ORIGINAL ARTICLE

Application of Quality Control Parameters and Model Dependent and Independent Approaches on Different Brands of Itopride HCL 250mg Available in Karachi, Pakistan

Hira Akhtar[1], Nighat Razvi[2], Shamroaz Khan[3], Kamil Khan[3], Saif Ullah[3], and Raza Ahmed Ansari[3]

ABSTRACT

Objective: To conduct Invitro Quality testing of five different brands Itopride HCl (250mg) available in Karachi, Pakistan to ensure that their quality meet the desired compendial standards.
Methodology: Several In-vitro tests were executed on five different brands of Itopride HCl coded as 11, 12, 13, I4 and I5. Sample of 20 tablets from individual selected brands were subjected to different tests including weight variation, hardness, thickness and diameter. Multiple point intervals dissolution were performed in 0.1N HCl medium in USP paddle type II apparatus and % dissolution data were subjected to several kinetic model including model dependent and model independent approaches utilizing DD solver add in program in Microsoft Excel.
Result: Weight variation of all five coded brands of Itopride HCl 250 mg were found to be 133- 311mg. The disintegration time of all test formulation was between 2 minutes 40 seconds and 9minutes 32 seconds, % friability of all tested tablets was found to be 0.21-0.57%. Multiple point dissolution studies samples were taken at 5, 10, 15, 20, 25 and 30 minutes and drug released was analyzed on UV spectrophotometer at the wavelength of 258nm.Similarity factor (*f1*)considering I2 as reference formulation were found to be in the range of 1.86-6.52 and dissimilarity factor (*f2*) values were found to be in the range of 61.80-84.87. Kinetic models were successfully applied to the dissolution profile of Itopride HCl.
Conclusion: Evaluation of the quality attributes of five different selected brands of itopride 250 mg tablets in Karachi, Pakistan, specifically assessing weight variation, hardness, thickness, diameter, dissolution, and disintegration was the primary objective of this study. By adhering to established Pharmacopeial standards ensure the product's quality, efficacy, and safety. Tablets ability to release active pharmaceutical ingredient in a timely manner improving patient compliance by providing optimum therapeutic activity. Invitro quality standards ensure the products accuracy in terms of weight, potency and performance. The study high light the importance of rigorous quality control in pharmaceutical manufacturing contributing to improved patient outcomes.

Keywords: Itopride HCl, multiple point dissolution, quality evaluation

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INTRODUCTION

Quality, safety and efficacy of any drug must be such that it improves human health and provides required therapeutic effect with no side effects. These standards must be reliable and reproducible and must not vary from batch to batch. The quality of pharmaceutical products is of major concern in developing countries[1]. An increase in number of counterfeit medicines in the market has affected low and middle income countries due to the lack of facilities[2]. All generics drugs that are pharmaceutically bioequivalent must meet the standards of quality, purity, potency and must be identical in all pharmacopeial evaluation tests[3]. Counterfeit and substandard drugs are major concern for human health as they increases morbidity and mortality rates[4]. The quality of pharmaceutical products must be such that it should be reproducible among batches and free from batch to batch variation[5]. It is the duty of all the pharmaceutical manufactures to check the quality of the product several time during the shelf life of the product[6]. Invitro quality tests or in

Lecturer[1] / Professor[2] /Student[3], Faculty of Pharmacy, Nazeer Hussain University, Karachi, Pakistan

Correspondence: Hira Akhtar, Lecturer, Faculty of Pharmacy, Nazeer Hussain University, Karachi, Pakistan

Email: dr.hiraakhtar@gmail.com

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process control of the pharmaceutical products during and after production according to the pharmacopeial test plays a significant role in maintaining the quality standards of the product[7].

