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Biopharmacotechnical and physical properties of solid pharmaceutical forms containing rutin commercially acquired in Juiz de Fora city, Brazil

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ABSTRACT. Rutin is a flavonoid used in clinical practice to treat capillary fragility and prevent bleeding due to its wide variety of pharmacological actions, including antioxidant, anti-inflammatory, anti-allergic, antiproliferative, and anticarcinogenic activities. In this study, the biopharmacotechnical and physical properties of film-coated tablets containing rutin marketed in drugstores were evaluated. Using samples from three batches called A, B and C, we determined the average weight, disintegration time, hardness, content and dissolution profile, and kinetics of the tablets. The samples demonstrated average weight of 457.45 ± 12.32 to 449.15 ± 8.95 mg; disintegration time, 30.17 ± 2.14 to 15.17 ± 2.14 min; hardness, 1.92 ± 0.55 to 1.69 ± 0.36 Kgf; and rutin content, 18.34 ± 1.21 to 15.66 ± 1.29 mg. After 90 min, the dissolution profile showed 52.65, 41.80, and 79.2% for A, B, and C, respectively. The results imply that the non-conformities of the tested products can significantly compromise the drug's therapeutic efficacy.

Keywords: rutin; quality control; physical-chemical characterization; dissolution profile; phytomedicines.

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Introduction

Flavonoids have attracted global attention of researchers for their great antioxidant potential and pharmacological properties, such as vasodilator, anti-inflammatory, anti-allergic, antiviral, and immune system-stimulating effects (Rana & Gulliya, 2019). Rutin (Figure 1), for example, is a glycosidic flavonol derived from its aglycon form quercetin. The formation of its structure occurs from a glycosidic bond at position 3 of the central pyran ring of a disaccharide (rhamnose + glucose) (Magar & Sohng, 2019). This flavonoid has been used to treat pathologies related to capillary fragility by preventing bleeding (Prasad & Prasad, 2019; Ganeshpurkar & Saluja, 2017). The compound with conspicuous antioxidant effects reduces low-density lipoprotein (LDL) oxidation, diabetes, inflammatory and thrombotic processes, and inhibits endothelial cell apoptosis (Choy et al., 2019; Ganeshpurkar & Saluja, 2017; Habtemariam & Lentini, 2015; Prasad & Prasad, 2019). In addition, rutin decreases the levels of hepatic cholesterol, triacylglycerol, and enzymes (Hsu, Wu, Huang, & Yen, 2009; Acquaviva et al., 2009) and protects oxidizing of enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase, which protect from cataract development (Isai, Sakthivel, Ramesh, Thomas, & Geraldine, 2009). The antioxidant effect of rutin makes it a suitable candidate to treat loss of spatial memory accompanied by damage to pyramidal neurons in the hippocampus (Prasad & Prasad, 2019). Moreover, this compound is active against septic arthritis caused by *Candida albicans* and inhibits the production of nitric oxide from the proliferation of macrophages and T cells (Ganeshpurkar & Saluja, 2017). It has a relaxing effect on the gastric muscle and exerts its anti-asthmatic effect by inhibiting histamine production and leukocyte recruitment, mainly neutrophils and eosinophils in the lungs (Prasad & Prasad, 2019).

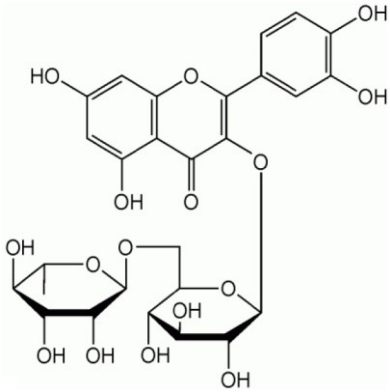

Figure 1. Chemical structure of rutin.

