ORIGINAL ARTICLE

Statistical Assessment of Drug Release Kinetics and Formulations Attributes of Ranitidine Tablets Available in Karachi, Pakistan

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ABSTRACT

Objective: To elucidate the in vitro equivalence of Ranitidine brands with other quality attributes to provide drug fate for interchangeability or replacement during prescription writing

Methodology: In the present study, quality assessment including range of physico-chemical parameters were evaluated for six selected brands of ranitidine (RT-1 to RT-6).

Result: Results were observed to be in satisfactory points of confinement. Additionally, disintegration profiles of all brands were resolved utilizing phosphate buffer pH 6.8. Information was investigated by factual strategies as recommended by FDA, for example, similarity factor ($f2$) and difference factor ($f1$) and one-way ANOVA technique. Consequences of one-way ANOVA showed no huge variation among the dissolution profiles of reference and test brands.

Conclusion: Correspondingly, results of $f1$ and $f2$ showed similar profiles of test and reference products. In addition, all the brands were found to be best fitted in Weibull model.

Key words: Ranitidine, Weibull model, Dissolution profiles, physico-chemical evaluation, pharmaceutical

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عنوان: پاکستان کے شہر کراچی میں دستیاب RanitidineTablets کی دواسازی اور اسکے اثرات کا شماریاتی جائزہ۔

تعارف: دواسازی میں خاص فعال جُز خاص مقدارِ خوراک میں معیار کے لحاظ سے متغیر ہوتا ہے۔ منہ کے ذریعے دی جانے والی ادویات کے جسم میں جانے کے بعد اثر انداز ہونے کی نوعیت کسی بھی خاص دوا کے معیار کے مستحکم ہونے کی نشاندہی کرتی ہے۔

طریقہ کار: اس تجزیہ میں چھ منتخب کردہ نامی گرامی ادویات کے معیار کا طبّی اور کیمیائی عوامل سے تخمینہ لگایا گیا۔

نتائج: حاصل ہونے والے نتائج اطمینان بخش تھے۔ تمام ادویات کے تحلیل ہونے کا عمل فاسفیٹ بفر پی۔ایچ (٦.٨) کے استعمال سے ہوا۔ اور معلومات کی تحقیق ایف۔ڈی۔اے کے تجویز کردہ شماریاتی طریقوں (Statistical measures) پر کی گئی۔

حاصلِ مطالعہ: f1 اور f2 کے نتائج ایک جیسے تھے۔ تمام ادویات weibull Model میں جانچنے کے لیے بہترین پائی گئیں۔

INTRODUCTION

Ranitidine belongs to H_2 receptor antagonist in pharmacological class of drug, utilized for the management of gastric and duodenal pathological conditions by blocking the acid secretion like in gastroesophageal reflux disease (GERD), peptic ulcer, gastritis, Zollinger-Ellison[1-3]. It is very soluble in water and less permeable to cell membrane. Ranitidine is crystalline in nature, has a whitish to pale yellowish colour with good solubility character in methanol, water, and few organic solvents[4,5]. Ranitidine is categorised in class III drug as defined by BCS recommended via FDA. It is well tolerable and shows atypical interactions and adverse effects and is approximately 50% bioavailable having 300-500 ng/ml serum level with dose of 150 mg observed after 2-3 hours of taken dose and 6% approximately excreted in urine[6,7].

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Currently, dissolution test data was used for drug profile comparison. In vitro evaluation of basic drugs plays an important role in bio-waiver assessment and alleviates the regulatory trouble of pharmaceutical industries for product development. UV spectrophotometer was used for analysis of ranitidine samples. Validated method demonstrates that dissolution test is appropriate for the assessment of ranitidine within pharmaceutical solid dosage form during in vitro studies explaining linearity, precision, and accuracy[8-10]. Use of statistical similarity methods helps in conclusion, which is based on concurrence or subjective assessments, but somewhat on scientific facts by controlling predefined maximum error probability i.e. significance limit[11-14].

