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In Vitro Stability Assessment of Ketoprofen Tablets Under ICHQ1A Guideline

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ABSTRACT

One of the critical components of the pharmaceutical industry is the capacity of pharmaceutical forms to remain stable over time and maintain their quality under different storage and transportation circumstances. Therefore, the amount of active components in the pharmaceutical form is evaluated following the ICHQ1A standards of the European Pharmacopoeia to ascertain the validity of the pharmaceutical product. This paper aims to investigate the stability of 100 mg ketoprofen tablets. Short-term stability experiments were conducted under accelerated conditions (6 months) at 40 ± 2 °C and 75 ± 5% relative humidity, while long-term stability studies (36 months) were conducted at 25 ± 2 °C and 60 ± 5% relative humidity. Using high-performance liquid chromatography, the amount of ketoprofen released from the 100 mg ketoprofen pills was ascertained. These investigations showed that 100 mg ketoprofen tablets have a shelf life of three years and after 36 months, the ketoprofen content of the tablets was more than 95%.

Keywords: Ketoprofen, Stability, *in vitro*, ICHQ1A norms

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Introduction

Data on the quality of medications and different pharmacological forms can be found in the European Pharmacopoeia's ICHQ1A standards [1, 2]. One essential prerequisite for achieving the desired therapeutic effect is the pharmaceutical forms' long-term stability and the preservation of product quality from preparation to usage [3]. The European Pharmacopoeia states that one of the most important steps in determining the legitimacy of a pharmaceutical product is to examine the stability of the active ingredients in different pharmacological forms [4]. A global stability study lead was established and tests were selected based on local climates to determine the active ingredient and final product. The conditions for those studies were as follows: for a long-term study (at least 12 months) at 25 ± 2 °C and relative humidity 60 ± 5%, and for a short-term study (6 months) at 40 ± 2 °C and relative humidity 75 ± 5% [4].

The stability test's objective is to demonstrate the quality of material in a certain pharmaceutical form and how external variables like temperature, humidity, and light affect that quality. The stability study's data must attest to the pharmaceutical product's continued compliance with its standards throughout its validity in the area where it is registered. The drug is evaluated by stress testing in high-humidity and high-temperature environments. The information gathered helps comprehend the drug's stability profile throughout production, storage, and transportation. These investigations shed light on the breakdown products and identify the processes that cause pharmaceutical drugs to deteriorate. When 5–20% of the active ingredient is gone, the stability under stress investigation should be stopped [4].

One medication with an anti-inflammatory effect that is a member of the non-steroidal anti-inflammatory drug class is ketoprofen. The Rhone-Poulenc Research Laboratories in Paris created ketoprofen for the first time in 1967, and in 1973 it received approval for usage in both France and the UK. The Food and Drug Administration (FDA) authorized the use of ketoprofen to treat rheumatoid arthritis a few years later.

Several acute and chronic inflammatory conditions, including rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis, are treated with ketoprofen, also known as 2- (3-benzoylphenyl) propionic acid [5-7]. Recent years have seen positive therapy outcomes in the prevention of neurological illnesses like Parkinson's and Alzheimer's as well as colorectal cancer [8]. This medication comes in the following forms: capsule, tablet, injectable solution, suppository, and gel [9].

It is described as a white, crystalline powder that melts between 93-96 °C [10, 11]. It dissolves in extremely alkaline solutions, methylene chloride, ethanol, and acetone [12]. It dissolves somewhat in acidic and watery solutions [13].

Numerous techniques, including electrophoresis [14], spectrophotometry [13], high-performance liquid chromatography (HPLC) [15-18], electrochemical approaches [19, 20], and FT-IR spectrometry [21] are used to identify ketoprofen in pharmaceutical formulations.

The purpose of this work is to demonstrate the in vitro stability of ketoprofen embedded in solid pharmaceutical forms (coated tablets) over time in the presence of stressors like high humidity and temperature. The stability investigations were conducted following European Pharmacopoeia ICHQ1A criteria. Both short-term (6 months) and accelerated settings (temperature 40 ± 2 °C and relative humidity 75 ± 5%) as well as long-term (36 months) and conditions with temperature 25 ± 2 °C and relative humidity 60 ± 5% were used to conduct stability experiments of ketoprofen tablets.

Under the same conditions, the average mass of the pills was monitored over time.

Based on the stability evaluations, it was decided if the evaluated pharmaceutical form satisfies the quality standards for the entire validity period specified at the time of pharmaceutical market placement.

