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Original Article

Impact of rifaximin potency after treatment with different solvents

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ABSTRACT

Rifaximin is an oral antibiotic used for the treatment of hepatic encephalopathy, ulcerative colitis, irritable bowel syndrome, *Clostridium difficile*, travelers' diarrhea and acute diarrhea. Production of rifaximin involves the use of different solvents. The performance of these solvents can affect the activity of this antimicrobial. The general objective of this work is to show the importance in the rigorous production of rifaximin raw material. The specific objectives of this work are to show that the use of different solvents or even a modification in the process of obtaining the raw material can lead to different activities of powder. A purposeful change in the process of obtaining the rifaximin raw material by recrystallization, using different solvents, resulted in significant changes in antimicrobial activity. This is an alert to the production of pharmaceutical inputs. The process of obtaining raw material must be standardized, aiming not only the quality of the medicine, but also, aiming the consequences of the use of non-quality medicines that generate a vicious cycle in the public health system.

Keywords: rifaximin, antibiotic, raw material, antimicrobial activity, quality.

INTRODUCTION

Rifaximin (Fig. 1) is a antimicrobial used for thetreatment of hepatic encephalopathy, ulcerative colitis, irritable bowel syndrome, *Clostridium difficile*, travelers' diarrhea and acute diarrhea [1-3].

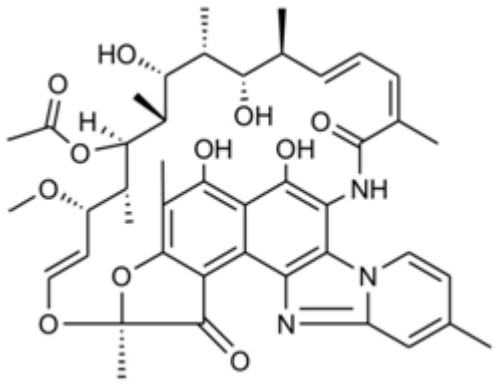

Figure 1. Chemical structure of rifaximin (CAS 80621-81-4).

On the market, tablets of rifaximin in crystalline form α are found, its systemic bioavailability is limited and this is one of the advantages of the use of this antimicrobial, which acts locally. The amorphous form showed significantly higher bioavailability and therefore lower tolerability [4]. The production of rifaximin involves the use of the following solvents: purified water, ethyl alcohol, chloroform, dichloromethane and ethyl acetate [5-8].

Does the change in any of these solvents, the time of exposure to them during the production of this raw material or a small change in the process of obtaining it can lead to differences in the activity of this antimicrobial? This work shows the importance of the rigorous production of the raw material of rifaximin against the results of antimicrobial activity obtained.

EXPERIMENTAL

Material: Rifaximin, form α, acquired of the company NutraTech Development Limited (China), was used.

Method: Rifaximin was solubilized in purified water, ethyl alcohol, acetone, chloroform, dichloromethane and ethyl acetate and re-obtained by recrystallization. The materials obtained are described in Table 1 [9].

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Table 1. Description of different forms of rifaximin obtained by recrystallization [9]

Material	Exposition	Form
I	ethyl alcohol + chloroform	amorphous
II	dichloromethane	α + β
III	ethyl alcohol + purified water	α + β
IV	acetone + purified water	β
V	ethyl alcohol + acetone + purified water	α + β
VI	ethyl alcohol + purified water + ethyl acetate	β + amorphous

The antimicrobial potency of materials from I to VI were evaluated by turbidimetric microbiological method [10] against rifaximin form α. The turbidimetric method was performed by strain of *Escherichia coli* ATCC 10536 at 8% in 3 concentration levels, 50, 70 and 98 μgmL^{-1} [10].
The results were statistically evaluated by Student t test.

RESULTS

The results of antimicrobial activity of each material obtained against rifaximin form α are described in Table 2. Table 3 shows the statistical comparison of the potency of each material against the potency of the rifaximin by Student t test.

Sample I formed by amorphous material showed the lowest potency. Its value, therefore, was statistically significant when compared to the potency of the rifaximin standard.

Sample IV formed by crystalline β material presented potency statistically equal to the potency of the form α (rifaximin standard).

The result of these two forms reinforces the theory that differences between crystalline and amorphous forms can be more problematic than the differences between crystalline forms [4].

