

ANALYTICAL APPLICATIONS OF MEFENAMIC ACID BY HYDROTROPE APPROACH: TITRIMETRIC ESTIMATION AND ULTRAVIOLET METHOD VALIDATION

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ABSTRACT

Objectives: Mefenamic acid is used as a modal nonsteroidal anti-inflammatory drug for analytical estimation. Due to the poor aqueous solubility, mefenamic acid liberated reduced bioavailability.

Methods: The hydrotropic solubilization technique is a promising technique used to improve the solubility of water-insoluble drugs. Experimentally, 2 M sodium benzoate has been employed in the prior titrimetric estimation of mefenamic acid and shows synergistic enhancement in the solubility of mefenamic acid by many folds as compared to the distilled water. Similarly, sodium benzoate approach was further applied in analytical estimation of marketed oral dosage forms in tablets, capsules, and suspension for checking the reproducibility of applied approach by ultraviolet (UV) method. Validation of UV method was further done and checked for linearity, accuracy, and precision. Drug degradation studies were also performed successfully to investigate the sustainability of mefenamic acid in various dosage forms under various stress conditions and to establish the preferred storage conditions for the drug.

Results: In the present experimental investigation, obtained mean % recoveries were close to 100 indicating the accuracy of the proposed approach. Similarly, in analytical estimation of mefenamic acid in oral marketed forms, results have reported lower values of standard deviation, % coefficient of variation, and standard error facilitated the reproducibility and precision of the proposed approach in the titrimetric estimation and analytical validation of UV method mefenamic acid in bulk and marketed forms.

Conclusion: Therefore, a new, simple, precise, and inexpensive proposed method was executed by validating the result statistically.

Keywords: Hydrotropy, Solubility enhancement, Titrimetric analysis, Ultraviolet method, Development, Validation, Mefenamic acid, Sodium benzoate.

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INTRODUCTION

Mefenamic acid as an individual from the anthranilic acid class or fenamates class of nonsteroidal anti-inflammatory drugs used in the treatment of gentle to direct pain and irritation in rheumatic illnesses, osteoarthritis, intense pain like muscle and back pain, toothache, and in menorrhagia. It acts by inhibiting both isoforms of the enzyme cyclooxygenase inhibitors and also focuses on the arrangement of prostaglandins that assume a part in pain affectability and aggravation, fever, additionally in hemostasis, kidney work, pregnancy, and in the assurance of the gastric mucosa [1-5]. As for bioavailability of the BCS Class II drugs, the solubility and dissolution rate are always the rate-determining step and as for mefenamic acid. Thus, the bioavailability problem with BCS Class II drugs thus can be overcome by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids [2,6-9]. As in this regard, improving the solubility of such drugs, the use of "Hydrotropes" has shown the remarkable ability in improving the bioavailability of mefenamic acid. In general, hydrotropes comprised a hydrophobic part and an ionic moiety responsible for forming the required water-soluble solution. Structure making or breaking phenomenon orients intermolecular hydrogen bonding and thus impacts solution properties, that is, solubility and surface tension. The mechanism of action of hydrotropes is generally based on the minimum concentration of the hydrotrope required to bring the aqueous solubility of the solute, which is related to the volume fraction solubility, the structure of the hydrotrope, and with drug (formed either due to structure breaking and making) and hence a polar group of the hydrotrope, which affects the water depression and the solute interactions [10-14]. A hydrotropic particle

collaborates with a less water-dissolvable atom through weak van der Waals cooperation, for example, π - π or dipole-dipole association. By representing weak van der Waals association and intermolecular hydrogen, authority assists in bringing striking dissolvability and effectiveness of the hydrotrope which dependent on its dissolvability improvement proportion of drug candidate and has an impact on their dissolvable properties. Hydrotrophy includes the utilization of effectively water-dissolvable mixes that assist with blocking the utilization of natural solvents [15-19]. The exploration of the analytical methods for mefenamic acid through titrimetric and ultraviolet (UV) method estimation using hydrotrope is the main objective of the present experiment for the routine analysis of the modal drug. Further, UV method was validated for their reproducible results. Hence, both methods are suggested to apply successfully for routine analysis of the drug.

