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Evaluation of Excipient Effects on Desloratadine Syrup formulation as Impurity and pH

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ABSTRACT

Objective: The aim of the research study is to compare the effects of excipient and pH and to develop a stable pharmaceutical product of desloratadine syrup formulation. For this stability study, 7 different formulation trial studies were prepared. In this study, different excipients were used and in this way different pH values were obtained to improve the product.

Methods: To improve the stability of desloratadine, 7 different formulations (F1-F7) were evaluated as different excipients, pH and impurities of desloratadine during the stability period. Each trial formulation was compared with pH and impurity results at different stability conditions at initial, 3rd month, 6th month.

Results: The most stable formulation study was evaluated within the pharmacopeia limits determined by comparing the stability results with each other in 7 different trial studies. According to the evaluation results, the F7 formulation was chosen as the most stable and best formulation in the studies.

Conclusion: According to the evaluation results, the F7 formulation was chosen as the most stable and best formulation in the studies.

Keywords: Drug formulation, desloratadine, syrup, excipient, pH, stability study, impurity, HPLC

INTRODUCTION

Desloratadine is a second-generation, tricyclic antihistamine which has a selective and peripheral H1-antagonist action. It is an effective descarboethoxy metabolite of loratadine (a second-generation histamine). Receptor-binding data specify that at a concentration of 2-3 mg/mL (7 nanomolars), desloratadine indicates significant interaction with the human histamine H1 receptor.[1] Desloratadines have a long-lasting effect and do not cause drowsiness because they do not readily enter into the central nervous system. Desloratadine belongs to the class of organic compounds known as benzocyclo-hepta-pyridines. These are aromatic compounds comprising a benzene ring and a pyridine ring fused to a 7-membered carbocycle. In general, many physical and chemical factors can have a negative effect on the stability of carbonic inhibitor.[2]

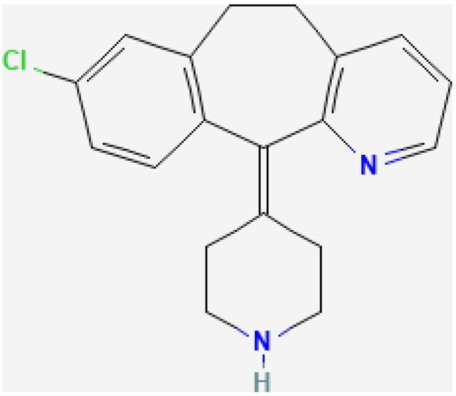

Figure 1. Desloratadine molecular structure[1]

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[1] https://pubchem.ncbi.nlm.nih.gov/compound/Desloratadine#section=2D-Structure

The chemical designation of desloratadine is 8-chloro-6,11-dihydro-11-(4-piperdinylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine. It is available as tablets and also available as syrup. It is a white to off-white powder that is slightly soluble in water but very soluble in ethanol and propylene glycol. The molecular formula of desloratadine is $C_{19}H_{19}ClN_2$ and the molecular weight is 310.8 g/mol. Desloratadine has a pyridine ring and a piperidine ring. A pyridine ring is a ring suitable for chemical interaction with ketone and aldehyde groups (Figure 1). Desloratadine molecular structure can be separated by proton donor. Because these groups are present in the molecule, Ethylenediamine Tetraacetic Acid (EDTA) should be used as the chelating aid. Due to its resistance to hydrolysis, EDTA can dissolve in water over a wide pH range with metal ions, which are not affected by temperature much, to form complexes. These complexes are particularly stable in the alkali environment and at high temperatures. EDTA provides the ligand function against the salts and ions in the raw materials in the product. Desloratadine and its compositions are prone to decomposition and oxidation by acidic excipients to form impurities such as deschlorodesloratadine, dehydrodesloratadine, and *N*-formyldesloratadine.[3] The desloratadine undergoes widespread degradation in the presence of common excipients such as lactose and stearic acid to form *N*-formyl desloratadine as a main degradation product. The basic salts of magnesium, calcium, or aluminum, plus avoidance of lactose and stearic acid, are used to control the degradation of desloratadine in liquid pharmaceutical compositions. Because of the widespread degradation of desloratadine in the presence of excipients such as lactose to form *N*-formyl desloratadine as a significant degradation product, the use of an effective stabilizer to increase the stability of the composition would be an important improvement in the field of therapeutic compositions.[4] The amount of EDTA to be used in the product is determined in the experiments for optimum impurity values. The buffering agents used for adjusting the product pH were quantified for experiments with minimum impurity. In addition, the pH of the product is investigated in the experiments made with the change of impurity.