Because of the low solubility of rutin in the aqueous media and in the human body, the lyophilized nanocrystalline tablet form shows 100% dissolution after 30 min, whereas the microcrystalline form and the commercialized tablets show 71% and only 55% dissolution after 30 min (Mauludin, Muller, & Keck, 2009). These data reveal that, in addition to the structural characteristics, the dissolution and absorption characteristics of this compound depend on the particle type used in the phytopharmaceutical formulation, which can cause a slow and irregular absorption in the gastrointestinal tract. Therefore, the incorporation of excipients, such as hydroxypropylmethylcellulose and sodium carboxymethylcellulose, into solid formulations containing rutin helps to improve the drug solubility in the body (Tambosi et al., 2018). On the contrary, biopharmacotechnical analyses are essential to determine the quality profiles of herbal product, because they are associated with the safety and efficacy of the drugs (Moreira, Teixeira, Monteiro, De-Oliveira, & Paumgartten, 2014). Thus, the biopharmacotechnical determinants, such as physicochemical parameters, manufacturing process, and physical characteristics, can decisively influence the drug bioavailability (Markl & Zeitler, 2017). Moreover, it has been highlighted that the absorption of a drug from solid pharmaceutical form significantly depends on the ingredients of its formulation. The ingredients can enable greater release and dissolution of the drug in the physiological environment and permeability through biological membranes to reach the target site and trigger the pharmacological effects (Markl & Zeitler, 2017; Li et al., 2019).

Any abnormality in the drug release process can have a hazardous effect on the treatment, leading to therapeutic inefficacy if the drug exceeds the release time to be absorbed or toxic effects if the drug is released and absorbed quickly. The release process of drugs manufactured for oral administration is a crucial factor for later absorption. This process considers two stages, disintegration and dissolution, which in turn are associated with the quality of processing and its excipients, such as particle size and shape, quantity and characteristics of disintegrating agents, aggregates and lubricants, mixing time, and compressive force (Markl & Zeitler, 2017). Therefore, inadequacies in the production of the pharmaceutical form will directly reflect on the drug bioavailability, affecting the speed and amount of drug absorption (Li et al., 2019).

Considering the importance of phytomedicines in treatment of various health concerns, we evaluated the physical and biopharmacotechnical properties of three batches of tablets in a phytotherapic formulation containing rutin. We analyzed the content, average weight, hardness, disintegration time, and dissolution profile to investigate quality deviations.

Material and methods

Samples

The batches of film-coated tablets containing rutin were obtained from drugstores located in Juiz de Fora city, Minas Gerais state, Brazil. These batches were called A, B, and C, and they were within their expiration date.

Composition of samples

The batches of tablet containing rutin had the following composition: dry extract of horse chestnut (*Aesculus hippocastanum* L.), 10 mg; dry extract of sarsaparilla (*Smilax papyracea* L.), 40 mg; rutin, 20 mg; dry extract of wormwood (*Polygonum acre* L.), 10 mg; excipient q.s.p. 1 tablet. Corn starch, calcium

carbonate, magnesium stearate, baby powder, sugar, gum Arabic, and erythrosine were the excipients described in the formulation.

Identification reactions

As other flavonoids, rutin was investigated through the identification procedures: $AlCl_3$, H_3BO_3, NaOH, and Shinoda reactions (Deshmukh & Theng, 2018).

Determination of average weight

Twenty tablets from each batch were weighed individually, then their average weight was determined using the AY 220 analytical balance (Shimadzu®). According to the average weight, the limit of variation specified was ±5.0%, because the film-coated tablets have a weight >300 mg (Agência Nacional de Vigilância Sanitária [ANVISA], 2019). Next, the standard deviation and coefficient of variation (CV) were calculated.

Quantification of the rutin contents

The quantification of the rutin contents was performed spectrophotometrically (Ramos, Bezerra, Ferreira, & Soares, 2017). Rutin® (⩾95%, Sigma-Aldrich, 2–30 μg mL^{-1}) was used as a standard to obtain the calibration line. The data were subjected to linear regression analysis using the least squares method, followed by the calculation of line equation and the determination coefficient (r^2). For this test, an absorption spectrum was obtained to define the wavelength to be used for rutin (10 μg mL^{-1}).

In this experiment, each tablet was individually used to prepare the test solution, totaling to 10 tablets (n = 10) per batch (A, B, and C). Next, the tablet was crushed in a porcelain gral and the powder was transferred to a beaker to which 20 mL of ethyl alcohol (P.A.) was added. After complete removal of the sample with the solvent, the alcoholic solution was filtered into a 100 mL flask, completing the volume of the container. In test tubes, the reaction was carried out using sample (0.4 mL), glacial acetic acid (0.12 mL), pyridine ethanol (2:8, 2 mL), and 8% aluminum chloride in ethanol (0.5 mL), making up to 5 mL with distilled water. The sample analysis was performed in triplicate at 418 nm using a spectrophotometer (Biochrom, mod. Libra S12).