In developing countries such as Pakistan, where a significant stretch of the population cannot afford to manage the cost of essential medical healthcare services, availability of substandard and spurious pharmaceutical formulations may exacerbate the situation. Studies like ours contribute importantly in prescription writing for alternative drugs at reasonable price. No such study concerning the pharmaceutical equivalence of ranitidine has been conducted in Pakistan. Therefore, this investigation is meant to explain the quality and dissolution effectiveness for correlations of different ranitidine brands available in the market in Karachi, Pakistan.

METHODOLOGY

Sanofi (Pvt) Ltd gifted the ranitidine reference. Sodium hydroxide, methanol, petroleum spirit, and potassium dihydrogen phosphate were used as analytical grade (Merck, Germany). In the present study, reference was chosen as RT-1 product amongst selected brands owing to its excellent physicochemical traits whilst RT-2 to RT-6 were designated as trial/test brands. Hardness tester (OSK Fujiwara, Ogawa Seiki Co. Ltd., Japan), and friabilator (H. Jurgens GmbH and Co., Germany). Thickness, weight, and diameter variation assessments were performed using vernier calliper and analytical balance (AUW-220, UNI Blog, Shimadzu, corp.) Basket Rack Assembly was utilized to perform the disintegration test (Erweka ZT-2 Husenstamn, Germany) (USP, 2003). UV-Visible spectrophotometer (UV-1800, Shimadzu Corp., Japan).

Evaluation for Pharmaceutical Equivalence and Quality Attributes of Ranitidine Tablets

Identification Test (IR Spectrum Technique): An amount was shacked of the powdered tablets containing 25 mg of ranitidine in 5 mL of methanol was soaked for a period of 5 minutes. The filtrate was separated and dried. Petroleum spirit 1 ml was added to the deposit, vessels sides were scratched to incite crystallization, dissipated to dryness. The infrared range of the dried deposit, as per Appendix II, is in good compliance with the reference range of RT[15].

Physicochemical Properties Evaluation: In current investigation, variety of parameters including weight variation, diameter, thickness, hardness, and friability were calculated for the six selected brands of ranitidine (RT-1 to RT-6).

Disintegration Test: Basket rack assembly was used to determine the disintegration time of all formulations. Tablets were introduced in each tube of assembly (N=6) and disintegration was observed. After completion of disintegration of all tablets (when no residue of tablet left on mesh of tube), time was noted in minutes. All brands were tested in similar manner[16].

Assay and Content Uniformity of Ranitidine HCl: Twenty tablets from each brand were accurately weighed. Mean weight of each brand was calculated and ground to powder form. An equivalent quantity of 150 mg of each sample was transferred to volumetric flask of 100 ml, methanol was added to make up the volume and samples were sonicated for 10 minutes and filtered. Filtrate was diluted with methanol to obtain 15 ìg/ml of ranitidine. The absorbance of each sample was observed at 325 nm. Standards were also prepared in the same concentration to calculate the percentage assay of each brand[17]. Content uniformity was also performed in similar way using 10 individual samples of each brand and %RSD values were calculated.

In Vitro Dissolution Study: In addition, RT-1 to RT-6 brands were also estimated for drug release potential by dissolution test. For this, dissolution apparatus II was used at $37^0C + 0.5^0C$; 50 rpm with 900 ml of phosphate buffer pH 6.8. Percentage amount of release contents were measured spectrophotometrically with UV-1800 Shimadzu Corporation Japan. Wave length was 325 nm for the set of experiment.

Comparison of Dissolution Profiles of Different Brands of Ranitidine: Ranitidine reference (RT-1) and test (RT-2 – RT-6) formulations were evaluated by multiple point dissolution method using apparatus II, at 50 rpm speed of rotation in 900 ml of pH 6.8 phosphate buffer. Temperature was adjusted at $37 + 0.5^0C$ throughout the experiment. Samples collection time was up to 120 minutes (5, 10, 15, 25, 30, 45, 60, 90 and 120 min). Ten ml samples were withdrawn at every point of sampling and consequently added with 10 ml fresh medium (previously maintained at 37 +

0.5^0C) in dissolution basket. Drug contents released were approximated by using spectrophotometer at 325 nm.

