Preparation and solubility profile study of sodium and potassium salts of mefenamic acid: the effect of pH and polarity

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Enhancing the solubility of active pharmaceutical ingredients became a fundamental concept in the manufacturing of different pharmaceutical dosage forms. This research aims to enhance the solubility of mefenamic acid by salt formation method and study the effect of polarity, pH, and temperature on the solubility of mefenamic acid and its salts. Two deferent salts of mefenamic acid (sodium and potassium salts) were prepared. Using the asymmetric factorial as an experimental design, the solubility of mefenamic acid (MA), sodium mefenamate (Na-MA), and potassium mefenamate (K-MA) were studied in different solvents, pH, and temperatures. It has been found that potassium mefenamate has the highest solubility among other derivatives in different media. Also, the mefenamic acid and its salts have a higher solubility in the polar aprotic solvent and the higher pH aqueous media.

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Keywords: Mefenamic acid, Sodium mefenamate, Potassium mefenamate, Mefenamic acid solubility, DSC, FTIR

1. Introduction

Mefenamic acid is derivatized from fenamic acid, derived from anthranilic acid [1]. Structurally, mefenamic acid is 2-[(2,3-Dimethylphenyl)amino]benzoic acid (IUPAC name) ($C_{15}H_{15}NO_2$) as shown in Figure 1. It is a weak organic acid that contains related 3-hydroxyanthranilic acid which is the natural metabolite of tryptophan (standard amino acid). This compound is a member of the NSAIDs family (one of five main families; salicylates, propionic acid derivatives, acetic acid derivatives, enolic acid derivatives, and fenamates)[2].

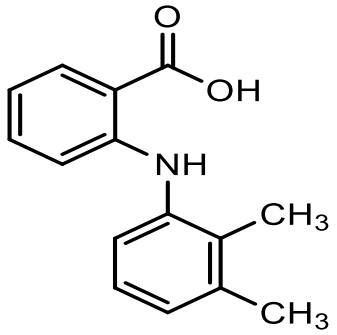

Fig. 1. Chemical structure of mefenamic acid.

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Mefenamic acid is a very potent and powerful antipyretic drug. Other therapeutic uses of the drug include treating mild to moderate pain such as headache, dental pain dysmenorrhea, rheumatoid arthritis, osteoarthritis as well as other joint disorders [3]. The overall mechanism of action of the drug is through binding to the prostaglandin synthetase receptors COX -1 and COX -2, potently inhibiting the action of prostaglandin synthetase. As both COX -1 and COX-2 receptors are major mediators of inflammation, the symptoms of pain are temporarily reduced. As with other NSAIDs, mefenamic acid is generally well tolerated and is found to be associated with mild side effects including headache, dizziness, nausea, diarrhea, abdominal discomfort, heartburn, peripheral edema, and hypersensitivity reactions [4]. It has also been found to be more effective and equally tolerable compared to paracetamol as an antipyretic in pediatric patients with febrile illness and can be the best alternative to paracetamol [5]. In terms of pain relief compared to other types of NSAIDs conflicting results have been reported, where Mefenamic acid has been reported, to be equally effective in alleviating pain in primary dysmenorrhea compared with several NSAIDs [6].

Mefenamic acid is white to off-white microcrystalline powder. It is a water-insoluble drug, sparingly soluble in chloroform and ether, slightly soluble in ethanol (4.6 mg/mL), with greater solubility in dimethylformamide (38.5 mg/mL) [7, 8]. The melting point of mefenamic acid is 230-231 °C. It is a liposoluble (logP = 5.12) with a pK_a equal to 4.2 [9].

Almost about 90% of the drugs are orally administered; in fact, the water solubility of the drug is considered one of the main physical properties that should be obtainable. Since 1995, it estimated around 40% of the recently approved biopharmaceutical substances (drugs) have poorly water-soluble properties [10]. The poor water solubility of the drugs directly affects the dissolution rate, drug permeability, chemical stability, drug-enzyme(s) stability, and ultimately, the bioavailability [11, 12].