Itopride HCl is the most extensively used prokinetic agent that increases GIT motility by reducing acetyl cholinesterase enzyme, has an anti-Dopamine receptor activity and decreases heart burn, dyspepsia, bloating, nausea and vomiting[8]. Dose of Itopride HCl is 50 mg three times a day with an elimination half-life of 6 hours. It does not cross blood brain barrier and does not impart any CNS effects[9]. The Drug is extensively absorbed and peak plasma concentration occurs in 35 minutes after the oral dosing[10]. Itopride HCl belongs to the BCS class I drug[11]. The present study aim is to perform the Invitro quality testing of several bands of Itopride HCl 250 mg available in Karachi Pakistan to ensure their standards meet the required compendial status.

METHODOLOGY

IRB/ERC Approval:

An exemption letter from the Ethical Review Board was obtained from Nazeer Hussain University, Karachi, under reference number NHU/ORIC/202/202401, dated July 22, 2024.

Five different brands of Itopride Hcl250mg were taken from Karachi, Pakistan's local market and each one was assigned a code for identification i.e. (11, 12, 13, 14 and 15).

Microsoft Excel 2016 software was used for data calculations and for the implementation of kinetic models on multiple point dissolution profile an add-in program DD Solver were utilized, Equipment used in the study included Vernier Caliper (Seiko, China), Friability Tester (Curio FB 2020, Pakistan), Digital Hardness Tester, USP Basket Rack Assembly (DA 6D, Veego, India), USP type 2 Paddle Dissolution Apparatus (Curio, Pakistan), UV Spectrophotometer (Shimadzu, Japan), Analytical balance (Shimadzu, Japan), and distilled water.

This study involved Pharmacopeial tests and non Pharmacopeial tests implementation such as weight variation, friability, disintegration, dissolution, assay, thickness, diameter and hardness. Model dependent and independent techniques were applied for multiple point dissolution. Model independent approaches included difference (*f1*) and similarity (*f2*) factors whereas Model dependent approaches included First-order, Higuichi, Hixson Crowell and Well model. Twenty tablets of Itopride HCl tablets from each selected five brands were taken and weighed separately. The average weight was then determined. The formula mentioned below can be applied for the estimation of weight variation.

Average weight=(X1+X2+X3+.....+Xn)/10

Weight Variation = (Individual weight-average weight) x 100/ average weight. (1)

To evaluate the tablets friability or tablets capacity to bear sufficient mechanical strength to with stand mechanical shock during transportation. Roche friabilitors were used. Twenty tablets were taken and their weight was noted down collectively (initial weight). The tablets were placed in friabilitor and rotated at 100 revolutions for 4 minutes. Once the test was completed, tablets were taken out dedusted, and weighed again (final weight).

The same procedure was repeated for other coded brands. Friability of the tablets were calculated by the following formula

$$\%F = (1-W/W0) \times 100\ \%$$

Friability of tablets <1% were noted as satisfactory.[12]

A Sample of twelve tablets was selected from every coded brands and observed for how well they disintegrated. Tablets of each coded brands were placed in the six tubes of the basket rack assembly of the disintegration tester within an open ended tube on a wire mesh that was fitted at one of its ends. The test consisted of being carried out using distilled water as medium at 37 ± 2°C for 15 minutes. To prevent the tablets from floating, perforated plastic discs were used. After the complete disintegration of the tablets, the time was noted. According to USP the disintegration time had to be 15 minutes or less. The same procedure was repeated for other coded brands I2, I3, I4 and I5.[13,14]

To evaluate the thickness and diameter Vernier calipers were utilized, Twenty tablets from all brand were taken and the thickness and diameter was measured individually, by sliding tablets between the jaws of Vernier calipers. Tablet thickness should not vary with in ±5% variation of a standard value.[15] Tests results were evaluated using Microsoft Excel 2019.