Ranitidine Release Kinetics

Model-Dependent Method: In current study, various model-dependent and independent tools were applied for the evaluation of drug release patterns of reference and test products. A number of authors have utilized such methods in their investigations to observe release profiles of various drugs (Hanif et al., 2011; Muhammad et al., 2012). Selected models for this study were presented in Table 2. DD-Solver software with Microsoft Excel™ 2007 was used to calculate these model values (Microsoft Corporation, USA). Numerous models were used in this study to analyze the drug release kinetics i.e. *First Order*[11], *Hixson-Crowell cube root law*[12], *Higuchi model*[13] and *Weibull model*[14]as given in Table 2. Model selection criteria were used as adjusted determination of coefficient (r^2), Model Selection Criterion (MSC) and Akaike Information Criterion (AIC).

Application of *Pair-Wise Approach:* Mathematical approaches are widely utilized to compute the profiles of formulations using similarity factor (f_2) and difference factor (f_1). These Pair-Wise techniques are most popular in their application in drug development and design research[14].

Statistical Assessment of Drug Release Kinetics: One-way Analysis of Variance (ANOVA)with Tukey's Post Hoc Test was carried out to conclude the variation in release trends of various brands in phosphate buffer pH 6.8. SPSS 20.0 (SPSS Inc.) was used to perform statistical evaluation.

Table 2: Various Model-Based and Model-independent Equations for Ranitidine Brands Release Kinetics Analysis

MODEL INDEPENDENT TERMS	
Difference factor (f_1)	$f_1 = \left[\frac{\sum_{t=1}^{n}(R_t - T_t)}{\sum_{t=1}^{n} R_t}\right] \times 100$
Difference factor (f_2)	$f_2 = 50 \times log\left\{\left[1 + \left(\frac{1}{N}\right)\sum (Ri - Ti)^2\right]^{-0.5}\right\} \times 100$
MODEL DEPENDENT TERMS	
Hixson–Crowell model	$Q_0^{1/3} - Q_t^{1/3} = K_{HC} \times t$
First Order kinetics	$\text{Log } Q = \text{Log} Q_0 - \frac{kt}{2.303}$
Weibull model	$m = 1 - \exp\left[-\frac{(t-Ti)^{\beta}}{\alpha}\right]$
Higuchi model	$Q = kt^{\frac{1}{2}}$

Physicochemical Attributes: Physicochemical features were estimated by calculating variety of parameters i.e., weight, diameter, thickness, and friability. The results of sample drugs were found to be within the acceptance range when compared with that of the reference. Disintegration, assay, and content uniformity test were performed on sample and reference drugs and results were found to be within range i.e. (within 30 mins), (95%–105%) and (95%–105%) respectively (Table 1). Figure 1 and 2 illustrate the drug release and weight based comparisons of selected brands.

RESULT

Identification Test: Identification test was performed for all the five samples (RT2-RT6) and reference brand (RT1) using IR spectrum technique and the results of the samples were found to be comparable with that of the reference.

Ranitidine Brands (N=20)	Hardness (kg) (N=20)	Thickness (mm) (N=20)	Diameter (mm) (N=20)	Disintegration Time (min) (N=6)	Weight (mg) (N=20)	Assay (%) (N=20)	Dissolution (%) (N=6)
RT-1	9.05 + 0.51	4.37 + 0.14	9.53 + 0.06	8.25	303.68 + 1.54	100.03+2.25	102.88+ 0.79
RT-2	9.81 + 0.52	5.14 + 0.05	8.05 + 0.28	9.00	259.24 + 2.51	99.46+ 1.29	101.07+1.05
RT-3	5.40 + 0.49	3.61 + 0.81	9.62 + 0.12	8.07	239.13 + 2.20	101.98+2.07	103.52+ 0.86
RT-4	9.17 + 0.43	5.51 + 0.12	9.71 + 0.28	3.67	329.88 + 2.13	100.56+2.98	101.69+0.96
RT-5	5.98 + 0.34	4.12 + 0.08	11.26 + 0.11	6.70	369.32 + 2.12	100.12+ 1.33	102.20+ 0.73
RT-6	5.18 + 0.35	4.10 + 0.09	11.33 + 0.15	6.77	297.48 + 2.44	101.73+2.02	103.31+ 0.98