METHODS [20-29]

Chemicals and reagents

Mefenamic acid was supplied as a gift sample by Akums Drugs and Pharmaceuticals Ltd., Raipur, Haridwar. All other chemicals and solvents were used as an analytical grade.

Infrared (IR) spectral studies

The infrared spectrum of pure mefenamic acid was recorded using Fourier-transform infrared (FTIR) spectroscopy involving neat analysis method. Here, in this method, the sample of drugs spreads on a KBr plate and pressed under hydraulic pressure. Thus, infrared radiation exposed into the sample and the signals are collected by the detectors

which sequentially liberated spectra provide the detailed functional groups exhibited in the molecule. Hence, the drug was detected by FTIR in which the spectra are recorded under the wavenumber of 4000 cm^{-1} – 650 cm^{-1} which have reported and obtained spectra were also compared with those in official compendia and shown in Fig. 1 and interpretation of IR spectra is mentioned in Table 2.

Preliminary drug solubility estimation

The equilibrium solubility studies were implemented in a variety of molar solutions of a screened hydrotropic agent. The aqueous solution of sodium benzoate as a hydrotrope was selected and prepared individually at 2 M molar concentration. This agent is accurately measured in their corresponding vial, and thus, an accurate amount of drugs is added and kept in a water bath shaker until a saturated solution is obtained. Then, the prepared solution in the vial was shaken on a water bath shaker for 12 h, allowed to equilibrate for 24 h to attain equilibrium solubility. The following formula was applied for measuring the solubility enhancement ratio for selected hydrotrope Table 1:

$$\text{Enhancement ratio} = \frac{\text{Solubility of drugs in hydrotropic solution}}{\text{Solubility of drugs in distilled water}}$$

Estimation of mefenamic acid bulk drug by IP method

For the analysis of Mefenamic acid from official method Indian Pharmacopoeia, drug sample solution was prepared by adding 100 mg of Mefenamic acid into 25 ml of ethanol (95%) neutralized previously to phenolphthalein as an indicator and final volume was achieved by adding 25 ml of water. It was then titrated with a 0.1 M sodium hydroxide solution. Each ml of 0.1 M sodium hydroxide is equivalent to 0.02543 g of $\text{C}_{16}\text{H}_{14}\text{O}_3$. Drug content was determined ($n=3$) and represented in Table 3.

Estimation of mefenamic acid bulk drug by the proposed method

In the proposed method for analysis: Weighed accurately 100 mg of mefenamic acid drug and transferred to a 250 ml conical flask. Twenty-five milliliters of a solution of 2 M sodium benzoate were added and the flask was shaken for about 10 min to dissolve the drug. 0.1 M sodium hydroxide solution was used to perform titration using phenolphthalein as an indicator. Blank titration was performed for necessary correction. Each ml of 0.1 M sodium hydroxide is equivalent to 0.02543 g of $\text{C}_{16}\text{H}_{14}\text{O}_3$. Drug content was determined ($n=3$) and presented in Table 3.

Application of the proposed (hydrotropes sodium benzoate) method

For the confirmation of utility and feasibility of the proposed method, mefenamic acid was determined in oral dosage forms (tablets, capsules, and suspension). For all samples assayed, the results obtained using official and proposed methods were compared and statistically evaluated ($n=3$). Each estimated value reported not exceeding any values of the theoretical values, proving no significant difference

