IOSR Journal Of Pharmacy *www.iosrphr.org*
(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219
Volume 8, Issue 3 Version. 1 (March 2018), PP. 19-31

Comparison of Pharmaceutical-Technological Properties of Commercially Available Ranitidine Tablets

Jasmina Hadžiabdić[1], Aida Bureković[1], Amra Demirović[2], Ognjenka Rahić[1], Alisa Elezović[1]

[1] *Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Sarajevo, Zmaja od Bosne 8, 71000 Sarajevo, Bosnia and Herzegovina*
[2] *Amsal Pharmaceuticals d.o.o. Sarajevo, Igmanska 38, 71320, Vogošća, Bosna i Hercegovina*
Corresponding Author: Jasmina Hadžiabdić1

Abstract: In this work, we compared the pharmaceutical-technological characteristics of ranitidine hydrochloride film coated tablets (tablets R1, tablets R2) of different manufacturers as well as the influence of excipients of the core tablet and/or film-coating. The results of assay (R1=97.55% ± 1.81%; R2=95.03% ± 0.82%), uniformity of dosage units (R1=267.55 mg ± 4.96 mg; R2=308.75 mg ± 2.67 mg), friability testing (R1=0.037%; R2=0.009%) and disintegration time (R1=239 sec; R2=317 sec) of tablets for both generic drugs meet pharmacopoeial requirements. Significant variations were observed in hardness testing for tablets R1 (RSD=26.69%) compared to hardness testing for tablets R2 (RSD=5.64%). Tested pharmaceutical equivalents may be considered bioequivalent because of the results of in vitro dissolution testing of ranitidine tablets (R1=97.17% ± 1.39%; R2=96.99% ± 3.76%). Tested tablets, containing various excipients, and having different pharmaceutical-technological characteristics, have met all requirements of the European and American pharmacopoeias. Tablets R2 were harder and had lower disintegration time, which resulted in the dissolution of more than 80% of ranitidine within 45 minutes. Patients with lactose intolerance have to be cautious when taking tablets R2, since these tablets contain lactose.

Keywords: characterization, excipients, pharmaceutical equivalents, ranitidine, tablets

---

Date of Submission: 22-02-2018 Date of acceptance: 10-03-2018

I. INTRODUCTION

As a result of various excipients generic drugs/pharmaceutical equivalents can differ in the pharmaceutical-technological properties due to application of various pharmaceutical and technological parameters in the production process which may influence the bioavailability of the active substance with the same concentration of the same pharmaceutical dosage form intended for the same route of administration [1]-[4].

Ranitidine hydrochloride is commercially available in the form of tablets as a generic drug under a variety of brand names, which complicates its selection by doctors, pharmacists and patients. It is used for short-term treatment of duodenal ulcer and benign stomach ulcers, in treatment of uncomplicated gastroesophageal reflux disease, in the occurence of the formation of stress-induced ulcer, as well as prevention and treatment of heartburn symptoms. It is a blocker of histamine H_2-receptors and it inhibits gastric acid secretion. Ranitidine leads to competitive inhibition of the action of histamine on all H_2 receptors on the basolateral membrane of the parietal cells of the stomach [5], [6]. By 1988. ranitidine hydrochloride was one of the most frequently prescribed medications. Chemically, it is N-[2-[[[5-[(Dimethylamino)methyl]furan-2-yl]methyl]sulphanyl]ethyl]-N′-methyl-2-nitroethene-1,1-diamine hydrochloride [7], [8]. Ranitidine was synthesized in 1976, but due to its poor solubility in water it was replaced by ranitidine hydrochloride in 1977.

The solubility of the ranitidine hydrochloride in water is 660 mg/mL [6]. According to the Biopharmaceutical Classification System (BCS), ranitidine hydrochloride had been classified as a class III drug (high solubility and low permeability). For Class III drugs permeability is rate limiting step for drug absorption [6]-[8]. Ranitidine hydrochloride is hygroscopic, and its hygroscopicity increases in the presence of light. It degrades in the presence of moisture because of its hygroscopic nature. Absorbed moisture can lead to the catalytic reaction like hydrolysis and oxidation which results in the degradation of the drug and hence decreases therapeutic efficacy of the drug. Therefore, it is necessary to protect ranitidine hydrochloride from moisture by using one of the following ways: by adequate production process, by coating (solid dosage forms), by specific packaging. Most often this problem is solved by coating the tablets [9].

Ranitidine hydrochloride film-coated tablets manufactured by two different producers available on the market of Bosnia and Herzegovina were tested. Those tablets were selected because of different excipients used in the core tablets as well as in the film coating of tablets. Pharmaceutical-technological characterization of the same pharmaceutical forms (tablets), intended for the same indication, having the same quantitative composition of the active substance (150 mg of ranitidine) but with different excipients, was performed in order to determine the influence of the excipients in the core tablets and/or film-coating on the tested pharmaceutical-technological parameters: assay, uniformity of dosage units, friability, disintegration time and hardness of the tablets and particularly on the dissolution of ranitidine. Dissolution test is considered to be significant *in vitro* method for assessing the bioequivalence/bioavailability of generic drugs/pharmaceutical equivalents. Tablets have been evaluated using the same pharmaceutical technological-tests in order to determine whether the obtained data comply with pharmacopoeial requirements [10], [11].

II. MATERIALS

Ammonium acetate, p.a., HPLC purity (Fisher chemical, United Kingdom), Methanol, p.a., HPLC purity (J.T.Baker, Netherlands), Ranitidine standard, 98.90% (Bosnalijek d.d., Bosnia and Herzegovina), Generic drug, ranitidine film coated tablets of manufacturer *x* (R1): each tablet contains ranitidine hydrochloride ($C_{13}H_{22}N_4O_3S{\cdot}HCl$, M_w=350.87 g/mol) equivalent to 150 mg ranitidine ($C_{13}H_{22}N_4O_3S$, M_w=314.40 g/mol) whose content is 90-110%. Excipients of core tablet R1: colloidal anhydrous silica, microcrystalline cellulose, croscarmellose sodium, magnesium stearate. Excipients of film coat R1: hypromellose, triacetin, titanium dioxide, talc, methylene chloride, ethanol 96%, v/v. Generic drug, ranitidine film coated tablets of manufacturer *y* (R2) contain an amount of ranitidine hydrochloride ($C_{13}H_{22}N_4O_3S \cdot HCl$, M_w=350.87 g/mol) equivalent to not less than 90.0% and not more than 110% to the labeled amount (150 mg) of ranitidine ($C_{13}H_{22}N_4O_3S$, M_w=314.40 g/mol). Excipients of core tablet R2: colloidal anhydrous silica, microcrystalline cellulose, corn starch, lactose monohydrate (70.7 mg), magnesium stearate, povidone, talc. Excipients of film coat R2: hypromellose, macrogol 400, titanium dioxide, ferric oxide yellow, talc, carnauba wax.