Uniformity method of content

For this test, 10 units from each batch were individually analyzed and submitted to the same process of sample preparation as mentioned in the "Quantification of the rutin content" section. Finally, the uniformity was determined as a percentage of rutin (ANVISA, 2019).

Hardness

To assess the resistance of the tablet against ruptures caused by transport, storage, among others, 10 tablets from each batch were subjected to the action of a device (Durometer, mod. 298 DGP, Nova Ética) that quantified the force required to crush a single tablet. The minimum acceptable force was 30 N (3 Kgf) (ANVISA, 2019).

Disintegration time

Six tablets from each batch were subjected to the action of a disintegrator (Erweka mod. ZT3) containing distilled water kept at 37 ± 1ºC as the immersion liquid. The time necessary for each tablet to disintegrate was noted, with the maximum limit being 45 min for sugar-coated tablets (ANVISA, 2019). Finally, the average disintegration time, standard deviation, and CV were calculated.

Dissolution profile

The dissolution profile was assessed according to the Brazilian Pharmacopoeia (ANVISA, 2019). Three units (tablets) from each batch were subjected to the dissolution test for 90 min. The dissolution equipment (Hanson Research SR6 Dissolution Bath) was used under the following conditions: apparatus 2 (shovel), agitation of the medium at 100 rpm, temperature 37 ± 0.5ºC, and medium of borate buffer (pH 8.78). During this period, aliquots (10 mL) were removed at 5, 20, 30, 40, 60, and 90 min. The rutin content was spectrophotometrically quantified each time at 418 nm as mentioned in the "Quantification of rutin content" section.

The dissolution profile was calculated as dissolution efficiency (DE) from the percent dissolved *versus* time curves (dissolution profile). The area under the curve (AUC) and the total area of the graph were obtained, and DE was calculated and expressed as a percentage by the ratio between these two parameters (Simionato, Petrone, Baldut, Bonafede & Segall, 2018). Kinetic models (zero-order, first-order, and Higuchi) were used to study the mathematical expression that best suited the dissolution process according to the equations provided in Figure 2 (Wójcik-Pastuszka et al., 2019). We obtained the line equation and the determination coefficient by using linear regression, least squares method.

Model	Equation
Zero-order	$Q_0 = Q_t + K_0.t$
First-order	$ln\ Q_t = ln\ Q_0 + K_1.t$
Higuchi	$Qt = K_H.t^{½}$

Figure 2. Mathematical models of dissolution kinetics. Q_t = quantity of drug released at time t; Q_0 = initial amount of drug in solution; K_0, K_1, K_H = constants of each model; t = time.

Statistical analysis

The results are expressed as mean ± standard error of mean (S.E.M.). Analysis of variance (ANOVA) followed by Tukey's honest significant difference (HSD) test was used to compare the means by measuring the degree of significance to $p < 0.05$. In addition, standard deviation and CV were determined using the Graph Pad Prism® software (version 5.0, Graph Pad Software, Inc.).

Results and discussion

The results revealed the presence of flavonol class following reactions with $AlCl_3$, H_3BO_3, NaOH, and Shinoda, indicating rutin in the samples of tablets.

Concerning average weight, batches A (453.50 ± 4.16 mg), B (455.10 ± 4.98 mg), and C (450.50 ± 3.64 mg) were statistically equal ($p < 0.05$) (Figure 3). However, although there was a variation, the weight of each tablet was within the specifications (ANVISA, 2019). Batch B demonstrated greater weight fluctuation between the units with CV of 2.69%, whereas batches A and C demonstrated CVs of 2.30 and 1.99%, respectively.

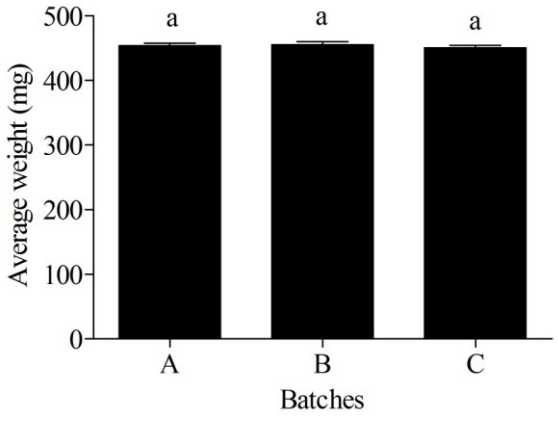

Figure 3. Average weight of 20 tablets from batches A, B, and C. Same letters, the means do not differ after ANOVA followed by the Tukey test ($p < 0.05$).

