Mefenamic acid (MA) is 2-[(2, 3-dimethylphenyl) amino] benzoic acid, belonging to the family of N-aryl anthranilic acid. This non-steroidal anti-inflammatory agent acts as Cyclooxygenase-I inhibitor. Although the drug is very effective in various inflammatory and rheumatic conditions, it is having certain disadvantages like main side effects including gastrointestinal disturbance, peptic ulceration and gastric bleeding. These gastroenteropathies are generally believed to be resulted from the direct contact mechanism appears to play an important role in the production of gastrointestinal lesions which is due to local irritation produced by free carboxylic acid group of NSAID's and local inhibition of cytoprotective action of prostaglandins on gastric mucosa. An ideal prodrug retains to achieve such a pharmacological profile and exhibit optimum physicochemical properties. The activity of the parent drug is retained while unwanted side effects are eliminated or notably reduced. The use of prodrugs to provisionally hide the acidic group of NSAIDs has been proposed as an approach to reduce or suppress the GI toxicity due to the direct contact effect. Literature reveals that many efforts had made to synthesize prodrugs via masking carboxylic acid group by forming glycolamide ester, methyl ester, ethyl ester and amide prodrug using various amino acids.

The objective of the present study was temporary masking of the free carboxylic acid group of NSAID’s which can ultimately improve the gastrointestinal tolerability of Mefenamic acid. Hence, the ester and amide prodrugs of Mefenamic acid were designed to achieve this objective. Synthesized compounds of ester and amide derivatives of Mefenamic acid were characterized by FTIR, $^1$H NMR, $^{13}$C NMR and Mass Spectroscopy. A study on their various physicochemical characteristics like melting point, Thin Layer Chromatography (TLC) was done. Anti-inflammatory activity and ulcerogenic activity of prodrugs were compared to that of MA. The synthesized compounds were evaluated for Anti inflammatory activity by carrageenan-induced hind paw oedema method and ulcerogenic activity by using fasted rat model. Pharmacokinetic characteristics were evaluated for solubility, partition coefficient and hydrolysis study.

A series of twelve ester prodrugs of Mefenamic acid were synthesized with different alcohols and phenols for esterification. The selection of alcohols and phenols was done on the basis of the varying degree of lipophilic characteristic. The selected alcohols were methanol, ethanol, propanol, isopropanol and n-butanol. The selected phenols were phenol, 3, 5-
dimethylphenol, 4-methylthiophenol, 2-methylthiophenol, 4-methoxyphenol, 4-flurophenol and 4-chlorophenol.

A series of twelve amide prodrugs of Mefenamic acid were synthesized with different aliphatic and aromatic amines for amidation. The selected aliphatic and aromatic amines were Aniline, 2,6-dichloro aniline, 2-hydroxy aniline, 3-hydroxy aniline, 3-methyl aniline, 4-fluro aniline, 4-hydroxyaniline, 4-methoxy aniline, 1-napthylamine, dimethylamine, ethylamine, methylamine.

Ester and amide Prodrug were prepared by reacting Mefenamic acid with alcohols, phenols, aliphatic and aromatic amines in presence of DCC & DMAP with the yields from 45-80%.

Synthesized compounds were characterized by FTIR, $^1$HNMR, $^{13}$C- NMR and Mass spectroscopy. Synthesized compounds were confirmed to the spectral analysis. The characteristics peaks for MA derivatives of substituted molecules were observed. For aromatic ring C=C str. at 1565-1585 cm$^{-1}$, C-H str at 3045-3085 cm$^{-1}$, C-H bend at 750-760 cm$^{-1}$, CH$_3$ aliphatic C-H str at 2945-2985 cm$^{-1}$, C-H bend at 1445-1485 cm$^{-1}$, C=O amide C=O str. at 1650 cm$^{-1}$; NH- str at 3300-3450 cm$^{-1}$, Ar C-N str at 1250-1300 cm$^{-1}$, C-O str of OH group at 1075-110 cm$^{-1}$, C-Cl at 678 cm$^{-1}$, C-F at 1160 cm$^{-1}$.

In $^1$H-NMR spectra of Mefenamic acid ester derivatives, various proton values for Methyl proton of A Ring (a), Methyl proton of A ring (b), Methyl proton of A Ring (c),Proton of Phenyl ring A, B, and C and NH proton.

The compound VE 6 showed NMR chemical shift value for 3(s) Methyl protons of A Ring (a) at 2.182 δ ppm, 3 (s) Methyl protons of A Ring (b) at 2.350 δ ppm; 12 (m) protons of Phenyl ring A, B and C at 6.658- 8.044 δ ppm; 1 (s) NH proton at 9.390.

The compound VE 7 showed NMR chemical shift value for 3(s) Methyl protons of A Ring (a) at 2.184 δ ppm, 3(s) Methyl protons of A Ring (b) at 2.338 δ ppm; 6(s) Methyl protons of C Ring at 2.610; 10(m) protons of Phenyl ring A, B and C at 6.660- 8.036δ ppm; 1(s) NH proton at 9.386

The compound VE 8 showed NMR chemical shift value for 3(s) Methyl protons of A Ring (a) at 2.188 δ ppm, 3(s) Methyl protons of A Ring (b) at 2.346 δ ppm; 3(s) Methyl protons of C Ring at 2.718 δ ppm; 11(m) protons of Phenyl ring A, B and C at 6.651- 8.059δ ppm; 1(s) NH proton at 9.384.

