METHOD OPTIMIZATION FOR KETOPROFEN TABLET DISSOLUTION: ENHANCED EFFICIENCY THROUGH MODIFIED TEST CONDITIONS

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Abstract: The continuous advancement of the pharmaceutical industry is not only marked by the discovery of novel therapeutic agents and innovative dosage forms but also by the need to improve existing analytical methodologies, especially those involved in process quality control. In modern pharmaceutical development, rapid, cost-effective, and reliable analytical techniques are essential to ensure the consistent performance and therapeutic efficacy of marketed drug products. One of the critical parameters in evaluating the bioavailability and therapeutic potential of solid oral dosage forms is their dissolution behavior, which directly correlates with drug solubility under physiologically relevant conditions. This research paper focuses on the optimization and modification of an existing UV-Vis spectrophotometric method for testing the dissolution of ketoprofen in tablet formulations, with the goal of simplifying and accelerating the dissolution testing protocol. The study involved the deliberate modification of several test conditions, including the pH of the dissolution medium (adjusted from pH 7.2 to pH 6.8), the rotation speed (reduced from 100 rotations per minute (rpm) to 75 rpm), and the sampling time points (shifted from a single 45 minute time point to three intervals of 15, 30, and 45 minutes). The choice of these parameters was based on their relevance to both physiological conditions and analytical efficiency. The results demonstrated that the modified method produced more favorable dissolution profiles, with significantly improved average solubility of the active pharmaceutical ingredient (API) even after just 15 minutes of testing. Such a rapid and consistent dissolution rate not only ensures better prediction of *in vivo* behavior but also offers a practical advantage for routine quality control testing by reducing analysis time without compromising reliability. Furthermore, this study highlights the need for ongoing evaluation and refinement of existing pharmacopoeia methods, recognizing that established procedures may benefit from scientifically supported improvements. The findings support a more flexible approach to method development, where alternative techniques when properly validated in line with official pharmacopeia standards can be considered for routine use. The study also emphasizes the broader relevance of method optimization in pharmaceutical analysis, demonstrating how minor but deliberate modifications to test conditions can lead to meaningful improvements in accuracy, speed, and efficiency. In conclusion, the proposed dissolution testing method presents a viable and promising alternative for the routine analysis of ketoprofen tablets, offering enhanced operational efficiency, practical utility, and alignment with modern industry demands for rapid, reliable, and cost-effective quality control strategies.
Keywords: ketoprofen, spectrophotometric methods, dissolution.

1. INTRODUCTION

Ketoprofen is a nonsteroidal anti-inflammatory drug (NSAID) that was first synthesized in France by the chemist Rhone Poulenc in 1967, only three years after the synthesis of ibuprofen. Clinical use of ketoprofen began in 1973 in France and the United Kingdom (Kantor, 1986; Mazumder et al., 2021). As an active pharmaceutical ingredient, ketoprofen is formulated into a wide range of dosage forms, including tablets of varying strengths, capsules, oral granules, suppositories, and topical creams (Ph. Eur. 11.0, 2023). Ketoprofen is a faintly colored, odorless and tasteless crystalline powder with irritating aerosols. It is soluble in polar organic solvents such as ethanol, methanol, octanol, acetone, chloroform, and ethyl acetate, while only partially soluble in water. Its molecular formula is $C_{16}H_{14}O_3$ and the molecular weight is 254.09. The IUPAC name is 2-(3-benzoylphenyl) propanoic acid. Structurally, it belongs to the class of benzophenones and monocarboxylic oxo acids (Kantor, 1986; Kumar et al., 2024; National Center for Biotechnology Information, n.d.).

From its chemical structure, it is evident that ketoprofen has one chiral center, which leads to the existence of two enantiomers that behave as mirror images of one another. The (+) enantiomer, which rotates plane-polarized light to the left, has the (S) configuration and exhibits pharmacological activity, while the (−) enantiomer rotates light to the right and possesses the (R) configuration. Although only the (S)-enantiomer is pharmacologically active, ketoprofen is commonly used in its racemic form (±). Since the two enantiomers do not exhibit antagonistic interaction, ketoprofen is typically formulated and administered as a racemic mixture (Jamali & Brocks, 1990; Liversidge G.G., 1981; Petrie & Camacho-Muñoz, 2021).