Many factors influence the drug solubility in different body media (stomach, intestine, etc.). Understanding these factors is essential for designing appropriate pharmaceutical dosage forms and achieving adequate absorption.

Generally, there are several techniques used to improve the solubility of poorly-soluble compounds. These include, solute-solvent interaction [13], particle size reduction [14], as well as elevation of temperature and pressure [15, 16]. Several studies were conducted previously, to enhance the solubility of mefenamic acid by using different techniques (i.e. chemical and physical modifications). [17-25]. Salt formation is one of the techniques that have been utilized to enhance and improve the solubility of water-insoluble acidic and basic drugs. This is because salts, in general, have a higher water-solubility compared with acidic compounds. This method offers a high level of chemical stability among other techniques, especially, in the formulation of parenteral dosage forms [26].

2. Materials and methods

2.1. Materials

Table 1 shows the description of materials used in this research as received. The instruments and apparatus used throughout this work are summarized in Table 2.

Table 1. Materials.

Material	**Manufacturer and Source**
Mefenamic acid	Sigma-Aldrich, CAS No. M4267, China
Sodium hydroxide	Sigma-Aldrich, CAS No. S8045, Poland
Potassium hydroxide	Loba Chemie Pvt. Ltd., CAS No. 1310-58-3, India
Hydrochloric acid	Sigma-Aldrich, CAS No. 30721, Austria
Methanol	Sigma-Aldrich (Chromasolv®), CAS No. 34860, Poland
Acetone	Sigma-Aldrich, CAS No. 32201, France
Dichloromethane	Sigma-Aldrich, CAS No. 32222, France
Ethanol	Sigma-Aldrich, CAS No. 24106, Brazil

Table 2. Instrument and apparatus.

Instrument/Apparatus	Specifications and Source
Analytical balance	Adam Equipment (PW254), UK
Ultrasonic bath	Branson Ultrasonics Corp. (M3800H-E), USA
Magnetic stirrer	HS-18 – HumanLab Instrument Co., Korea
Centrifuge	Thermo Fisher Scientific (Her. Meg. 16R), Germany
Rotary evaporator	IKA® (RV 10 Control), Germany
Shaking water bath	ThermoLab (1083 GFL), Germany
Freeze dryer	Christ (BETA 2-8 LD *plus*), Germany
Differential Scanning Calorimetry	NETZSCH (DSC 214 *polyma*), Germany
FTIR spectrophotometer	Agilent Technologies (Cary 630), Malaysia
UV-Visible spectrophotometer	Thermo Fisher Scientific (Evolution 60S), USA

2.2. Methods

2.2.1. Preparation of mefenamic acid together with its sodium and potassium salts

2.2.1.1. Preparation of sodium mefenamate (Na-MA)

The method adapted was modified from a previous study done by Bani-Jaber et al [27] following the chemical reaction as shown in Fig. 2, in which 1 g of sodium hydroxide (NaOH) was dissolved in 300 mL of distilled water at room temperature. This was followed by the gradual addition of 6 g of mefenamic acid (MA) into NaOH solution in a bath sonicator. The formed solution was then filtered and the clear solution was concentrated into 100 mL using a rotary evaporator at 60 °C. The formed solution was kept overnight in the freezer (-20 °C). The frozen solution of Na-MA was then dried using a freeze dryer for 24 hours, and the resulting powder was kept at room temperature (22 °C).

2.2.1.2. Preparation of potassium mefenamate (K-MA)

Using the same previously modified method [27] for the preparation of sodium mefenamate was made taking into consideration the difference in molecular weight between the sodium and potassium molecules as shown in Fig. 2. 1.5 g of potassium hydroxide (KOH) was dissolved in 350 mL of distilled water at room temperature. Following this, 6.45 g of mefenamic acid (MA) was added gradually into a KOH solution in a bath sonicator. The formed solution was filtered, and the clear solution was concentrated into 100 mL using a rotary evaporator at 60 °C. The formed solution was kept overnight in the freezer (-20 °C). The frozen solution of M-MA was then dried by freeze dryer for 24 hours, and the resulting powder was kept at room temperature (22 °C).