METHODS

All trials are produced by using desloratadine of Vasudha Pharma Chem Ltd, Hindistan. Physical and chemical tests are made to justify the suitability of active substance to its specifications. As excipients, sodium methyl parahydroxybenzoate and sodium propyl parahydroxybenzoate are produced by Clarient, Switzerland, glycerol by Vance Bioenergy, Malezya, propylene glycol by Dow, United States, citric acid monohydrate by Jungbunzlauer, Basel Switzerland, sucrose by Çallı Gıda, Ataşehir/İstanbul, and orange flavor by Firmenich, Switzerland.

The syrup production method generally consists of a raw material weighing process, heating–cooling, solution preparation, mixing, and analytical analysis. A mechanical mixer, heater, and weighing device were used during the production of the product.[5] All production steps are detailed below. All excipients used in the trials are conventional raw materials used in pharmaceutical syrup formulations. In the stability analysis, the batch size is 150 mL for each trial. At the end of these trials, the product is placed in a 150 mL amber-colored glass bottle.

General Description of Production Process

1. Pure water is taken 40% of the total volume and to the main production tank and heated at 75-80°C.
2. Antimicrobial agents and sweeteners are added to the main production beaker of the heated 40% water. It is stirred until it becomes a clear solution.
3. In another preparation beaker, the stabilizer is heated at 40-50°C. Desloratadine raw material is added to the solution in the another production beaker in heated water.
4. The main production tank containing the solution obtained in step 2 is cooled to 40-50°C. Buffering and stabilizing agents are added to the solution obtained. It is stirred until it becomes a clear solution. The solution obtained in step 3 is added to the main solution by constant stirring. It is stirred until it becomes a clear solution.
5. A lubricant is added to the solution obtained in step 4, and with stirring, the solution is cooled to 30 ± 2°C.
6. Flavor is added to the solution obtained in step 5. It is stirred until it becomes a clear solution. A coloring agent is added to the solution obtained. The resulting solution is made up to volume and mixed for 10 minutes.
7. The solution obtained is filtered through 20 µm filters and filtered into the storage bottle.

Formulation trials from the desloratadine syrup F1-F7 are shown in Table 1. The combination of trials for minimum impurity with different excipients is presented below.

Through this experiment, we find that by adding a pH regulatoragent, a stable buffer system is formed. The pH value of the syrup and the kind of buffer system all can have an influence on the stability of formulation.[6] In these studies, all trials are prepared at optimum pH values and filtered. The prepared syrup is in the process of long-term stability. A significant change in pH and results above the pharmakope limits as impurities mean that the experiment is inappropriate..[7]

Trials are performed at different pH values. Various trials are performed with buffering agents (sodium citrate dihydrate and citric

Table 1. Formulation Trials

Function	Ingredients	F1 (g/150 mL)	F2 (g/150 mL)	F3 (g/150 mL)	F4 (g/150 mL)	F5 (g/150 mL)	F6 (g/150 mL)	F7 (g/150 mL)
API	Desloratadine	0.075	0.075	0.075	0.075	0.075	0.075	0.075
Sweet agent	Sucrose	90.00	90.00	90.00	90.00	90.00	90.00	90.00
Lubricant	Glycerol	7.50	7.50	7.50	7.50	7.50	7.50	7.50
Preservative	Sodium methyl hydroxybenzoate	0.15	0.15	0.15	0.15	0.15	0.15	0.15
Preservative	Sodium propyl hydroxybenzoate	0.015	0.015	0.015	0.015	0.015	0.015	0.015
Antimicrobial agent	Propylene glycol	12.60	12.60	12.60	12.60	12.60	12.60	12.60
Buffering agent	Sodium citrate dihydrate	–	–	–	–	0.189	0.189	0.189
Buffering agent	Citric acid monohydrate	0.35	0.35	0.35	0.75	–	0.350	0.150
Chelating agent	EDTA	0.0375	0.075	0.150	0.0375	0.0375	0.0375	0.0375
Flavoring agent	Orange flavor	0.0075	0.0075	0.0075	0.0075	0.0075	0.0075	0.0075
Coloring agent	Sunset yellow	0.0012	0.0012	0.0012	0.0012	0.0012	0.0012	0.0012
Solvent	Purified water	To 150 mL	To 150 mL	To 150 mL	To 150 mL	To 150 mL	To 150 mL	To 150 mL

