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(REVIEW ARTICLE)



## An insight of non-steroidal anti-inflammatory drug mefenamic acid: A review

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### Abstract

This review focuses on the design, synthesis and pharmacological effects of non-steroidal anti-inflammatory (NSAIDs) mefenamic acid which is an anthranilic acid derivative. Mefenamic acid is a non-steroidal anti-inflammatory drug used to treat pain, including menstrual pain. Exploitation of the prodrug approach has the potential to achieve a reduction of mefenamic acid GI (gastrointestinal) intolerance, enhance its bioavailability, mask its unpleasant sensation and prolong its duration of action. Mefenamic acid, an effective NSAID has always been used as an anti-inflammatory and analgesic agent. A brief note on various marketed formulations of mefenamic acid provides an insight of the potential capability of this drug and its future scope.

**Keywords:** Anti-inflammatory drugs; Mefenamic acid; Rheumatoid arthritis; Dosage formulations

### 1. Introduction

Mefenamic acid (MA) is an anthranilic acid derivative. In particular, it is structured as *N*-(2,3-xylyl) anthranilic acid. This drug shares relatedness to 3-hydroxyanthranilic acid, a naturally occurring metabolite of tryptophan [1].

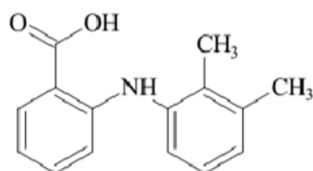
Its physicochemical properties, especially the extremely low solubility in water ( $\ll 1 \text{ mg mL}^{-1}$ ) and distinct adhesive properties give rise to major challenges during dosage form development and manufacturing. Hence, serious effort was made to increase dissolution characteristics of MA to improve its biopharmaceutical performance [2].

The short biological half-life of Mefenamic acid is 2h. Conventionally it is available as tablets, capsules and suspensions. Because of short half-life oral dose required to frequent administration of drug to maintain the desired steady state level. The available dose for this drug is 250mg thrice a day. MA is classified as class II on the basis of biopharmaceutical classification system, because of its poor solubility over the pH range 1.2-7.5. It is inherently highly permeable through biological membranes, but exhibits low aqueous solubility. Due to its low solubility, various researches were done to improve the low solubility or bioavailability such as solid dispersion and micronization. Mefenamic acid is widely used in mild to moderate pain including headache, dental pain, dysmenorrhea, rheumatoid arthritis, osteoarthritis and other joint disorders also leads to side effects such as gastrointestinal disorders, like gastrointestinal bleeding and gastric upset.

Drug delivery at specific site is affected by carriers used. Carrier used should be biocompatible and immunogenic in nature. Also, suitable for route administration and desired release profile of drug. Eudragit RL 100 and Ethyl cellulose have been used as drug carriers to achieve sustained and controlled drug delivery for the past few decades [3].

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**Figure 1** Structure of mefenamic acid

**Table 1** Characteristic feature of mefenamic acid

Characteristic feature	Description
Molecular formula	C <sub>15</sub> H <sub>15</sub> NO <sub>2</sub>
Molecular weight	241.28
Chemical name	2-[(2,3-dimethylphenyl)amino]benzoic acid
Volume of distribution	1.06 L/kg
Protein binding	90%
Half life	2 h
LD50	740 mg/kg
Solubility	0.0137 mg/mL
log P	5.4
pKa	3.89
Refractive index	71.88 m <sup>3</sup> .mol <sup>-1</sup>
Melting point	230-231
Color	White to off-white, crystalline powder
Boiling point	398.8
Density	1.2gm/cm
Molar volume	200.6 cm

### 1.1. Mode of action

MA binds the prostaglandin synthetase receptors COX-1 and COX-2, inhibiting the action of prostaglandin synthetase. As these receptors have a role as a major mediator of inflammation and/or a role for prostanoid signaling in activity-dependent plasticity, the symptoms of pain are temporarily reduced.

**Cox-1:** Cyclooxygenase-1, an enzyme that acts to speed up the production of certain chemical messengers, called prostaglandins, in a variety of areas of the body such as the stomach, kidneys, and sites of inflammation. In the stomach, prostaglandins promote the production of a protective natural mucus lining. They also interact within certain cells that are responsible for inflammation and other functions.