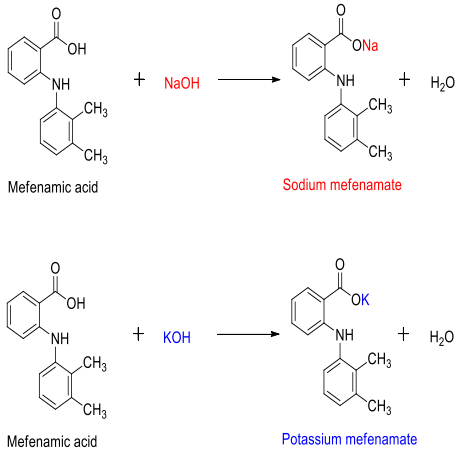


Fig. 2. The chemical reaction of MA with sodium and potassium hydroxides.

2.2.2. FT-IR Spectrometry

All samples of MA, Na-MA, and K-MA were subjected to FT-IR spectrophotometry for qualitative identification. The spectrums of all samples were then analyzed to compare them with standard IR spectrums of MA [28] in the literature.

2.2.3. Differential Scanning Calorimetry (DSC)

The thermodynamic properties of MA, Na-MA, and K-MA were determined by DSC that was pre-calibrated using indium calibration standard. About 5-10 mg from each sample (MA, Na-MA, and K-MA) were placed into an aluminum crucible (pan) and analyzed by the DSC in a temperature range of 150-330 °C at a heating rate of 10 °C/min using nitrogen as a purging gas in a flow rate of 40 mL/min. Following this, all SDC patterns were determined.

2.2.4. Determination of solubility profile of mefenamic acid and its salts

2.2.4.1. Calibration curve of mefenamic acid and its salts

All tools and glassware were washed by chromic acid and double washed using distilled water, they were then washed again by ethanol and dried for 24 hours in a 40°C oven. Stoke solutions of 100 µg/mL of MA, Na-MA, and K-MA in ethanol were prepared and scanned in the UV-spectrophotometer (190-500 nm) for determination of maximum absorption (λ_{max}) for each one. The prepared stock solutions were diluted into 50, 25, 10, 5, and 1 µg/mL. Then, the absorption (*A*) of diluted solutions of each compound (MA, Na-MA, and K-MA) were measured in the UV-spectrophotometer. Finally, a calibration curve was devolved by plotting the absorbance (*A*) versus sample concentration (µg/mL), and the correlation coefficient was detected.

2.2.4.2. Design of experiment

Fabrications of the three variables within this study were conducted following $2^1 3^1 6^1$ asymmetric factorial design. The first factor (F_1) was a temperature (examined at 2 levels; 25 °C and 37.5 °C), the second factor (F_2) was the mefenamic acid and its salts (examined at 3 levels; MA, Na-MA, and K-MA), and the third factor (F_3) was the type of solvent (examined at 6 levels; 0.1N HCl, phosphate buffer pH 5.8, phosphate buffer pH 6.8, methanol, acetone, and dichloromethane), respectively. The design was composed of 36 experimental runs and the layout is shown in Table 3 [29].

Table 3. Experimental runs layout for the 213161 asymmetric factorial design.

ID	**F_1** **Temp.**	**F_2** **MA & its salts**	**F_3** **Type of the solvent**	**Experiment layout**
Run 01	0 = 25°C	0 = MA	0 = 0.1N HCl	000
Run 02	0	0	1 = Phosphate buffer pH 5.8	001
Run 03	0	0	2 = Phosphate buffer pH 6.8	002
Run 04	0	0	3 = Methanol	003
Run 05	0	0	4 = Acetone	004
Run 06	0	0	5 = Dichloromethane	005
Run 07	0	1 = Na-MA	0	010
Run 08	0	1	1	011
Run 09	0	1	2	012
Run 10	0	1	3	013
Run 11	0	1	4	014
Run 12	0	1	5	015
Run 13	0	2 = K-MA	0	020
Run 14	0	2	1	021
Run 15	0	2	2	022
Run 16	0	2	3	023
Run 17	0	2	4	024
Run 18	0	2	5	025
Run 19	1 = 37.5°C	0	0	100

