

# PEDIATRIC FORMULATION OF RANITIDINE USING FROM COMMERCIALY AVAILABLE TABLETS IN ALBANIA

Briseida Dosti \*, Ledjan Malaj

University of Medicine Tirana, Faculty of Pharmacy, Department of Pharmaceutical Technology;

Str. Kongresi i Manastirit, No. 133, 1005 Tirana, Albania

Telephone: +368 40 30 426;

\* Email: brizidosti@yahoo.com

## ABSTRACT:

**Background:** Ranitidine Hydrochloride is H<sub>2</sub> – receptor antagonist indicated for duodenal ulcer. It is used for the treatment of gastric/duodenal ulcer and GERD for both neonates and children, in respective dosage 1.5-2mg/kg/24h, q12h and 1-5mg/kg/24h, q6-8h. For use in children is needed cutting into smaller parts to obtain appropriate units, since are missing more appropriate pharmaceuticals forms, such as liquid formulations.

**Objectives:** The purpose of this study was to evaluate the accuracy of splitting ranitidine hydrochloride 150 mg tablets, in dosage for children. Prepare extemporaneous Ranitidine syrup from commercially available tablets and determine it stability.

**Methods:** This study was conducted with three different types of ranitidine tablets, chosen based on the presence or not of the score line. For the preparation of Ranitidine syrup were pulverized tablets of Ranitidine 150 mg and suspended in base solution distilled water and simple syrup. This mixture was diluted to a total volume of 120 ml; resulting in a final ranitidine concentration of 15 mg/ml. A UV-VIS spectrophotometer (Cary 100, Varian) was used to determine ranitidine concentration at wavelength 315 nm.

**Results:** Cutting Ranitidine TBL into halves and quarters lead to large deviations. These deviations were related to the presence or not of the score line. It was shown that prepared formulations retain minimum 98% of initial Ranitidine concentration after 7 days of storage at 25°C and 4°C.

**Keywords:** extemporaneous, ranitidine, splitting tablets, stability, pediatric

## INTRODUCTION:

Many drugs administered to children are not available in formulations for pediatric use. Most marketed oral medicines are intended for adults and are solid dosage forms. Solid dosage forms present problems as children have difficulty swallowing whole tablets (TBL). Sometimes tablets are cut into smaller parts to obtain appropriate units for children. Ranitidine oral is used for the treatment of gastric/duodenal ulcer and GERD for both neonates and children, in respective dosage 1.5-2mg/kg/24h, q12h, and 1-5mg/kg/24h, q6-8h (1).

The study was made with ranitidine hydrochloride 150 mg TBL, from 3 different manufacturers present in Albanian market. Products have been chosen based on the presence or not of the score line: scored on one side (S), scored on both sides (BS) and not scored (NS).

In Albania, there isn't available in the market liquid formulation of Ranitidine Hydrochloride (RH) for pediatric administration.

The purpose of this study was to evaluate the accuracy of splitting ranitidine hydrochloride 150 mg TBL, in dosage for children. Prepare extemporaneous RH syrup from commercially available tablets and determine it stability.

## MATERIAL AND METHODS:

### Split of ranitidine hydrochloride 150 mg TBL, in dosage for children:

This study was conducted with three different types of ranitidine tablets commercially available on the Albanian market. They have been chosen based on the presence or not of the score line. For simplicity, the different types will be referred to as S (line score on one side of the tablet), NS (No line score) and DS (line score on both sides of the tablet). Of each product, 100 TBL were taken at random and weighed using a Denver Instrument APX – 200 analytical balance and mean weight (MW) was calculated. Then the TBL were divided into halves and quarters by using a pill-splitter. From each TBL one-half and one-quarter was weighed and means weight was calculated. The range of 85% to 115% and 75% to 125% confidence intervals (CI) was determined based on the

mean weight. For the whole TBL, halves and quarters, the weight deviation from the average weight were compared to the above interval (2, 3, 4, 5).

#### Preparation of extemporaneous Ranitidine hydrochloride syrup for pediatric use:

RH syrup was prepared from marketed 150 mg tablets. For the preparation of Ranitidine syrup were pulverized 12 tablets of Ranitidine 150 mg and suspended in base solution distilled water and simple syrup. This mixture was diluted to a total volume of 120 ml. The final concentration of Ranitidine in the formulation was 15 mg/ml (6). Samples of the formulation were stored in glass bottles protected from light and kept on 25°C and 4°C. Stability was determinate at 0, 3, 7 and 14 days using Varian Cary UV-VIS spectrophotometer, absorption maxima at 315 nm.