In addition to ketoprofen, the NSAID group also includes ibuprofen, indomethacin, naproxen and others. In general, these drugs work by reducing the concentration of prostaglandins, chemical mediators responsible for pain, fever, and inflammation. The mechanism of action of ketoprofen involves inhibition of the cyclooxygenase (COX) enzymes, which are key enzymes in the metabolism of arachidonic acid, the precursor to prostaglandins. Among NSAIDs, ketoprofen is considered one of the most potent COX inhibitors, and studies indicate that it is up to six times more effective than naproxen (Jamali & Brocks, 1990). According to the Anatomical Therapeutic Classification (ATC), ketoprofen is classified as M02AA10 (RxReasoner, n.d.), a topical non-steroidal anti-inflammatory drug for the musculoskeletal system.

When administered orally, ketoprofen is rapidly absorbed, with peak plasma concentrations achieved within 0.5 to 2 hours. The rate of absorption depends on the dosage form, for example solutions are absorbed more quickly than tablets. After absorption, the drug binds to plasma albumin, allowing for systemic distribution (Jamali & Brocks, 1990). One of the most critical pharmaceutical parameters influencing drug absorption is the dissolution of the API from its dosage form, as drug release and dissolution are frequently the rate-limiting steps in gastrointestinal absorption (Abdulrahman A. Alagga, Mark V. Pellegrini, 2024). Even the most pharmacologically potent compound can fail therapeutically if it does not sufficiently dissolve during gastrointestinal transit, as inadequate dissolution often results in poor bioavailability and suboptimal clinical performance (Muenster et al., 2011).

While solubility refers to the inherent ability of a substance to dissolve in a solvent, dissolution describes the rate and extent to which the drug is released from its solid dosage form into solution. For oral tablets, ensuring proper dissolution is essential for achieving bioavailability, the fraction of the administered dose that reaches systemic circulation. Dissolution is therefore a critical parameter in both pharmaceutical development and quality control, as it directly influences therapeutic efficacy. Factors related to the nature of the active substance and the dosage form (e.g., chemical structure and physical form), as well as factors associated with the instrumentation used for dissolution testing (e.g., pH of the dissolution medium, temperature, rotation speed), can all impact the dissolution behavior of the active substance. (Nashed et al., 2023).

According to the European Pharmacopoeia, dissolution testing for ketoprofen tablets is performed using a paddle apparatus at 100 rpm, in 900 mL of phosphate buffer solution at pH 7.2 and a temperature of 37 °C, with a total test duration of 45 minutes (Ph. Eur. 11.0, 2023). The amount of drug released is determined using UV-Vis spectrophotometry. A dissolution result is considered acceptable if it meets or exceeds Q + 5% (Rahman et al., 2021), where Q = 75%. In this study, we investigate the impact of modifying key dissolution test parameters, specifically, reducing the paddle rotation speed to 75 rpm, adjusting the pH of the medium to 6.8, and introducing sampling at 15, 30, and 45 minutes instead of a single endpoint. These changes are designed to evaluate the method's sensitivity to physiological variation and to assess the robustness of ketoprofen release under modified conditions. A comparative analysis with the pharmacopoeia method will help determine whether the adjusted procedure remains within acceptable quality standards and offers any analytical or practical advantages.

2. MATERIALS AND METHODS

The dissolution analysis of ketoprofen was performed using pharmaceutical-grade reagents and certified reference materials. The active substance, Ketoprofen CRM (purity 99.8%, batch LRAD1874), was used as the standard.

Methanol of analytical grade (Fisher Chemical, batch 2522422/48) served as the primary solvent, while solid potassium dihydrogen phosphate (KH_2PO_4, VWR Chemicals, batch 24H304119), freshly prepared 5 mol/L sodium hydroxide (NaOH) solution, and distilled water were used for buffer preparation. All weighing procedures were conducted using a precision Analytical balance (Mettler Toledo XPR10, Model 538), with accuracy to six decimal places.

For the preparation of the standard solution, 10 mg of Ketoprofen CRM were accurately weighed and transferred into 100 mL volumetric flasks. Methanol was added to approximately half the volume, and the solution was sonicated for 2 minutes to ensure complete dissolution. Each flask was then brought to volume with methanol. From the resulting stock solution, 3 mL were transferred into a 50 mL volumetric flask, combined with 7 mL of methanol, and filled to the mark with the dissolution medium to achieve a final working concentration of approximately 0.0059 mg/ml.

Dissolution testing was carried out on six ketoprofen tablets for each condition using the Hanson Vision G2 Classic 6 dissolution apparatus (paddle method). For the validated method, the test was performed in 900 mL of phosphate buffer at pH 7.2, maintained at a temperature of 37 ± 0.5 °C, with a paddle rotation speed of 100 rpm and a total duration of 45 minutes. In the optimized method, the buffer pH was adjusted to 6.8, the paddle speed was reduced to 75 rpm, and samples were collected at three time points: 15, 30, and 45 minutes.