To quantify the rutin content, a spectrophotometric analysis was performed between wavelengths 382 and 520 nm with a rutin standard solution (10 µg/mL) to obtain the absorption spectrum (Figure 4A). After defining the peak of maximum absorption (λ = 418 nm), a calibration line (Figure 4B) was established using rutin (2–30 µg/mL). The data was subjected to linear regression analysis to produce the equation of the line $y = 0.02251x + 0.009323$ and the coefficient of determination $r^2 = 0.9993$ (Figure 3B).

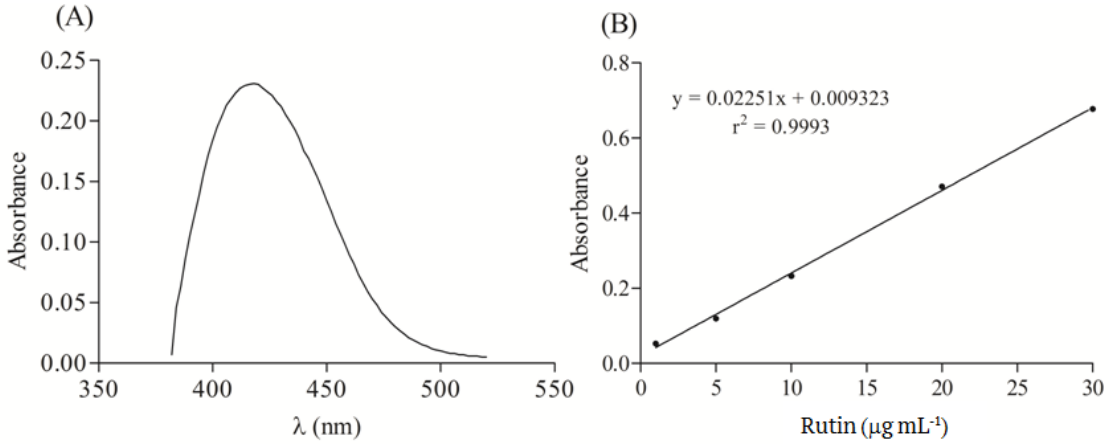

Figure 4. Absorption spectrum (A) and rutin calibration curve (B).

From the line equation (Figure 4B), batches A, B, and C, on average, revealed 18.03 ± 1.17, 17.50 ± 0.85, and 15.42 ± 1.24 mg of rutin, respectively (Figure 5A). These values are lower than the quantity described on the packaging, which reported the presence of 20 mg of rutin. Based on this parameter, on average, batches A, B, and C showed 94.88, 92.10, and 81.14% of rutin, respectively (Figure 6A). Because the commercialized rutin is 95% pure, ~19 mg of pure rutin must be present in each tablet. However, considering the lower and upper limits of 10% (17.10 and 20.9 mg, respectively), the tablets (batches A and B) are in accordance with the specifications (purity > 90%) (Figures 5B and 6B). For instance, a study on tablets containing *Ginkgo biloba* presented a rutin content of 97.90–98.40%, in accordance with the values recommended in the literature (Dubber & Kanfer, 2004). In addition, the dosages of the tablet from batches A, B, and C revealed standard deviations of 1.17, 0.91, and 1.24 and CVs of 6.49, 5.19, and 8.04%, respectively. Our results suggest that the decrease in rutin content in the tablets could be attributed to the degradation by physical or chemical agents related to the pharmaceutical formulation (Bhattarai & Gupta, 2016; Costa et al., 2011).

