IN-VITRO EVALUATION STUDIES OF SEVERAL BRANDS OF DESLORATADINE AVAILABLE IN KARACHI, PAKISTAN WITH APPLICATION OF MODEL DEPENDENT & MODEL INDEPENDENT APPROACHES: KINETIC MODELS

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Abstract:

Objective: The basic purpose of this study is to evaluate different brands of Desloratadine 5mg tablets available in local market of Karachi Pakistan through various pharmacopeial and non pharmacopeial test, for this study only random 3 brands were selected. **Methodology**: Twenty tablets were selected from each brand and different test suggests weight variations, hardness thickness, diameter, disintegration, friability, assay and their data analysed through MS excel (2013) and multiple point dissolution studies were conducted and dissolution studies were subjected to several models such as model dependent approaches and model independent approaches. **Results:** Study revealed that weight variation of selected brand coded as P1, P2, P3 were found to be (224.58±0.90, 224.48±0.94 and 224.27±0.98), thickness and diameter were found to be with in the limit of 5%, hardness of all the three brands were found to be within the limit according to USP 3 to 6 kg, disintegration of selected brands P1, P2 and P3 were found to be 4 min 7 sec, 5 min 9 sec and 7 min 20 seconds. All the selected brands friability were found to be less than 1%, assay of three selected brands were performed in 0.1N HCL and the results were found to be 101.8%, 100.9% and 101.9%. Multiple point Dissolution studies were performed such as 5 min, 10min, 15 min, 20 min, 30 min and 45 min according to USP more than 80% of the drug must be released at 45 minutes results reveals that at 45 minutes percentage of Drug release for P1, P2 and P3 were found to be 99.9%, 98.9% and 98.6% then the dissolution data were subjected to several kinetic models such as model independent and model dependent approaches. Model independent consist of similarity (*f2)* and dissimilarity (*f1)* factors by choosing P1 as reference formulation on the basis of high drug release at 45 minutes. Results of P2 and P3, *(f2)* were found to be 66.75 and 64.56 and (*f1)* were found to be 4.67 and 4.95. Model dependent approaches consist of several kinetic models such as First order kinetics, Higuchi Kinetics, Hixon Crowell cube root law and Weibull model which were calculated using DD solver on the basis of r^2 value it was concluded that all the three brands P1,P2 and P3 followed First order and Weibull kinetics. **Conclusion:** Successful In-vitro Pharmacopieal and Non-Pharmacopieal tests were applied to three different brands of Desloratadine available in Karachi, Pakistan and large sample size need to be analysed.

Key Words: Desloratidine, Multiple point Dissolution, Independent & Dependent approaches, In-vitro studies of Desloratidine.

Introduction:

Several Enhancement has been made to improve the quality of pharmaceutical products. Concerns about the quality of medicines are widespread, especially in developing nations. Poor manufacturing procedures, drug fraud, or improper storage methods can all lead to inadequate pharmaceuticals. Due to drug quality problems, there are more hospital admissions and fatalities. The use of subpar drugs puts therapeutic treatment at risk and increases the likelihood of treatment failure. Pharmaceuticals are important for enhancing human health and fostering happiness. According to the WHO, producers are accountable for the quality of the medications they produce. To produce the desired pharmacological effect, it is necessary to ensure the safety, efficacy, and quality of drugs. A global survey of countries found that the prevalence of allergic rhinitis (AR), a common immune- mediated disorder, can reach up to 28.9%. The signs and symptoms of allergic rhinitis, such as sneezing, rhinorrhoea, nasal congestion/ stuffiness, and nasal pruritus, must be relieved with the right treatment in order to improve patient's quality of life and to make it easier to manage conjunctivitis, otitis media, sinusitis, and asthma as well as other associated conditions. As a first line of defence against allergic rhinitis, non-sedating antihistamines are advised. In individual studies, a variety of non-sedating antihistamines have demonstrated their efficacy in treating the symptoms of AR. These agents may also inhibit the actions of other mast cell and basophil mediators that cause nasal obstruction and inflammation of nasal mucosa. Desloratadine is an antihistamine that doesn't cause drowsiness and was first made accessible in 2001 to treat AR. It is the main active metabolite of loratadine. Desloratadine is a powerful, non- sedating H1-receptor antagonist with antiallergic and anti-inflammatory properties. It belongs to the biopharmaceutical classification system BCS II drug. This drug is metabolized to 3-hydroxydesloratidine by liver metabolism but the rate of its first pass less than loratadine. Plasma protein binding of Desloratadine is 82-87%. Desloratadine inhibit the production or release of a variety of inflammatory mediators, including IL-4, IL-6, IL-8, IL-13, PGD2, leukotriene C4, tryptase, histamine, and the TNF induced chemokine RANTES. Its demonstrated capacity to stop the release of cytokines, chemokine, and cellular adhesion molecules linked to the late-phase response may be a factor in its decongestant effects. Desloratadine pharmacokinetic characteristics have been investigated in single- and multiple-dose trials, and the results showed that the drug is quickly absorbed and has a substantial half-life of about 27 hours.(Geha and Meltzer 2001) Its bioavailability and absorption are not significantly impacted by food, it can be administered with or without food. The main purpose of this study was to compare different brands of desloratadine tablets met the commercially available tablet form marketed by various manufactures in Karachi, Pakistan. All pharmacopeial as well as non-pharmacopeial test were applied to evaluate desloratadine in In-vitro quality and kinetic models' evolution. However, it's important to note that the study had limitations due to a small sample size, and a larger number of samples would be required for more accurate estimations.(Canonica, Tarantini et al. 2007)

