Mefenamic Acid Conjugates Based on a Hydrophilic Biopolymer Hydroxypropylcellulose: Novel Prodrug Design, Characterization and Thermal Analysis

[1] Muhammad Ajaz Hussain*, [1] Rukhsana Kausar, [1] Muhammad Amin and [2] Muhammad Raza Shah
[1] *Department of Chemistry, University of Sargodha, Sargodha 40100, Pakistan*
[2] *International Center for Chemical and Biological Sciences, University of Karachi, Karachi 75270, Pakistan.*
majaz172@yahoo.com*

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Summary: Macromolecular prodrugs (MPDs) of mefenamic acid were designed onto a cellulose ether derivative hydroxypropylcellulose (HPC) as ester conjugates. Fabrication of HPC-mefenamic acid conjugates was achieved by using *p*-toluenesulfonyl chloride as carboxylic acid (a functional group in drug) activator at 80°C for 24 h under nitrogen atmosphere. Reaction was preceded under homogeneous reaction conditions as HPC was dissolved before use in DMAc solvent. Imidazole was used as a base. Easy workup reactions resulted in good yields (55-65%) and degree of substitution (DS) of drug (0.37-0.99) onto HPC. The DS was calculated by acid-base titration after saponification and UV/Vis spectrophotometry after hydrolysis. DS by both of the methods was found in good agreement with each other. Aqueous and organic soluble novel prodrugs of mefenamic acid were purified and characterized by different spectroscopic and thermal analysis techniques. The initial, maximum and final degradation temperatures of HPC, mefenamic acid and HPC-mefenamic acid conjugates were drawn from thermogravimetric (TG) and derivative TG curves and compared to access relative thermal stability. The TG analysis has indicated that samples obtained were thermally more stable especially with increased stability of mefenamic acid in HPC-mefenamic acid conjugates. These novel MPDs of mefenamic acid (*i.e*., HPC-mefenamic acid conjugates) may have potential applications in pharmaceutically viable drug design due to wide range of solubility and extra thermal stability imparted after MPD formation.

Keywords: Hydroxypropylcellulose, Mefenamic acid, Macromolecular prodrugs, Polysaccharides, Thermal analysis

Introduction

To decrease the ulcerogenic effects (by gastric lesions) of mefenamic acid, *i.e*., a non-steroidal anti-inflammatory drug (NSAID), it is desirable to design its prodrug [1-4] by converting its carboxylic acid into ester. Polysaccharide based prodrugs of NSAIDs proved to be much effective and safer as compared to parent NSAIDs as it is evident from several studies [5-8].

Nowadays, growing interests are focused in studies related to physiochemical characteristics of polysaccharides and especially their ether derivatives. Material and medicinal chemists are keenly interested in cellulose ether derivatives from polysaccharides particularly because of their plethora of applications in pharmaceutical, biomedical devices and nanomedicines [9-12]. Recently, macromolecular prodrug design (MPDD) and applications based on etherified renewable polysaccharides especially cellulose, *e.g*., hydroxypropylcellulose (HPC) [2], hydroxypropylmethylcellulose (HPMC) [5, 9], hydroxyethylcellulose [13], *etc*., have emerged as thrust area of research. An important factor of their use in MPDD of NSAIDs in particular is the presence of inbuilt oligohydroxyalkyl moieties that act as a potential linker between cellulose and NSAIDs. By this way, drug loading capability can be increased on sterically hindered cellulose chains. Therefore, a pharmaceutically viable proportion of NSAIDs onto biopolymers can be achieved due to expected high DS of carboxylic acid containing NSAIDs. The same is evident in this context in a recent study [2, 3] where useful results were achieved.

By making mefenamic acid prodrugs, the stomach can be kept safe from its ulcerogenic effects. Therefore, our aim was focused on mefenamic acid prodrugs formation on to a versatile cellulose ether derivative, *i.e*., HPC which is non-toxic, neutral, non-ionic, biodegradable and biocompatible polymer. For this purpose, homogeneous and moderate reaction conditions were selected in order to keep the native properties of biopolymers intact. Another aim of present work is to study the thermal properties of newly designed MPD of mefenamic acid onto HPC because thermally stable prodrugs generally show higher shelf life.

