International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 4 July-Aug 2023, pp: 1570-1575 www.ijprajournal.com ISSN: 2249-7781

Analytical Reviewon Butenafine Hydrochloride

Dr. Rajveer Bhaskar, Dr. Monika Ola, Dr. Pankaj Nerkar, Dr.Bhushan Bhairav,Mr. Mahesh Shantaram Patil*, Mr. Mahesh Sharad Patil
Department of Regulatory Affairs, R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur 425405, MS, India.

Submitted: 01-08-2023 Accepted: 10-08-2023

ABSTRACT
A novel synthetic antifungalbutenafine, a new benzylamine antimycotic drug, has significant in vitro action against dimorphic fungi, Candida and other yeasts, and dermatophytes. It is a benzylamine derivative whose molecular makeup and action method are comparable to antifungals based on allylamine. It alters the cellular sterol composition, increasing the outer layer's susceptibility to attacks. This review includes the different comparisons and affirmative discussion of ten analytical procedures, including HPLC, Stability-Indicating, UV-Spectrophotometry, and Bioanalytical Methods. To offer accurate results for regulatory submissions, analytical development must be confirmed. Pharmaceutical advancements ushered in a new era in human health.

Keywords: Butenafine hydrochloride; Review Article; Analytical Methods;

I. INTRODUCTION

A novel synthetic antifungal drug called butenafine hydrochloride (BFH) **Fig. 1**treats various fungal infections. butenafine hydrochloride is a member of the benzylamine drug category**[1, 2, 3]**. It is 4-tert-Butylbenzyl-N-methyl-1-naphthalene methylamine hydrochloride chemically. The empirical formula of this compound is $C_{23}H_{27}N$. HCl and its molecular weight is 353.93 gm/mol. Water is only modestly soluble compared to methanol, ethanol, and chloroform. It is highly effective against dermatophytes, such as aspergilli, dimorphic fungi, and dematiaceous fungi, in vitro**[4, 5, 6]**. Butenafine, a new benzylamine antimycotic drug, has significant in vitro action against dimorphic fungi, Candida, other yeasts, and dermatophytes **[7]**. It is a benzylamine derivative whose molecular makeup and action method are comparable to antifungals based on allylamine. It alters the cellular sterol composition, increasing the outer layer's susceptibility to attacks. It is the only benzylamine that has received approval in the U.S. **[8]**

Additionally, butenafine prevents Candida albicans from squalene epoxidation, perhaps by promoting the production of intracellular inorganic orthophosphate, which damages the Candida albicans cell wall **[1]**. According to a review of the literature, while there are a few chromatographic methods to identify butenafine hydrochloride in pharmaceutical formulations, there aren't many analytical procedures for evaluating butenafine hydrochloride with betamethasone and betamethasone dipropionate in a formulation or biological fluids. Butenafine hydrochloride is not listed as a specific medication in any pharmacopeia. **[5, 9]**

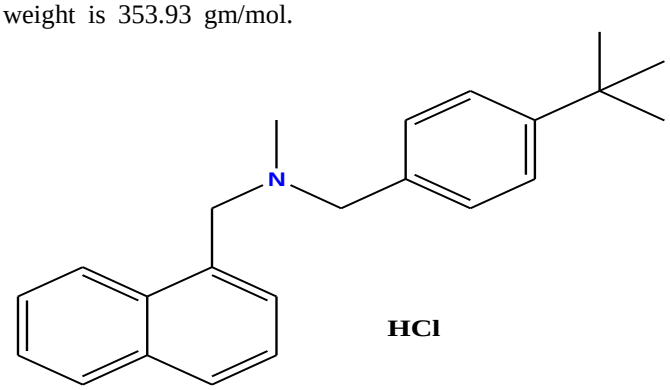

Fig. 1 Chemical Structure of Butenafine Hydrochloride

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Various Analytical Approaches for Butenafine Hydrochloride

The literature survey revealed a few analytical techniques viz U.V./VisibleSpectrophotometry, HPLC, and LC-MS for determining butenafine hydrochloride in bulk and pharmaceutical formulations. The reported methods describe the estimation of butenafine hydrochloride in various dosage forms as a single constituent and combination with betamethasone. Total analytical methods describe in **fig no 2.**