Equipment's:

Analytical balance (Shimadzu, Japan), Vernier Calliper (Seiko, China), Roche friability tester (Curio FB 2020, Pakistan), Dissolution Apparatus, digital hardness tester, USP Basket-rack assembly (DA 6D, Veego, India), UV spectrophotometer (Shimadzu, Japan).

Materials:

In this study three different brands of Desloratadine were selected from market of Karachi Pakistan. Selected brand tablets were evaluated using various invitro quality control tests such as weight variation, hardness, thickness, diameter, assay, and in vitro dissolution. To ensure ethical considerations, the manufacturer's identity was blinded, and only the researcher had knowledge of it. The study utilized pharmaceutical-grade reagents like Phosphate buffer pH 5.8 and 0.1 M NaOH.

Method's:

Weight Variation:

For the purpose of performing weight variation test 20 tablets of each brand were weighted individually (P1, P2, P3) and the average weight were calculated by using formula below.(Huque, Brishti et al. 2017)

$$\text{Average weight} = \frac{(P1+P2+P3. \quad +Pn)}{20}$$

Weight variation= (individual weight – average weight)/ Average weight ×100

If more than two tablets of individual weight will deviate from average weight the test should be repeated again.

Limits According to USP:

Mean weight of tablets	% Difference
Less than 130 mg	+ 10
Greater than 130 and 324 mg	± 7.5
Greater than 324 mg	+ 5

Hardness:

Twenty tablets of selected brands were individually placed place in digital hardness tester. Result was evaluated using Microsoft excel 2010.Mean hardness and standard deviation were also calculated.(Huque, Brishti et al. 2017)

Limit: Hardness of Desloratadine should be between 3 to 6 kg.

Diameter & Thickness Inspection:

Twenty tablets from each brand were selected for diameter and thickness test. Diameter and thickness were determined by using Vernier calliper. Mean thickness, diameter and their standard deviations (SD) were calculated using Micro soft excel 2010.(Huque, Brishti et al. 2017)

Limit: The percentage deviation for both tests should not be more than ± 5%

Tablet Friability Comparison:

Friability test is now included in United State Pharmacopeia as a compendial test. The compendia specification for friability is 1%. 10 tablets of (each brand) given sample were selected and weighed. All tablets were put into the drum of the friability tester. The rate of rotation was set to 25 rpm, time to 4 minutes and start the operation. At the end of the operation, all the tablets were removed and ensure freedom from dust or powder (use the brush). The tablets were reweighed. The percentage loss of weight was determined by using the formula below.(Huque, Brishti et al. 2017)

(Initial weight – Final weight) / Initial weight) x 100.

Limits: Compressed tablet should not lose more than 1% of its weight.