Excipients in core tablets R1

During tablet manufacturing colloidal anhydrous silica is used as glidant in concentrations from 0.1 to 1%. It is also used as tablet disintegrant [12]-[14]. Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tableting and capsule filling [12]. Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant [15] and disintegrant properties that make it useful in tableting [12], [14]. Magnesium stearate is most frequently used lubricant in tablet and capsule manufacturing. It is hydrophobic powder and can slow down the release of the active substance from solid pharmaceutical form, therefore it is used in the lowest possible concentrations. Physical properties of magnesium stearate may vary from manufacturer to manufacturer, due to the characteristics of the powder that are affected by the production conditions [12]. Croscarmellose sodium is a crosslinked polymer of carboxymethylcellulose sodium. It is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets and granules [12]. In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process. Croscarmellose sodium belongs to the group of „super disintegrants“. This name is derived from its ability to have full efficacy in low concentrations (1-4%) [14].

Excipients in film-coating of tablets R1

Hypromellose is used as an ingredient of the coating solutions for pharmaceutical forms. This polymer is soluble in water and organic solvents.Hypromellose concentration in coating formulation depends on the nature of the solvent for coating, ie.whether it is water or organic solvent. Low viscosity forms of this polymer are used in the aqueous solutions, while high-viscosity forms are used in organic solvents for the coating [12], [16], [17]. Talc is used as diluent and lubricant in solid pharmaceutical forms [12]. As a lubricant it is used in concentrations up to 5% (1-5%) [14], [18], and the amount is restricted by its hydrophobic characteristics (high concentrations of talc lead to decreased wetting of tablets and slow down the dissolution rate) [18]. Titanium dioxide, inorganic color, has a high degree of opacity. In the pharmaceutical forms is used as a white pigment in aqueous solutions for the coating, alone or in a mixture with the other pigments [12]. As a water insoluble pigment it is used to reduce the permeability of the coating to moisture and light, and thus to improve the

stability of the product. It also serves as a bulking agent, and the total content of solids in the dispersion for coating without an excessive increase in viscosity [19]. Triacetin is excipient which is used as humectant, plasticizer and solvent. It is a colorless, viscous liquid with a slightly fatty odor. Triacetin is used as a hydrophilic plasticizer in both, aqueous and organic solvent-based polymeric coating of capsules, tablets and granules in concentrations from 10 to 35% w/w [12]. Methylene chloride is a colorless, clear, non-flammable liquid with sweet, pleasant odour. Ethanol is a clear, colorless liquid which is used as a solvent and a preservative in the manufacturing of pharmaceutical forms. Methylene chloride (boiling point of 39 °C) and ethanol (boiling point of 78 °C) evaporate at low temperatures and are used as solvents in the pharmaceutical industry for coating of solid pharmaceutical forms [20].

Excipients in core tablets R2

In addition to colloidal anhydrous silica, microcrystalline cellulose, magnesium stearate and talc, tablets R2 contain corn starch as a binder, a disintegrant and diluent. Corn starch is used as a binder in the tablet formulations for wet granulation. By using granulated starch in the preparation of tablets by direct compression, the tabletting process is facilitated and tablet disintegration time is shorter [12]. Corn starch has a great affinity for water, it swells and thus facilitate release of the active substance from the pharmaceutical form. Is added in concentrations of 5%, and even 10-15% in the manufacture of immediate-release forms [14]. Corn starch can be used in both capsules and tablets to improve flowability, enhance disintegration and improve hardness [12]. Lactose is one of the most commonly used excipients in tablets. In the pharmaceutical industry lactose monohydrate is used as a diluent and binder. As a diluent, it is used in many preparations because of its pleasant tast and high water solubility. Orally taken lactose by the action of the enzyme lactase is disintegrated in small intestine villi into glucose and galactose. One of the major side effects of lactose is lactose intolerance which can be seen in people with a lack of intestinal enzyme lactase. Such a person will not digest lactose, which can cause cramping, bloating, bowel distension and diarrhea [12]. These effects are the result of the transformation of undigested lactose to lactic acid or high osmotic pressure in the intestine, which occurs as a result of production of carbon dioxide and hydrogen by bacterial fermentation of nonabsorbed carbohydrates [21]. Lactose intolerance is a common occurrence throughout the world [22]. It is not expressed equally among all individuals. In some age groups (children, adults) above mentioned symptoms may occur after ingestion of lactose in a dosage of 3 g or less [21]. The amount of lactose in the majority of pharmaceutical dosage forms is rarely greater than 2 g per day [12]. Povidone is commonly used in the manufacture of solid pharmaceutical forms. It is used as a binder, a disintegrant, and an agent for improving solubility (a solubilizer) [12].

Excipients in film-coating of tablets R2

In addition to hypromellose, talc and titanium oxide, film-coating of tablets R2 also contains macrogol 400 (macrogol 400, synonym polyethylene glycol 400), which is used in coating formulations as an agent for polishing and as a plasticizer in combination with the film-forming polymers [12], [23]. The presence of polyethylene glycols in film coats, especially of liquid grades (eg. makrogol 400), tends to increase their water permeability and may reduce protection against low pH in enteric-coating films [12]. Coatings containing polyethylene glycols are solid, smooth and tasteless. Polyethylene glycols are used to enhance the stability of drugs which are susceptible to influence from the surroundings [24]. Ferric oxide yellow is used as coloring agent in pharmaceutical forms. Carnauba wax is used as an ingredient of the coating solution. Polished, shiny pills without mechanical treatment can be obtained by the application of carnauba wax [12].

III. METHODS

3.1. Assay

Assay testing was performed using the apparatus HPLC Agilent Technologies, Santa Clara, USA. Chromatography was conducted with a mixture of methanol and 0.1 M ammonium acetate as a mobile phase (85:15) [11]. 0.1 M ammonium acetate solution was previously prepared (magnetic stirrer, Hotplate Stirrer, Stuart, Stone, United Kingdom) and filtrated through nylon filter (LLG-Syringe Filter, nylon) with pore diameter of 0.2 μm. Mobile phase flow rate was 2 mL/min, injection volume 2 μL, oven temperature 25 °C, and detection was performed at 322 nm. Analysis was conducted on a column ZORBAX Eclipse Plus C18 (Agilent Technologies, Santa Clara, USA) as a stationary phase. 13.440 mg of ranitidine standarda was weighted (Analytical balance type XS 204 DR, METTLER TOLEDO, Greifensee, Schwizerland), transferred to 100 mL-volumetric flask and half of the volumetric flask was filled. It was stirred in the ultrasonic bath (Ultrasons H-D SELECTA, Barcelona, Spain). After stirring the volumetric flask was filled up to the mark with the mobile phase. Concentration of ranitidine standard solution was 0.1204 mg/mL. Ten ranitidine hydrochloride tablets were transferred into 250 mL-volumetric flask, mobile phase was added to the mark and stirred in the ultrasonic bath (Ultrasons H-D (SELECTA, Barcelona, Spain). 1 mL of prepared samples was diluted to 50 mL with

mobile phase, in a volumetric flask, in order to obtain concentration of 0.12 mg/mL.–Solutions were filteret through nylon filter (LLG-Syringe Filter, nylon, pore diameter 0.2 μm). Afterwards, solutions were injected in triplicate, while standard solution was injected five times. Based on recorded chromatograms, the identification and quantification of ranitidine in standard and test solutions was performed. Identification was performed according to retention time, and quantification on the basys on the area under the signal of the chromatographic peak.