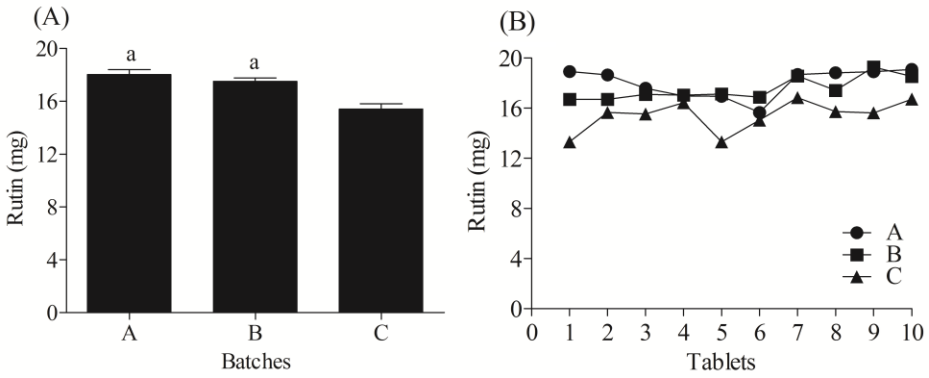

Figure 5. Average contents of rutin (mg) in batches A, B, and C (n = 10) and rutin content (mg) in each tablet of the batches. Same letters, the means do not differ after ANOVA followed by the Tukey test ($p < 0.05$).

Considering the purity degree of rutin at 95%, on average, the uniformity of content (Figures 6A and B) of batches A (94.88 ± 6.16%) and B (92.10 ± 4.45%) was significantly equal ($p < 0.05$), but differed from batch C (81.14 ± 6.55%). Batch A, on average, had the rutin levels according to the established specifications. However, uniformity revealed distinct CVs and outside the parameters recommended by the Brazilian Pharmacopoeia (ANVISA, 2019), which imposes a maximum limit of 6%. It is worth mentioning that batch B showed a CV of 1.15%, which complies with the legislation.

The hardness test (Figures 7A and B) revealed that the average values of A (1.92 Kgf), B (1.69 Kgf), and C (1.87 Kgf) did not differ from each other ($p < 0.05$) (Figure 7A). Thus, on average, none of the batches met the requirements of the Brazilian Pharmacopoeia (ANVISA, 2019), which recommends a minimum hardness value of 3 Kgf. However, one tablet in batch A had a hardness of 3.40 Kgf (Figure 7B). The lack of uniformity in the hardness test may be related to conditions such as transport, storage, and handling, which can induce changes in the structure of solid drugs (Kumar, Singh, Antil, & Kumar, 2016). Typically, a film-coated tablet must have a higher degree of hardness than conventional tablets, because they are affected during the

dredging process with more intense physical and mechanical shocks (Kumar et al., 2016; Dasari, Kala, & Nadendla, 2017). In addition, batches A, B, and C showed CVs > 21%, indicating a lack of homogeneity between the units. These results also allow us to infer that lower hardness values presented by formula C did not necessarily imply shorter disintegration times (Kumar et al., 2016; Dasari et al., 2017).

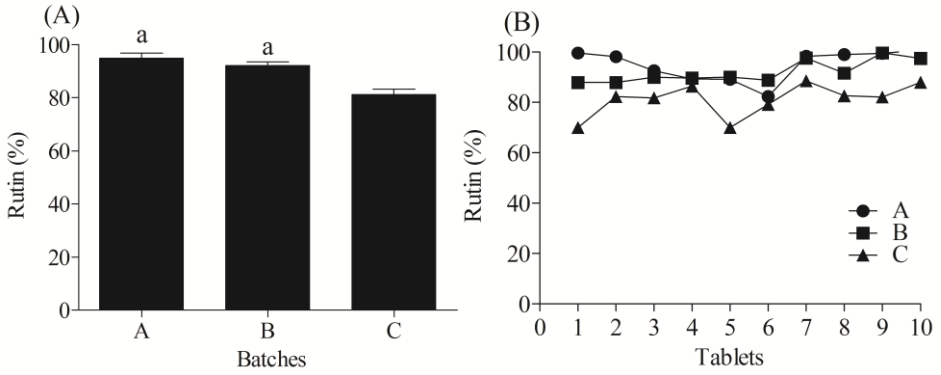

Figure 6. Average percentage of rutin in batches A, B, and C (A) and percentage of rutin per tablet in batches (B). Same letters, the means do not differ after ANOVA followed by Tukey test ($p < 0.05$).