Only ten methods have been described for quantifying butenafine hydrochloride in the biological matrix and pharmaceutical dosage form. For butenafine hydrochloride, separation was achieved utilizing gradient and isocratic modes.The separation of butenafine hydrochloride in varying proportions is often accomplished using a maximum RP-HPLC system with a separate C_{18} column as the stationary phase and polar solvents, including acetonitrile, methanol, water, and buffer solutions having an acidic pH.butenafine hydrochlorides were estimated using 280 and 283 nm detection wavelengths. The information concerning the drug samples, Methods, pharmaceutical or biological matrix, and Experimental condition (such as Stationary phase, mobile phase, flow rate, mode of analysis, and wavelength detection) are all summarized in **Tables 1[5, 10-16]**

Vaditake K.T. et al. reported a single formulation of butenafine hydrochloride in bulk and cream, and a straightforward, precise, accurate, and accurate UV-Spectrophotometric method was established. According to ICH guidelines, the technique has been validated for linearity, accuracy, precision, robustness, and ruggedness. The drug's maximum absorption was determined to be 252 nm using methanol as the solvent. With a regression coefficient of 0.999, it was discovered that the linearity for butenafine hydrochloride was in the range of 10 - 60 g/ml. Force degradation analysis was used to determine the butenafine hydrochloride's stability. **[10]**

Baviskar A. et al. reported the HPLC method for estimating butenafine HCl in nanolipidgel. Chromatographic separation was accomplished using a Cosmosil C18 (250 x 4.6, 5) column and an HPLC 3000 binary gradient system with a mobile phase of methanol: water (80:20%) with a pH adjusted to 3.0 by ortho-phosphoric acid. At 0.8 ml/min, the flow rate was kept constant. Data collection was placed at 283 nm. According to ICH criteria, the established RP-HPLC method was created.**[11]**

Song, L. et al. reported an HPLC/MS/MS method for estimating butenafine hydrochloride in human plasma with testosteronepropionate as the internal standard was developed and validated. Plasma samples were extracted withan n-hexane/diethyl ether (1:2, v/v) mixture and separated using a C_{18} column by a gradient elution withthe mobile phase containing acetonitrile and five mM ammonium acetate buffer. Quantification wasperformed using multiple reaction monitoring (MRM) modes with a transition of m/z 318.4 → 141.0 forbutenafine hydrochloride and m/z 345.5 → 97.0 for testosterone propionate (I.S.). This method was validatedin terms of specificity, linearity, precision, accuracy, and stability per ICH guidelines. **[12]**

Ansari, M.J. et al. reported a simple, rapid, sensitive, accurate, and precise Reverse-phase RP-HPLC method with a wide range of estimations todetermine butenafine hydrochloride in nanosponges. This method has been validated as per ICH norms. Separation was achieved by utilizing the most commonly used reverse phasecolumn (C-18, 5 µm, 150 mm x 4.6 mm) set at 30ºC and quantified by U.V. detection at 280 nm afterisocratic elution from a mobile phase (70:30 v/v of methanol: phosphate buffer pH 3.0) flowing at 1ml/min.The assay or determinations were accurate, precise, and reproducible withmean accuracy and mean relative standard deviation of precision of 101.53 ± 0.43% and 0.51 ±0.11%, respectively. **[13]**

SUN, L. et al. establish RP-HPLC method for determination of butenafine hydrochloride in cream.The samples were separated by Waters C18 column4.60 mm×150 mm, 5 µmwith methanol: tetra-n-methylammonium hydroxide solutionadjusted (pH to 6.8) using phosphoric acid (85:15%, v/v)as mobile phase and detected with UV 282 nm and a flow rate of 1.0 mL·min-1.The calibration curve was linear in the 80.1-400.7 µg·mL-1 concentration range. The average recovery rate was 99.47%. The detection limit was 2.5 ng.**[14]**

Barth, A.B. et al. reported a new stability-indicating liquid chromatography method for determining the butenafine hydrochloridein cream developed and validated using the Plackett-Burman experimental design for robustness evaluation. Also, thedrug photodegradation kinetics was determined. The analyticalcolumn was operated with acetonitrile, methanol, and a solution