3.2. Uniformity of dosage units

The term uniformity of dosage unit is defined as the degree of uniformity in the amount of the active substance among dosage units. The uniformity of dosage units can be demonstrated by either of two method: content uniformity or mass variation [10], [11]. Since the quantity of ranitidine, as an active, is higher than 50 mg, mass variation test is performed [11]. Mass variation of ranitidine tablets was determined by weighing (XS 204 DR, METTLER TOLEDO, Stockholm, Sweden) each of ten randomly selected dosage units. Then assay was determined, as well as average mass of tablets and acceptance value (*AV*) was calculated.

Acceptance value is calculated on the basis of the formula (1):

$$\left|M - \overline{X}\right| + ks \qquad (1)$$

where:
M - reference value,
$\bar{X}$ - mean of individual contents expressed as a percentage of the label claim,
k - acceptability constant,
s - standard deviation [10].

Individual content in dosage unites was calculated by using formula (2):

$$x_i = w_i \times \frac{A}{\overline{W}} \qquad (2)$$

where:
$x_1, x_2,..., x_n$ - individual estimated contents of the dosage units tested,
$w_1, w_2,..., w_n$ - individual masses of the dosage units tested,
A - content of active substance (percentage of label claim) obtained using an appropriate analytical method (assay),
$\overline{W}$ - mean of individual masses ($w_1, w_2, ..., w_n$) [10].

Tablets comply with requirements if *AV* of 10 tested dosage units equals or is less than maximum allowed *AV*, that is L1 (L1=15 unless specified otherwise). If *AV* is greater than L1, additional 20 dosage units must be tested and new *AV* must be calculated. Tablets comply with requirements if *AV* of all 30 dosage units is less than or equals L1 [10].

3.3. Friability test

In order to determine friability, number of tablets that have cumulative weight of 6.5 g [10] was weighted on analytical balance (XS 204 DR, METTLER TOLEDO, Stockholm, Sweden). Before placing in the drum of friability tester (250 Friability tester, Agilent Technologies, Santa Clara, USA), tablets were carefully de-dusted and weighted on analytical balance (XS 204 DR, METTLER TOLEDO, Stockholm, Sweden). De-dusting was performed by placing the tablets onto a sieve Nr. 1000 (the length of the side of aperture 1000 nm). Fine particles of the powder have been removed using a soft brush. Drum rotation speed was 25 rpm ± 1 rpm (during 4 minutes). After 4 minutes of rotation, the tablets were taken out, de-dusted again and weighted with accuracy of 1 mg. Maximum weight loss after friability test must not be greater than 1% [10], [11], [25], [26].

3.4. Disintegration test

Six randomly selected ranitidine coated tablets are transferred into a cylindrical glass tubes of the apparatus for testing the disintegration time of tablets, 100 Automated Disintegration Apparatus (Agilent Technologies, Santa Clara, USA). As a medium for tablet disintegration test 900 mL of purified water heated to a temperature of 37 °C ± 0.1 °C were used the . Cylinders with the samples moved rhythmically in the up - down direction, until the tablets were completely disintegrated [10], [27]. The whole process of tablet

disintegration, the detection of the end of the disintegration process, as well as the determination of the disintegration time of tablets, is monitored and assessed visually. The disintegration time of tested coated tablets was read from the apparatus display.

3.5. Hardness test

Measuring the force needed to crush the tablet was performed on ten randomly selected ranitidine film coated tablets. Before each following measurement, a soft brush was used to eliminate fragments of previously broken tablets from the tray of apparatus (Tablet Hardness Tester - VK 200, Vankel Technology Group, Cary, USA). During the tests, the force needed to crush the tablet was read from the scale of the apparatus The results were expressed as the minimum and maximum values of the force required for breaking the tablet The obtained values, expressed in kiloponds (kp) have been transformed into Newtons (N).

3.6. Dissolution test

The dissolution test of ranitidine from coated tablets was performed using apparatus 2 (rotating paddle - Dissolution Apparatus 708-DS, Agilent Technologies, Santa Clara, USA). Rotating speed was 50 rpm ± 4%. Purified water, heated up to 37 °C ± 0.5 °C, was used as a dissolution medium. Samples of 10 mL were collected after 5, 10, 15, 30 and 45 minutes. After each sampling, the volume of the sample was replaced with equal volume of dissolution medium having specified temperature. 1 mL of each solution was transferred to 10 mL volumetric flask and diluted with purified water. The samples were filtered through a nylon filter (LLG-Syringe Filter, nylon, pore diameter 0.2 μm). The absorbances of samples were measured at wavelength of 314 nm in 1 cm cuvette using spectrophotometer (Cary Series UV-Vis Spectrophotometer, Agilent Technologies, Santa Clara, USA), using water as blank [11].

Preparation of ranitidine standard solution: 18.848 mg of ranitidine standard was weighted (XS 204 DR, METTLER TOLEDO, Stockholm, Sweden) and transferred into 100 mL volumetric flask and filled with purified water to the mark. Volumetric flask was placed in ultrasonic bath (Ultrasons H-D SELECTA, Barcelona, Spain) for 10 minut in order to dissolve ranitidine standard. 1 mL of obtained solution was transferred into 10 mL volumetric flask and diluted with purified water. Aqueous solution of ranitidine standard was filtered through nylon membrane (LLG-Syringe Filter, nylon, pore diameter 0.2 μm). The absorbances of standard solution were measured at wavelength of 314 nm in 1 cm cuvette using spectrophotometer (Cary Series UV-Vis Spectrophotometer, Agilent Technologies, Santa Clara, USA), using water as blank.

Ranitidine hydrochloride assay was calculated using external standard method. Quantification was conducted with respect to the working standard solution of ranitidine in the purified water, with concentration of 0.01667 mg/mL. Percentage of dissolved ranitidine was calculated using formula (3):

$$content\,(\%) = \frac{A_s \times w_{st} \times d_s \times k \times 900}{A_{ss} \times V_{ss} \times w_s \times d_{ss}} \qquad (3)$$

where:
A_s - absorbance of sample solution,
w_{st} - weight of standard (mg),
d_u - dilution of sample solution,
A_{ss} - absorbance of standard solution,
V_{ss} - volume of standard solution (mL),
w_s - weight of sample (mg),
d_{ss} - dilution of standard solution,
k - correction factor for ranitidine (0.896).

The percentage of dissolved ranitidine in selected time intervals is expressed as a percentage of ranitidine in relation to the declared content of ranitidine in film coated tablet (150 mg). Not less than 80% of the declared content of ranitidine has to be dissolved within 45 minutes [11]. Based on the obtained results, the dissolution profile was constructed: time (t), expressed in minutes, was applied to the abscissa and the percentage of the ranitidine was applied to the ordinate.