Samples II, III and V are composed of a mixture of material α and β. Sample III, exposed to ethyl alcohol and purified water, presented potency statistically equivalent to the potency of the rifaximin form α. However, the potencies of samples II and V were statistically different from the potency of form α. These two samples were treated with dichloromethane and acetone which, despite maintaining crystalline form, affected the antimicrobial activity.

Sample VI, although composed of amorphous material and a small part of crystalline material in form β, showed antimicrobial potency statistically equivalent to the potency of the rifaximin form α. The opposite result was expected for this sample, but exposure to ethyl acetate certainly had its influence.

Table 2. Potency of each material against rifaximin form α

Material		Potency (%)
I	amorphous	83.15
II	α + β	93.33
III	α + β	99.20
IV	β	94.73
V	α + β	85.06
VI	β + amorphous	96.44

Table 3. Statistical comparison of the potencies of rifaximin

Material		Potency (%)	Student t test	
			$t_{calulated}$	$t_{critical}$
I	amorphous	83.15	12.69*	4.30
II	α + β	93.33	9.16*	
III	α + β	99.20	0.82	
IV	β	94.73	1.86	
V	α + β	85.06	11.26*	
VI	β + amorphous	96.44	2.66	

*statistically significant value, considering 95% confidence

DISCUSSION

A purposeful change in the process of obtaining the raw material by recrystallization using different solvents resulted in rifaximin composed of the forms α, β, amorphous and the mixture of them (Table 2). This impacted in significant change of antimicrobial activity in some samples (Table 3).
These tests were performed to prove that changes in the processes of obtaining pharmaceutical inputs influence directly the activity of the product. Activities range from 83.15 to 99.20 % (Table 3).

This is an alert to the production of pharmaceutical inputs. The processes of obtaining raw materials must be standardized aiming not only the quality of the medicine, but also in what it entails: public health, overload of the public health system, contribution to the increase of microbial resistance (Figure 2).

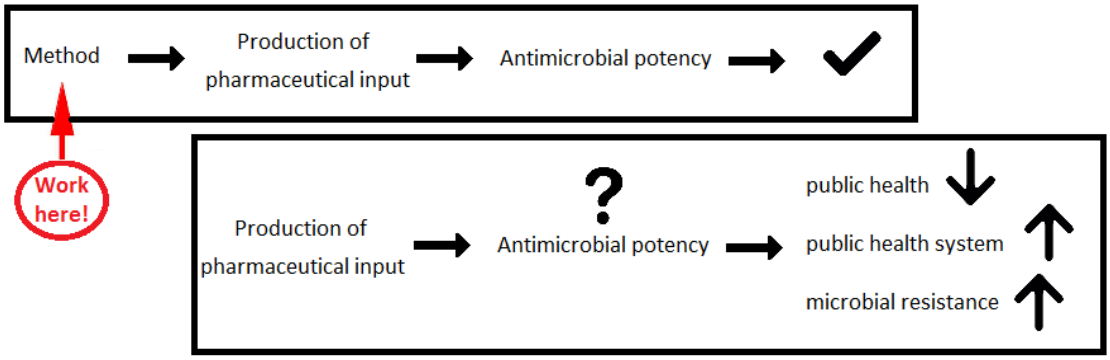

Figure 2. Consequences of the lack of a method for the production of pharmaceutical inputs.

Increasingly, physico-chemical methods are being improved for drug analysis, detection of impurities and degradation products, however if drugs were produced with good practices and with standardized way this might not be so primordial and critical.

The idea and message that must be disclosed is to avoid intellectual waste. Do not treat why the difference in potency occurs if you use one solvent or another, but treat the standardization of the manufacturing of pharmaceutical inputs. Do not treat the effect but the cause! We must standardize methods and not spend time trying to understand why it did not work out right. We must do it right in the first time, this is the mindset! This is a basic teaching of Quality Management that should be adopted by any process [11].

The impact of solvent change in obtaining rifaximin or change in the process or duration of this process proved to be significant in antimicrobial activity. The exposure of rifaximin to acetone and ethyl alcohol concomitantly decreased the potency of the antimicrobial by approximately 15 % (Table 3). This is an example of how important is the adoption of good practices in the production of pharmaceutical inputs.

CONCLUSION

The production of pharmaceutical inputs should be standardized aiming the quality of the medicine and its consequences on public health. Physico-chemical methods are more and more targeted for analysis of impurities, however if the drugs were produced in a standardized way and with good practices this might not be so worrying.

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DECLARATION OF INTEREST

The authors report no declarations of interest.

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