**Cox-2:** Cyclooxygenase-2, an enzyme that acts to speed up the production of certain chemical messengers, called prostaglandins that play a key role in promoting inflammation. When cox-2 activity is blocked, inflammation is reduced. Unlike cox-1, cox-2 is active only at the site of inflammation, not in the stomach.

### 1.2. Pharmacokinetics

#### 1.2.1. Absorption

Mefenamic acid is rapidly absorbed after oral administration. Mean extent of absorption was 30.5 mcg/h/mL.

### 1.2.2. Distribution

Apparent volume of distribution was found to be 1.06 L/Kg for 500 mg tablet.

### 1.2.3. Metabolism

Mefenamic acid is metabolized by cytochrome P450 enzyme CYP2C9 to 3-hydroxymefenamic acid (Metabolite I). Further oxidation to a 3- carboxymefenamic acid (Metabolite II) may occur.

### 1.2.4. Excretion

Approximately 52% of a mefenamic acid dose is excreted into urine primarily as glucuronides of mefenamic acid (6%), 3- hydroxymefenamic acid (25%) and 3- carboxymefenamic acid (21%). The fecal route of elimination accounts for up to 20% of the dose. The elimination half-life of mefenamic acid is approximately 2 h [4].

## 1.3. Drug interaction

(R)-warfarin: the risk or severity of gastrointestinal bleeding can be increased.

(S)-Warfarin: The risk or severity of gastrointestinal bleeding can be increased.

2, 5-Dimethoxy-4-ethylamphetamine: The risk or severity of hypertension can be increased.

4-Bromo-2, 5-dimethoxyamphetamine: The risk or severity of hypertension can be increased.

4-hydroxycoumarin: The risk or severity of gastrointestinal bleeding can be increased.

### 1.3.1. Side effect

- Cardiovascular thrombotic
- GI Bleeding, Ulceration
- Hepatotoxicity
- Hypertension
- Renal toxicity and Hyperkalemia
- Serious skin reaction
- Hematologic toxicity

### 1.3.2. Contraindication

- Methotrexate- Neutopenia, Renal dysfunction,
- Aspirin- GI bleeding, Ulceration
- Cyclosporine- Increase cyclosporine's nephrotoxicity
- Other NSAIDs- GI bleeding, Ulceration

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## 2. Formulations of mefenamic acid

The suitable formulation for the synthesized drugs is always a challenge for the researchers. The compatibility of all the components including pharmaceutical active ingredients plays significant role in designing the formulation so always it is taken into consideration. The developed formulation should be cost effective, stable and physiologically the active ingredients should be available on release [5].

### 2.1. Mefenamic acid suspension

Drugs dispensed as suspensions because of poor aqueous solubility (BCS class II). Drug formulated as suspensions are more bioavailable than solid dosage form [6]. Possible modification of the drug's bioavailability can be another advantage of this dosage form, The prodrugs were already reported as chemically stable and bio-labile so for the suspension first there is preparation of prodrug of mefenamic acid which results in delayed drug release, provides clinically useful plasma concentration of the drug [7].

### 2.1.1. Material

Mefenamic acid, Tween-80, Potassium chloride, Methyl cellulose, Sodium CMC, Sodium citrate, Sodium benzoate, Glycerine, etc.

### 2.1.2. Preparation of suspensions of prodrugs

The weighed quantities of prodrugs were wetted by trituration with aqueous solution of wetting agent. Glycerin was added by trituration to form smooth paste. Now water soluble ingredients (sodium citrate, sodium benzoate) were dissolved in water and added slowly and triturated. Potassium chloride dissolved in water added with trituration. Thereafter aqueous solution of suspending agent and syrup was added to above mixture with trituration. Then flavor was added and mixed. The suspension so formed transferred to a measuring cylinder and volume was made to 100 mL.

**Table 2** List of marketed products of Mefenamic acid suspension

Sr. No.	Marketed product (Brand name)	Manufacturing company
1	Meftal-P	Blue I Cross Laboratories
2	Paramol-M	Parkinson Pharma
3	Panston	Pfizer
4	Meftagesic	Blue Cross Laboratories
5	Alide P	Altar Life Sciences
6	Nimucet MF	Intas laboratories Pvt. Ltd.
7	Zuesic Forte	Zodak Health Care Ltd.
8	M Gesic	Cure Quick Remedies
9	Pyritec M DS	Innovative Pharmaceuticals
10	Parafit M	Medlab Pharmaceuticals Pvt. Ltd.