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oftriethylamine 0.3% adjusted to pH 4.0 (6:3:1) at a 1 mL/min flow rate and detection at 283 nm. BTF extraction from the creamwas done with n-butyl alcohol and methanol in an ultrasonic bath. Theperformed degradation conditions were: acid and primary media withHCl 1M and NaOH 1M, respectively, oxidation with H2O2 10%,and exposure to UV-C light. The BTFphotodegradation kinetics was determined for the standard and the cream in methanolic solution under U.V. light at 254 nm.The degradation process can be described by first-order kinetics inboth cases. **[15]**

Ankam R. et al. reported that a fast, specific, accurate, and precise reverse-phase high-performance liquid chromatographic method was developedto determine butenafine hydrochloride and betamethasone in a cream formulation. Thedetermination was carried out on microcars microsphere RP-select B (250×4.6 mm, 5 µ) column in isocratic mode,the mobile phase consisting of 50 mM ammonium acetate buffer and acetonitrile in the ratio of 60:40, adjustedto pH 4.5 ± 0.1 with glacial acetic acid. The flow rate was 2.0 ml/min, and eluents were monitored at 254 nm. Theretention times of butenafine hydrochloride and betamethasone were 4.70 min and 7.76 min, respectively, and theresolution factor was more significant than 4.0. Linearity of butenafine hydrochloride and betamethasone were 100-300 µg/ml and 5-15 µg/ml, respectively. The proposed method is also precise and robust fordetermining butenafine hydrochloride and betamethasone in a cream formulation. **[16]**

Bhosale, S.D.,et al. developed an RP-HPLC method for simultaneous estimation of butenafine hydrochloride and betamethasone dipropionate usingInertsil C18 column (250 x 4.6 mm 5 ids) as stationary phase and methanol and water used as mobile phase in gradient flow, at a flow rate of 1 mL/min. Detection was carried out at 254 nm. The method was validated concerning specificity, linearity, accuracy, precision, ruggedness, and robustness. This method is simple, precise, sensitive, and applicable for simultaneous quantifying butenafine hydrochloride and betamethasone dipropionate in a cream formulation. **[5]**

Mitra, A. et al. reported a bioanalytical method for the estimation ofbutenafine hydrochloride using an in vitro human skin permeation study,whether changes in the excipients of butenafine hydrochloride cream would have any effect onthe performance of the formulation. Such in vitro data would be a surrogate for any requirement of abioequivalence study to demonstrate formulation similarity. An LC-MS/MS method for quantitating butenafine in various matrices was developed and validated. The results of the study comparing the two formulations showed that therewas no statistically significant difference in the extent of butenafine permeation into human skin. Inconclusion, these in vitro data demonstrated that the formulation change would likely not significantly impact the performance of 1% (w/w) butenafine hydrochloride cream.**[1]**

Table no 1 Pharmaceutical Analysis of butenafine hydrochloridein alone and combination.

Sr. No.	Drugs	Methods	Pharmaceutical or Biological Matrix	Experimental Conditions	Ref.
1.	BFH	UV-Spectrophotometric Method	Bulk Material & Cream	**Detection –** 252 nm **Linearity (µg/mL) –** 10-60 **Correlation coefficient-** 0.999	10
2.	BFH	RP-HPLC Method	Bulk Material & Nanolipidgel	**S.P- Cosmosil**C18 (250 × 4.6 mm, 5µ) Column, **M.P.-**Methanol:Water, (80:20, v/v), **Flow rate** –0.8 mL/min **Mode of analysis –** Isocratic **Detection –** 283 nm	11
3.	BFH	HPLC/MS/MS method	Bulk Material& Human plasma	**S.P.-** RP C18 Column, **M.P.-**acetonitrile and 5 mM ammonium acetate buffer (1:2, v/v) **Flow rate** - 1.0 mL/min **Mode of analysis –** Gradient	12
4	BFH	RP-HPLC	Bulk Material	**S.P-** RPC18 (150 × 4.6 mm,	13