IV. RESULTS

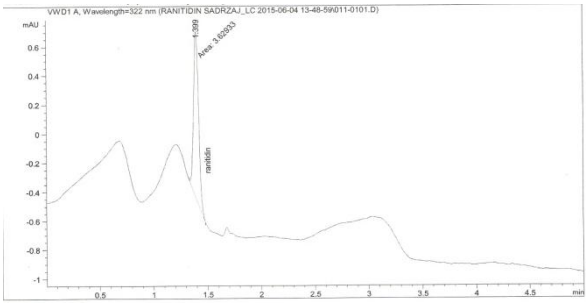
4.1. Assay

The chromatographic data obtained for diluent, standard solution (Ss 1-5, n=5) and test solution of tablets R1 ($Rs_{1.1.}$- $Rs_{1.3.}$, n=3) and tablets R2 ($Rs_{2.1.}$- $Rs_{2.3,}$ n=3) are presented in Table 1.

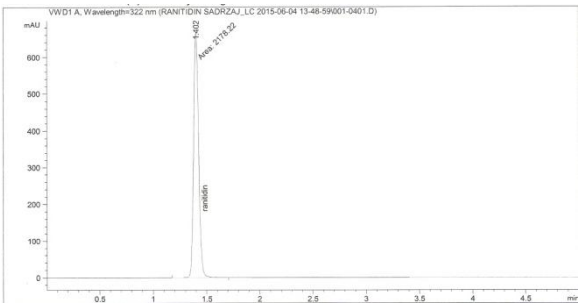
Table 1: Chromatographic parameters of tested tablets

Solution	Retention time (min)	Surface (mAU*s)	Height (mAU)	Symmerty	Widht (min)	Number of of theoretical attics
Diluent	1.399	3.62933	1.15121	0.87	0.0493	4453
Ss. 1	1.402	2178.21851	668.22321	0.90	0.0504	4270
Ss. 2	1.402	2188.95605	668,85797	0.88	0.0503	4298
Ss. 3	1.403	2187.66846	670.71924	0.90	0.0504	4295
Ss. 4	1.404	2190.76709	670.29688	0.90	0.0505	4289
Ss. 5	1.403	2192.00830 $\bar{x}$=2187.8 RSD = 0.22%	671.28687	0.90	0.0504	4293
$Rs_{1.1.}$	1.404	2113.22095	645.39825	0.89	0.0505	4285
$Rs_{1.2.}$	1.404	2196.39502	672.16901	0.90	0.0504	4298
$Rs_{1.3.}$	1.404	2141.69800	652.97614	0.88	0.0504	4303
$Rs_{2.1.}$	1.404	2039.11951	625.24359	0.90	0.0504	4301
$Rs_{2.2.}$	1.405	2101.86841	642.54260	0.90	0.0505	4290
$Rs_{2.3.}$	1.606	2143.56348	656.35254	0.90	0.0505	4294

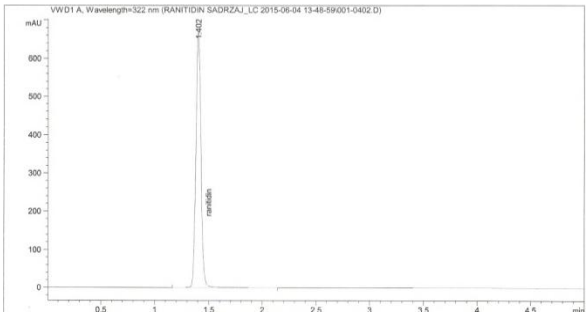
On the basis of the obtained results, three parameters for the system suitability were checked out: tailing factor (TF), the efficiency of the column (number of theoretical plates) and relative standard deviation. System suitability was checked by recording chromatograms of five standard solutions in order to verify the correctness of the apparatus, columns and others. Fig. 1 presents the chromatograms of diluent and ranitidine standard solution.



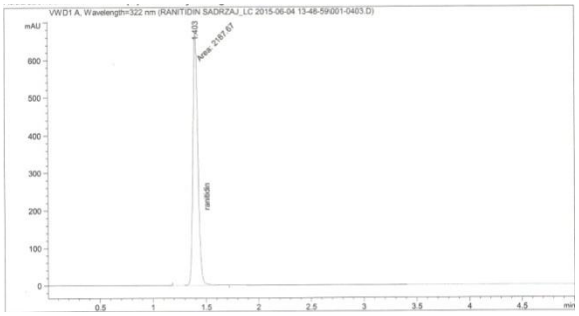
Chromatogram of diluent



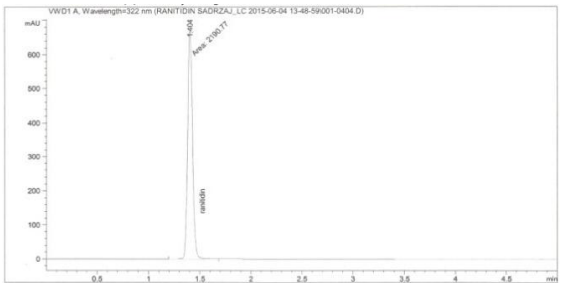
Chromatogram of Ss 1



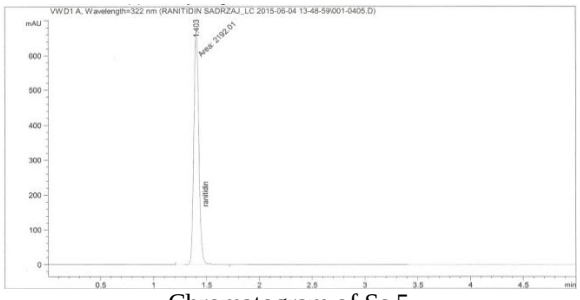
Chromatogram of Ss 2



Chromatogram of Ss 3



Chromatogram of Ss 4



Chromatogram of Ss 5

Fig. 1: Chromatograms of the ranitidine standard solution and diluent

TF must not be greater than 2 [11] calculated by the formula (4).

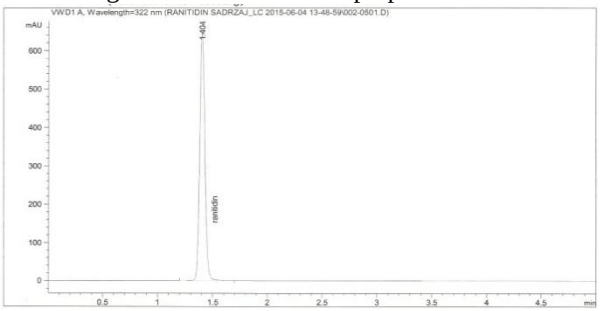
$$TF = \frac{1}{symmetry} \qquad (4)$$

Assymetry for all five standard solutions is satisfactory (TF_1=1.11; TF_2=1.14; TF_3=1.11; TF_4=1.11; TF_5 = 1.11). The efficacy of the column determined from the peak of ranitidine hydrochloride should not be less than 700 theoretical plates (TP) [11]. In this case, number of theoretical plates of all five standard solutions was not less than 700 (TP_1=4270; TP_2=4298; TP_3=4295; TP_4=4289; TP_5=4293). Relative standard deviation (RSD) of standard solutions must not be greater than 2% [11]. In this case, RSD of all five standard solutions was 0.22 %. Afterwards, the assay of ranitidine was determined in samples prepared from the tablets R1 and tablets R2. Assay is calculated according to formula (5):