Ten tablets from each selected brand were taken and placed in hardness tester. The force needed to crush the tablet was noted in kgF^2. Average crushing force and SD was calculated using Microsoft Excel 2019. Itopride HCl Spectroscopic method is one of the easiest, the least time and cost consuming method for the determination of Itopride HCl. Take Twenty tablets

were taken and note their average weight then crush the tablets in mortar and pestle and the amount equivalent to 50 mg was taken in 100 ml volumetric flask and diluted with 0.1N HCl. Sample was analyzed in UV spectrophotometer at 258 nm using 0.1N HCl as blank.

The percentage of assay should not be less and more than 90% - 110%.

Dissolution testing was carried out using type II USP dissolution Paddle apparatus at 50 rpm using 0.1N HCl as medium. Samples were taken multiple time as 5, 10, 15, 20, 25 and 30 minutes. Each time 10ml of freshly prepared sample was added after sample withdrawal. By using U.V spectrophotometer at wavelength of 258nm using 0.1N HCl as blank and absorbance of the samples from each point interval were noted and % of drug release was compared with reference[14]. Not less than 80% of the drug released at 30 minutes[8]. Dissolution data were subjected to various Model dependent approaches as shown in Table 4.

First order kinetics model[16,17]

$$\text{Log } Q = \text{Log}Q_0 - \frac{kt}{2.303} \quad (2)$$

Higuchi model [17]

$$Q = kt^{\frac{1}{2}} \quad (3)$$

Hixson Crowell model [18]

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} \times t \quad (4)$$

Weibull model [19]

$$m = 1 - \exp - \frac{(t - Ti)^{\beta}}{\alpha} \quad (5)$$

This pair wise method Difference factor (*f1*) and similarity factor (*f2*) compares the two dissolution profiles such as reference and test formulation[20,21]. Reference formulation was selected from the test formulations I1-15 on the basis of high drug release I2 was selected as reference formulation as show in Table 3.

$$f_1 = \frac{\sum_{t=1}^{n} R_t - T_t}{\sum_{t=1}^{n} R_t} \times 100 \quad (6)$$

$$f_2 = 50 \times \log \left[1 + \frac{1}{N} \left(Ri - Ti\right)^{2}\right]^{-0.5} \times 100 \quad (7)$$

n = number of samples
Rt = percent release of the reference drug
Tt = percent release of test drug
The value of difference factor (*f1*) should be between 0 and 15,

While the Similarity factor (*f2*) is between 50 and 100.

DISCUSSION

The aim of the study was to evaluate the different brands of itopride HCl 250 mg available in the market of Karachi, Pakistan. Weight variation indicates the sustainability of good manufacturing practice by the manufacturer as well as the presence of the quantity of an active ingredient in the formulation[22]. Weight variation tests of all the tablets were found to be in the range of 130.5±6.04-311±15.18 as shown in **Table 1.** Hardness of the tablet indicates the quality of the product. If the tablet is not too hard it will fail in friability test and will be difficult to handle during coating. And if the tablet is too hard, it will not disintegrate in the body which results in poor bioavailability of the product Hardness results of the itopride tablet were found to be between 2.59±0.11 - and 8.5±0.17. shown in **Table 1**. The tendency of the tablet to crumble during manufacturing, handling and transportation can be determined through friability as tablets sliding over one another result in the removal of particles from the surface of the tablet[23]. Friability of the test tablets were found to be in the range of 0.29-0.40%. Diameter and thickness plays an important role in terms of tablet swallowing, tablet weight and uniformity of content can be easily detected. Appearance and packing can be affected by the diameter and thickness of the tablet[24]. The values of diameter found to be in the range of 3.5±0.05- 9.8±0.04 and thickness values were found to be in the range of 2.05±0.03 - 3.3±0.02 as shown in **Table 1.** Disintegration time is considered to be one of the crucial steps for the tablet as it plays an important role in the dissolution of the drug. If the drug does not disintegrate with-in the specified time, it will not be available for dissolution, hence the concentration and efficiency of the disintegrant plays a significant role in the dissolution of the drug[25]. The disintegration of the test tablets were found in the range of 2 minutes 40 seconds - 9 minutes 32 seconds. Assay indicates the amount of the drug in the tablets and their stability as well[26]. The Assay of the given the itopride HCl tablets were found to be 100.2 %- 102.32% as shown in **Table 2.** In-vitro in vivo dissolution provides useful information regarding the bioavailability and batch to batch consistency. It is a compendial requirement for the license of the drug. This test is also utilized to specify stability and development characteristics[27]. It is a surrogate point in development of a formulation and to predict the bioequivalence[28]. In this study multiple point dissolution were performed to evaluate the maximum drug release. At 30 minutes, the percentage dissolution of the drug was found to be 98.49% to 101.32% of the test formulations as shown in **Figure 1**. Similarity (*f2*) and dissimilarity *(f1*) factors represent