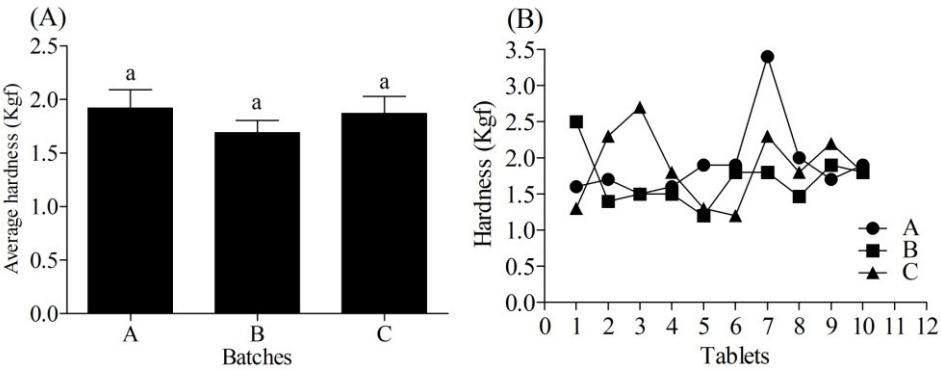

Figure 7. Average hardness (Kgf) of batches A, B, and C (A) and hardness of each tablet in batches (B). Same letters, the means do not differ after ANOVA followed by Tukey test ($p < 0.05$).

The disintegration test (Figures 8A and B) revealed that the tablets of all the batches satisfactorily met the requirements of the Brazilian Pharmacopoeia (ANVISA, 2019) with disintegration times of <45 min (A = 28.17 min; B = 30.17 min; C = 15.17 min). However, on average, batch C demonstrated shorter disintegration time than batches A and B ($p < 0.05$), which can be important for the dissolution and absorption of the drug. The CVs of batches A and C were ~14%, whereas batch B presented a CV of ~7%, indicating a lack of homogeneity between the batches and units (Markl & Zeitler, 2017). This fact was reflected in the dissolution profile and, consequently, in the absorption process, as well as in the hardness of the tablets (Quodbach & Kleinebudde, 2015).

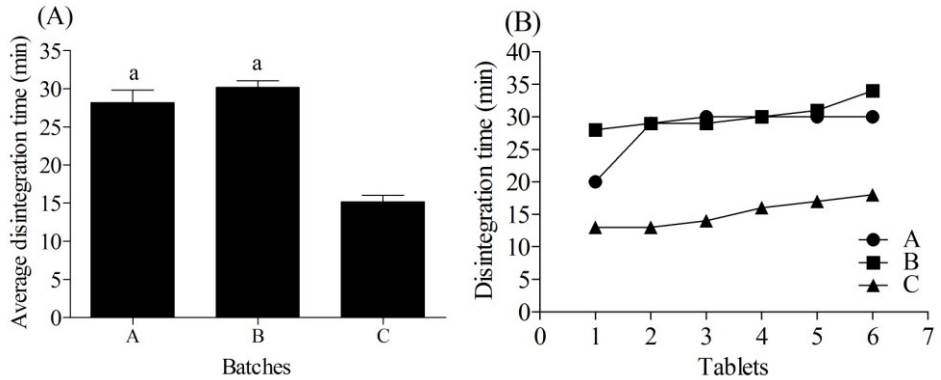

Figure 8. Average disintegration time for batches A, B, and C (A) and disintegration time for tablets of each batch (B). Same letters, the means do not differ after ANOVA followed by Tukey test ($p < 0.05$).

The dissolution profile of the rutin tablets analyzed from 5 to 90 min is shown in Figure 9A. After 90 min, only batch C released the active ingredient being >70% (79.2%), considered as the minimum value (Mitrevska et al., 2019). Batches A and B did not reach this value and were not in accordance with the reference value. Thus, after 90 min, the percentage of the released rutin was as follows: A = 52.65 ± 0.10%, B = 41.80 ± 0.10%, and C = 79.20 ± 0.10% (Figure 9B). During this analysis, we observed that the tablets from batches A and B did not disintegrate or completely dissolve, presenting themselves as a dense beige mass, where there was possibly an appreciable amount of rutin. In this case, it is assumed that the ingredients of the formulation did not satisfactorily meet the performance of the pharmaceutical form, probably due to the lack of the disintegrating agent (Markl & Zeitler, 2017; Bhattarai & Gupta, 2016). Therefore, there is a need to reassess the composition of the pharmaceutical form.