Table 3: Outcomes of Pharmaceutical Equivalence Studies for Reference and Brands of Ranitidine Formulations

Parameters	Specifications	RT-1 (Comparator)	RT-2 (Brand)	RT-3 (Brand)	RT-4 (Brand)	RT-5 (Brand)	RT-6 (Brand)
Identification Test	Complies	Passable	Passable	Passable	Passable	Passable	Passable
Dissolution (%) (n=6)	NLT 80%	Suitable	Suitable	Suitable	Suitable	Suitable	Suitable
Disintegration Test (min) (n=6)	Within 30 minutes	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
Assay (%) (n=20)	95-105%	Conformed	Conformed	conform	Conformed	Conformed	Conformed
Content Uniformity (%) (n=20)	95-105%	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate

Table 4: Kinetics Evaluation of Ranitidine Brands (RT-1 to RT-6) at pH 6.8

Formulation	First Order		Higuchi		Hixson-Crowell		Weibull model		
	r^2	$K_1(h^{-1})$	r^2	$K_H\ (h^{-1/2})$	r^2	$K_{HC}\ (h^{-1/3})$	r^2	α	β
RT-1	0.986	0.056	0.779	10.49	0.977	0.011	0.986	15.124	0.946
RT-2	0.973	0.040	0.845	11.35	0.986	0.012	0.988	19.36	1.273
RT-3	0.990	0.045	0.867	10.86	0.994	0.011	0.989	23.42	1.020
RT-4	0.985	0.056	0.769	10.88	0.979	0.012	0.984	22.03	1.069
RT-5	0.985	0.067	0.639	10.54	0.925	0.012	0.989	21.65	1.134
RT-6	0.987	0.049	0.814	10.96	0.989	0.011	0.987	25.83	1.080
Model Selection Criteria									
CODE	MSC	AIC	MSC	AIC	MSC	AIC	MSC	AIC	
RT-1	4.091	41.45	1.202	67.46	3.499	46.79	3.968	42.56	
RT-2	3.403	51.48	1.557	68.09	3.980	46.29	4.163	44.64	
RT-3	4.471	39.57	1.707	64.45	4.944	35.32	4.259	41.42	
RT-4	3.974	43.71	1.158	69.05	3.593	47.13	3.860	44.73	
RT-5	4.022	42.64	1.710	72.45	2.283	58.28	4.243	40.64	
RT-6	4.138	42.74	1.373	67.62	4.263	41.62	4.089	43.18	

Dissolution Profile Comparison: Multiple point dissolution method was used to compare dissolution profiles of different brands of ranitidine (RT2-RT6) with the reference brand (RT1) at 325 nm by using pH 6.8 phosphate buffer and the results were found to be within range i.e. (NLT 80%). Table 3 describes the outcomes of pharmaceutical equivalence studies for reference and brands of ranitidine formulations. Table 4 depicts the kinetics evaluation of ranitidine brands (RT-1 to RT-6) at pH 6.8 alongwith model selection criteria. Furthermore, results reveal that Weibull model was found to be best fitted when evaluated on the basis of model selection criteria.

Model-Dependant, Independent, and ANOVA Results: Release profile comparison of the test and reference products was made using ANOVA-one way technique, model-dependent and model-independent techniques using phosphate buffer pH 6.8 as dissolution media. Results obtained from model-independent technique like difference factor ($f1$) and similarity factor ($f2$) showed similarity in the release profile of test products when compared with the reference. (Table 5) Results obtained from ANOVA detected an insignificant variation between the test (RT2-RT6) and reference product (RT1) as the value of p was found to be 0.997 (Table 6).