RESULTS

Table 1: Invitro Quality Parameters Weight variation, Thickness, Diameter, Hardness, Friability, Disintegration and Dissolution of Itopride Hcl (250mg) I1-I5

Codes	weight (mg) Mean ± SD	Thickness (mm) Mean ± SD	Diameter (mm) Mean ± SD	Hardness (kg) Mean ± SD	Friability (%)	Disintegration Time (min) (not >15 min)	Dissolution Studies of Itopride HCl (250mg) in 0.1N HCL at 30 minutes
I1	133±7.32	3.12±0.06	7.3±0.02	8.5±0.17	0.40	5 min 40 sec	99.89
I2	131.5±7.45	2.4±0.04	3.5±0.05	6.12±0.26	0.57	9 min 32 sec	101.32
I3	130.5±6.04	2.05±0.03	7.4 ±0.06	2.59±0.11	0.29	6 min 19 sec	99.87
I4	179.5±14.6	3.1±0.07	8.2±0.02	4.07±0.57	0.37	5 min 22 sec	98.49
I5	311±15.18	3.3±0.02	9.8±0.04	6.6 ±0.62	0.21	2 min 40 sec	99.84

Table 2: Percentage Assay of Several Brands of Itopride Hcl (250mg) available in Karachi, Pakistan Itopride Hcl (250mg) I1-I5

No.of Tablets	I1 (%)	I2 (%)	I3 (%)	I4 (%)	I5 (%)
20	99.98	99.89	101.24	99.67	99.87
20	100.9	102.6	99.96	101.4	103.35
20	99.97	99.90	100.78	100.45	99.99
Mean	100.2	102.32	100.66	100.50	102.24
SD	0.53	0.98	0.64	0.86	0.54

Table 3: Application of model independent approaches similarity factor(f2) and dissimilarity factor (f1) on selected brands of itopride 250 mg with I2 brand is selected as Reference (I1-I5)

Similarity *(f2)* and Dissimilarity *(f1)* factor at 0.1N HCl	I1	I3	I4	I5
f1	3.16	3.91	6.52	1.86
f2	76.94	74.55	61.80	84.87

Table 4: Application of kinetic models (model dependent approaches) on the multiple Dissolution data of the selected brands Itopride (250 mg) I1-I5

Code	r^2	k_1(m)	r^2	kH(m-1/2)	r^2	kHC(m-1/3)	r^2	B	A
I1	0.9628	0.081	0.9756	17.450	0.9520	0.022	0.9630	1.019	12.971
I2	0.9599	0.085	0.9734	17.902	0.9652	0.023	0.9639	1.086	14.701
I3	0.9699	0.081	0.9663	17.526	0.9776	0.022	0.9767	1.115	16.762
I4	0.9737	0.099	0.9276	18.630	0.9467	0.026	0.9750	1.047	11.306
I5	0.9753	0.008	0.9850	18.045	0.9701	0.023	0.9768	1.051	12.974