Experimental

Reagents and Chemicals

Pre-dried HPC (110°C under vacuum for 8 h) with MS 3.46, *i.e*., 60% HP moieties was procured from Nanjing Yeshun Industry and International

*To whom all correspondence should be addressed.

Trading Co. Ltd (Jiangsu China-Mainland). Imidazole and *p*-toluenesulfonyl chloride (Tos-Cl) were obtained from Fluka. Other chemicals used were of analytical reagent grade and used as received. Mefenamic acid (US Pharmacopoeia standard) was gifted by Candid Pharmaceuticals, Sialkot, Pakistan.

Measurements

The ^{1}H-NMR (DMSO-d_6) spectra of HPC-mefenamic acid conjugates were acquired on Bruker 400 MHz NMR instrument. The FTIR (KBr) spectra were recorded on IR Prestige-21 (Shimadzu, Japan) using the pellet technique and pellets were dried under vacuum before analysis at 50°C for 2 h. The UV/Vis spectrophotometric analyses were carried out on UV PharmaSpec 1700 (Shimadzu, Japan) in order to determine the degree of substitution (DS) of mefenamic acid in HPC-mefenamic acid conjugates. Thermal decomposition temperatures (Tdi, Tdm, Tdf) of the products were determined by thermo-gravimetric analysis using TA Instruments (SDT Q600 USA). For this purpose, a weighed sample was taken and temperature effects were noted at the rate of 10°C/min in temperature range of ambient to 800°C.

Dissolution of HPC in N,N-Dimethylacetamide (DMAc)

For a typical preparation, HPC (2.0 g) was added in DMAc (30 mL) and kept under stirring and heating continuously for 30 min at 80°C till the optically clear solution of the polymer was obtained.

Synthesis of HPC-Mefenamic Acid Conjugate **2**

To the solution of HPC (2.0 g, 5.5 mmol) in DMAc, carboxylic acid activating reagent *p*-toluenesulfonyl chloride (3.16 g, 16.5 mmol) was added in parts and dissolved. A base imidazole (2.25 g, 33.0 mmol) was added followed by the addition of mefenamic acid (3.99 g, 16.5 mmol) in parts. This mixture appeared very viscous however along with continuous stirring at 80°C, it became less viscous after 3 h. Reaction was preceded for 21 h further under same reaction conditions. Isolation of the product was carried out by precipitation of reaction mixture into 300 mL methanol. The precipitates of sample **2** were washed with methanol three times to remove any of the un-reacted drug contents and impurities. Precipitates of sample **2** were dried under vacuum at 50°C overnight. Degree of substitution (DS): 0.80; Yield: 58%; FTIR (KBr): 2913 ν(OH), 1738 ν(CO Ester), 1466 ν(CH_2), 1057 ν(C-O-C polymer chain) cm^{-1}. ^{1}H-NMR (DMSO-d_6, 400 MHz): 7.14-7.80 (aromatic-Hs), 2.99-4.96 (AGU-Hs), 2.05 (two CH_3 of drug), 1.02 (CH_3 of HPC).

Analytical Data of HPC-Mefenamic Acid Conjugate **1**

Degree of substitution: 0.37; Yield: 55%; FTIR (KBr): 3447 ν(OH), 2926 ν(C-H arom and OH H-bonded), 1742 ν(CO Ester), 1452 ν(CH_2), 1051 ν(C-O-C) cm^{-1}

Analytical Data of HPC-Mefenamic Acid Conjugate **3**

Degree of substitution: 0.97; Yield: 60%; FTIR (KBr): 2895 ν(OH, C-H), 1724 ν(CO Ester), 1483 ν(CH_2), 1040 ν(C-O-C) cm^{-1}.

Analytical Data of HPC-Mefenamic Acid Conjugate **4**

Degree of substitution: 0.99; Yield: 65%; FTIR (KBr): 2940 ν(OH, C-H), 1728 ν(CO Ester), 1467 ν(CH_2), 1053 ν(C-O-C) cm^{-1}.