ID	F_1 Temp.	F_2 MA & its salts	F_3 Type of the solvent	Experiment layout
Run 20	1	0	1	101
Run 21	1	0	2	102
Run 22	1	0	3	103
Run 23	1	0	4	104
Run 24	1	0	5	105
Run 25	1	1	0	110
Run 26	1	1	1	111
Run 27	1	1	2	112
Run 28	1	1	3	113
Run 29	1	1	4	114
Run 30	1	1	5	115
Run 31	1	2	0	120
Run 32	1	2	1	121
Run 33	1	2	2	122
Run 34	1	2	3	123
Run 35	1	2	4	124
Run 36	1	2	5	125

2.2.4.3. Determination of saturated solubility of MA, Na-MA, and K-MA

The applied technique for measuring the solubility profile of MA and its sodium and potassium salts is based on previous studies by Qandil et al [30] and Assaf et al [31] with few modifications.

The solubility of MA, Na-MA, and K-MA were determined in 6 different solvents: (i) 0.1 N HCl (stomach media); (ii) phosphate buffer pH 5.8 (small intestine pH); (iii) phosphate buffer pH 6.8 (small intestine pH); (ix) methanol (polar protic solvent); (x) acetone (polar aprotic solvent); and (xi) dichloromethane (nonpolar solvent). For each compound (MA, Na-MA, and K-MA), the solubility profile was determined at room temperature (25 °C) and human body temperature (37.5 °C).

An excess amount of each material (MA, Na-MA, or K-MA) was added into 5 mL of the solvent in a glass vial and shacked very well by a shaker for 1 hour. The vials were then incubated in a shaker water-bath under a controlled temperature of 25 °C and 37.5 °C for 48 hours.

After 48 hours of incubation, the samples were centrifuged for 15 minutes (9000 rpm) and the supernatants were filtered using syringe filter (WhatmanTM 0.2 µm PTFE). The obtained clear solutions were measured in the UV-spectrophotometer for the determination of the solute concentrations.

3. Results and discussion

3.1. FTIR Spectrometry of MA, Na-MA, and K-MA

All samples were scanned at a wave-number range of 4000-650 cm^{-1}. The spectra of MA, Na-MA, and K-MA are shown in Figure 3. The MA IR spectrum shows a small peak at 3308 cm^{-1} which indicates an overtone to the fundamental sharp peak of carbonyl (C=O) stretch at 1684 cm^{-1}. Also, there is a broad-band (3098-2551 cm^{-1}) representing the O-H stretching. The aromatic C=C and hydroxyl (O-H) bending appear at 1577 cm^{-1} and 1439 cm^{-1}, respectively.

The comparison of the three spectra reveals the presence of hydroxyl (O-H) stretching and bending bands in the MA spectrum only. The absence of these two bands in the NA-MA and K-MA spectra confirms the formation of both salts.