Table 2. The pH Values of the Finished Product Trials

	F1	F2	F3	F4	F5	F6	F7
pH	3.8	3.8	3.8	3.0	8.9	4.6	5.7

acid monohydrate) and chelating agent (EDTA). Since the amount of citric acid is 0.35 g/150 mL in the first 3 trials, the product is measured at acidic values. Sodium citrate dihydrate was used instead of citric acid in the F5 experiment for more basic pH results, whereby pH 8.9 was measured (Table 2). In the F6 trial, citric acid monohydrate and sodium citrate dihydrate were used together and the pH measured is 4.6. In the last trial, it is aimed to increase the pH to neutral level by reducing the amount of citric acid according to F6.

Preparation of Formulations for Stability Test

Product stability studies have been tested at 3 different temperature and humidity values. These values were taken according to the ICH guide. Long-term period (25°C ± 2°C; 60% ± 5% Relative humidity (RH)), Intermediate period (30°C ± 2°C; 65% BN ± 5% RH) Accelerated stability (40°C ± 2°C; 75% RH ± 5% RH). Samples were tested at the beginning of the stability, at the third month, and at the sixth month by impurity and pH tests.

Analytical Methods

Chemicals and Reagents

The pharmaceutical grade sample of desloratadine, impurity-A (methyl loratadine), impurity B (loratadine), and impurity-C (n-formyl loratadine) is purchased from Vasudha Pharma Chem Ltd. The injection water (0.05 µc) is produced by the Sartorius system as High Performance Liquid Chromatography (HPLC) grade.

HPLC Chromatographic Conditions of Desloratadine-Related Substances

HPLC, Av. Headlight. According to the current publication, monograph 2.2.29 limit is below.

Impurity A: 1.0%
Impurity B: 1.0%
Impurity C: 1.0%
Unknown impurity: 0.4%
Total impurity: 3.0%

Column	Inertsil ODS-2 5µm 150 mm × 3.0 mm or equivalent
Flow rate	0.7 mL/min
Dedector	UV, 278 nm
Injection volume	20 µL
Column temperature	40°C
Autosampler temperature	25°C
Filter	0.45 µm Polytetrafluoroethylene (PTFE)
Dilution solution	Moving phase B

Mobile phase A: 1.36 g KH_2PO_4 and 0.96 g pentane-1-sulfonic acid sodium salt are weighed and dissolved in 1000 mL distilled water. The pH was adjusted to 3.0 ± 0.05 with 2M phosphoric acid. It is mixed and degasified.

Mobile phase B: 0.5 mL trifluoroacetic acid is taken into a 1 L flask and filled with pure water.

The solution is mixed with methanol at a ratio of 90 : 10 (v/v). It is degassed.

Mobile phase C: Acetonitrile[8]

Preparations of a Standard Solution

About 25 mg desloratadine Working standart (WS) is exactly weighed and transferred into a 100 mL volumetric flask. It is dissolved in an ultrasonic bath for 5 minutes by adding 70.0 mL of solvent to it. This is made up to 100 mL volume with solvent. About 1 mL of this solution is taken and transferred to a 100 mL volumetric flask. The flask is made up to the volume by filling with the solvent. It is thoroughly mixed. About 4 mL of this solution is transferred to a 10 mL volumetric flask and filled with solvent in volume. It is mixed well. It is filtered through 0.45 µm PTFE filter and taken into the HPLC vial ($C_{Desloratadine}$: 0.001mg/mL).[9]

Sample Solution (2 Parallel sample solution prepared)

The syrup sample equivalent to 2.50 mg desloratadine is exactly weighed and transferred to a 10 mL volumetric flask. It is dissolved in an ultrasonic bath for 5 minutes by adding dilution solution to it. Make up to its volume with dilution solution. It is filtered through 0.45 µm PTFE filter and taken into the HPLC vial ($C_{Desloratadine}$: 0.25 mg/mL).

Procedure

After the column is equilibrated, dilution solution (1 time), standard solution (6 times), placebo solution (1 time), and sample solutions (once) are injected.