### RESULTS AND DISCUSSIONS:

#### Split of ranitidine hydrochloride 150 mg TBL, in dosage for children

From the study were found that all the whole TBL were conformed to the Eur.Pharm mass uniformity requirements (5). And only halves from S and BS tablets complied with the Eur.Pharm. 37% of halves from NS tablets deviated more the 15% from the mean (Table 1).

Table 1: Percentage of halves, that weight falls in the CI.

Deviation from MW	% of halves fall in CI		
	S	BS	NS
$X < 15\%$	100	100	63
$15\% \leq X < 25\%$	0	0	29
$25\% \leq X$	0	0	8

The results were worse with quarters. None of the quarters from evaluated products complied with Eur. Pharm requirements. Only 73% of quarters from S and BS tablets and 62% of the quarter from NS tablets were within the CI of 15% (Table 2).

Table 2: Percentage of quarters, that weight falls in the CI.

Deviation from MW	% of quarters fall in CI		
	S	BS	NS
$X < 15\%$	73	73	62
$15\% \leq X < 25\%$	20	23	25
$25\% \leq X$	7	4	13

#### Stability of extemporaneous Ranitidine hydrochloride syrup

##### Determination of $\lambda_{\max}$ and Working standard solution:

Weighed an amount 100 mg of Ranitidine Hydrochloride was dissolved in 100 ml of distilled water to obtain a 1 mg/ml concentration of Ranitidine Hydrochloride in solution. From this solution were taken 1 ml and was dissolved in 100 ml distilled water to obtain concentration 0.01 mg/ml. This solution was subjected to scanning between 300 – 400 nm and absorption maxima at 315 nm were determined (7, 8, 9).

##### Calibration curve for Ranitidine Hydrochloride:

The aliquots working standard solution (1 mg/ml) was diluted serially with distilled water to obtain the concentration range of 0.01 – 0.03 mg/ml. A calibration curve for Ranitidine Hydrochloride was obtained by measuring the absorbance at the  $\lambda_{\max}$  of 315 nm. And were determined statistical parameters like the slope, intercept, coefficient of correlation, standard deviation, relative standard deviation, and standard error (10).

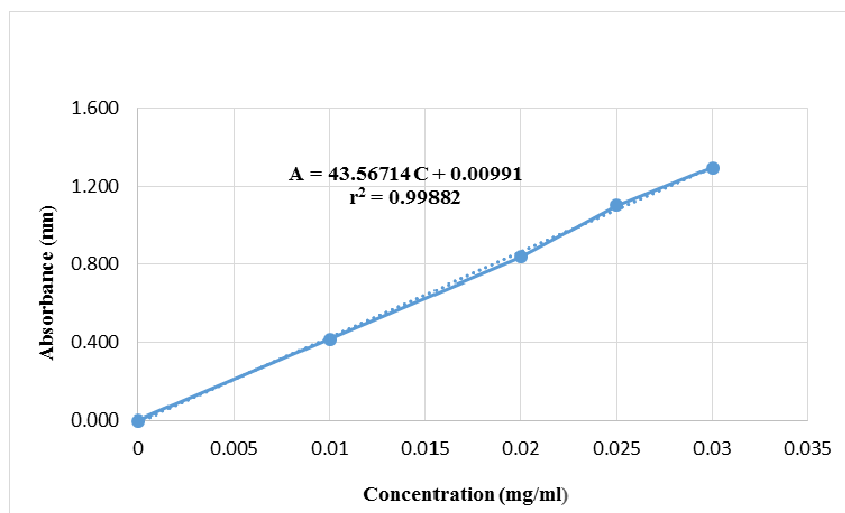


Fig. 1: Calibration curve for Ranitidine Hydrochloride

**Analysis of extemporaneous Ranitidine hydrochloride syrup:**

From prepared syrup was accurately weighed 1 ml, equivalent to 15 mg of Ranitidine. This solution was transferred to 100 ml volumetric flask and added distilled water and made the volume mark with the same, obtaining concentration 0.15 mg/ml. This mixture was sonicated for 15 minutes and then filtered. Again for last solution were removed samples (1 ml) and diluted with 10 ml distilled water, obtaining concentration 0.015 mg/ml ranitidine hydrochloride. For each aliquot ( $C = 0.015$  mg/ml) was determined the respective absorbance at 315 nm against the distilled water as blank.