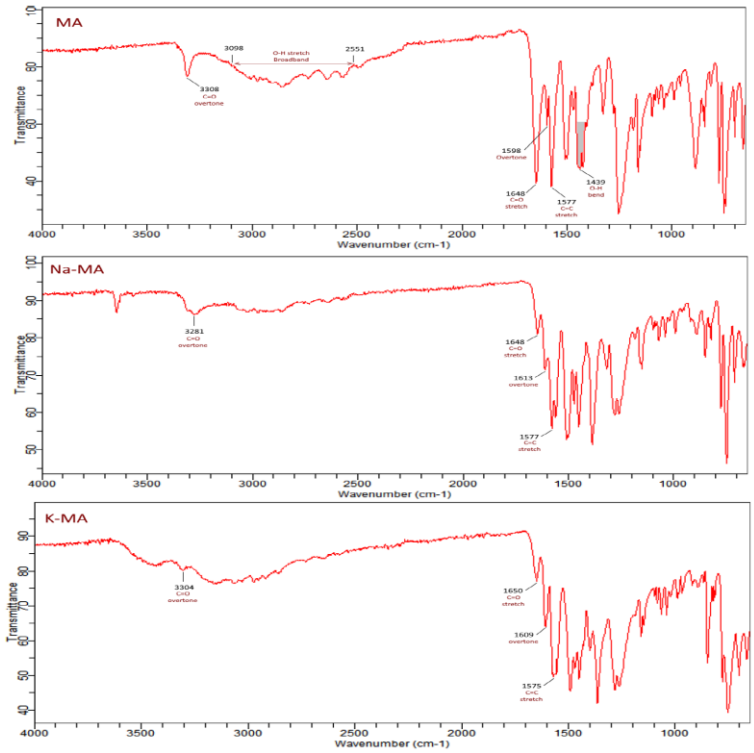


Fig. 3. FTIR spectrum of MA, Na-MA, and K-MA.

3.2. Differential Scanning Calorimetry (DSC) patterns MA, Na-MA, and K-MA

The DSC patterns of MA, Na-MA, and K-MA are shown in Fig. 4, in which the DSC thermogram showed endothermic (melting) peaks at 234.9 °C, 258.2 °C, and 311.1 °C for MA, Na-MA, and K-MA, respectively. MA showed higher a melting point compared to the recorded value in the literature (230-231 °C) [9], this difference may be attributed to the difference in instrumentation and/or experimental conditions. Also, the sodium and potassium salts of mefenamic acid showed higher melting points than MA, consistent with the fact that organic acid salts have a higher melting point than their corresponding acids due to the new constructed ionic bond(s) [32]. Furthermore, The Na-MA exhibited a lower melting point and/or decomposition temperature than K-MA, such finding is aligned with a thermodynamic property of another NSAID compounds; diclofenac sodium (284 °C) [33] and potassium salts (287 °C) [34].

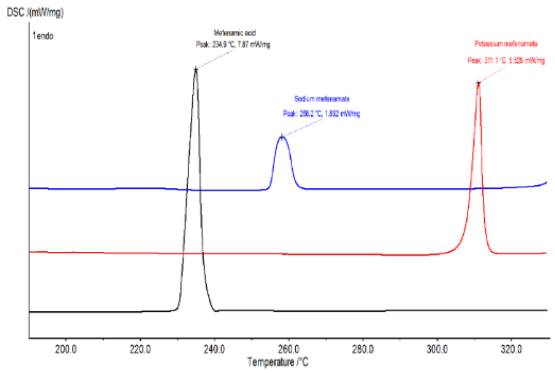


Fig. 4. DSC patterns of MA, Na-MA, and K-MA.

3.3. Solubility profile of mefenamic acid and its sodium and potassium salts

3.3.1. Calibration curves of MA, Na-MA, and K-MA

The stock solutions of 100 µg/mL of MA, Na-MA, and K-MA were scanned in UV-spectrophotometer, and the absorption spectrums are shown in Fig. 5. The maximum absorptions (λmax) were determined as 281 nm for MA, 297 nm for Na-MA, and 299 nm for K-MA.

Five diluted solutions (50, 25, 10, 5, and 1 µg/mL) were prepared from the stock solution (100 µg/mL) of MA, Na-MA, and K-MA. Plotting of absorbance (A) versus concentration (µg/mL) for each compound were obtained calibration curves of MA, Na-MA, and K-MA as shown in Fig. 6.