System Compatibility

"The area relative standard deviation (RSD) of the desloratadine peak in the standard solution of 6 consecutive injections should not be more than 5.0%."

The theoretical plate number for desloratadine should be at least 2000.

About Relative Retention Time (RRT)

- Desloratadine (approximately RT 11.5) 1.0
- Impurity A: (methyl loratadine) 1.2
- Impurity B (loratadine) 2.6
- Impurity C (*N*-formyl loratadine) 1.6
- The peaks from the placebo and blank chromatograms and those below 0.05% are ignored.

Calculation:

% Known and unknown impurity:

$$\frac{A_n}{A_s} \times \frac{W_s}{100} \times \frac{1}{100} \times \frac{4}{10} \times \frac{P}{100} \times \frac{100-WC}{100} \times \frac{10}{W_n} \times \frac{d}{L} \times 100$$

An, area of known and unknown impurity peak in sample solution; As desloratadine mean peak area in standard solution; Ws, desloratadine required for standard solution WS weight, mg; Wn the weight of the sample required for the sample solution, g; P, desloratadine WS dry potency, %; WC, desloratadine WS water amount, %; d, density of the sample, g/mL; Label value, 2.5 mg/5 mL.

Validation of Related Substance Method by HPLC

The optimized HPLC method is validated according to guideline vspecificity, linearity, accuracy, precision (system, method, and intermediate precision), and robustness. It's shown in Table 6.

Table 3. Initial Column Area, Second Column Area, and Percent Change

	Initial Column Area	Second Column Area	% Change
Desloratadine	47 616	48 506	1.87
İmpurity A	112 024	111 688	0.30
İmpurity C	124 900	123 118	1.43
İmpurity B	110 344	108 590	1.59

Table 4. This Solution Is Analyzed After Changing the Initial pH of Desloratadine Mobile Phase to pH 2.95

	Initial Area (pH:3.00)	After change Area (pH:2.95)	% Change
Desloratadine	47 616	48 528	1.92
Impurity A	112 024	111 410	0.55
Impurity C	124 900	123 173	1.38
Impurity B	110 344	108 597	1.58

Table 5. This Solution Is analyzed After Changing the Initial pH of Desloratadine Mobile Phase to pH 3.05

	Initial Area (pH:3.00)	After change Area (pH:2.95)	% Change
Desloratadine	47 616	48 841	2.57
Impurity A	112 024	111 095	0.83
Impurity C	124 900	123 312	1.27
Impurity B	110 344	108 592	1.59

Table 6. Relative Standard Deviation (RSD) Parameters and Results

Parameter		Result
Linearity	Range	LOQ-140.0%
	Equation	$y = 12\ 117\ 723.7107x\ 333.0610$
	Correlation coefficient	$r^2 = 1.0000$
Accuracy	Range average	80.0%-120.0%
	95% confidence interval limits	99.29-100.15
Precision	System precision	RSD = 0.31%
	Method precision	Total impurity RSD = 0.95%
	Intermediate precision	Total impurity RSD = 7.02%

LOQ, Limit of Quantification.

Column

The standard solution is prepared as specified in the desloratadine method.

This solution is analyzed in the starting column and after column change. Results are compared to baseline and the percent change was calculated. It's shown in Tables 3, 4 and 5.

pH of Mobile Phase

The standard solution is prepared as specified in the method.

System precision is conducted with 6 repeated injections of stock solutions prepared at 100% concentration, and the RSD of peak areas is found to be below 10%. Method precision is performed by preparing 6 sample solutions described in validation of Related Substance Method by HPLC part. Relative standard deviations were calculated, and the results were found to be below 10.0%. Intermediate precision is studied by different analysts and with different devices. Each analyst prepared 1 standard solution and 6 sample solutions. All the results were compared and RSD is calculated (Table 6).

To validate the sturdiness of the developed method, system parameters were certified, and standard solutions were tested. Hplc column temperature was changed to 40°C ± 2°C and mobile phase ratio was changed to 100 ± 5.0 mL and different lot numbered columns were used. Percent variations were calculated, and no important difference was found between initial and changed conditions.