Disintegration:

Six tablets were taken from each brand of desloratadine and place it in basket rack assembly distilled water was taken as medium and the temperature was maintained at 37±0.5 centigrade. Note the time when the tablets were completely disintegrated(Etman, Gamal et al. 2014)

Limit: not more than 15 minutes.

Dissolution:

Dissolution test of desloratiidne was performed in USP type ii paddle apparatus 0.1N/HCL were selected as dissolution medium temperature of the medium was kept at 37±0.5 centigrade. 10 ml of Sample were taken at multiple point interval 5, 10, 15, 20, 30 and 45 minutes each time sample was replaced with freshly prepared medium. Filter 10 ml sample in Whatmann filter paper 0.45um and take the absorbance of the sample at 282 nm taking 0.1 NHCL as blank.(Falcão, de Melo Teixeira et al. 2017)

Limit: Not less than 80%.

Assay:

20 tablets were taken and weigh individually and note their average weight crush 20 tablets in morter and pestle take out powder equivalent to average weight and sonicate it 100 ml 0.1 N HCL for 5 minutes filter the sample through whatmann filter paper and take the absorbance at 280 nm using 0.1 N HCL as blank.(Abbas, Abbas et al. 2020)

Limit: 93.0%–105.0%.

Model Dependent Approach:

For the determination of absorption, distribution, metabolism, excretion, release from the porous system as well as change in surface area during dissolution and release from the matrix system can be accomplished by following kinetic model which included:

FIRST ORDER KINETIC:

Q_0 and Q_t represent the initial amount of drug in dosage form and amount release at time t.(Jain and Jain 2016)

$$\mathbf{Log\ Q = LogQ_0 - \frac{kt}{2.303}} \quad \mathbf{(1)}$$

Here,

t = time

K = First Order Rate constant

Higuchi model:

Higuchi constant is represented by $K_{HZ.}$(Jain and Jain 2016)

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

Hixson Crowell model:

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

Here,

KHC = Hixson–Crowell Rate constant.

Weibull model:

$$\mathbf{m = 1 - [- (t - Ti)\ \beta /\ ]} \quad \mathbf{(4)}$$

M = amount of drug dissolved as a function of time t.

M0 = total amount of drug being released.

T = lag time.

This model is useful in comparing the release patterns of matrix system

Eq.5 is arranged as follows:

$$\mathbf{Log\ [-(l - m)] = b\ log(t - Ti) - log\ \alpha} \quad \mathbf{(5).}$$

Model independent Approaches:

Difference factor (*f*1) and Similarity factor of (*f*2) of dissolution data will be accessed by following equations

$$\mathbf{f1 = [\sum_t^n = 1(R_t -) / \sum_t^n = 1R_t] \times 100} \quad \mathbf{(6)}$$

$$\mathbf{f2 = 50 \times log\ \{[1 + (1/N)\ \sum(Ri - Ti)^2]^{-0.5}\} \times 100} \quad \mathbf{(7).}$$

Number of samples (n), % release of the reference (Rt) and test (Tt) products.

Limits of Difference factor (f1) is 0-15 and Similarity factor of (f2) is 50 -100.

Table 1: Pharmacopeial and Non- Pharmacopeial Test of Desloratadine.

Code.	Weight (mg) Mean+SD (n=20)	Hardness(kg) Mean+SD (n=20)	Thickness (mm) Mean +SD (n=20)	Diameter (mm) Mean+SD (n=20)	Friability (%) (n=20)	Disintegration not> 15 (minutes)	ASSAY
P1	224.58±0.90	4.57±0.2	1.94±0.2	2.91±0.3	0.7%	4min7sec	101.8%
P2	224.48±0.94	4.48±0.3	1.95±0.1	2.35±0.3	0.9%	5min9sec	100.9%
P3	224.27±0.98	4.55±0.4	1.85±0.3	2.95±0.2	0.8%	7min20sec	101.9%

Table 2: Multiple Dissolution Studies of Desloratidine (5mg) at 0.1N HCL

TIME	P1	P2	P3
5	37.5	43.2	45.6
10	50.8	59.8	59.8
15	67.9	67.8	68.7
20	78.4	79.8	79.8
30	85.6	83.2	85.4
45	99.9	98.9	98.6

Table 3: f1 and f2 Tests With Reference Formulation P1.