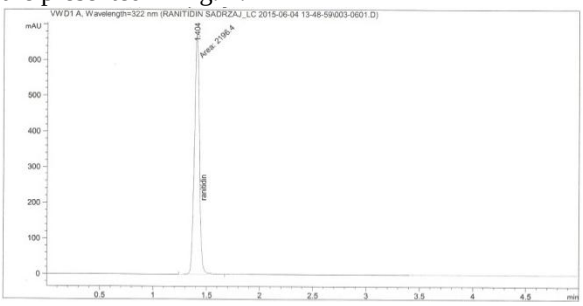
$$content\,(\%) = \frac{A_s \times c_{ss}}{A_{ss} \times c_s} \times p \qquad (5)$$

where:
A_s - area of ranitidine peak in test solution,
c_{ss} - concentration of standard solution,
A_{ss} - area of ranitidine peak in standard solution,
c_s - concentration of sample solution,
p - purity.

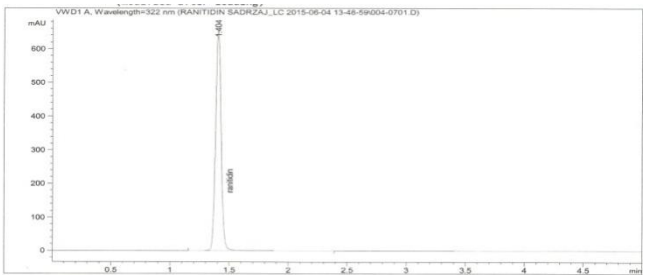
Chromatograms of test solutions prepared from tablets R1 are presented in Fig. 2.



Chromatogram of $Rs_{1.1.}$



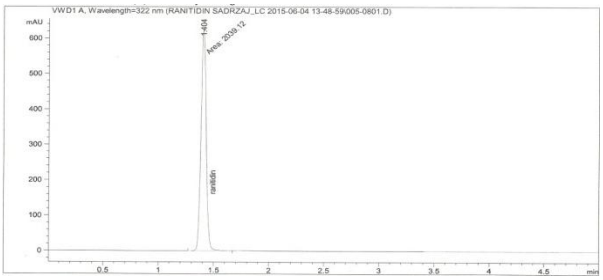
Chromatogram of $Rs_{1.2.}$



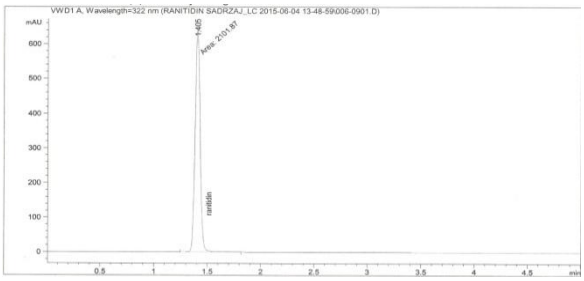
Chromatogram of $Rs_{1.3.}$

Fig. 2: Chromatograms of test solutions prepared from tablets R1

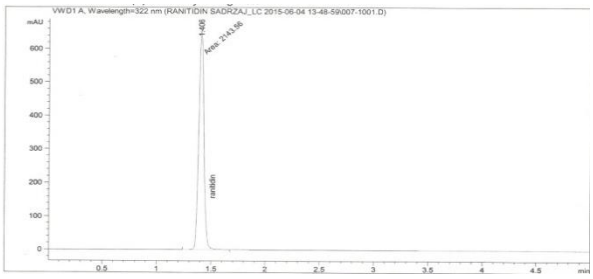
Chromatograms of test solutions prepared from tablets R2 are presented in Fig. 3.



Chromatogram of $Rs_{2.1.}$



Chromatogram of $Rs_{2.2.}$



Chromatogram of $Rs_{2.3.}$

Fig. 3: Chromatograms of test solutions prepared from tablets R2

Assay of ranitidine in tablets R1 and tablets R2 (%), standard deviation (SD, %) and relative standard deviation (RSD, %) of ranitidine assay in tablets R1 and tablets R2 are presented in Table 2.

4.2. Uniformity of dosage units

Table 2 also contains results for the average mass (mg) of tablets R1 and R2. Average mass of tablets, as well as SD (mg) and RSD (%) were calculated after weighing ten randomly selected tablets. Calculation of ranitidine content in individual tablet is performed according to formula (2). Average individual content of ranitidine (content uniformity, %), SD of ranitidine content in ten individual tablets, as well as RSD are presented in Table 2. To confirm the content uniformity using variation of masses, accepted value (*AV*) should be less than 15. Since $\overline{X}$ <98.5 for both generic drugs, according to Ph. Eur. M=98.5 (reference value, M (case 1)), the *AV* is calculated by the formula (6) [10]:

$$AV = \left| 98.5 - \overline{X} \right| + ks \qquad (6)$$

therefore *AV* for R1 is:

$$AV = \left| 98.5 - 97.55 \right| + 2.4 \times 1.564445 = 4.7$$

4.7 < 15

and *AV* for R2 is:

$$AV = \left| 98.5 - 95.03 \right| + 2.4 \times 1.947739 = 8.14$$

8.14 < 15

Content uniformity calculted using variation of masses test for both generic drugs comlies with pharmacopoeial requirements, which menas that tablet have uniform individual content of active substance.

4.3. Friability

Friability (%) of film-coated tablets R1 and film-coated tablets R2 are shown in Table 2. Initial weight (x_1) of tablets R1 was 6.6994 g, while their final mass (x_2) was 6.6969 g. Initial weight (x_1) of tablets R2 was 6.7666 g, while their final mass (x_2) was 6.7660 g.

Friability (F) is calculated using formula (7):

$$F\,(\%) = \frac{(x_1 - x_2)}{x_1} \times 100 \qquad (7)$$

where:

F - friability (%),

x_1 - initial weight of tablets (g),

x_2 - final weight of tablets (g).

Obtained results comply with pharmacopoeial requirements [10].

4.4. Disintegration

Tablets R1 disintegrated within 239 seconds, while disintegration time for tablets R2 was 317 seconds (Table 2).

4.5. Hardness

Results of hardness test for tablets R1 and R2 are shown in Table 2. They are expressed as average force (N) needed to crush ten randomly selected tablets.