Table 5: Evaluation of Difference Factor (f_1) and Similarity Factor (f_2) of RT-1 to RT-6

Ranitidine Brands	f_1	f_2	Comments
RT-1 and RT-2	10.86	50.01	Similar
RT-1 and RT-3	6.40	60.47	
RT-1 and RT-4	3.45	72.74	
RT-1 and RT-5	5.67	63.29	
RT-1 and RT-6	4.43	66.04	

Table 6: Statistical Assessment (ANOVA) of Dissolution Profiles of Ranitidine 150 mg Tablets (RT-1 to RT-6)

	Between Groups	Sum of Squares	df	Mean Square	F	Sig.
pH 6.8	Within Groups	831.454	5	166.291	0.190	0.965
	Total	36772.433	42	875.534		
	Between Groups	37603.887	47			
time	Within Groups	0.000	5	0.000	0.000	1.000
	Total	34800.000	42	828.571		
		34800.000	47			

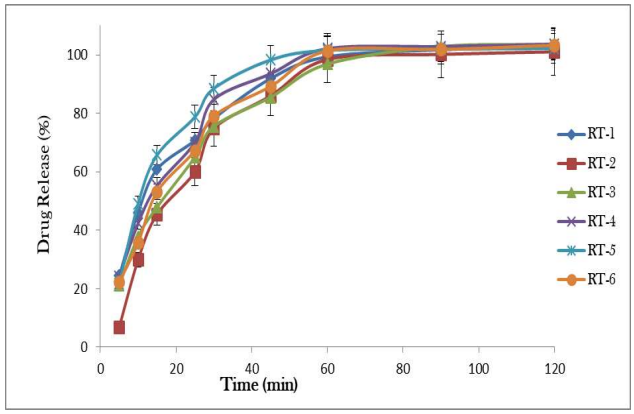

Figure 1: % Drug Release of Ranitidine 150 mg Tablets in Buffer pH 6.8 (RT-1 to RT-6)

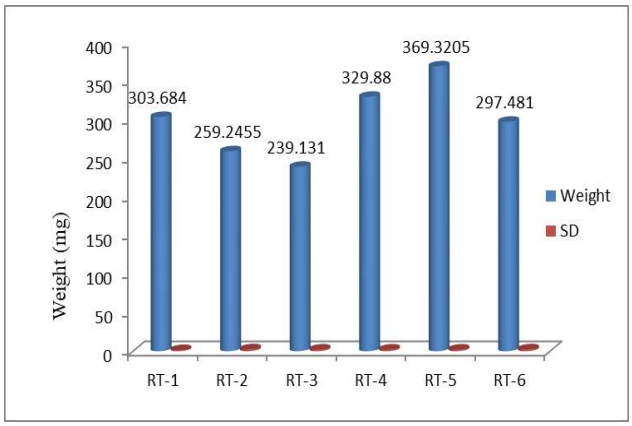

Figure 2: Weight Comparisons of Various Brands of Ranitidine (RT-1 to RT-6)

DISCUSSION

Dissolution test is the way to assess basic parameters, for example, satisfactory bioavailability values and gives necessary information to the formulator in designing of more efficient and restoratively ideal formulations. Dissolution investigation of pharmaceuticals has developed as the absolute most essential test that will guarantee the nature of a product[18]. It is a key explanatory test utilized for identifying physical changes in a functioning pharmaceutical ingredient and in the final product[19]. Pharmaceutical equivalents are defined as indistinguishable measurement forms that contain a similar dynamic fixing i.e. same ester or salt, utilize a similar mode of administration, are interchangeable in concentration and strength and meet the same compendial norms (i.e. identity, quality and purity)[20]. When appropriate, pharmaceutical counterparts must meet a similar substance consistency, disintegration, and dissolution values[21].

In the current study, five commercially available brands of ranitidine (RT2-RT6) were methodically estimated for their physical features and compared with reference brand (RT1) owing to the fact of excellent quality features. Results showed that Hardness (kg) (5.18 ± 0.35 – 9.81 ± 0.52), Thickness (mm) 3.61±0.81 – 5.51 0.12), Diameter (mm) 8.05±0.28–11.33±0.15, Disintegration time (min) 3.67-9, Weight (mg) 239.13±2.20-369.32±2.12, parameters were in acceptable ranges. Result values for assay studies were also found to be in satisfactory ranges (99.46 1.29 – 101.98 2.07). (Table1) Tablets were premeditated for invitro dissolution behaviour for 120 minutes using dissolution apparatus II with 900 ml of phosphate buffer pH 6.8 and the values were found to be in the satisfactory ranges (101.07 1.05-103.52 0.86). (Table 1) In the present study, dissolution profiles of all the brands were evaluated and compared to that of the reference by applying different comparison methods. Techniques applied for comparison were statistical evaluation using ANOVA method, model-independent method including difference factor (f_1) and similarity factor (f_2), model-dependent method. ANOVA followed by the Tukey post hoc multiple comparison test was used to decide statistical worth.