Determination of DS by Acid Base Titration

DS of mefenamic acid onto HPC-mefenamic acid conjugates was calculated by a standard acid-base titration after saponification. Sample (100 mg each) was dissolved in 1.0 M NaOH solution (50 mL) and the solution was kept under stirring overnight and pH was monitored by pH meter. Afterwards, the pH of the solution was maintained at 7 by the addition of 0.01 M HCl. Then a known quantity of 1.0 M NaOH solution was added. Excess of the base was then back titrated against 0.1 M HCl solution till the pH again became 7. DS was then calculated by using following formula.

$$DS = [n.NaOH \times M(RU)] / [Ms-(MRCO) \times n. NaOH)]$$

where, n.NaOH is number of moles of NaOH after saponification, M(Ru) is molar mass of repeating unit, *Ms* is mass of sample, M(RCO) is molar mass of ester functionality.

Determination of DS by UV/Vis Spectrophotometric Analysis

Standard (pure mefenamic acid) was taken and 10-100 ppm solutions were prepared in fresh 0.1 N aq. NaOH and absorbance was noted using UV spectrophotometer. Calibration curve was plotted to calculate amount of drug contents in conjugates in terms of mg of drug in 100 mg conjugate. For sample solution, 10 mg of sample (conjugate) was dissolved 0.1 N aq. NaOH (10 mL). The solution was heated at 80°C for 3 h for hydrolysis in order to get free mefenamic acid. The volume of sample was made up to 10 mL with 0.1 N aq. NaOH. Resultant solution (1.0 mL) was diluted up to 10 mL to obtain 100 ppm solution then absorbance was noted for all the

samples, likewise. Drug content of samples was drawn from calibration curve of standard.

Thermal Analysis and Degradation Kinetics

Initial, maximum and final thermal decomposition temperatures (Tdi, Tdm, Tdf) were calculated from TGA data. The thermal data were analyzed by MS Excel® 2010 and Universal Analysis 2000 software v 4.2E. Friedman [14], Broido [15] and Chang [16] models were used to determine the degradation kinetics.

Friedman model uses equation 1, whereas, mathematical form of Chang model is given in equation 2. *Ea* and *Z* were also calculated from Broido kinetic model as per equation 3.

$$ln\left(\frac{d\propto}{dt}\right) = lnZ + nln(1-\propto) - \frac{Ea}{RT} \qquad eq.\ 1$$

$$ln\left(\frac{\frac{d\propto}{dt}}{(1-\propto)^n}\right) = lnZ - \frac{Ea}{RT} + constant \qquad eq.\ 2$$

$$ln\left(ln\frac{1}{y}\right) = -\frac{Ea}{RT} + constant \qquad eq.\ 3$$

where (in eq. 1-3), *dα*/*dt* is the rate of weight loss directly taken from DTG curve; *n* is the reaction order; *Ea* is the activation energy; *Z* is the frequency factor of decomposition reaction; *R* is the gas constant; *1-α* is the weight of sample left at a certain temperature taken from the TG curve; *T* is the absolute temperature recorded.

Results and Discussion

In case of less reactive carboxylic acids, activators of carboxylic acids are used in order to make their esters with alcohols. Previously, heterogeneous esterification was carried out using carboxylic acid anhydrides [17, 18]. However, homogeneous reaction methodologies are in high demand nowadays because native properties of the polymers remain intact by this way. *p*-Toluenesulfonyl chloride (Tos-Cl) is one of the most famous COOH activator which is widely used under homogenous esterification reaction conditions. Therefore, esterification reaction between hydroxypropylcellulose (HPC) and mefenamic was carried out by using Tos-Cl [19]. As several studies have shown that homogeneous reaction conditions are important to acquire native properties of water soluble polysaccharides (20,21) in their ester derivatives [22-24]. Hence, homogeneous reaction conditions for the synthesis of HPC-mefenamic acid conjugates were maintained by carrying out reaction in *N,N*-dimethylacetamide (DMAc). Reactions were proceeded as a one pot synthesis. The general reaction scheme for the acylation of HPC with mefenamic acid to form HPC-mefenamic acid conjugates **1-4** is outlined in Fig. 1.

Mefenamic acid reacts with OH groups available on oligohydroxypropyl functions on cellulose chains in HPC by the addition of Tos-Cl to form HPC-mefenamic acid conjugates. Different molar ratios of mefenamic acid to HPC biopolymer were used during the reactions and the esters were homogenously synthesized at 80°C for 24 h. By this way different mefenamic acid prodrugs with various DS were synthesized. Tos-Cl appeared very useful activator for mefenamic acid for the synthesis of its ester (prodrugs) with HPC. The conditions and results for HPC-mefenamic acid conjugates are summarized in Table-1. All of the products were purified by washing with methanol thrice to remove any of the side products and unreacted drug as all the expected side products (tosic acid) and unreacted reactants (*e.g.*, drug) are soluble in methanol. Moreover, purified HPC-mefenamic acid conjugates were characterized by using different spectroscopic and thermogravimetric (TG/DTG) analyses.