Table 2: Values of pharmaceutical-technological parameters of tablets R1 and R2

Parameters	R1	R2
Assay (%) ± SD RSD (%)	97.55 ± 1.56 1.60	95.03 ± 1.95 2.05
Average weight (mg) ± SD RSD (%)	267.55 ± 4.96 1.85	308.75 ± 2.67 0.86
Content uniformity (%) ± SD RSD (%)	97.55 ± 1.81 1.86	95.03 ± 0.82 0,86
Friability (%)	0.037	0.091
Disintegration time (seconds)	239	317
Hardness (N) ± SD RSD (%)	68.43 ± 1.86 26.69	159.82 ± 0.92 5.64

4.6. In vitro dissolution studies

Absorbances of previously prepared standard solutions of ranitidine (n=5) were measured by spectrophotemetrically using Cary Series UV-Vis Spectrophotometer, Agilent Technologies, Santa Clara, USA. Average absorbance of standard solution was 0.8398. This absorbance value was used to calculate % of released ranitidine. Percent of ranitidine release in tested samples was calculated using formula (3). Table 3 presents the average values of absorbance (A) of ranitidine, ranitidine release (%) from commercially available film-coated ranitidine tablets R1 and R2, standard deviation (%) and relative standard deviation (%) of released ranitidine from tablets R1 and R2. samples for testing were wtihdrawn from dissolution vessels after 5, 10, 15, 30 and 45 minutes.

Tabela 3: Average values of absorbances and ranitidine released from film coated tablets R1 and R2

R1					
Time	5 minutes	10 minutes	15 minutes	30 minutes	45 minutes
A ± SD (n=6)	0.1911 ± 0.019	0.4982 ± 0.028	0.8129 ± 0.011	0.8109 ± 0.017	0.8144 ± 0.012
Ranitidine release (%) ± SD (n=6)	22.80 ± 2.29	59.44 ± 3.31	97.01 ± 1.38	96.54 ± 1.98	97.17 ± 1.39
RSD (%)	10.05	5.09	1.41	2.05	1.43
R2					
Time	5 minutes	10 minutes	15 minutes	30 minutes	45 minutes
A ± SD (n=6)	0.3378 ± 0.037	0.7113 ± 0.063	0.7877 ± 0.035	0.8153 ± 0.032	0.8129 ± 0.031
Ranitidine release (%) ± SD (n=6)	40.29 ± 4.36	84.86 ± 7.51	93.99 ± 4.14	97.28 ± 3.82	96.99 ± 3.76
RSD (%)	9.88	8.07	4.01	3.58	3.53

In Fig. 4 represents *in vitro* dissolution profiles of ranitidine film coated tablets (R1 and R2).

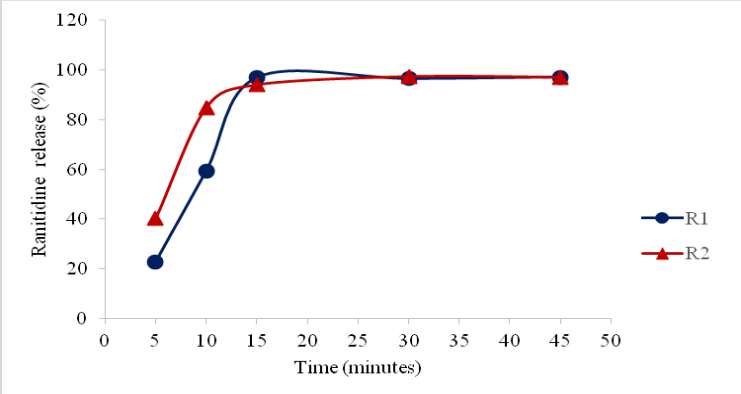


Fig. 4: Dissolution profiles of ranitidine film coated tablets

Obtained results comply with pharmacopoeial requirements.

V. DISCUSSION

Tested ranitidine film-coated tablets are distinguished by their pharmaceutical-technological properties. Different properties are a consequence of the application of various pharmaceutical and technological parameters in the course of the manufacturing process and due to the use of various excipients as constituent components of tested generic drugs. Core tablets R1 and core tablets R2, in addition to 150 mg of ranitidine hydrochloride, have three common excipients: hydrophobic colloidal silica as a glidant, microcrystalline cellulose as a diluent and magnesium stearate as a lubricant. Other ingredients vary: R1 tablets contain croscarmellose sodium as disintegrating agents, while R2 tablets contains povidone (povidone may also have the role of binding agent) and corn starch (which may have the role of the diluent and binder). Additionally, the core tablets R2 further contain 70.7 mg of lactose in the form of monohydrate (lactose monohydrate) which acts as diluent and binder, as well as the talc which has the role of a lubricant and glidant [12]. Side effects of excipients may be manifested to all or only to some patients and may or may not be expressed, depending on dose [21]. R2 tablets contain lactose monohydrate and special caution is required in the administration of this pharmaceutical form to patients who showed intolerance to lactose. The quantity of lactose used as the excipient in this tablet formulation is significantly lower than in the standard portions of milk products used in the nutrition [28]. However, in a randomized, double-blind, cross-over study, which was conducted Monalto et al. [28], [29] patients who were considered to be very intolerant to lactose, attributed the side effects in the gastrointestinal tract (GIT) to lactose even when it was not an integral part of the preparation which used. Each person has an individual tolerance to lactose (from less sensitive to the hypersensitive), so that it is difficult to determine whether a small amount of lactose used in formulation of drugs may cause side effects in intolerant individuals [28]. There are differences in the composition of the film coat of tested tablets. The mutual ingredients are hypromellose as a film-forming polymer, talc as a lubricant, and an inorganic color titanium dioxide. In addition, the film coating of tablets R1 contains triacetin as a plasticizer, ethanol and methylene chloride as a solubilizing agents. Apart from titanium dioxide, film coating of tablets R1 contains iron oxide as coloring agent, macrogol 400 as plasticizer and carnauba wax which gives gloss to a tablet without mechanical treatment [12]. Based on the constituent components tablets R1 have simpler formulation than tablets R2.

Having in mind that ranitidine hydrochloride is highly hygroscopic, tablets containing ranitidine hydrochloride must be protected from moisture [9]. The method for manufacturing these tablets exclude the presence of water, and the final product is coated film coating. Ranitidine is susceptible to photodegradation. In the presence of light its hygroscopicity increases. Chemical instability of ranitidine in tested tablets was resolved by coating them with opaque film coating and packaging them in opaque packaging.

All tested tablets were subjected to visual inspection and it was determined that there weren't any damage, discoloration, or changes in the shape of tablets. It could be observed visually that the tablets R2 were darker than tablets R1, ie they have a more pronounced pale brown-yellowish color. The dark color is derived from the use of the iron oxide yellow pigment (as addition to titanium dioxyde) in the film coating of tablets R2, in contrast to the tablets R1 in which manufacturer specified that film formulation contains only titanium dioxide, a white pigment.