Table 8. pH of Desloratadine Syrup Formulations During the Initial Stability Period

	F1	F2	F3	F4	F5	F6	F7
pH	3.8	3.8	3.8	3.0	8.9	4.6	5.7

Table 9. Impurity of Desloratadine Syrup Formulations During (40°C±2°C; 75%+5 RH) the Third-Month Stability Period

	ICH Limits	F1 (g/150 mL)	F2 (g/ 150 mL)	F3 (g/150 mL)	F4 (g/150 mL)	F5 (g/150 mL)	F6 (g/150 mL)	F7 (g/150 mL)
Impurity A	1.0%	ND	ND	ND	ND	ND	ND	ND
Impurity B	1.0%	ND	ND	ND	ND	ND	ND	ND
Impurity C	1.0%	ND	ND	ND	ND	ND	ND	ND
Unknown impurity	0.4%	1.62%	1.56%	1.50%	2.23%	0.38%	0.63%	0.05%
Total impurity	3.0%	1.72%	1.66%	1.60%	2.34%	1.28%	0.73%	0.05%

ND, not detected.

Table 10. pH of Desloratadine Syrup Formulations During (40°C±2°C; 75%+5 RH) the Third-Month Stability Period

	F1	F2	F3	F4	F5	F6	F7
pH	3.9	3.8	3.9	3.1	8.8	4.6	5.7

Also, solution stability is evaluated by pursuing the peak area response. Sample and standard solutions were analyzed shortly after their preparation 12, 24, and 48 hours after at room temperature. Results were compared and percent variations were calculated, and all results were below 10%.

RESULTS

Our studies are formulated with different excipients from F1 to F7. The syrup is made as described in the description of production process in general. Initial impurity and pH results in desloratadine syrup formulation trials are shown in Tables 7 and 8.

Product stability studies were performed on the stability batch according to the ICH requirements. Samples are stored at 40°C/75% RH for 3 and 6 months. No trends are observed during storage, and the results were not affected by the fill volume or storage position. Trials are stored at 40°C and 75% RH relative humidity for 3 and 6 months. The bottles are in an upright position during storage.[10]

Desloratadine syrup trials are carried out in amber-colored glass bottles.

In the production of Trials F1, F2 and F3, edta, whose chelator and antioxidant synergist properties were used in the product composition, was used as a multiplexed dose in these 3 formulations. By catalyzing the autoxidation reactions, it is thought to reduce the oxidation of desloratadine during stability by forming chelates with trace amounts of metal ions. In these 3 trials, the pH value was targeted to an acidic pH of 3.8 with Citric acid monohydrate and 0.35 g/150 mL was used in the F1, F2, F3 trials.

The effect of the amount of citric acid and sodium citrate dihydrate used as buffering agent on the changes of impurity and pH is investigated by keeping the EDTA amount constant in F4, F5,

Table 7. Impurity of Desloratadine Syrup Formulations During the Initial Stability Period

	ICH Limits	F1 (g/150 mL)	F2 (g/150 mL)	F3 (g/150 mL)	F4 (g/150 mL)	F5 (g/150 mL)	F6 (g/150 mL)	F7 (g/150 mL)
Impurity A	1.0%	ND	ND	ND	ND	ND	ND	ND
Impurity B	1.0%	ND	ND	ND	ND	ND	ND	ND
Impurity C	1.0%	ND	ND	ND	ND	ND	ND	ND
Unknown impurity	0.4%	0.05%	0.05%	0.05%	0.05%	0.05%	0.03%	0.06%
Total impurity	3.0%	0.05%	0.05%	0.05%	0.05%	0.05%	0.03%	0.06%

ND, not detected.

Table 11. Impurity of Desloratadine Syrup Formulations During (40°C ± 2°C; 75% RH ± 5% RH) the Sixth-Month Stability Period

	ICH Limits	F1 (g/150 mL)	F2 (g/150 mL)	F3 (g/150 mL)	F4 (g/150 mL)	F5 (g/150 mL)	F6 (g/150 mL)	F7 (g/150 mL)
Impurity A	1.0%	ND	ND	ND	ND	ND	ND	ND
Impurity B	1.0%	ND	ND	ND	ND	ND	ND	ND
Impurity C	1.0%	ND	ND	ND	ND	ND	ND	ND
Unknown impurity	0.4%	5.1%	5.4%	5.3%	5.6%	0.5%	3.0%	0.16%
Total impurity	3.0%	5.1%	5.4%	5.3%	5.6%	1.5%	3.0%	0.27%

Out-of-limit results are shown in red.

