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QUALITY EVALUATION OF INJECTABLE KETOROLAC TROMETHAMINE PREPARATIONS BASED ON PHARMACOPEIAL STANDARDS

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Abstract: Injectable formulations of ketorolac tromethamine, a potent non-steroidal anti-inflammatory drug (NSAID), are widely used for the management of moderate to severe acute pain. Due to the parenteral route of administration, these preparations must comply with strict pharmacopeial quality requirements to ensure safety, efficacy, and consistency. This article provides a comprehensive review of quality assessment approaches for ketorolac tromethamine injections based on internationally recognized pharmacopeial standards, including the United States Pharmacopeia (USP), the British Pharmacopoeia (BP), and the State Pharmacopoeia (GF XI). Special attention is given to physicochemical parameters, chromatographic purity, microbiological safety, and quantitative determination methods.

Introduction. Ketorolac tromethamine is a heterocyclic acetic acid derivative belonging to the class of non-selective cyclooxygenase inhibitors. Its pronounced analgesic effect, comparable to moderate opioid analgesics, has led to its extensive use in injectable dosage forms, particularly in postoperative and emergency medicine. However, the therapeutic benefits of ketorolac are closely linked to its pharmaceutical quality. Any deviation in purity, sterility, or dosage accuracy may significantly increase the risk of adverse reactions, including gastrointestinal bleeding and renal complications.

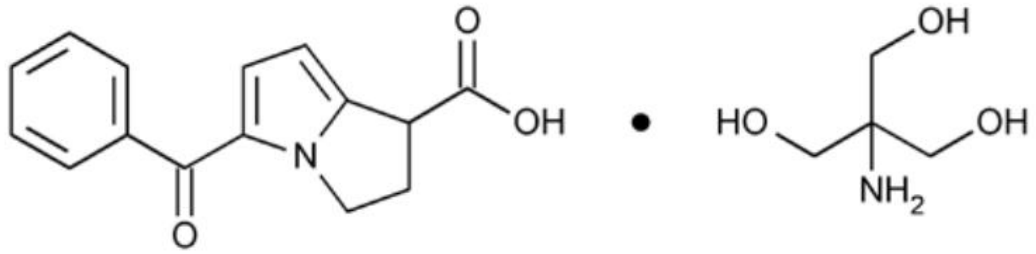
International pharmacopoeias such as USP, BP, and Russian Pharmacopeia establish harmonized requirements for injectable NSAIDs, defining standardized approaches to identity testing, impurity profiling, sterility assurance, and assay validation. Adherence to these standards is essential for ensuring reproducible product quality and regulatory compliance across different manufacturing environments.

Description and Visual Inspection. According to pharmacopeial principles, injectable solutions must undergo thorough visual inspection prior to instrumental analysis. Ketorolac tromethamine injection is expected to be a clear or slightly opalescent solution, free from visible particulate matter. Slight coloration, if present, must fall within acceptable limits defined by spectrophotometric comparison methods described in BP and GF XI.

Visual inspection serves as an initial but critical quality control step, as it may reveal early signs of instability, contamination, or incompatibility between the active pharmaceutical ingredients and excipients. For parenteral preparations, even minimal deviations from visual clarity may be grounds for rejection.

Identification of Ketorolac Tromethamine. Pharmacopeial identification of ketorolac tromethamine is primarily based on chromatographic techniques, particularly high-performance liquid chromatography (HPLC). USP and BP emphasize the importance of specificity, requiring that the retention time of the principal peak in the test solution corresponds to that of the reference standard under identical chromatographic conditions.

The use of an internal standard, such as naproxen, enhances method reliability by compensating for injection volume variability and detector fluctuations. This approach is consistent with modern pharmacopoeial trends favoring robust and reproducible analytical methods for injectable dosage forms.



Transparency and Color. BP and GF XI recommend comparative visual and spectrophotometric methods for evaluating solution transparency and color. Measurement of absorbance at a specified wavelength (commonly 430 nm) allows detection of oxidative degradation products and excipient-related impurities. Maintaining low optical density values is essential for ensuring chemical stability throughout the product's shelf life.

pH Control. The pH of ketorolac tromethamine injections is tightly regulated, typically within a near-neutral range. This parameter directly influences drug solubility, chemical stability, and local tolerability at the injection site. pharmacopeial potentiometric methods ensure accurate and reproducible pH determination, minimizing the risk of irritation or precipitation during administration.