Verifying the suitability parameters of the chromatographic system (asymmetry, the column efficiency, relative standard deviation), it was found that system was suitable and that repeatability was satisfactory (RSD value was 0.22% in relation to the permitted deviation of 2%). Assay of ranitidine tablets R1 (97.55%) was somewhat higher than the assay of the ranitidine tablets R2 (95.03%) (Table 2), while RSD was higher for the tablets R2 (2.05% for R2; 1.60% for R1). The differences may be due to uneven distribution of ranitidine during the mixing proces [29]. If there is a segregation of the active substance mass can remain uniform, but the content in this case varies [18]. From the data obtained by determining the average weight of the tablets, individually determined content of ranitidine and ranitidine assay it was observed that there was no segregation of the active substance, as the results complied with the requirements of USP38-NP33. Variation in the content may result in a variation in disintegration and the dissolution rate of the active substance from the tablet [18]. According to USP38-NF33 requirements, ranitidine tablets contain not less than 90% and not more than 110% of ranitidine hydrochloride of the declared content ranitidine. Based on these results it was found that tablets R1 and tablets R2 correspond to the requirements of USP38-NP33. Mass variation may be due to the different specific density (poor flowability of the powder/granulate), an non-uniform particle size distribution of the tablet composition, the lack of the lubricant, or glidant, or their inadequate mixing [18]. The average tablet weight R1 (267.55 mg) was less than the average weight of the tablets R2 (308.75 mg) (Table 2), whereas the RSD (%) of tablets R1 greater than the RSD (%) of tablets R2 (RSD 1.85% for R1; 0.86% for R2). Determined individual content based on a predetermined content of ranitidine in the tablets also showed a difference. Tablets R1 have a higher value of ranitidine content (97.55%) than tablets R2 (95.03%) (Table 2). After calculating accepted value (*AV*) of tested ten dosage units, obtained values meet Ph. Eur. Requirements (*AV* of tablets R1 and tablets R2 was of less than 15).

Friability test is performed in order to test the strength of tablets after their exposure to external factors during manufacture, handling, packaging and usage [31], [32]. After performing the test, maximum weight loss must not be greater than 1% [10], [26]. In this case, the tablets R1 and tablets R2 showed no weight loss, and therefore have met the requirements of Pharmacopoeia (Table 2).

After the disintegration test of both the generic ranitidine tablets, it was found that the tablets R1 (239 sec) disintegrated faster than tablets R2 (317 sec) (Table 2). The differences in the disintegration time between the tablets can be a result of various disintegrants used in manufacturing of tested tablets. Tablets R1 contained croscarmellose sodium, known as superdezintegrator, in contrast to the tablet R2 which contained corn starch and povidone as disintegrants.

Hardness testing of tablets is performed in order to, under different conditions, evaluate tablet's resistance to crush under the physical factors during the production, packaging, transportation and handling before use. This way, the information about the force needed to crush the tablet can be obtained [32]. In order to obtain a satisfactory tablet hardness minimum force required is 4 kg [13], [25]. Tablet hardness depends on the distance between the top and bottom piston during compression and the applied pressure, duration of the compression, weight of the mixture used for tabletting, the concentration of binding agent [27]. Based on the results of hardness testing of tablets R1 and tablets R2, it was observed that tablets R2 are harder 2.34 times more than tablets R1 (Table 2). The differences in hardness between tested tablets may be the result of using different excipients and materials in film coatings. A higher value of hardness of the tablets R2 affects disintegration time which is longer than the disintegration time of tablets R1 (Table 2). Excessive amounts of disintegrator can reduce the hardness of tablets [18]. Decreased hardness of tablets R1 may be the result of using „superdisintegrant", croscarmellose sodium. The compression force applied during the manufacturing process of tablets has influence on final tablet hardness. For less hard tablets (tablets R1) is expected to have decreased disintegration time. This is important in *in vivo* conditions, since this is the parameter that affects the disintegration of tablets after ingestion. The relative standard deviation of hardness of tablets R2 is 5.62%, which does not exceed required 6% („in-house" Amsal Company). Based on the values of relative standard deviation of tablets R1 (26.69%) it has been observed that there are great variations in the hardnesses of the individual tablets (Table 2).

In vitro dissolution rate of the active ingredients from solid dosage forms is one of the most important tests for testing and verifing the quality of pharmaceutical forms, since drug efficacy depends on the rate of dissolution of the active substance in the GI tract prior to absorption into the systemic circulation [33]. According to USP38-NF33, it is required that not less than 80% of the declared content of ranitidine need is dissolved in 45 minutes. By analyzing the test results, the dissolution rate of the active substance, it has been found that after 45 minutes tablets R1 as well as the tablets R2 released approximately the same amount of ranitidine in relation to the declared content (Table 2), therefore both pharmaceutical equivalent of ranitidine tablets meet the pharmacopoeial requirements [11]. This confirmed quality and efficacy of tested tablets.

VI. CONCLUSIONS

After performing the pharmaceutical-technological testing of ranitidine film coated tablets, it is observed that tablets R1 and tablets R2 comply with pharmacopoeial requirements, and the results of conducted tests (tablets mass variation, ranitidine assay, friability, disintegration time) are within specified limits. Although tablets R1 contain only one substance as a disintegrant (croscarmellose sodium), and tablets R2 contain two disintegrants (corn starch and povidone), tablets R1 disintegrated more rapidly than tablets R2, since croscarmellose is superdisintegrator. Tablets R2 are harder than tablets R1, and it is one of the reasons why the tablets R2 disintegrate more slowly, although this did not affect the dissolution rate of the active substance. Considerable variations in the hardnesses of the individual tablets R1 compared to the values obtained upon testing tablet R2 hardness were observed. Tested pharmaceutical equivalents may be considered effective, bioequivalent after conduction of *in vitro* dissolution tests. Higher hardness and slower disintegration of tablets R2 did not affect the dissolution rates of these tablets of ranitidine. Tested tablets of both manufacturers comply with all European and U.S. Pharmacopoeial requirements. Given that the tablets R2 contain lactose monohydrate pharmacist has obligation, prior to use of the tablets R2, to warn the patient to their use, especially if doctor stated that there is intolerance to certain sugars in patients in question.

REFERENCES

[1]. L. Shargel, I. Kanfer, Introduction to generic drug product development, in L. Shargel, I. Kanfer (Eds.), *Generic drug product development: solid oral dosage forms* (New York: Marcel Dekker, 2005) 1-16.

[2]. S. Mastan, T.B. Latha, and S. Ajay, The basic regulatory considerations and prospects for conducting bioavailability/bioequivalence (BA/BE) studies-an overview, *Journal of Comparative Effectiveness Research, 2011 (1),* 2011, 1-25.