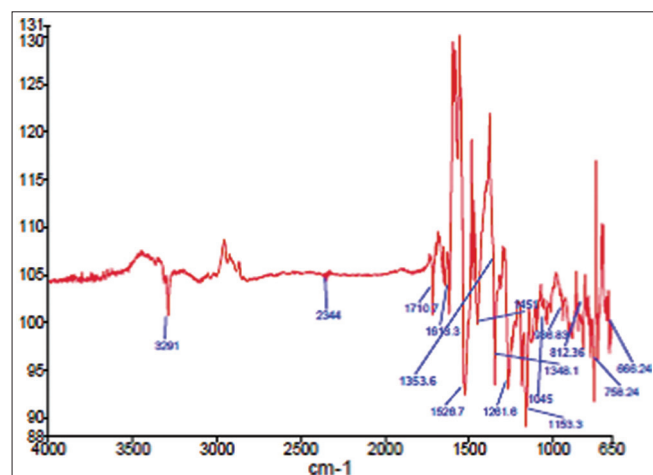


Fig. 1: Fourier transform infrared spectrum of mefenamic acid

between applied methods concerning precision and accuracy in the estimation of mefenamic acid in oral dosage forms. Based on estimated recoveries, proposed method was further validated.

Spectrophotometric determination of mefenamic acid in marketed oral dosage forms for routine analysis

Tablets

Five marketed brands of tablets (Ponstan [250 mg], Mefac [250 mg], Mefacid [100 mg and 250 mg], Meflup Forte [250 mg], and Flexiwin [100 mg]) were purchased from different medical store located in Kanpur, India. The five brands selected with 5 years shelf life labeled to contain 10 mg per tablet of mefenamic acid.

Standard drug solution

The solution of 1000 μg prepared by transferring accurately weighed 50 mg of mefenamic acid to 100 ml of volumetric flask. For drug solubilization, 40 ml of 2.0 M sodium benzoate was added and final volume was achieved by distilled water and successive shaking for 10–15 min was performed. Similarly, stock solutions of 100 $\mu\text{g}/\text{ml}$ of drug were prepared by dilution method and scanning was done in UV over the range of 400 nm–200 nm.

Assay procedure

Tablets (20) were accurately weighed and powdered. Powdered tablets equivalent to 100 mg were taken and dissolved in 20 mL 2M sodium benzoate solution swirled and sonicated for 2 min. For complete mixing, solution was shaken for 15 min. Filtration of prepared solution was done in Whatman No. 42 filter paper followed by rejecting the first few ml of solutions. The clear supernatant was further used for preparing suitable aliquots followed by dilution sodium benzoate (hydrotropic solution) to get final concentration of 20 $\mu\text{g}/\text{mL}$ and corresponding absorbances were measured Table 6.

Capsules

The different brands (Ponstan, Silaxin) were purchased from different medical store located in Kanpur, India.

The mortar and pestle were used to triturate the capsules of mefenamic acid to convert into powdered form (20 capsules). A powder part equivalent to one capsule weight was dissolved in 2 M sodium benzoate and solution was shaken for 2 h and sonicated for 15 min for complete dissolution of solution. The filtrate was diluted by water and a 20 $\mu\text{g}/\text{mL}$ solution was prepared. Similar procedure was further applied as used for other formulations for the mefenamic acid content estimation.

Table 1: Preliminary solubility study of mefenamic acid

Drug (mg)	Solvent system	Solubility (%w/v)	Temperature (°C)	Solubility enhancement ratio
Mefenamic acid	Distilled water	0.12	25°C	-
	2 M sodium benzoate	9.2	25°C	76.6

Table 2: FTIR spectrum for mefenamic acid identification

S. No.	Functional group	Range (cm^{-1})	Observed frequency (cm^{-1})
1.	Alkanes	600–1500	758.24
2.	Aromatic ring	1500–1600	1528.7
3.	Alcohol	1000–1300	1261.6
4.	Amines	3300–3500	3291
5.	Carboxylic acid	1680–1760	1710.7

FTIR: Fourier transform infrared

Suspensions

One hundred milligrams (Mefmol Suspension) were transferred into a 100 mL calibrated flask dissolved in 20 mL 2 M sodium benzoate followed by sonication same as other formulations.