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		Method	&Nanosponge	5µ) Column, **M.P-** Methanol: Phosphate buffer (pH 3.0), (70:30, v/v), **Flow rate** –1.0 mL/min **Mode of analysis –** Isocratic **Detection –** 280 nm	
5	BFH	RP-HPLC Method	Bulk Material & Cream	**S.P-** Waters RPC18 (150 × 4.6 mm, 5µ) Column, **M.P-** Methanol: tetra n-methyl ammonium hydroxide (pH 6.8), (85:15, v/v), **Flow rate** –1.0 mL/min **Mode of analysis –** Isocratic **Detection –** 282 nm	14
6	BFH	Stability-Indicating LC Assay	Bulk Material & Cream	**S.P-** RPC18 (150 × 4.6 mm, 5µ) Column, **M.P-** Acetonitrile: Methanol : a solution of triethylamine 0.3% adjusted to pH 4.0 (6:3:1), **Flow rate** –1.0 mL/min **Mode of analysis –** Isocratic **Detection –** 283 nm	15
7	BFH + BMT	Simultaneous HPLC Method	Bulk Material & Cream	**S.P-** licrocartlicrosphere RP-select B C18 (150 × 4.6 mm, 5µ) Column, **M.P-** 50 mM ammonium acetate buffer and Acetonitrile, (60:40, v/v), **Flow rate** –2.0 mL/min **Mode of analysis –** Isocratic **Detection –** 254 nm	16
8	BFH + BMT	Simultaneous HPLC Method	Bulk Material & Cream	**S.P**Inertsil C18 (150 × 4.6 mm, 5µ) Column, **M.P.**-Methanol : Water, **Flow rate** – 1.0 mL/min **Mode of analysis –** Gradient **Detection –** 254 nm	5

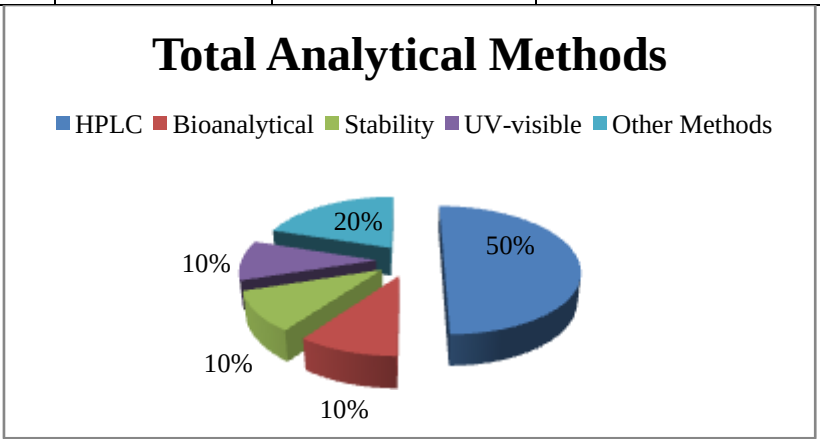

Fig. 2Total Analytical Methods for Butenafine Hydrochloride

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II. DISCUSSION

The butenafine hydrochloride in pharmaceutical formulations and bulk drugs can be determined using various Analytical techniques. Only ten analytical methods, such as simple HPLC, bioanalytical, and stability-indicating, can be used to estimate the concentrations of butenafine hydrochloride alone and in combination with betamethasone. Total analytical methods describe in **fig no 2.**

III. CONCLUSION

The examination of analytic methods for detecting butenafine hydrochloridein pharmaceutical formulations, human plasma, and bulk form utilizing HPLC. Among the most often used solvents for sample processing is the acetonitrile, water, and methanol mixture. Some of the solvents used to separate butenafine hydrochlorideinclude acetonitrile, methanol, and different buffer solutions with acidic pH levels. Isocratic mode is used for most HPLC operations for reverse phase chromatography analysis. The current review study contains essential information that the researcher may find helpful regarding the many methods applied for butenafine hydrochlorideanalysis. Likewise, it can get knowledge of the numerous possibilities for butenafine hydrochloride**.**

Acknowledgment
The authors thank to Principal R.C. Patel Institute of Pharmaceutical Education and Research Shirpur, (MS) 425 405, for providing necessary library facilities.

Abbreviations Used

- HPLC- High-performance liquid chromatography
- L.C.- Liquid chromatography
- M.P. – Mobile Phase
- pH- Power of hydrogen
- S.P.- Stationary phase
- BTF HCL- Butenafine Hydrochloride
- BTM- Betamethasone
- BTM DPP-Betamethasone dipropionate

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