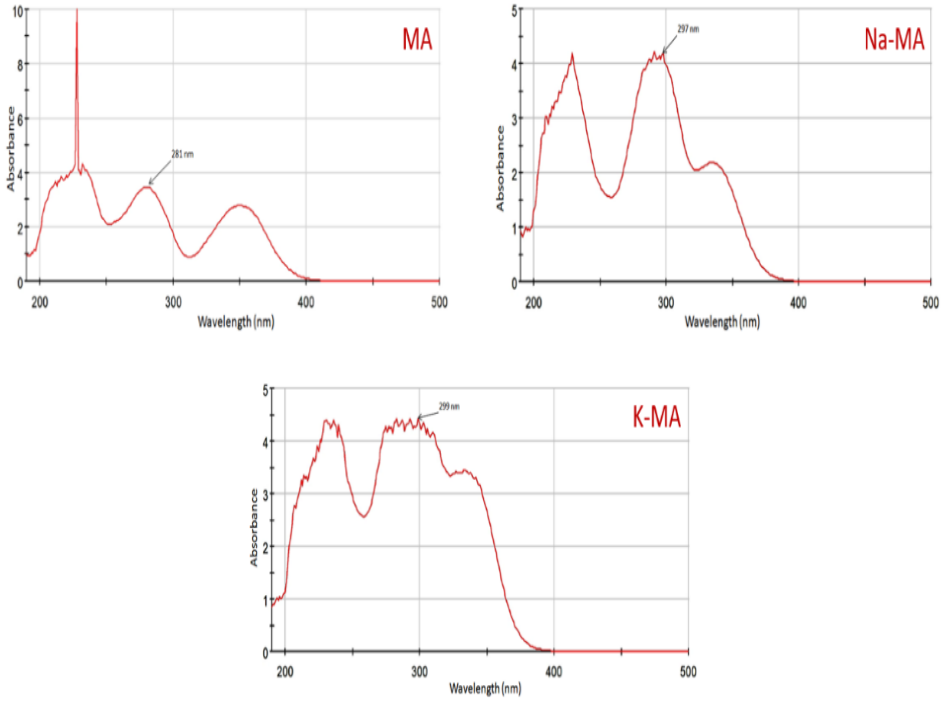
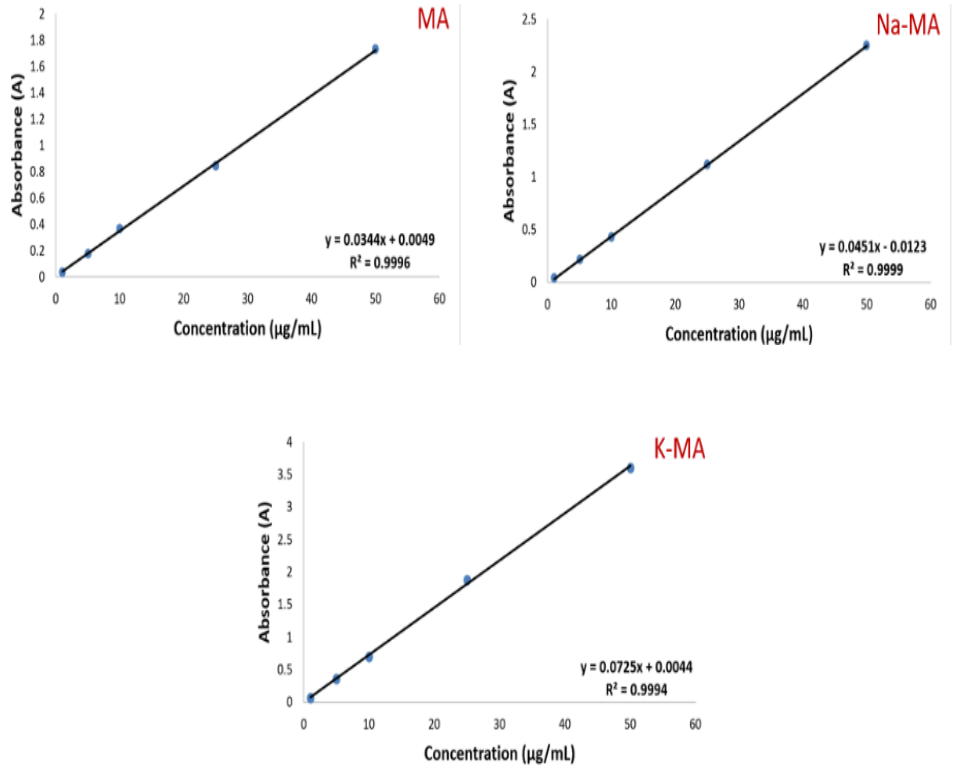


Fig. 5. The UV absorption spectrum of MA, Na-MA, and K-MA solutions (100 µg/mL).