Following dissolution, each sample was filtered using blue filter paper to remove undissolved excipients. A 3 mL aliquot of the filtrate was transferred into a 50 mL volumetric flask and diluted with 10 mL methanol, then brought to volume with the dissolution medium. The UV-Vis spectrophotometric analysis was conducted using a Shimadzu UV-1800 instrument (Model A11635372302). Measurements were taken at λ_{max} = 260 ± 2 nm, previously confirmed by scanning the full absorbance spectrum of both the standard and sample solutions. The blank consisted of a 5:25 (v/v) mixture of methanol and the corresponding dissolution medium. All measurements were performed in duplicate, and the absorbance data were processed using the instrument's dedicated software for quantitative interpretation.

3. RESULTS AND DISCUSSIONS

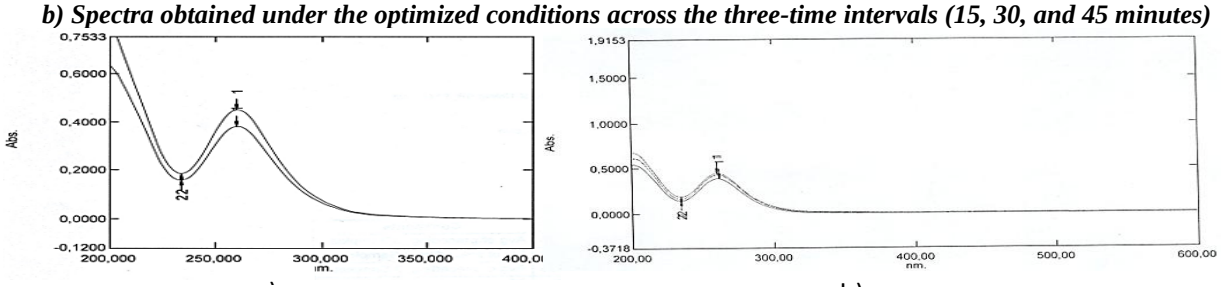
To establish a reference for evaluating the optimized dissolution method, initial analyses were conducted using the officially validated pharmacopoeia procedure. The UV-Vis spectra of both the standard and sample solutions obtained via this method were consistent with established literature data, confirming the identity of ketoprofen and the reliability of the validated procedure.

Subsequently, comparative analyses were performed using an optimized method, in which two variables were adjusted: the pH of the dissolution medium was modified from 7.2 to 6.8, and the paddle rotation speed was reduced from 100 rpm to 75 rpm. All other experimental parameters, including temperature, dissolution volume, and instrumentation, were held constant to isolate the effects of these specific changes.

The UV-Vis spectra recorded for the optimized method at 15, 30, and 45 minutes showed no observable deviation from the validated method. The spectral profiles were virtually identical, with no evidence of bathochromic or hypochromic shifts. This indicates that the moderate change in pH and number of rotations did not alter the electronic absorption characteristics of ketoprofen in phosphate buffer. The consistent absorption behavior confirms that ketoprofen remains chemically stable and spectroscopically unaffected across the studied conditions.

This spectral consistency supports the robustness of the method and suggests that variations in pH within this physiological range, as well as reduced hydrodynamic stress, do not compromise the spectroscopic integrity of the API. Figure 1a presents the spectra obtained using the validated method, while Figure 1b illustrates those obtained under the optimized conditions across the three time intervals (15, 30, and 45 minutes).

Figure 1. a) Spectra obtained using the validated method;
b) Spectra obtained under the optimized conditions across the three-time intervals (15, 30, and 45 minutes)



Source: Authors' research

Once the spectral identity and maximum absorption wavelength (λ_{max} = 260 nm) of ketoprofen were confirmed, quantitative absorbance measurements were performed to assess dissolution efficiency under both test conditions. Notably, the optimized method, employing a lower paddle rotation speed (75 rpm) and a dissolution medium of pH 6.8, consistently produced higher absorbance values compared to the validated method, even at the earliest time point (at 15 minutes).

This trend was observed for both the standard and the test solutions, indicating enhanced dissolution performance under the modified parameters. The increase in absorbance suggests a higher concentration of ketoprofen released into solution, which may be attributed to improved wettability or reduced mechanical shear, allowing for a more uniform and complete disintegration of the tablets over time.

Table 1 summarizes the absorbance values for all samples analyzed using both the validated and optimized methods at 15, 30, and 45 minutes. These results provide the quantitative foundation for further evaluation of the dissolution profile and comparison with pharmacopoeia acceptance criteria.