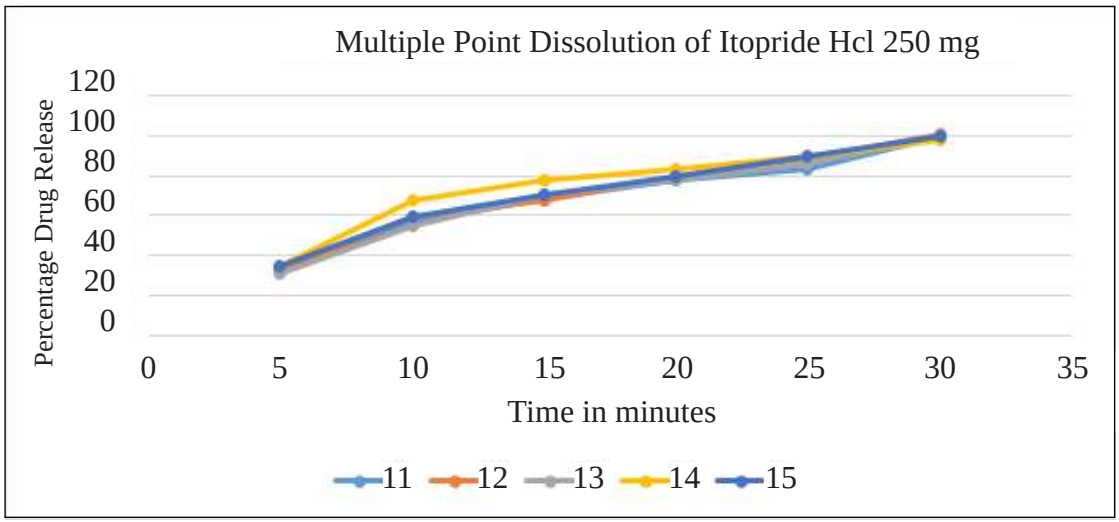

Figure 1: Graphical presentation of multiple point dissolution studies of Itopride HCl 250 mg at 0.1N HCL for 30 minutes

the difference and similarity between the two dissolution profiles[29]. The difference factor f1 is also called as Fit factors, and the similarity factor f2, first proposed by Moore and Flanner. The factor f1 quantify the difference in drug released between the dissolution profiles at multiple time points the profiles of the test and reference are identical when f1 is zero dissimilarity between the two profiles increases, as the value increases and usually a value of 15 or below indicates fair similarity[30]. The f2 values are between 0 and 100, and if the calculated value is greater than 50, the test and reference formulations are similar. The similarity factor f2 is achieving popularity due to its recommendation by regulatory authorities for the assessment of similarity between dissolution profiles[31]. In this study reference formulation was I2 and the test formulations were I1, I3, I4 and I5. (*f2*) value was found to be 84.87 to 61.80 and *(f1)* value was found to be 1.86 to 3.9 as shown in **Table 3**. In this study several kinetic models (dependent approaches) were applied successfully as shown in **Table 4.**

CONCLUSION

This study demonstrates the importance of rigorous quality control measures in ensuring the efficacy, safety, and reliability of pharmaceutical products. The evaluation of quality control parameters such as weight variation, hardness, thickness, diameter, dissolution, and disintegration, emphasize the importance of following Pharmacopeial standards. These tests are important in ensuring that each tablet contains the accurate amount of active ingredient, with weight variation and hardness tests authenticates uniformity and mechanical strength, respectively. The rationality of this research lies in the requirements to guarantee that pharmaceutical products meet high quality requirements, thereby optimizing therapeutic outcomes and enhancing patient compliance. This study contributes to the advancement of high-quality pharmaceutical products by highlighting the significance of quality control for both manufacturers and regulatory agencies.

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Authors' Contributions: HA; conceptualized the study, led the manuscript write-up, and handled correspondence. **NR;** supervised the study and provided critical guidance and review of the final draft. **SK, KK, SU,** and **RAA**; actively contributed by conducting in-vitro quality tests. Each author has reviewed and approved the final version of the manuscript.

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