The results showed that the dissolution profiles of the reference and sample drugs were not significantly different as the P value was greater than 0.05 i.e. 0.997 (Table 6).

The mean of the values were used to calculate the difference factor and similarity factor and the results

for $f1$ and $f2$ were found to be in order of (3.45-10.86) and (50.01-72.74), respectively (Table 5). $f1$ values equal to 15 (0-15) and $f2$ range of 50-100 guarantees similarity or proportionality of the two brands and subsequently the sameness of the test and reference[22]. In case, if the estimation of $f2$ is 50, 90% comparability in the profile was shown and the value up to 40, then 80% likeness might be demonstrated. Thus, the outcomes from this investigation uncovered similitude in the medication release.

The slope and coefficient of determination (r^2) values were identified using each model. For First Order and Higuchi models, the r^2 values were in the range of 0.973-0.990 and 0.639-0.867 respectively. Using Hixson-Crowell model, values of r^2 lied in the range of 0.925-0.994. Weibull model gave best curve fitting with highest values of coefficient of determination (0.984-0.989). The determination of the fitting model in the medication discharge behaviour is important to guarantee the viability of the investigation. Different criteria for the choice of the numerical models which depend on the factual treatments are reported in multiple literatures. The most generally utilized strategy uses the coefficient of assurance, r^2 to determine the best fit equation condition. This strategy can be utilized when the parameters of the model conditions are comparable[19,21,22].

Other widely accepted techniques include Model Selection Criteria (MSC) and Akaike Information Criterion (AIC). The AIC, as characterized above, is reliant on the extent of the data points and additionally the quantity of perceptions. What is more, the most fitting model is the one with the littlest estimation of the AIC. The MSC will give an indistinguishable ranking between models from the AIC and has been standardized with the goal that it is autonomous of the scaling of the information focuses. Besides, the most fitting model will be that with the biggest MSC (to boost the "data content" of the model)[24].

As observed from Table 4, Weibull model proves to be the best fit model followed by First-Order, Hixson-Crowell, and Higuchi models. The values of AIC and MSC for Weibull model are in the range of (40.64-44.64) and (3.860-4.259) respectively. AIC values for First-Order, Hixson-Crowell, and Higuchi models are found to be (39.57-51.48), (35.32-58.28) and (64.45-72.45), respectively. Hixson-Crowell model gave MSC value in the range of (2.228-4.944) whereas the MSC values observed for First Order and Higuchi model are in the range of (3.403-4.471) and (1.202-1.710) respectively. Other investigations conducted by Ali et al. and Naqvi et al. also reported Weibull as prominent model for description of drug release of Gatifloxacin tablets[22,23].

CONCLUSION

All the selected products (RT-1 to RT-6) of ranitidine brands verified the adequate physico-chemical characteristics and confirmed the satisfactory in vitro drug release profiles. Such studies not only offer exceptional avenues for choice of superior alternatives accessible in drug market as prominent products but also assist in the most favourable care of patients in developing countries, where ease of access and affordability of these products influence swift healthcare provision.

Authors'contributions: Prof. Huma Ali conceived the idea, worked on data collection, data analysis and review, and also worked on introduction and discussion. Dr Shaheen Parveen and Dr Fozia Israr worked on literature search, results, and discussion. Dr Maria Sodagar and Dr Amber Nawab reviewed the literature, worked on discussion and edited the manuscript. Dr Anum Tariq reviewed the literature, result and conclusion in the discussion. All authors contributed to the final manuscript.

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