[3]. A.H. Kibbe, Generic drugs and generic equivalency, in J. Swarbrick (Ed.), *Encyclopedia of pharmaceutical technology*, 3 (New York: Informa Healthcare, 2007) 1891-1896.
[4]. S. Dunne, B. Shannon, C. Dunne, and W. Cullen, A review of the differences and similarities between generic drugs and their originator counterparts, including economic benefits associated with usage of generic medicines, using Ireland as a case study, *BMC Pharmacology and Toxicology, 14(1),* 2013, 1-19.
[5]. A.W. Hoogerwerf, J.P. Pasricha, Pharmacotherapy of gastric acidity, peptic ulcers, and gastroesophageal reflux disease, in L.L. Brunton, S.J. Lazo, L.K. Parker (Eds.), *Goodman and Gilman's the pharmacological basis of therapeutics*, 11 (New York: McGraw-Hill, 2006) 967-981.
[6]. H. Kortejärvi, M. Yliperttula, B.J. Dressman, H.E. Junginger, K.K. Midha, V.P. Shah, and D.M. Barends, Biowaiver monographs for immediate release solid oral dosage forms: ranitidine hydrochloride, *Journal of Pharmaceutical Science, 94(8),* 2005, 1617-1625.
[7]. V.P. Shah, and G.L. Amidon, G.L. Amidon, H. Lennernas, V.P. Shah, and J.R. Crison. A theoretical basis for a biopharmaceutic drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability, Pharm Res 12, 413-420, 1995-backstory of BCS, *Journal of the American Association of Pharmaceutical Scientists, 16(5),* 2014, 894-898.
[8]. F.A.S.Júnior, I.S. Barbosa, V.L. Santos, R.L. Silva, and E.C. Junior, Test of dissolution and comparison of *in vitro* dissolution profiles of coated ranitidine tablets marketed in Bahia, Brazil, *Brazilian Journal of Pharmaceutical Sciences, 50(1),* 2014, 83-89.
[9]. P. Patel, A. Dave, A. Vasava, and P. Patel, Formulation and characterization of sustained release dosage form of moisture sensitive drug, *International Journal of Pharmaceutical Investigation, 5(2), 2015*, 92-100.
[10]. European Directorate for the Quality of Medicines and Healthcare, *European Pharmacopoeia, 8th Edition*, 2014, 285-359, 810, 3154-3155.
[11]. United States Pharmacopeial Convention, *The United States Pharmacopeia, 38th Edition*, 2015, 5141, 5189.
[12]. R.C. Rowe, J.P. Sheskey, E.M. Quinn, *Handbook of pharmaceutical excipients* (Pharmaceutical Press, 2009).
[13]. M. Turkoglu, A. Sakr, Tablet dosage forms, in A.T. Florence, J. Siepmann (Eds.), *Modern pharmaceutics*, 1 (New York: Informa Healthcare, 2009) 482-497.
[14]. A.A. Sakr, K.F. Alanazi, Oral solid dosage forms, in L. Felton (Ed.), *Remington: essentials of pharmaceutics*, 1 (London: Pharmaceutical Press, 2013) 581-610.
[15]. J. Shah, M. Tomar, A.K. Singh, and A.R. Sinha, Study of microcrystalline cellulose as a substitute of magnesium stearate towards functionality of lubricant in aspirin formulation, *International Journal of Development Research, 7(10),* 2017, 15879-15884.
[16]. G.C. Cole, Introduction and overview of pharmaceutical coating, in G. Cole, J. Hogan, M. Aulton (Eds.), *Pharmaceutical Coating Technology*, (London: Taylor and Francis, 2002) 1-5.
[17]. J.E. Hogan, Film-coating materials and their properties, in G. Cole, J. Hogan, M. Aulton (Eds.), *Pharmaceutical Coating Technology*, (London: Taylor and Francis, 2002) 6-52.
[18]. P. Davis, Čvrsti farmaceutski oblici, in M. Gibson M (Ed.), *Preformulacija i formulacija lekova*, 1 (Beograd: Univerzitet u Beogradu, 2012) 389-450.
[19]. S.C. Porter, Coating of pharmaceutical dosage forms, in L. Felton (Ed.), *Remington: essentials of pharmaceutics*, 1 (London: Pharmaceutical Press, 2013) 611-621.
[20]. R.Q. Cao,W.Y. Choi,H.J. Cui, and B.J. Lee, Effect of solvents on physical properties and release characteristics of monolithic hydroxypropylmethylcellulose matrix granules and tablets, *Archives of Pharmacal Research, 28(4),* 2005, 493-501.
[21]. American Academy of Pediatrics: Committee on Drugs, "Inactive" ingredients in pharmaceutical products: update (subject review), *Pediatrics, 99 (2),* 1997, 268-278.
[22]. P.J. Crowley, L.G. Martini, Excipients for pharmaceutical dosage forms, in J. Swarbrick (Ed.), *Encyclopedia of pharmaceutical technology*, 3 (New York: Informa Healthcare, 2007) 1609-1619.
[23]. A. Roy, A. Ghosh, S. Datta, S. Das, P. Mohanraj, J. Deb, and M.E. R. Bhanoji, Effects of plasticizers and surfactants on the film forming properties of hydroxypropyl methylcellulose for the coating of diclofenac sodium tablets, *Saudi Pharmaceutical Journal, 17(3),* 2009, 233-241.
[24]. D.A. Miller, W.J. McGinity, Aqueous polymeric film coating, in L.L. Ausburger, W.S. Hoag (Eds.), *Pharmaceutical dosage forms: tablets*, 3 (New York: Informa Healthcare, 2008) 399-437.
[25]. S.A. Qureshi, Tablet testing, in J. Swarbrick (Ed.), *Encyclopedia of pharmaceutical technology*, 3 (New York: Informa Healthcare, 2007) 3707-3716.
[26]. S. Porter, G. Sackett, L. Liu, Development, optimization, and scale-up of process parameters: pan coating, in Y. Qiu, Y. Qiu (Eds.), *Developing solid oral dosage forms*, 1 (London: Academic Press, 2009) 761-805.

[27]. K.A. Dash, Solid dosage forms, in K.A. Dash (Ed.), *Pharmaceutics: basic principles and application to pharmacy practice*, (Sand Diego: Academic Press, 2014) 161-180.
[28]. M. Monalto, A. Gallo, L. Santoro, F. D´onofrio, V. Curigliano, M. Covino, G. Cammarota, A. Grieco, A. Gasbarrini, and G. Gasbarrini, Low-dose lactose drugs neither increases breath hydrogen excretion nor causes gastrointestinal symptoms, *Alimentary Pharmacology and Therapeutics*, *28(8)*, 2008, 1003-1012.
[29]. T.H. Vesa, A.R. Korpela, and T. Sahi, Tolerance to small amounts of lactose in lactose maldigesters, *The American Journal of Clinical Nutrition*, *64(2)*,1996, 197-201.
[30]. P. Thapa, N.M. Barakoti, A. Khan, B. Kafle, P. Mahara, and R.K. Thapa, A comparison of the technical quality of Nepalese and Indian ranitidine hydrochloride tablets available in Pokhara, *World Journal of Pharmacy and Pharmaceutical Sciences*, *3(2)*, 2014, 1855-1866.
[31]. G. Alderborn, G. Frenning, Mechanical strength of tablets, in L.L. Augsburger, S.W. Hoag (Eds.), *Pharmaceutical dosage forms: tablets*, 3 (New York: Informa Healthcare, 2008) 207-236.
[32]. T. Rhines, Non-chromatographic methods to support stability purposes, in K. Huynh-Ba (Ed.), *Handbook of stability testing in pharnmaceutical development*, (New York: Springer Science-Business Media, 2009) 201-222.
[33]. U.S. Food and Drug Administration/Center for Drug Evaluation and Research, *Guidance for industry: Dissolution testing of immediate release solid orale dosage forms*, Rockville MD, 2007.

IOSR Journal of Pharmacy (IOSR-PHR) is UGC approved Journal with Sl. No. 5012

Jasmina Hadžiabdić "Comparison of Pharmaceutical-Technological Properties of Commercially Available Ranitidine Tablets. ”IOSR Journal of Pharmacy (IOSRPHR), vol. 8, no. 3, 2018, pp. 19-31