λmax are 281 nm, 297 nm, and 299 nm for MA, Na-MA, and K-MA respectively

Fig. 6. Calibration curves of MA, Na-MA, and K-MA.

3.3.2. Effect of salt formation on the solubility profile of mefenamic acid in different temperatures

Using UV-spectrophotometer and constructed calibration curves, the saturated solubility of MA, Na-MA, and K-MA was determined by measuring the maximum concentrations of the solute in the selected solvent. Results obtained are listed in Table 4 based on the 213161 asymmetric factorial experimental design described previously in Table 3. Because of the insignificant increase in the solubility grade from 25 °C to 37 °C, the average values have been used to analyze the data.

The result was analyzed by STATISTICA© V7.0 and the layout was showed in Figure 7, in which the higher saturated solubility was obtained from K-MA in acetone (110.7 µg/mL). Furthermore, results showed that the solubility of mefenamic acid and its salts is significantly ($p < 0.05$) higher in organic solvents (51-110 µg/mL) rather than aqueous media (5-17 µg/mL). Moreover, the temperature increased the solubility in all studied solvents. However, there was no significant ($p > 0.05$) difference in the solubility between the two temperature grades (25 °C and 37.5 °C).

As a result, the salt formation method enhanced the solubility of MA in all aqueous and organic solvents in a range of 1.2-2.2 folds.

Table 4. The saturated solubility of MA, Na-MA, and K-MA in different solvents at 25°C and 37.5°C.

Drug	Solvent	Saturated solubility (µg/mL)	
		25 °C	**37.5 °C**
MA	0.1N HCl	3.026	3.113
	Phosphate buffer pH 5.8	5.933	6.311
	Phosphate buffer pH 6.8	10.904	11.253
	Methanol	58.259	60.613
	Acetone	70.497	71.980
	Dichloromethane	39.625	41.020
Na-MA	0.1N HCl	5.350	5.395
	Phosphate buffer pH 5.8	7.080	7.169
	Phosphate buffer pH 6.8	15.905	16.282
	Methanol	80.118	82.468
	Acetone	100.494	102.623
	Dichloromethane	51.049	52.645
K-MA	0.1N HCl	6.822	6.850
	Phosphate buffer pH 5.8	7.732	7.801
	Phosphate buffer pH 6.8	17.719	17.994
	Methanol	86.574	87.181
	Acetone	110.298	111.084
	Dichloromethane	55.236	57.912

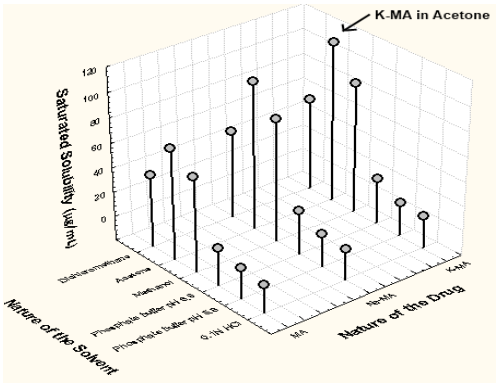


Fig. 7. 3D scattered plot of solubility profile of MA, Na-MA, and K-MA in a different type of solvents.

3.4. Influence of pH and polarity on solubility profile of MA, Na-MA, and K-MA

In order to explore the effect of pH of the aqueous media on the solubility profile of MA, Na-MA, and K-MA, the 3D surface plot of saturated solubility versus pH of the media versus mefenamic acid/salt was developed by STATISTICA© V7.0 software as shown in Fig. 8. The plot showed that K-MA has a higher solubility than Na-MA and MA in different pH grades. Furthermore, increasing the pH value revealed an increase in solubility of both MA and its salts.