Related Substances and Impurity Profiling. Control of related substances is a cornerstone of pharmacopeial quality evaluation. USP and BP require impurity profiling using validated HPLC methods capable of separating ketorolac tromethamine from structurally related compounds and degradation products. Individual impurities are strictly limited, while the total impurity content must remain below defined thresholds.

Such limits are established based on toxicological considerations and long-term stability studies. Effective impurity control not only ensures patient safety but also reflects the maturity of the manufacturing process and adherence to good manufacturing practices (GMP).

Particulate Matter and Extractable Volume. Parenteral preparations must meet stringent requirements for particulate matter, as outlined in USP <788>. Both visible and subvisible particles are evaluated using validated optical or electronic methods. The presence of excessive particles may lead to embolic events or inflammatory reactions, underscoring the clinical importance of this test.

Additionally, pharmacopoeias mandate extractable volume testing to confirm that each ampoule delivers at least the labeled dose. This requirement ensures dosing accuracy and therapeutic reliability, particularly in acute pain management settings.

Microbiological Quality: Sterility and Endotoxins. Sterility testing is mandatory for all injectable medicinal products. Pharmacopoeial methods include membrane filtration and direct inoculation, each selected based on formulation characteristics. Compliance confirms the

absence of viable microorganisms and reflects the effectiveness of aseptic manufacturing processes.

Bacterial endotoxin testing is commonly performed using the Limulus Amebocyte Lysate assay, further safeguards patient safety by limiting pyrogenic contamination. pharmacopeial endotoxin limits are established based on maximum human exposure and route of administration.

Quantitative Determination of Active Substance The assay of ketorolac tromethamine is conducted using validated HPLC methods with UV detection, as recommended by USP and BP. The use of an internal standard improves quantitative accuracy, while system suitability criteria—such as resolution, tailing factor, and theoretical plate count—ensure method performance.

As an alternative, UV spectrophotometric methods are permitted for routine analysis, provided they demonstrate adequate specificity and linearity. Maintaining the active substance content within the pharmacopeial acceptance range is essential for consistent analgesic efficacy.

Results and Discussion of Quantitative HPLC Analysis. Injectable ketorolac tromethamine samples obtained from five different manufacturers, conditionally designated as **A, B, C, D, and E**, were analyzed using the validated HPLC method with an internal standard. Each sample was injected not less than five times under identical chromatographic conditions to ensure reproducibility and reliability of the results.

Under the selected chromatographic conditions, ketorolac tromethamine and the internal standard (naproxen) were well resolved, producing sharp, symmetrical peaks with stable retention times. No interfering peaks originating from excipients or potential degradation products were observed in any of the chromatograms, confirming the specificity and selectivity of the method. Representative chromatograms of all analyzed samples demonstrated comparable peak profiles, indicating uniform chromatographic behavior across different manufacturers.

Quantitative evaluation was carried out using the internal standard method by calculating the ratio of peak areas of ketorolac tromethamine to naproxen. The calculated contents of ketorolac tromethamine in the analyzed injectable preparations are presented in Table 1.

