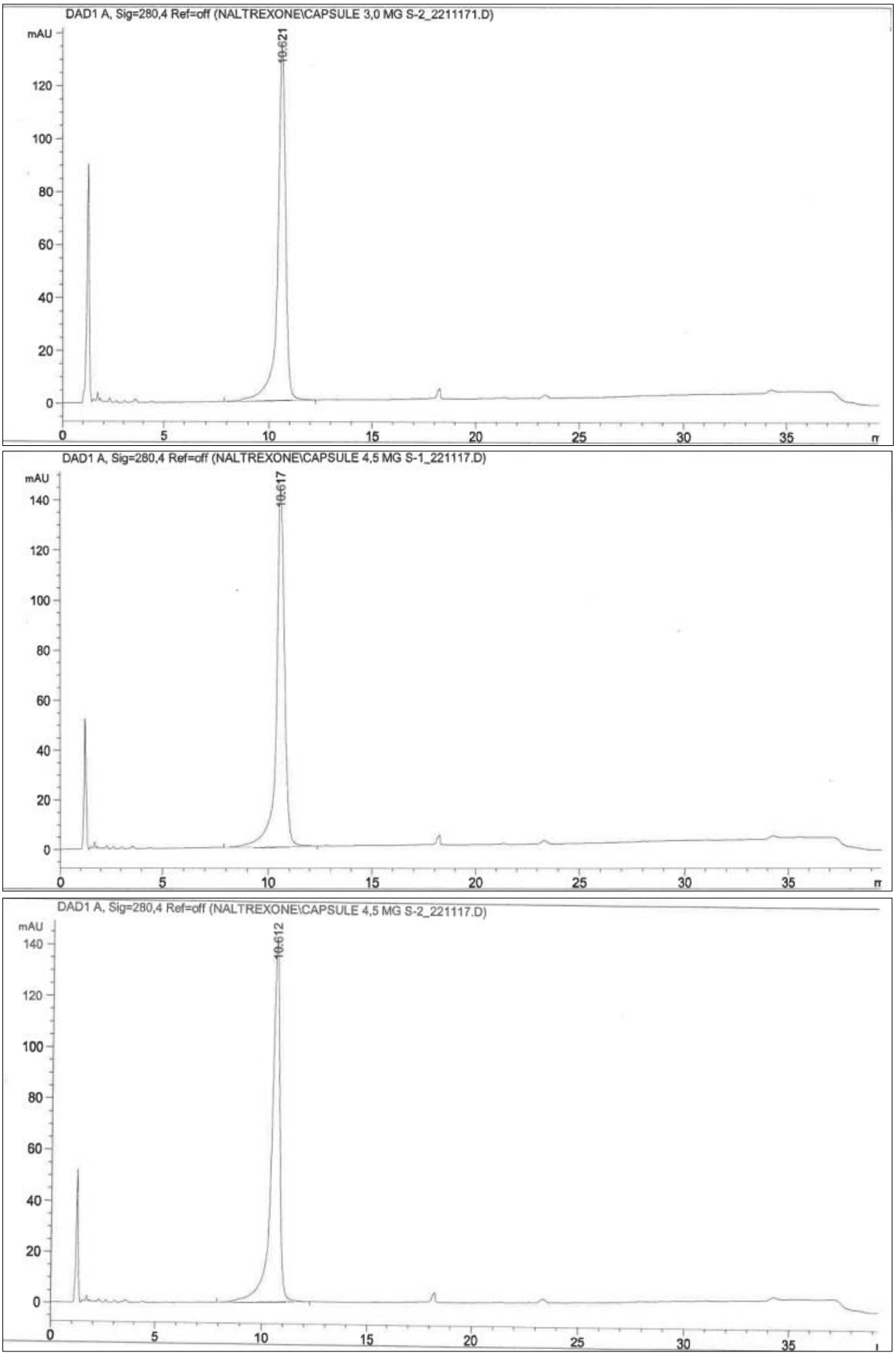


Figure 3: The chromatograms of NLX HCl 3.0 mg and 4.5 mg capsules.

CONCLUSION

The naltrexone hydrochloride quantification in pharmaceutical dosage form using the suggested RP-HPLC method is rapid, straightforward, linear, accurate, and precise. The quality-control of bulk medication and its preparations can therefore be carried out using the current RP-HPLC technique. The experiment was done successfully, the process was performed twice for each sample to get a great result. According to the USP, NLX HCl capsules contain not less than 90% and not more than 110% of the labeled amount of NLX HCl. The new formulated 3.0 mg and 4.5 mg NLX HCl capsules are in between the acceptance criteria.

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