Similarity *(f2)* and Dissimilarity *(f1)* factor at 0.1N HCl	**P2**	**P3**
f1 difference factor	4.67	4.95
f2 similarity factor	66.75	64.56

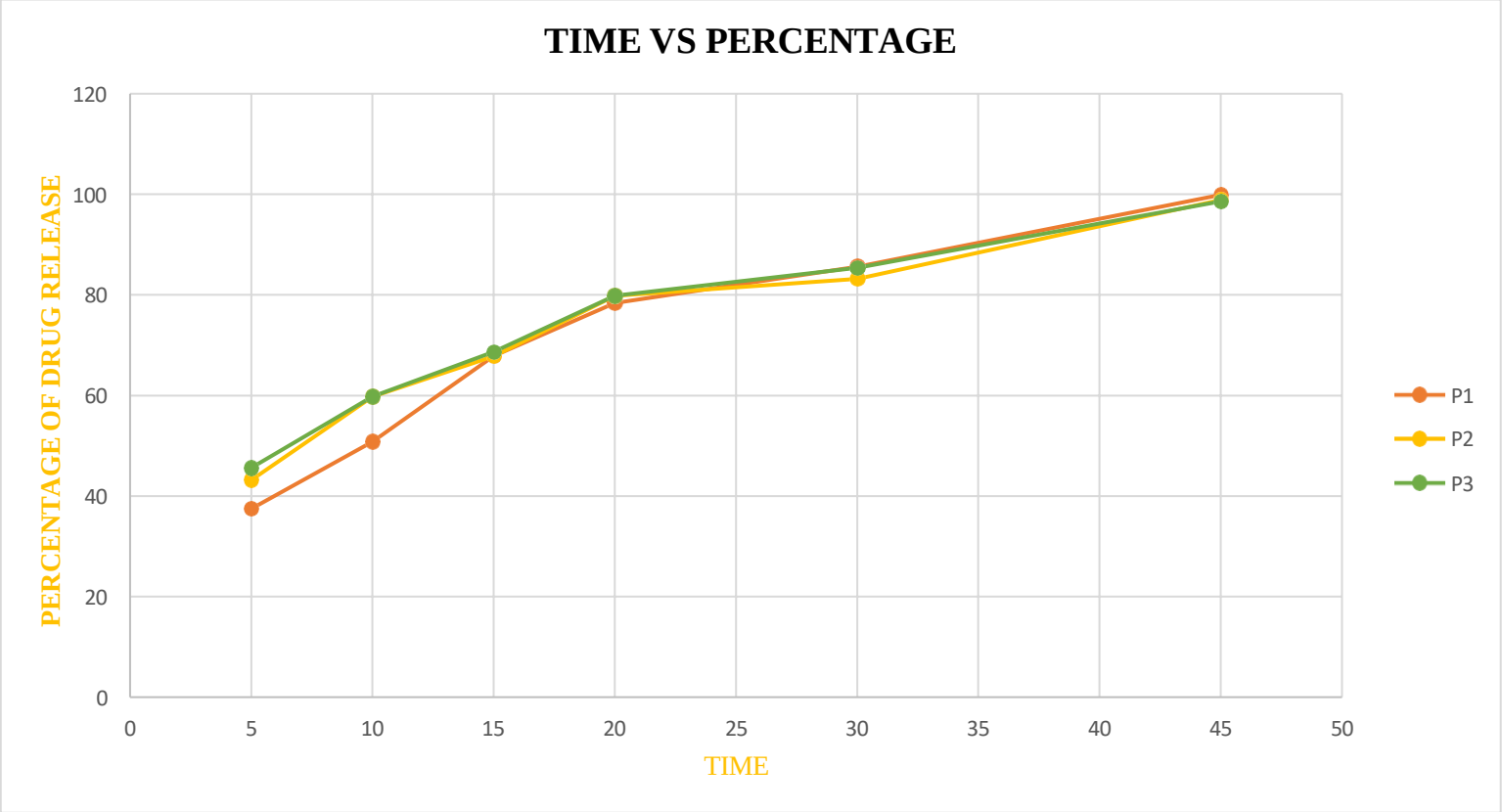

Table 4: Release kinetics of Coded Tablets of Desloratidine (5mg)