Table 12. pH of Desloratadine Syrup Formulations During (40°C±2° C; 75%+5 RH) the Sixth-Month Stability Period

	F1	F2	F3	F4	F5	F6	F7
pH	3.9	3.7	4.0	3.1	8.8	4.7	5.7

and F6. In these trials, pH 3.8 in F4, pH 8.9 in F5, and pH 4.6 in F6 were measured.

In F7 trial, impurity results at different pH values were evaluated over F6 formulation. Compared to the F6 trial, citric acid monohydrate was used to make the pH 5.7 in the F7 trial. Initial, 3rd month and 6th month stability impurity and pH results of all trials are shown in the Tables 8-12.

As shown in Table 7 of the initial impurity results, all results are within the limit. The initial results were analyzed on the day of production. The assays were tested at room temperature. When the results are examined, it is seen that other experiments give similar results. In the initial impurity results, the unknown impurity disregard value is 0.05%, which can be considered due to contamination during production.

According to the results of the third month analysis, edta was used in amounts of F1 (0.0375 g/150 mL), F2 (0.075 g/150 mL) and F3 (0.150 g/150 mL). Increasing edta concentration in the trials did not significantly change the desloratadine impurty results. Increasing the amount of citric acid in F4 caused impurity increase. In the first 4 trials, the unknown impregnation of desloratadine at 40°C±2°C 75% RH is beyond the limit. In these 3 trials, the product is degraded by the reaction of amine groups in the molecule due to the acidic pH value of the product to the highly unknown impurity. Citric acid monohydrate was not used in experiment F5 because it was desired to evaluate the impurity performance of alkaline solution as opposed to acidic solution in this trial. High pH value caused impurity C increase. In the F6 trial using citric acid monohydrate and sodium citrate dihydrate, the unknown impurity limit is within the total impurity limit. In the last trial, the level of unknown and total impurity disregard is 0.05%.

Basing on the results of sixth-month analysis, in F1, F2, F3, and F4 trials, unknown impurity and total impurity values are above ICH limits. This is due to the degradation of the pyridine and piperidine groups which exhibit basic character in the acidic product. This situation has increased the unknown impurity not called impurity A, impurity B, and impurity C.

In the F5 trial, the unknown impurity decreased by 90% compared to the F1, F2, F3, and F4 trials. However, the unknown impurity is 40% above the ICH limits. Total impurity is within the limit. Such a reduction in the unknown impurity depends on the alkaline pH of the product.

In the F6 trial, the product is used as much as citric acid monohydrate used in F1, F2, and F3 trials. In this experiment, unlike F1, F2, and F3, the buffering agent sodium citrate dihydrate is used, and the pH is around 4.6. This is 750% higher than the upper limit of unknown impurity. Factors causing such a high impregnation caused degradation of desloratadine by oxidation of the pyridine group.

Since the product is known to increase impurity when it is acidic in the F7 trial, the product is made at 5.7—a pH close to neutral pH. Citric acid monohydrate amount has been reduced in order to provide this pH value in F7. Thus, unknown impurity and total impurity are within the limit and at minimum values. In all experiments, unknown impregnation problem in desloratadine syrup formulation is completed with trial studies. As a result of the experiments, the optimum pH value of the product is found.

The research study is aimed at developing a syrup form of a desloratadine formulation during the stability impurity period. Based on the physicochemical properties of desloratadine and buffering and chelating excipients, the impurity parameter is optimized combination F7 formulation. The F7 formulation was selected for stability studies (40°C±2°C; 75%+5RH) for a time period of 3 and 6 months.[11] The formulations were appraised for the pH and related substances. From 3. month stability data, F7 formulation was found to be more stable than other trials in Impurity A, B, C, unknown Impurity and Total Impurity parameter. As shown in the tables, the stability data of the F7 formulation are suitable for ICH specifications. With the amount of excipients and formulation trials, impurity has been improved and the pH value has been brought to pH 5.5-6.0 values, and product safety and stability have been increased.

Ethics Committee Approval: This study has not been tested on a patient for whom an indication study has not been performed. only as a formulation, it has been made more stable with certain parameter changes.

Informed Consent: This study has not been tested on a patient for whom an indication study has not been performed. only as a formulation, it has been made more stable with certain parameter changes. therefore, patient consent is not required.

Peer-review: Externally peer-reviewed.

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