## 2.2. Controlled release tablets containing mefenamic acid

Oral drug delivery system have the advantages that these are easy to administer, ease of manufacturing and higher patient compliance. In oral drug delivery systems the most profound objective was to maintain constant drug plasma concentrations for a certain period of time to reduce the dosage frequency and this goal achieved by the development of controlled drug delivery system [8].

Oral sustain/controlled release drug delivery systems is dominating the market and have an increased safety and patient compliance. These dosage forms can deliver the drug in a predetermined manner to the site of action following drug release from matrices occurs by diffusion or degradation mechanism.

- Polymers, Polyurethanes for elasticity.
- Polysiloxanes or silicones for insulating ability.
- Polymethyl methacrylate for physical strength and transparency.
- Polyvinyl alcohol for hydrophilicity and strength.
- Polyethylene for toughness and lack of swelling.
- Polyvinyl pyrrolidone for suspension capabilities.

To be successfully used in controlled drug delivery formulations, a material must be chemically inert and free of leachable impurities, controls release of drug in a slow and nearly constant manner to obtain nearly constant peak plasma level [9, 10].

### 2.2.1. Material

Mefenamic acid, sodium hydroxide, mono basic potassium phosphate, caboxy methyl cellulose, starch, lactose and magnesium stearate.

### 2.2.2. Formulation of tablets

Mefenamic acid 200 mg controlled release matrix tablets were prepared using 100 mg drug and weighing concentrations of polymer and excipients. Starch was used as filler and magnesium stearate was used a lubricant.

### 2.2.3. Preparation of tablets

Drug and polymer was taken in mortar and was grind to fine powder than all other excipients were added except lubricant. This mixture was passed through 20 sieve size mesh for three times and then lubricant was added and again passed through the same sieve. The prepared powder was compressed to tablets using single punch tableting machine at an average hardness of 7 kg/cm<sup>2</sup>.

**Table 3**List of marketed products of Mefenamic acid tablet

Sr. No.	Marketed products (Brand name)	Manufacturing company
1	Abdrot Plus	CaptabBiotec
2	Alide-P	Altar Pharma
3	MefProxyvon	Wockhardt
4	Meflup	Lupin
5	Meflup Forte	Lupin
6	Ponstan	Pfizer
7	Meftal 500	Blue Cross Laboratories
8	Biospas Forte	Biochem
9	Mictal 250	Biochem
10	Meff P	Bastochem

## 2.3. Mefenamic acid emulgel for topical delivery

Gels are a relatively newer class of dosage form created by entrapment of large amounts of aqueous or hydroalcoholic liquid in a network of colloidal solid particles, which may consist of inorganic substances, such as aluminum salts or organic polymers of natural or synthetic origin. They have a higher aqueous component that permits greater dissolution of drugs, and also permit easy migration of the drug through a vehicle that is essentially a liquid, compared with the ointment or cream base. In spite of many advantages of gels a major limitation is in the delivery of hydrophobic drugs [11].

So to overcome this limitation, emulgels are prepared and used so that even a hydrophobic therapeutic moiety can enjoy the unique properties of gels [12]. When gels and emulsions are used in combined form the dosage forms are referred as EMULGELS [13].

In recent years, there has been great interest in the use of novel polymers with complex functions as emulsifiers and thickeners because the gelling capacity of these compounds allows the formulation of stable emulsions and creams by decreasing surface and interfacial tension and at the same time increasing the viscosity of the aqueous phase [14]. Emulgels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, long shelf life, bio-friendly, transparent and pleasing appearance [15].

### 2.3.1. Material

Mefenamic acid, carbopal 940, liquid paraffin, tween 20, span20, propylene glycol, methyl paraben, ethyl paraben, mentha oil, clove oil, water.