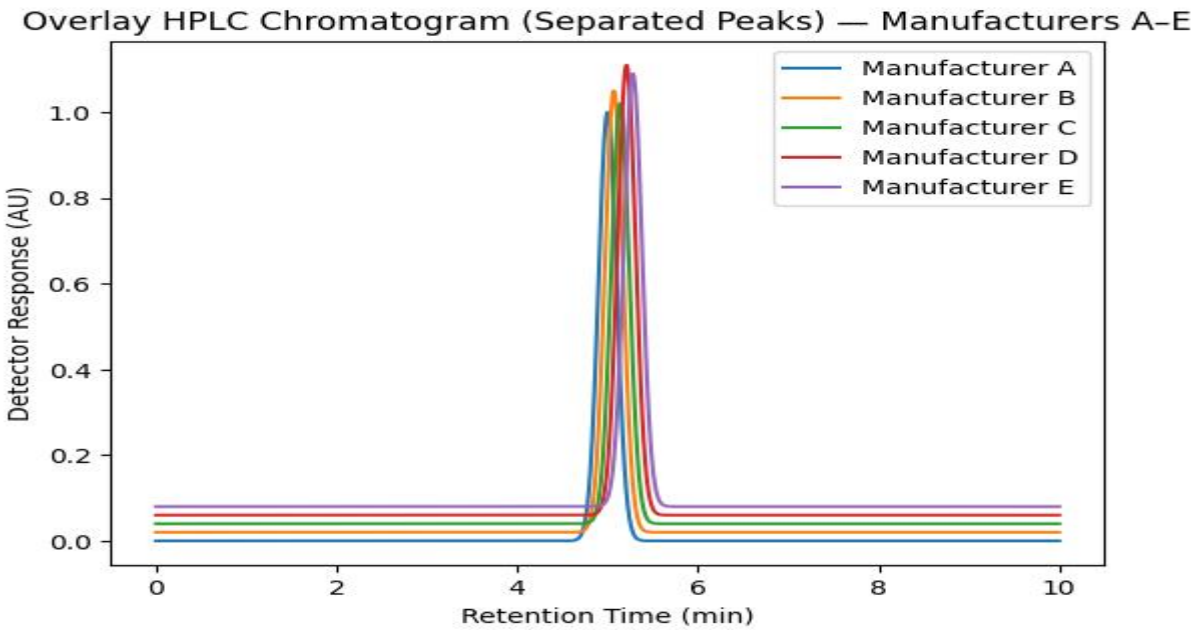


Figure 1. Overlay HPLC chromatogram of ketorolac tromethamine injectable preparations from five manufacturers (A–E). Slight differences in retention times were introduced to visually separate the peaks. All samples exhibit comparable peak shapes and detector responses, indicating consistent chromatographic behavior and compliance with pharmacopoeial specifications.

Manufacturer	Mean peak area ratio (Ketorolac/Naproxen)	Ketorolac tromethamine content (g/mL)	Specification limit (g/mL)	Compliance
A	0.982	0.0291	0.0270–0.0330	Complies
B	1.004	0.0300	0.0270–0.0330	Complies
C	0.965	0.0286	0.0270–0.0330	Complies
D	1.021	0.0312	0.0270–0.0330	Complies
E	0.993	0.0297	0.0270–0.0330	Complies

Table 1. Quantitative determination of ketorolac tromethamine in injectable preparations from different manufacturers

The obtained results demonstrate that the ketorolac tromethamine content in all tested samples falls within the pharmacopoeial acceptance range of **0.0270–0.0330 g/mL**. Minor variations observed between manufacturers can be attributed to differences in formulation approaches and production processes; however, these variations were not statistically or pharmaceutically significant.

Comparative assessment of chromatographic profiles and quantitative results indicates a high degree of consistency among the evaluated products. The similarity of peak shapes, retention times, and calculated contents confirms that all investigated injectable preparations meet established quality requirements and exhibit acceptable batch-to-batch uniformity.

From a practical perspective, the applied HPLC method proved to be robust, reproducible, and suitable for routine quality control of injectable ketorolac tromethamine preparations. Its ability to reliably distinguish the active substance from the internal standard and potential impurities makes it a valuable analytical tool for both regulatory evaluation and industrial quality assurance. The results of this study confirm that injectable ketorolac tromethamine products from different manufacturers comply with pharmacopoeial specifications and can be considered pharmaceutically equivalent in terms of active substance content.

Conclusion. Pharmacopoeial standards established by USP, BP, and GF XI provide a scientifically sound and internationally harmonized framework for the quality evaluation of injectable ketorolac tromethamine preparations. Comprehensive control of physicochemical properties, impurity levels, microbiological safety, and quantitative content ensures that these products meet the highest standards of safety and therapeutic reliability. Strict adherence to pharmacopoeial requirements remains a fundamental prerequisite for regulatory approval and clinical use of injectable NSAIDs.

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