Table 1. Detailed absorbance data for all measured samples under both methods

Validated method measurements		**Optimized method measurements / 15 min**		**Optimized method measurements / 30 min**		**Optimized method measurements / 45 min**	
Sample	**Absorbance**	**Sample**	**Absorbance**	**Sample**	**Absorbance**	**Sample**	**Absorbance**
Standard 1	0.3813	Standard 1	0.3896	Standard 1	0.3896	Standard 1	0.3896
Standard 2	0.3859	Standard 2	0.3901	Standard 2	0.3901	Standard 2	0.3901
Test sample 1	0.4502	Test sample 1	0.4490	Test sample 1	0.4275	Test sample 1	0.4354
Test sample 2	0.4301	Test sample 2	0.4469	Test sample 2	0.4275	Test sample 2	0.4359
Test sample 3	0.4321	Test sample 3	0.4299	Test sample 3	0.4266	Test sample 3	0.4255
Test sample 4	0.4183	Test sample 4	0.4300	Test sample 4	0.4267	Test sample 4	0.4264
Test sample 5	0.4277	Test sample 5	0.4481	Test sample 5	0.4253	Test sample 5	0.4259
Test sample 6	0.4178	Test sample 6	0.4268	Test sample 6	0.4252	Test sample 6	0.4264

Source: Authors' research

The quantitative assessment of ketoprofen dissolution in tablet form was determined using Equation (1), which calculates the relative release percentage (RR %) based on spectrophotometric data. This calculation expresses the proportion of ketoprofen released into solution relative to a reference standard under identical analytical conditions.

$$RR\ \% = \frac{A \cdot m_s \cdot 3 \cdot 900 \cdot 50 \cdot 100}{A_s \cdot 100 \cdot 50 \cdot 100 \cdot 3} \quad (1)$$

Where:

RR % denotes the relative release of the API expressed as a percentage; A represents the absorbance of the test solution; m_s is the accurately weighed and corrected mass of the standard substance and A_s corresponds to the absorbance of the standard solution measured under identical conditions.

For the optimized method, additional volume corrections were applied during the calculation of ketoprofen release, in order to account for the cumulative sampling over the course of the dissolution test. Specifically, while the calculation formula remains consistent after the 15-minute sampling point, subsequent aliquot withdrawals reduce the effective volume of the dissolution medium. Therefore, at 30 minutes the corrected volume is 890 mL, and at 45 minutes it is 880 ml. These adjustments are essential to ensure accurate determination of the released drug fraction and to maintain the validity of comparative analysis across time points.

Using the appropriate calculation formulas and the absorbance values presented in Table 1, the following average dissolution values were obtained: 99.53% for the validated method, and 100.32%, 96.49%, and 96.03% for the optimized method at 15, 30, and 45 minutes, respectively. Remarkably, the optimized method achieved superior dissolution at the 15 minute mark compared to the validated method, which required a full 45 minutes to approach

comparable dissolution levels. This indicates that the buffer with a lower pH used in the optimized method facilitates a more efficient release and dissolution of ketoprofen in a shorter time frame.

While ketoprofen, as a weak acid, typically exhibits enhanced solubility under more basic conditions, our results indicate that prolonged exposure to such conditions may actually reduce apparent solubility. This can occur due to **precipitation from supersaturation, ionic interactions with buffer constituents, and surface adsorption phenomena**. Similar in vitro findings show that weak acid drugs can precipitate after initial rapid dissolution when transitioning to higher pH environments (Gan et al., 2023). Although not yet confirmed specifically for ketoprofen, it is reasonable to consider that the ionized form of the molecule may interact with buffer components or adsorb onto the dissolution vessel surface, potentially contributing to the observed reduction in apparent solubility over time.

The observed decline in dissolution after 30 and 45 minutes in the optimized method may therefore be attributed to such stability-related phenomena. Consequently, based on the dissolution efficiency, analyte stability, and practical workflow considerations, the 15 minute sampling point under the optimized conditions appears to be the most suitable for routine analysis of ketoprofen in solid dosage forms.

4. CONCLUSION

The optimized dissolution method demonstrated superior performance, achieving complete ketoprofen release within 15 minutes, three times faster than the validated method, without compromising analytical reliability. While this suggests significant time-saving potential in pharmaceutical quality control, further biopharmaceutical studies are essential to confirm whether such rapid release at pH 6.8 aligns with therapeutic efficacy and physiological relevance. If proven appropriate, this method could serve as a strong candidate for future validation and implementation.

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