

# Stability assessment of isoniazid and rifampin liquid dosage forms in a national referral center for tuberculosis

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## Abstract

**Objectives:** Although liquid dosage forms of antituberculosis drugs can be prepared extemporaneously; the physical and chemical stability of the formulations should always be assessed. At our tuberculosis referral center, isoniazid and rifampicin oral liquid forms were compounded for the first time. Our objective was to determine the stability of compounded oral liquid forms of isoniazid and rifampicin. **Methods:** Isoniazid 10 mg/mL and rifampicin 10 mg/mL were prepared using sorbitol and simple syrup base respectively. The suspensions were then placed in glass bottles and stored at 5°C for 28 days. Samples were collected on days 0, 7, 14, 21, and 28 after preparation and analyzed by high performance liquid chromatography. **Results:** A mean of at least 90% of the initial drug concentration was retained for 28 days after the formulations were made. No substantial changes in the appearance, odor, and uniformity were observed. **Conclusion:** Isoniazid and rifampicin were stable in liquid dosage forms prepared for 4 weeks during storage at 5°C.

**Keywords:** Compounding, Extemporaneous, Isoniazid, Rifampicin, Stability

## Introduction

Administration of solid dosage forms is difficult in patients who are unable to swallow tablets or capsules. Children, in particular, pose a challenge for medication administration as do patients that require non-standard doses. Most antituberculosis agents are not available in liquid formulations and so isoniazid tablets are often crushed or rifampicin capsules are opened to administer the medication [1]. However, administration of crushed isoniazid tablets with food may be associated with impaired gastrointestinal absorption and the opening of rifampicin capsules may lead to error in delivery of doses [2, 3].

Pharmacists in hospital pharmacy practice can extemporaneously prepare liquid dosage forms of antituberculosis drugs but stability data are limited for such preparations [1]. In developing countries however, extemporaneous compounding is a big challenge due to lack of equipment, resources such as ingredients, and trained personnel [4]. In our country, the oral liquid dosage forms of many essential medications are not commercially available and unfortunately, pharmacists are not trained in extemporaneous compounding. We established an extemporaneous pharmacy area in the inpatient pharmacy to prepare oral liquid dosage forms for pediatric, elderly, or critically ill patients [5]. The extemporaneous preparation was done under the supervision of the pharmaceutical care department of the hospital. This setting was also used to train other hospital pharmacists. Isoniazid and rifampicin liquid oral forms are used frequently in our center. These formulations were extemporaneously prepared in the pharmacy. The aim of this study was the determination of the stability of isoniazid and rifampicin liquid dosage forms as compounded in our limited resource setting.

## MATERIALS AND METHODS:

### Preparation of oral liquid dosage forms

Isoniazid 10 mg/mL was compounded according to a previously reported formula [6]. For 100 mL solution, 200 mg methylparaben and 20 mg propylparaben were dissolved in four mL of purified water. One gram isoniazid, 50 mL sorbitol 70% and sufficient purified water were added while mixing. For extemporaneous preparation of 120 mL rifampicin 10 mg/mL, the contents of four rifampicin 300 mg capsules were triturated in simple syrup into a paste. The remaining syrup was added while retrituring and mixing the suspension [7]. The six fold volume of each formulation was prepared and stored in six amber glass bottles at 5°C for 28 days.

### High performance liquid chromatographic analysis

Samples were drawn from each bottle immediately after mixing (day 0), and on days 7, 14, 21, and 28 of storage. All bottles were analyzed in triplicate (n=18) on each day of analysis.

Assessments were done by means of a high performance liquid chromatography SHIMADZU (Shimadzu Corporation) equipped with a detector (SPD 20A), pump (LC-10A), degasser (DGLU-14A), and system controller (SCL 10A). Assay methods were based on USP monograph and an in-house HPLC method for rifampicin [8] and isoniazid respectively (Table 1).

Stability was determined as the retention time of not less than 90% of the original drug concentration.

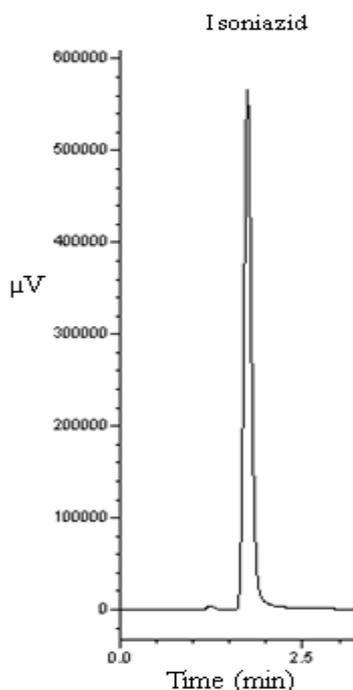
### Microbiological and physical stability