Mefenamic acid degradation studies

As per the ICH guidelines, stress studies of mefenamic acid were performed by various stress conditions to observe the effects over wide range of pH, heat, and oxidation, photodegradation, and storage temperature.

Acid degradation

Twenty milliliters of diluent were used to dissolve 20 mg of mefenamic acid with 10 ml of 1 N hydrochloric acid (1 mg/ml) and refluxed in round bottom flask on boiling water bath for 8 h (25 ml used) followed by keeping the solution at room temperature condition.

Alkali degradation

To study the effect of alkali degradation, 20 mg of mefenamic acid was dissolved in 20 ml of solvent with 10 ml of 0.1 N NaOH (1 mg/ml) followed by refluxing 25 ml of solution in round bottom flask on boiling water bath for 8 h by keeping solution in room temperature.

Oxidative degradation

Approximately 10 ml of 30% H₂O₂ (1 mg/ml) was used to dissolve 20 mg of mefenamic acid in 20 ml of diluent to study oxidative stress and refluxed 25 ml of the above solution in round bottom flask on boiling water bath for different time durations, that is, 45 min, 2 h, and 6 h.

Photodegradation

Mefenamic acid (20 mg) was placed in covered Petri dishes as a thin layer and put under the sunlight for different time intervals and for blank observations Petri dishes placed in dark conditions.

Thermal degradation

By placing 20 mg of mefenamic acid in different weighing bottles and keeping them at 105° for different time intervals was done to observe the thermal degradation effects on drug.

Storage conditions

To study the effects of storage conditions on mefenamic acid for the prediction of best storage conditions for the drug, it was placed at room temperature conditions and saved for a day in the refrigerators temperature for several days, that is, 1 day, 7 days, and 14 days. Using IR spectroscopy, the percentage of the active substance was calculated under these circumstances.

Analytical applications and validation of proposed method

The proposed method was successfully applied for quantitative determination of mefenamic acid in different pharmaceutical preparations and further validated as per ICH guidelines and good recoveries were obtained, as shown in Tables 4 and 7.

Accuracy

Accuracy of the developed method was checked by scanning in the UV range of 400 nm–200 nm. For interference of formulation additives, recovery experiments were carried out by standard addition method (80, 100, and 120 mg drug). A percentage recovery was calculated from total amount of drug found.

Repeatability precision test

To check the degree of repeatability of the methods, suitable statistical evaluation was carried out. Five samples of the tablet formulations were analyzed for the repeatability study. The standard deviation coefficient of variance and standard error was calculated.

Precision studies (interday and intraday precision)

The intra- and inter-day precision was calculated by assay of the sample solution on the same day and on different days at different time intervals, respectively.

Recovery study

The recovery study was also carried out by the addition of different amounts of drugs to pre-analyze solution (50 µg/ml). From the stock solution of 100 µg/ml of each drug, 1 ml solution was taken in each of four volumetric flasks (10 ml), then 1.2, 0.8, and 0.4 ml of mixed standard stock solution (100 µg/ml of MA) added in three flasks so that remaining one flask contains no added solution and scanned in 285 nm. Good percentage recovery was reported Table 7.

RESULTS AND DISCUSSION

IR spectral studies

IR spectra confirmed the drug mefenamic acid with observed frequencies.

Preliminary solubility studies of drug

The enhancement in solubility of 100-fold was reported for mefenamic acid in hydrotropic mixture solution of 2 M sodium benzoate as compared to solubility in distilled water. The aqueous solubility of pure mefenamic acid in distilled water was 0.012%w/v, whereas in 2 M sodium benzoate, the solubility was found to be approximately 9.2%w/v. Hence, the stability of mefenamic acid in sodium benzoate solution was evaluated by keeping the solution at room temperature conditions for 24 h of duration. Further, the proposed method was optimized and UV method was developed for analytical estimation in marketed oral dosage forms.