### 2.3.2. Preparation of emulgel

The gel phase in the formulations was prepared by dispersing Carbopol 940 in purified water with constant stirring at a moderate speed using mechanical shaker, then the pH was adjusted to 6–6.5 using tri ethanol amine (TEA). The oil phase of the emulsion was prepared by dissolving span 20 in light liquid paraffin while the aqueous phase was prepared by dissolving tween 20 in purified water. Methyl and ethyl parabens were dissolved in propylene glycol whereas mefenamic acid was dissolved in ethanol, and both solutions were mixed with the aqueous phase. Clove oil and mentha oil were mixed in oil phase. Both the oily and aqueous phases were separately heated to 70–80°C, then the oily phase was added to the aqueous phase with continuous stirring until it got cooled to room temperature. The obtained emulsion was mixed with the gel in 1:1 ratio with gentle stirring to obtain the emulgel [16].

**Table 4** List of marketed products of NSAIDS emulgel

Sr. No.	Marketed products (Brand name)	Manufacturing company
1	Volini GEL	Ranbaxy Laboratories
2	DiclonEmulgel	Med Pharma
3	Voltaren	Novartis Pharma
4	Voltarol Emulgel P	Glaxo Smith Kline Pharma
5	Isofen Emulgel	Beitjala Pharma

### 2.4. Topical gel containing microsponges of mefenamic acid

The microsphere delivery system is patented polymeric system consisting of porous microsphere. They are tiny sponge like spherical particles that consist of myriad of inter connecting void within a non-collapsible structure through which active ingredient are released in a controlled manner. Microsphere surrounded by the vehicle acts like microscopic sponges, storing the active ingredient until its release is triggered by skin application. Release of drug into the skin is triggered by a variety of stimuli, including rubbing and higher skin temperature than ambient one. Their high degree of cross linking results in particles that are insoluble, inert and of sufficiently strong strength to withstand the high shear commonly used in creams, lotions, and powders [17, 18].

The microsponges were prepared by free radical suspension method or quassi emulsion solvent diffusion method. It was shown that the drug: polymer ratio, stirring rate, volume of dispersed phase influenced the particle size and drug release behavior of the formed microsponges and that the presence of emulsifier was essential for microsphere formation [19].

#### 2.4.1. Material

Mefenamic acid, eudragit RS100, eudragit RL 100, ethyl cellulose, polyvinyl alcohol, ethanol, carbopol 934P, triethanolamine, distilled water

#### 2.4.2. Formulation of mefenamic acid loaded microsponges

Microsponge were prepared by quasi-emulsion solvent diffusion method using an external phase of distilled water and polyvinyl alcohol (PVA), and internal phase consisting of drug, ethyl alcohol, polymer(ethyl cellulose, eudragit RS100 & eudragit RL 100) and glycerol (which was added at an amount of 20% of the polymer in order to facilitate the plasticity). For preparing microsphere, the internal phase was prepared and added to the external phase at room temperature. After emulsification process is completed, the mixture was continuously stirred for 2 h at 500 rpm. Then the microsponges were separated by filtration. The product was washed and dried under vacuum oven at 40°C for 12 h [20, 21].

#### 2.4.3. Mefenamic acid microsphere gel

Accurately weighed amount of carbopol 934 P was taken and dissolved in water using propeller. Microsphere formulations containing mefenamic acid was added to the above solution with constant stirring. This final solution was neutralized slowly adding triethanolamine with constant stirring until the gel is formed [22].

**Table 5** List of other marketed products of Mefenamic acid

Sr. No.	Marketed products (Brand name)	Manufacturing company
1	Mefpra (Syrup)	Immune Life Sciences
2	Ladex P (Syrup)	Allenge India
3	Migesic (Syrup)	Hauz Pharma Pvt. Ltd.
4	Nimley P (Syrup)	Zodley Pharmaceutical Pvt. Ltd.
5	Zuesic P (Syrup)	Zodak Health Care
6	Nukind M (Syrup)	Ambic Aayurchem
7	Mifucet (Suppository)	Intas Pharmaceuticals Ltd.
8	Armed Forte (Capsule)	Ardor Drugs Pvt. Ltd.

### 3. Conclusion

Mefenamic acid, a BCS class II drug gives a reason to improve its solubility and by studying about its formulations it gives major goal for formulation development of modified drug delivery system such as Nanocrystals, Nanostructured lipid carriers etc. for improved bioavailability of the drug at desired site of action.

### Compliance with ethical standards

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#### *Disclosure of conflict of interest*

The review article bears no conflict of interest.

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