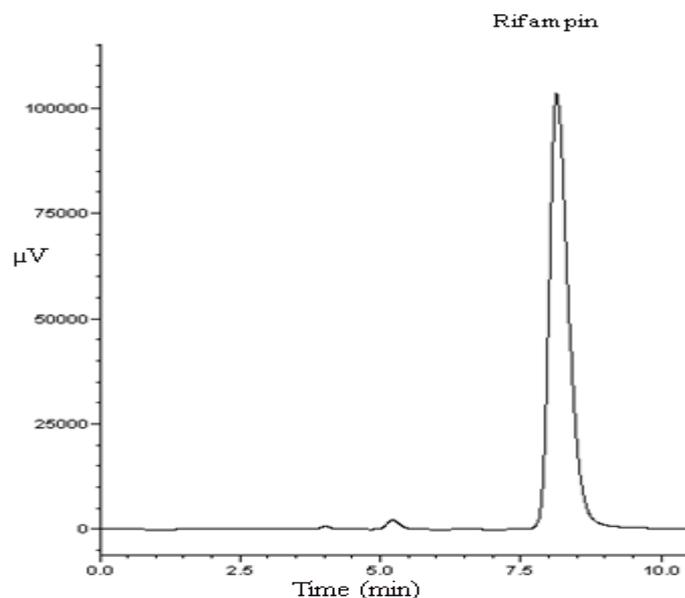
Bacterial contamination of the suspensions was assessed at baseline, and 1, 7, 14, 21, 28 days after preparation. Aliquots of 100  $\mu$ L from each bottle were plated in duplicate on 5% sheep blood agar plates and stored aerobically at 37 °C for 24 hours. Following the 24-hour incubation, agar plats were inspected for microbial grow and colony formation. Each sample was inspected for uniformity, color and odor change at each time point.

### Results:

Visual and olfactory observations did not reveal any substantial changes during the study period.

The chromatogram for isoniazid and rifampicin are shown in Figures 1 and 2 respectively. We checked the peaks belong to the blank syrup and standard solution. There was no interference with the assay procedure from the inactive ingredients present in the syrups. Table 2 shows the percentage of isoniazid and rifampicin remaining in the mixtures during the study period. There were no significant changes in isoniazid concentrations during 28 days at 5°C but rifampicin concentrations fell to 93.79 % on day 28.





### Discussion:

The results for isoniazid 10 mg/mL oral solution were in agreement with those determined by Gupta et al [9] who demonstrated that the oral liquid dosage form of isoniazid prepared according to the formulation reported by Allen [6] was stable for at least 42 days when stored in an amber glass bottle at room temperature. However, we showed increased isoniazid concentrations from day 7 to day 21. This finding may be related to different storage condition as both preparation method and storage can effect concentration [10]. Storage in refrigerator can also have an effect on dispersion of drug in the syrup.

Our findings for the 28 day stability of rifampicin 10 mg/mL suspension in simple syrup were similar to those determined in other studies. Allen [11] reported a stability period of four weeks for 1% rifampicin suspensions prepared using simple syrup, wild cherry syrup or fruit-flavored syrup and stored under refrigeration. Krukenberg et al [12] also showed a four week stability period for 1% rifampicin suspensions formulated using syrup NF, two commercially available simple syrup, wild cherry syrup and fruit-flavored syrup and stored at room temperature or refrigerated.

Nahata et al [7] found that rifampicin was stable in suspension for 8 weeks during storage in room temperature. They reported increasing rifampicin concentrations with storage time which could be due to the binding of rifampicin powder to the plastic bottle, and incomplete wetting and dispersion of drug in the syrup. The powder gradually release to the suspension and result in increasing concentration. This effect was not detected in our study since we didn't use plastic bottles and carefully triturated the powder.

Although the use of an appropriate suspending agent has been recommended to prepare a more concentrated and dispersed suspension [13], suspending agents are not commercially available in Iran; so we had to compound rifampicin suspension using a simple formulation. Rifampicin injection vial is also a proper ingredient to make homogeneous syrup [7, 10] but it costs are significantly higher than the capsule.

Since antituberculosis drugs are not commercially available in oral liquid dosage forms in our country, extemporaneous preparation of liquid formulations is an effective method of administering isoniazid and rifampicin at appropriate dose when tablet or capsule cannot be used. Although our physicians do not usually aware of this method and they usually order to crush tablets or open capsules; despite the limitations that exist in developing countries pharmacists can prepare extemporaneous medications using simple and modified formulations. The stability of compounded products should always be evaluated to ensure the proper dose.

### Conclusions:

Extemporaneous preparations of isoniazid and rifampicin liquid dosage forms were stable for 4 weeks during storage at refrigerator.

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Table 1: High Performance Liquid Chromatographic Conditions

Drug (Dilution)	Column	Mobile Phase	Flow Rate (mL/min)	Detector Setting (nm)	Retention Time (min)	Range of standard Curve ( $\mu\text{g/mL}$ )
Rifampicin (1:100)	C18	Water: acetonitrile: phosphate buffer (136.1 g of monobasic potassium phosphate, 6.3 mL of phosphoric acid diluted to 1 L with water): 1.0 M citric acid solution: 0.5 M sodium perchlorate solution (500:360:100:20:20)  45% water: 55% methanol	1	254	8	50-300
Isoniazid (1:100)	C18		1	254	1.7	20-150

Table 2: Stability of isoniazid and rifampicin up to 28 days at 5°C

Day	Isoniazid Concentrations Average $\pm$ SD	Rifampicin Concentrations Average $\pm$ SD
1	93.09 $\pm$ 3.47	105.58 $\pm$ 6.34
7	111.28 $\pm$ 3.43	102.84 $\pm$ 4.34
14	112.90 $\pm$ 3.43	100.57 $\pm$ 5.34
21	108.71 $\pm$ 3.51	101.47 $\pm$ 2.88
28	104.82 $\pm$ 4.25	93.79 $\pm$ 2.33