Materials and Methods

Dosage of ketoprofen from 100 mg film-coated tablets by HPLC-UV method

Using an Able and Jasco chromatograph made up of the following modules: PU-1580 pump module, LG-980-02S ternary gradient module, DG-980-50 degasser module, UV 1575 detector module, and Rheodyne manual injector, the analyses to ascertain the concentration of ketoprofen were carried out using HPLC chromatography [15, 22]. It was a Nucleosil 150 C18, 5μm, 150 x 4.6 mm chromatographic column. At a flow rate of 0.5 ml/min, the mobile phase was composed of acetonitrile, double-distilled water, and 1% acetic acid. At λ = 254 nm, detection was carried out.

Ten tablets containing 100 mg of ketoprofen were combined (at various intervals). Next, methanol and powder equal to one tablet's weight (about 311 mg) are combined in a 100 ml volumetric flask. After a methanol dilution yields a solution with a concentration of 0.1 mg/ml, it is filtered and its content of ketoprofen is calculated using the following equation and the calibration curve created using ketoprofen (pure substance): y = 1.1159 x.

Stability study in accelerated conditions in the short term

At a temp of 40 ± 2 °C and relative humidity of 75 ± 5%, samples were obtained at three as well as six months, correspondingly, to check for stability [3]. Using the above-described working procedure, the HPLC method was used in the research to establish the amount of ketoprofen. Ten pills were utilized for each series, and all analyses were carried out in triplicate.

Long-term stability study

The samples were kept in climatic chambers with a temperature of 25 ± 2 °C and a relative humidity of 60 ± 5% throughout the investigation. Assessments were conducted at the start and 3, 6, 9, 12, 18, 24, and 36 months [3]. Three sets of ten tablets each were used for the determinations.

Determination of the variation of the average mass per film-coated tablet with the concentration of 100 mg ketoprofen in accelerated short-term and long-term stability study conditions

The average mass per tablet, expressed in milligrams, was calculated under the previously mentioned conditions for the short-term and long-term assessment of the stability of 100 mg film-coated ketoprofen tablets. As a result, 20 film-coated tablets were weighed separately and consecutively at 3, 6, 9, 12, 18, 24, and 36 months for the long-term stability research, and at 3 and 6 months for the short-term stability study under accelerated settings [22, 23].

No more than two tablets should deviate from the average mass by more than 7.5% to satisfy the quality requirements for film-coated tablets containing 100 mg of ketoprofen [4].

Results and Discussion

The resulting outcomes, which are shown in **Figure 1**, were attained at the designated intervals of 3 and 6 months after the stability research method was applied to ketoprofen in the form of film-coated tablets under accelerated and short-term settings.

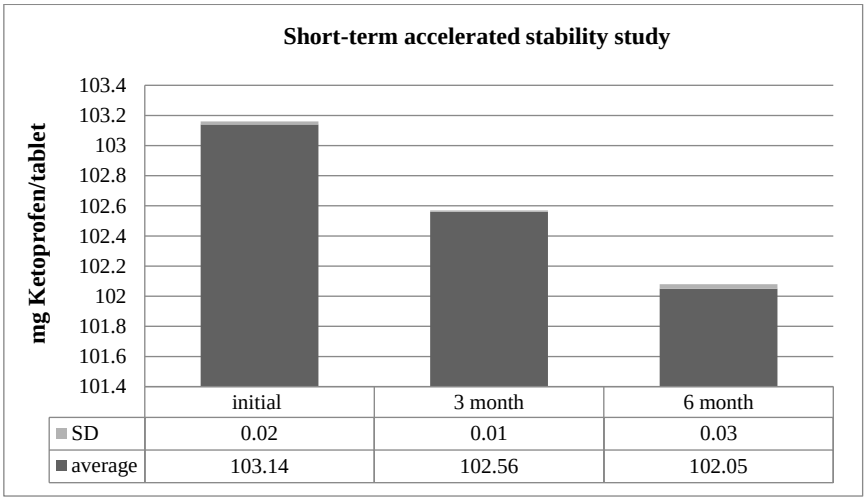


Figure 1. Findings from the study on the temporal stability of ketoprofen tablets at 40 ± 2 °C and relative humidity of 75 ± 5%.