Table 3: Stability of Ranitidine syrup at temperature 25°C and 4°C

	Concentration of Ranitidine (mg/ml)			
	Day 0	Day 3	Day 7	Day 14
Temperature 25°C	0.01497	0.01517	0.01475	0.01267
Temperature 4°C	0.01508	0.01525	0.01482	0.01317

Table 4: % Initial concentration remaining at temperature 25°C and 4°C

		Concentration of Ranitidine (%)			
	Initial concentration of sample	Day 0	Day 3	Day 7	Day 14
Temperature 25°C	15 mg/ml	99.8%	101.1%	98.3%	84.5%
Temperature 4°C	15 mg/ml	100.5%	101.6%	98.8%	87.8%

The spectrum of Ranitidine Hydrochloride in distilled water showed the absorption maxima at 315 nm. The statistical analysis of data obtained from the calibration curve of Ranitidine Hydrochloride in pure solution indicated a high level of precision and coefficient of correlation was 0.99882. The linearity range was observed between 0.01 – 0.03 mg/ml. The plot clearly showed a straight line passing through origin ( $A = 43,56714C + 0.00991$ ).

Stability was determinate at 0, 3, 7 and 14 days using Varian Cary UV-Vis spectrophotometer. It was shown that prepared formulations retain minimum 98% of initial RH concentration after 7 days of storage at 25°C and 4°C.

**CONCLUSION:**

By breaking Ranitidine TBL into halves and quarters were observed large deviations. These deviations were related to the presence or not of the score line. Such inadequate breaking of TBL may result in dose variability and complicate therapeutic outcome. In small markets where the introduction of lower doses may not have a commercial interest, appropriately scored TBL (scored both sides) can ensure more flexible dosage. There is a need for pediatric formulations and dose adaptation based on child body weight.

Extemporaneous RH syrup 15 mg/ml were stable for 7 days when stored in glass bottles protected from light, at two controlled temperature. Such formulations may provide an option in situations where the marketed liquid formulations for pediatric use are unavailable.

# REFERENCES:

- [1] D. Bebeçi. *Pediatrics, botim i katërt*. Expo Vision Albania, Tiranë, 2006.
- [2] *European Pharmacopoeia*. Supplement 7.4, 2011. Council of Europe, Strasbourg, France.
- [3] Lieven Van vooren, B. De Spiegeleer, T. Thonissen, P. Joye, J. Van Durme, G. Slegers. Statistical analysis of tablet breakability methods. *J. Pharm. Sci.*, 2002, 5(2), pp. 190-198.
- [4] Tablets, monograph 0478, *Pharmaceutica* 2004 Apr, 16 (2), 250-253.
- [5] Freund RJ, Littell RC, Spector PC. *SAS system for linear models*. Cary, NC: SAS Institute, Inc., 1986:78-82.
- [6] Karnes HT1, Harris SR, Garnett WR, March C. Concentration uniformity of extemporaneously prepared ranitidine suspension. *Am J Hosp Pharm.* 1989 Feb;46(2):304-7.
- [7] P. Salve, D. Gharge, R. Kirtawade, P. Dhabale, K. Burade. Simple Validated Spectroscopic Method for Estimation of Ranitidine From Tablet Formulation. *International Journal of PharmTech Research*, 2010, 2(3);2071-2074.
- [8] Walash M, Sharaf – E1 DM, Metwalli ME, et al. Spectrophotometric determination of nizatidine and ranitidine through charge transfer complex formation. *Arch Pharm Res*, 2004; 27:720-6.
- [9] Osol A, ed. *Remington's pharmaceutical sciences*. Easton, PA: Mack Publishing Company; 1980:306-7.
- [10] Vandenberghe HM, Soldin SJ. Analysis of ranitidine by high-performance liquid chromatography. In: Sunshine I, ed. *Methodology of analytical toxicology*, volume 3. Boca Raton, FL: CRC Press, Inc.; 1985:169-73.