Coded Tablets	First Order		Higuchi		Hixon Crowell		Weibull Model		
	r^2	k_1(m)	r^2	kH (m-1/2)	r^2	kHC (m-1/3)	r^2	β	α
P1	0.97	0.076	0.94	15.97	0.93	0.021	0.98	1.35	57.34
P2	0.90	0.084	0.82	16.19	0.78	0.023	0.97	1.03	18.76
P3	0.89	0.087	0.79	16.34	0.76	0.023	0.98	1.24	44.65

Discussion:

The study conducted in Karachi, Pakistan, aimed to evaluate the quality of different brands of Desloratadine 5mg tablets available in the local market through a series of pharmacopeial and non-pharmacopeial tests. The findings of this research provide valuable insights into the quality and consistency of these pharmaceutical products. The study encompassed a comprehensive range of tests, including weight variation, hardness, thickness, diameter, disintegration, friability, and assay were also evaluated. As Weight variation is a critical process for the dose accuracy of tablets it reduces side effects of the drug and improve patient compliance (Etman, Gamal et al. 2014). In this study Weight variation were found to be 224.27±0.98-224.58±0.90 as shown in table 1. Frequent measurements of tablet diameter and thickness hold significant importance since the weight of a compressed tablet is intricately linked to parameters such as density, diameter, and thickness. This proactive approach to overseeing tablet dimensions at various stages of production acts as a pre-emptive strategy to avert potential challenges associated with tablet weight and uniformity in content, thereby addressing issues at an early stage of the manufacturing process (Akgeyik, KAYNAK et al. 2016) . In this study diameter and thickness were found to be in the range of 2.35±0.3 -2.95±0.2 and 1.95±0.1- 1.85±0.3 as shown in table 1. Disintegration shows that the time at which the drug is disintegrate in body into granules as it enhances dissolution of the drug and the drug will be bioavailable in the body (Du and Hoag 2003). According to USP the disintegration time of Desloratadine must be less than 15 minutes in our study the disintegration time of all the three brands were found to be 4-7 minutes as shown in table 1. Friability of the drug shows that the tablets withstand with the jerk and shocks it faces during transportation according to the USP Friability of the tablet should be less than 1% (Rockville 1995).In this study friability was found to be 0.7-0.8% as show in table 1. The assay results, performed in 0.1N HCL, showed that all three selected brands were close to 100%, with values ranging from 100.9% to 101.9% as shown in table 1, as assay indicates that how much active drug present in the tablet (Parmar, Tandel and Rabari 2015).This suggests that the tablets contained the expected amount of Desloratadine, reinforcing their potency. Dissolution indicates at how much time maximum drug will dissolve in the body and be bioavailable for further process such as absorption distribution , metabolism and excretion dissolution studies are crucial for understanding how quickly the drug is released from the tablets. According to the USP, more than 80% of the drug should be released at 45 minutes for Desloratadine. The findings revealed that all three brands met this criterion, with percentages of drug release ranging from 98.6% to 99.9% at 45 minutes as shown in table 2. This indicates that these tablets are likely to provide effective therapeutic outcomes. Kinetic The use of kinetic models, both model-dependent and model-independent, adds depth to the analysis. The tablets followed first-order and Weibull kinetics, which is valuable information for pharmaceutical manufacturers and regulatory agencies. It suggests that the drug release from these tablets follows predictable patterns. The study concludes by acknowledging the need for a larger sample size to be analysed. This implies that while the three selected brands appear to meet the required standards, it is essential to expand the scope of testing to ensure the generalizability of the findings to other brands in the market. In summary, this study provides a rigorous assessment of the quality of Desloratadine tablets in the Karachi market. The findings are largely positive, indicating that the selected brands are in compliance with pharmacopeial standards and release the drug efficiently. However, the call for a larger sample size underscores the importance of continuous monitoring and quality assurance in the pharmaceutical industry. Consumers can take confidence in the fact that these brands have passed stringent tests for quality and efficacy.

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