Degradation study

In this regard, further study was performed for isolating and characterizing the degradants by exposing to different stress conditions. Susceptibility of mefenamic to acid, alkali, oxidative, thermal, and photolytic degradation in the marketed formulation was investigated. To establish the probable storage conditions for mefenamic acid, storage condition prediction studies were performed by storing the drug in room temperature for the 1st day the reported percentage of active ingredient 100.7% and similarly under refrigerator condition, the active ingredient percentage was remained same, that is, 100.7%. Consequently, storage condition prediction studies were further continued for next several days to 14 days and the active percentage ingredient reported approximately was 98.7%, in the refrigerator; it was 96.8%. For day 14, the percentage of the active ingredient was found 95.8% and in the refrigerator condition 91.9%. Thus, it was concluded that temperature has affected the stability of active drug in marketed forms. The suggestive best storage condition for mefenamic acid was at room temperature away from sunlight and moisture Table 5.

S. No.	Sample	Estimated percentage
1.	Normal	99.99
2.	Acid	77.51
3.	Alkali	93.52
4.	Oxide	92.21
5.	Heat	98.86
6.	Sunlight	100.00

Accuracy and reproducibility of the proposed method were further confirmed by recovery studies. The results of the study confirmed that any little change in the drug concentration in the solution could be possible to estimate by the applied proposed method.

Repeatability results indicated the precision under the same operating conditions over a short interval of time and interassay precisions. Intermediate precision study expresses variation within laboratory conditions in different days. The results of intra- and inter-

Table 3: Analysis data of bulk drug sample with statistical evaluation (n=3)

Amount of bulk drug taken (mg)	Method of analysis	% drug estimated (Mean±SD)	Coefficient of variation (%)	Standard error
100	IPM	97.29±0.63	0.647	0.368
100	PTM	98.26±0.66	0.671	0.383

IPM: Indian Pharmacopoeia method, PTM: Proposed titrimetric method

Table 4: Marketed formulation estimation of mefenamic acid

Formulation	Label claim (mg)	Calculated amount	% recovery proposed method	% recovery reference method
Tablets				
Mefacid (F1)	100	99.56±0.5	99.67	99.09
Flexiwin (F2)	100	99.84±0.11	99.73	98.83
Meflup Forte (F3)	250	254.5±0.23	102.16 ± 1.5	101.96
Mefac (F4)	250	253.8±0.21	101.52 ± 0.62	101.68
Ponstan (F5)	250	252.6±0.15	100.64 ± 0.69	100.96
Mefacid (F6)	250	253.4±0.51	100.96 ± 0.42	101.12
Capsules				
Silaxin Cap.*	250	253.8±0.54	100.99±0.48	101.24
Ponstan Cap.*	250	252.8±0.17	100.7±0.72	101.06
Suspension				
Mefmol Susp.*	5.3±0.2	10.6±0.25	5.2±0.7	104.00

*Susp: Suspension; *Cap: Capsules

Table 5: Stress condition

Storage temperature conditions	Day 1	Day 7	Day 14
4°C	100.7%	96.8%	91.9%
25°C	100.7%	98.7%	95.8%

Table 6: Analytical parameter

Parameters	Values
Observed, λ max	285 nm
Beer's range µg/ml	5-60
Slope	0.0426
Intercept (c)	0.0038
Correlation coefficient	0.9899

day precision and intersubject variation study were reported not more than 2.0% variance reflected good recoveries and results are indicated in Table 8:

Analytical methods comparison (proposed and standard method)

Table 9 shows the comparative analysis between fewer analytical parameters of the present method with recent spectrophotometric methods:

DISCUSSION

The methods developed and discussed in the present work provide a unique, convenient, reproducible, and accurate way for analytical estimation of mefenamic acid in its bulk and pharmaceutical oral dosage form. The results of applied titrimetry approach demonstrated that the mean percent drug content of mefenamic acid in the bulk sample was measured by the standard pharmacopoeial method and found that values were 97.29±0.63. Similarly, the proposed method (2 M sodium benzoate hydrotrope) was successfully applied for the analysis of bulk drug and 98.26±0.66 was found as the mean percent drug content of mefenamic acid. Results of studies have indicated that aqueous solubility of mefenamic acid was appreciatively enhanced in the