As shown in **Figure 2**, the fluctuation in the amount of ketoprofen in pills as a consequence of time is therefore represented by a line with the equation: y = -0.18 x + 103.1 (where x = time expressed in months and y = ketoprofen content expressed in mg ketoprofen per tablet).
Using similar test conditions, the line that shows the variation in the amount of ketoprofen in tablets after dissolution has an equation as follows with a 95% confidence factor (the lowest allowed by the quality criteria of the European Pharmacopoeia):
y = -0.2117 x + 103.15

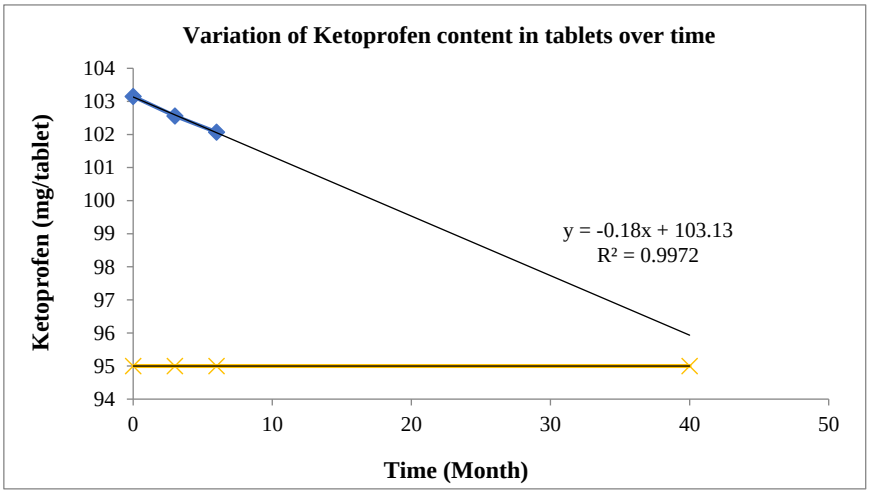
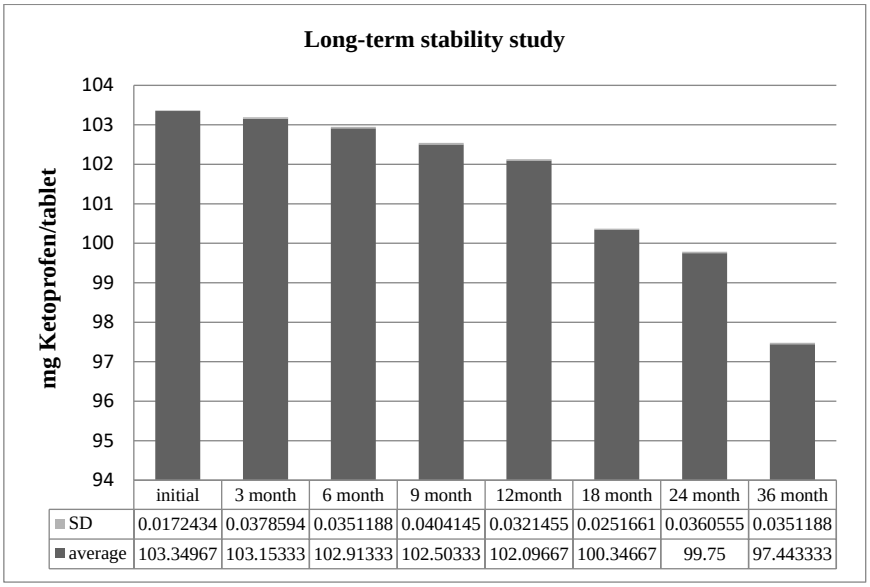


Figure 2. How the HPLC method changed the amount of ketoprofen in tablets over three and six months under temporary accelerated settings.

The following results were obtained for film-coated tablets of ketoprofen utilizing the long-term technique of stability study at 25 ± 2 °C and 60 ± 5% relative humidity at the specified time intervals (3, 6, 9, 12, 18, 24, 36 months). These data are displayed in **Figure 3**.



	initial	3 month	6 month	9 month	12month	18 month	24 month	36 month
SD	0.0172434	0.0378594	0.0351188	0.0404145	0.0321455	0.0251661	0.0360555	0.0351188
average	103.34967	103.15333	102.91333	102.50333	102.09667	100.34667	99.75	97.443333

Figure 3. The outcome of the ketoprofen time stability investigation in tablets at 25 ± 2 °C and 60 ± 5% relative humidity.

The long-term stability research aimed to verify the validity period by looking at how the quality metrics developed. The fluctuation of the tablets' ketoprofen content as a function of time is depicted by a line with the equation y = -0.1724 x + 103.77, where y = ketoprofen content expressed in mg/tablet and x = time expressed in months **(Figure 4)**.

At a 95% confidence level, the equation for the line that shows the variation in the amount of ketoprofen in the tablets is y = -0.1731 x 36 + 103.35.