Solubility of MA, Na-MA, and K-MA were measured in three pH grades (pH 1.0, 5.8, and 6.8) as tabulated in Table 4 simulating the gastrointestinal tract system (stomach, small intestine, and duodenum). Plotting of 3D surface plot (saturated solubility vs. pH vs. drug) revealed a sharp slope that indicates a significant impact of the pH on the solubility profile of mefenamic acid and its salts as shown in Figure 8.

From the 3D surface plot, Na-MA and K-MA had a higher solubility than MA in all tested pH. As the medium pH value increase from pH 1 to pH 6.8, solubility of MA increased by 3.6-folds and ~2.7-folds for K-MA and Na-MA, respectively. The high elevation in MA solubility is due to the nature of the molecule (acid) that resists solubility in an acidic medium (pH 1).

This theory has been confirmed previously by Patil et al. [22] with a lower solubility grade of mefenamic acid in pH 6.8 (7.01 µg/mL) compared to our finding (11.08 µg/mL). Such difference is most properly referred to the difference in the source and purity grade of used chemicals in this work.

To select the suitable organic solvent that can load the highest amount of mefenamic acid and its salts, three organic solvents with different polar properties have been tested. The resultant data (Table 4 and Fig. 9) confirms that MA, Na-MA, and K-MA have high solubility in the polar aprotic solvent (acetone), moderate solubility in the polar protic solvent (methanol), and poor solubility in a nonpolar solvent (dichloromethane).

This result is referred to the chemical structure of mefenamate (M-1) which consists of polar protic characteristic groups (carboxylic and amine groups) as well as nonpolar characteristic groups (aromatic and methyl groups). During the solubility process, a hydrogen atom will be donated by the carboxylic group (and not by the amine group) due to its high electro-negativity to form a hydrogen bond between mefenamic acid and solvent. But firstly, mefenamic acid should break these bonds and replaces them with bonds having a similar strength. A stronger hydrogen bond leads to high solubility. This result was agreed by Mullin [35].

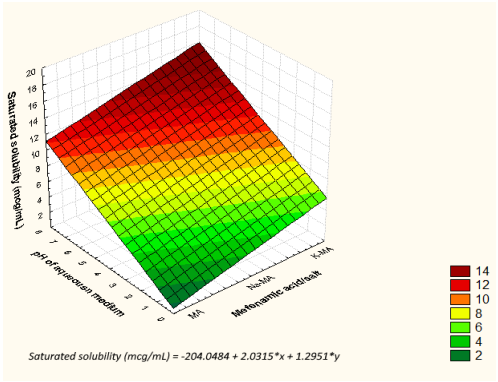


Fig. 8. 3D surface plot for the effect of pH on solubility profile of MA, Na-MA, and K-MA.

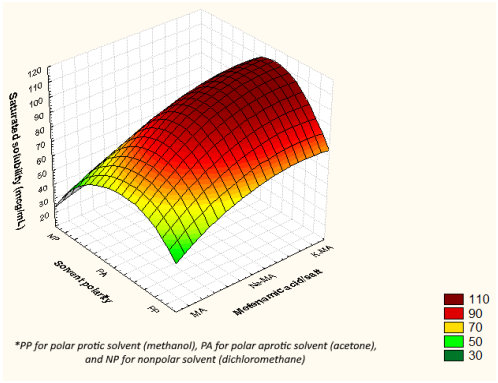


Fig. 9. 3D surface plot for the effect of polarity of organic solvent on solubility profile of MA, Na-MA, and K-MA.

4. Conclusion

The salt formation technique has improved the solubility of mefenamic acid in a wide range of aqueous and organic solvents. Moreover, it has been approved that potassium salt of mefenamic acid has a higher solubility than sodium salt, offering superior pharmaceutical applications over mefenamic acid. In general, the solubility of mefenamic acid and its salts is significantly ($p < 0.05$) higher in organic rather than aqueous solvents. The mefenamic acid and its

sodium and potassium salts have high solubility in polar aprotic solvent (acetone), moderate solubility in polar protic solvent (methanol), and poor solubility in nonpolar solvent (dichloromethane). The solubility of all mefenamic acid and its salts is increased by the increase of temperature and pH values in all tested solvents.

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