Table 7: Recovery studies for the prediction of accuracy

Drug	Label claim	Amount added/ tablet weight	% Recovery±SD	Percentage coefficient of variance
F1	100	80	100.02	0.221
		100	98.99	0.543
		120	103.02	0.154
F2	100	80	100.28	0.253
		100	101.24	0.287
		120	99.89	0.336
F3	100	80	100.15	0.165
		100	99.97	0.659
		120	99.91	0.255
F4	100	80	101.05	0.876
		100	98.78	0.109
		120	99.98	0.436
F5	100	80	100.07	0.245
		100	99.95	0.206
		120	99.94	0.278

*F1: Formulation 1, *F2: Formulation 2, *F3: Formulation 3,

*F4: Formulation 4, *F5: Formulation 5

Table 8: Repeatability

Method	Drug	Intraday precision % coefficient of variance (n=3)	Interday precision % coefficient of variance (n=3)		
			Day 1	Day 2	Day 3
F1	MF	0.966	0.676	0.427	0.286
F2	MF	0.672	0.554	0.434	0.243
F3	MF	0.846	0.785	0.456	0.674
F4	MF	0.571	0.432	0.265	0.152
F5	MF	0.432	0.354	0.238	0.159

MF*: Mefenamic acid

Table 9: Comparative analysis of different methods

Analytical parameter	Proposed method	Reference method
λmax (nm)	285	283
Medium	Aqueous	Non-aqueous
Solvent	Water	Organic solvent
Beers range	5-60 µg/mL	5-25 µg/mL
RSD %	99.73	98.83
Application	Applied for estimation of mefenamic acid in different dosage forms tablet, capsule, and in suspension	Used for estimation of mefenamic acid in tablet formulation

hydro-tropic solution of 2 M sodium benzoate as compared to solubility in distilled water based on the analysis done by the proposed method values found to be closed enough of the standard method proving the accuracy of the applied method. Further, for the validation of proposed method, UV spectrophotometry method was applied and developed for the analytical estimations of mefenamic acid in different marketed oral dosage forms. Wavelength of 285 nm was selected as absorbance maxima of mefenamic acid analysis. Linearity range 5-60 µg/ml was shown for the analysis. The % RSD for repeatability (n=3), intraday and interday (n=3) precision was found to be <2% indicating the precision of method. Similarly, for the accuracy of proposed method, recovery studies were carried out and the results were found within the range of 99% and 100% with lower values of standard deviation and coefficient of variation. Further, the prediction of storage conditions and stress conditions was performed for active drug in marketed formulations. The mefenamic acid was best stored at room temperature away from

sunlight and moisture whereas the drug was found to be susceptible to acid, alkali, oxidation, and heat conditions.

CONCLUSION

Hence, the proposed method is effortless, unique, acceptable, reproducible, and environment support. Evidently, from the applied approach, no interference of drug was reported with 2 M sodium benzoate in analytical estimation at 285nm, hence an attempt could be manifested for analytical estimation of poorly aqueous soluble drugs having λ_{max} above 250 nm by proposed approach provided their preliminary solubility studies confirm the enhancement of solubility in 2 M sodium benzoate. As it is found to be cheaper than most of the organic solvents and thus suggested as a better substitute for expensive organic solvents. Thus, therefore it is concluded that proposed method can save much time and money hence, suggested to be applied in small laboratories for routine analysis of drugs.

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AUTHORS' CONTRIBUTIONS

Dr. Dinesh Kumar Sharma and Dr. Jagannath Sahoo have investigated and supervised the findings of this presented experiment. Ms. Devika Tripathi carried out all the experimental work and wrote the manuscript with support of Dr. Dinesh Kumar Sharma and Dr. Jagannath Sahoo. All authors discussed the results and contributed to the final manuscript.

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None.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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