In $^1$H-NMR spectra of Mefenamic acid amide derivatives, various proton values for methyl proton of A Ring (a),Methyl proton of A ring (b), Proton of Phenyl ring A,B, and C, NH proton and NH of CONH.
The compound \( \text{V2} \) 3(s) Methyl proton of A Ring (a) at 2.187 \( \delta \) (ppm); 3(s) Methyl proton of A ring (b) at 2.342 \( \delta \) (ppm); Proton of Phenyl ring A, B, and C at 6.666-8.047 \( \delta \) (ppm); 1(s) NH proton at 9.386 \( \delta \) (ppm); 1(s) NH of CONH at 10.198 \( \delta \) (ppm).

The compound \( \text{V4} \) 3(s) Methyl proton of A Ring (a) at 2.185 \( \delta \) (ppm); 3(s) Methyl proton of A ring (b) at 2.340 \( \delta \) (ppm); 11(m) Proton of Phenyl ring A, B, and C at 6.658-8.032 \( \delta \) (ppm); 1(s) NH proton at 9.370 \( \delta \) (ppm); 1(s) OH proton of Ar ring at 6.392 \( \delta \) (ppm); 1(s) NH of CONH at 10.218 \( \delta \) (ppm).

The compound \( \text{V9} \) 3(s) Methyl proton of A Ring (a) at 2.190 \( \delta \) (ppm); 3(s) Methyl proton of A ring (b) at 2.345 \( \delta \) (ppm); 14(m) Proton of Phenyl ring A, B, and C at 6.654-8.060 \( \delta \) (ppm); 1(s) NH proton at 9.382 \( \delta \) (ppm); 1(s) NH of CONH at 10.210 \( \delta \) (ppm).

\(^{13}\text{C} \text{NMR} \ (\delta, \text{ppm}) \ (\text{DMSO}): \) spectra of Mefenamic acid amide derivative \( \text{V4} \) showed the 21 peaks for 21 different carbon atoms. (13.58ppm & 20.45ppm) was assigned to methyl carbon, (168.22 ppm) assigned to carbonyl carbon of amide group, (120.82, 122.02, 122.64, 123.95, 127.28, 129.91, 130.62, 131.17, 133.61, 138.05, 139.58, 147.44, 147.61, 159.78) other all are aromatic carbon.

\(^{13}\text{C} \text{NMR} \ (\delta, \text{ppm}) \ (\text{CDCl}_3): \) spectra of Mefenamic acid ester derivative \( \text{VE6} \) showed the 21 peaks for 21 different carbon atoms. (13.53ppm & 20.93ppm) was assigned to methyl carbon, (165.2 ppm) assigned to carbonyl carbon of ester group, (120.93, 122.16, 122.67, 123.93, 127.38, 129.94, 130.68, 131.24, 133.65, 138.17, 139.63, 147.45, 147.69, 163.17) other all are aromatic carbon.

The confirmation of the molecular structure was done by mass spectra. The molecular ion peak and the base peak, in all compounds, were clearly obtained in mass spectral study. The molecular ion peaks were found to be in agreement with molecular weight of the respective compounds.

The synthesized compounds of ester and amide derivatives of Mefenamic acid were evaluated for anti-inflammatory activity by carrageenan-induced hind paw oedema method. This method indicated that some prodrugs have comparable activity to parent drugs. The prodrugs with significant anti-inflammatory activity were selected for the further evaluation of ulcerogenicity. The Ulcerogenic activity was done on fasted rat model and screened by one way ANOVA followed by Dunnet’s T-Test. The synthesized Prodrugs showed lower ulcer index value than Mefenamic acid thus indicating decrease in gastrointestinal side effects through successful masking of free carboxylic group of drug.
The synthesized ester prodrugs of Mefenamic acid were subjected to solubility studies. Prodrugs were found insoluble in water and 0.1M HCl, slightly soluble in 0.1M NaOH and moderately to highly soluble in various solvents such as methanol, ethanol, chloroform and benzene. The greater solubility of the standard drug MA in 0.1M NaOH may be mainly due to the presence of free carboxyl group, which forms a sodium salt and makes the compound ionic. But prodrug showed moderate to high solubility in various organic solvents, which indicates lipophilic behavior of the compound. Partition coefficient of Mefenamic acid and prodrugs were evaluated in octanol-aqueous buffer (pH 7.4) system. The results indicate that synthesized esters were found to be more lipophilic than parent drug. The in vitro hydrolysis studies were designed in a manner to mimic the gastrointestinal tract pH, hence as a primary requirement, calibration curve in the experimental pH value related for the study were made. The hydrolysis study was carried out in simulated gastric fluid (SGF) at pH 1.2 for representing the condition of stomach, in simulated intestinal fluid (SIF) at pH 7.4 and in 80% human plasma at pH 7.4. The minimum reversion was observed at gastric pH (SGF, pH 1.2) suggesting the stability of synthesized prodrugs in gastric pH. However at higher pH values i.e. in SIF representing intestine, the percentage reversion was significantly higher, thereby making the free drug available for absorption in the intestine. A much higher value was observed in 80% human plasma due to the enzyme dependant hydrolysis taking place in blood. Also the process of reversion increases almost linearly with time at intestinal pH and physiological pH of blood. Hence, prevention of contact of free carboxylic group with gastric mucosa resulted in reduction in ulcerogenicity, while rapid hydrolysis of prodrugs in human plasma caused retention of activity. As a result, the objective of synthesis of prodrugs with comparable anti-inflammatory activity with significantly reduced ulcerogenicity is achieved.

The present investigation on the synthesis of prodrugs of Mefenamic acid for the reduced ulcerogenic potential may represent a potentially useful method for developing compounds with equipotent activity and reduced toxicity than the parent compounds.