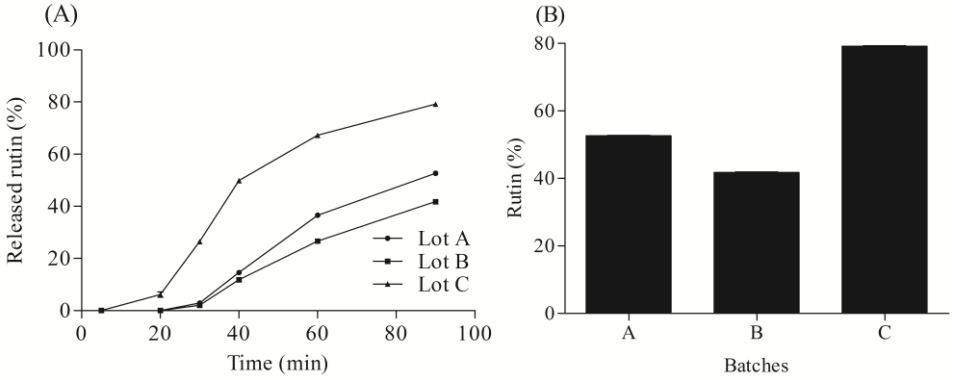

Figure 9. Tablet dissolution profile for batches A, B, and C (A) and dissolution of each batch after 90 min (B).

To evaluate the dissolution profiles of the three batches of tablets, kinetic models (zero-order, first-order, and Higuchi) were used to study the mathematical expression that best suited the dissolution process after linear regression. We observed that batches A and C followed the kinetic process according to the first-order model (Figures 10A and C), which is characteristic of the quick release pharmaceutical forms and the results of a destructive process from disintegration and dissolution. However, the amount of undissolved rutin is less in batch A compared to batch C, which releases more slowly. Batch B was closer to the Higuchi model (Figure 10B), in which the drug is released predominantly by diffusion. Regarding the DE that represents the area under the curve of the dissolution profiles, it was found that batch C revealed a DE of 54.35%, whereas batches A and B revealed a DE of 26.93 and 20.56%, respectively, indicating that batch C had better performance.

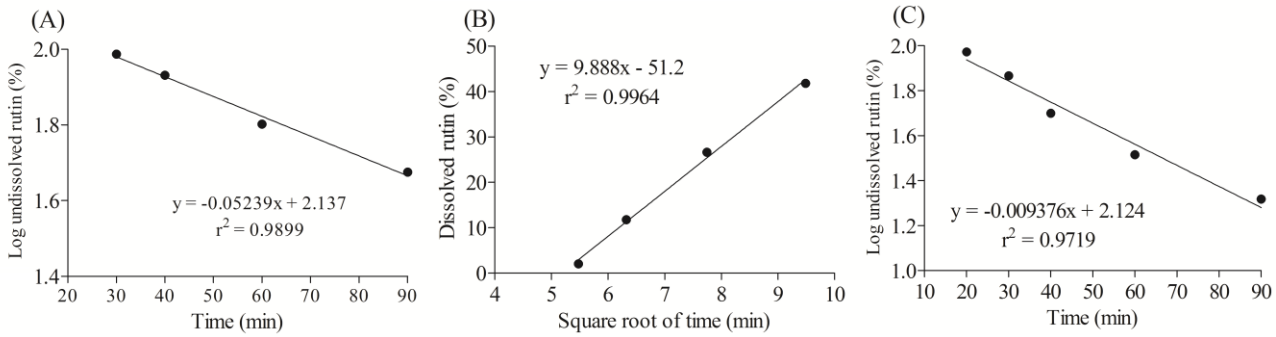

Figure 10. Kinetic models adapted to batches A (A), B (B), and C (C).

According to Figure 2, the first order model equation is linked to a higher dissolution efficiency, while the Higuchi model equation is related to slower release, with a low drug solubilization characteristic. In addition, the Higuchi model describes the drug release mechanism as a diffusion process based on Fick's law, being dependent on the square root of time. This model can be applied with greater accuracy to one-dimensional poorly soluble matrices, which do not have swelling capacity, such as cellulose acetate, in which a very soluble drug is incorporated. For other systems, such as matrices made up of HPMC, this equation is also used. However, when one wants to have a more accurate idea of the release mechanisms, it is necessary to pay attention to other physical-chemical factors (Li et al., 2019).

Conclusion

The results revealed that rutin tablets had quality deviations in the parameters of rutin content, hardness, and dissolution profile. Batches A and C followed the kinetic process according to one-order model, whereas batch B was closer to the Higuchi model. Therefore, for therapeutic use, tablets containing rutin must be submitted to different quality parameters to guarantee their therapeutic action and clinical efficacy.

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