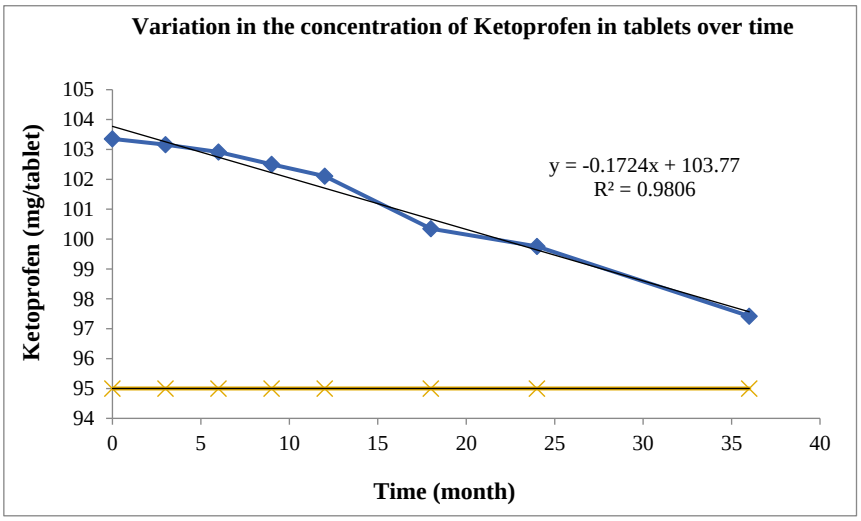


Figure 4. Variation of ketoprofen content in tablets over 3, 6, 9, 12, 18, 24, and 36 months in long-term accelerated conditions determined by HPLC method.

According to the European Pharmacopoeia, it is crucial to preserve a uniform mass of the solid pharmaceutical form as part of similar testing conditions while analyzing the stability of the active ingredients in various pharmaceutical types in addition to modifications in the active ingredient's concentration at various temperature and humidity conditions. In the case of the 100 mg ketoprofen tablets, it is therefore recommended to determine the variation of the average mass per film-coated tablet. Both short-term and long-term accelerated stability research settings were used for this test, and the results are displayed in **Table 1**.

These statistics indicate the mean of 20 pill weights recorded across time.

Table 1. The mean mass variation, measured in milligrams, for film-coated tablets containing 100 milligrams of ketoprofen indicated stability in both short-term and long-term accelerated experiments.

	Short-term accelerated stability study (months)			**Long-term stability study (months)**							
	Initial	3	6	Initial	3	6	9	12	18	24	36
Average mg/tablet	311.5	311.44	311.37	311.51	311.51	311.5	311.5	311.49	311.48	311.48	311.48
± SD	0.57	0.69	0.79	0.57	0.57	0.57	0.57	0.56	0.56	0.57	0.57

Estimating the validity duration and any adverse consequences was the goal of the short-term stability investigation.

At three and six months, respectively, the change in the amount of ketoprofen in the tablets over time was brought to light. The confidence factor, based on the actual norms, is ninety-five of the overall quantity of ketoprofen reported (in this case, 100 mg per tablet).

The proportion of active ingredients in tablets is 95.53% following six months, The findings of this study on the dependability of ketoprofen tablets under brief, accelerated temperature and humidity conditions indicate that there has been no exceeding of the confidence factor. Accordingly, after 36 months (the recommended validity period), the proportion of ketoprofen in tablets consumed at accelerated settings would be precisely 94.93% (value deemed permissible), which is slightly less than the confidence coefficient.

Following the European Pharmacopoeia's ICHQ1A criteria, long-term studies are conducted to assess the stability of ketoprofen over three years, which is designated as the investigated tablets' validity period. Therefore, values of 97.12% were also reached by conducting investigations over a lengthy period (0-36 months), which does not surpass the confidence factor set by the European Pharmacopoeia's quality standards. This indicates that the active ingredient content of the 100 mg ketoprofen tablets examined here is consistent throughout the validity period.

Over three years, the amount of ketoprofen, the active ingredient, has steadily declined by 1.7%, according to a long-term stability study. This result is much smaller than the 3 mg/tablet amount observed in the tablet stability research.

We also showed that the mass of the tablets stayed constant for three to six months and three to thirty-six months, respectively. This means that the tablets coated with 100 mg ketoprofen meet quality criteria, with an average mass of the tablets that did not deviate by more than 7.5%, the limit specified by the European Pharmacopoeia [4].

Conclusion

The stability research results demonstrated that, throughout their validity, the 100 mg ketoprofen tablets satisfied the quality standards established by the European Pharmacopoeia's ICHQ1A recommendation. Even after 36 months (the package's maximum validity term), the percentage of active ingredients is higher than the necessary 95%.

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Conflict of Interest: None

Financial Support: None

Ethics Statement: None

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