Solubility of the MPD of mefenamic acid was achieved in different organic solvents, *i.e.*, DMSO, DMAc and acetone. However, sample **1** was found soluble in water rather than acetone, perhaps due to low drug DS. Whereas, samples **2-4** were soluble even in acetone which is indicative of high hydrophobic drug DS.

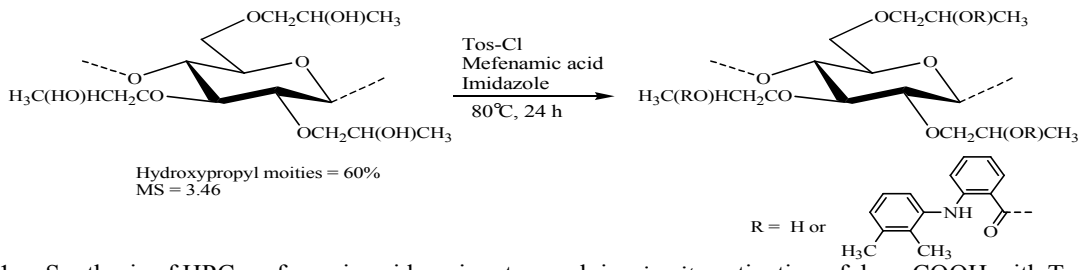

Fig. 1: Synthesis of HPC-mefenamic acid conjugates applying *in situ* activation of drug-COOH with Tos-Cl.

Table-1: Conditions and results of reactions of HPC (2 g) with *in situ* activated mefenamic acid with Tos-Cl at 80°C for 24 h.

Sample	Molar ratio[a]	Yield (%)	DS[b]	DS[c]	Solubility
1	1:2:2:4	55	0.37	0.41	Water, DMSO, DMAc
2	1:3:3:6	58	0.80	0.74	Acetone, DMAc, DMSO
3	1:4:4:8	60	0.97	0.87	Acetone, DMAc, DMSO
4	1:6:6:12	65	0.99	0.89	Acetone, DMSO, DMAc

[a] HPC repeating unit:Tos-Cl:mefenamic acid:Imidazole; [b] DS calculated by acid base titration after saponification; [c] DS calculated by UV/Vis spectrophotometry

The FTIR spectroscopic studies of the products were carried out by using KBr pellet technique to confirm the appearance of new ester carbonyl absorptions. Distinct ester peaks appeared in the range *v* 1724-1742 cm^{-1} for HPC-mefenamic acid conjugates **1-4** synthesized with varying DS of drug. The FTIR spectrum of sample **2** (DS 0.80) is being shown in Fig. 2 as a typical example along with spectra of mefenamic acid drug. The success of reaction was confirmed by the presence of a peak observed at *v* 1738 cm^{-1} of ester along with other characteristic peaks of some free OH at about *v* 2913 cm^{-1} and COC of polymer backbone at about *v* 1057 cm^{-1}. All of the signals of different CH_2 appeared at *v* 1466 cm^{-1}. Presence of ester signal (*v* 1738 cm^{-1}) and absence of mefenamic acid carbonyl (*v* 1657 cm^{-1}) signal indicates the successful synthesis of MPD of mefenamic acid on HPC as HPC-mefenamic acid conjugate.

The ^{1}H-NMR spectra of HPC-mefenamic acid conjugates were recorded in DMSO-d_6. Appearance of aromatic protons at δ 7.14-7.80 ppm for sample **2** (Fig. 3) provides the information about the attachment of aromatic ring to HPC polymer backbone. These results showed that the unsaturated system is not destroyed during the reaction. Signals for two methyl groups of mefenamic acid moiety appeared at δ 2.05 ppm. Whereas, NH proton signal was overlapped with the AGU signals. Protons of HPC polymer backbone/anhydroglucose unit (AGU) were detectable in the range of δ 2.99-4.96 ppm. The protons of methyl at hydroxypropyl moiety of HPC polymer were detectable at δ 1.02 ppm. The signals of -CH_2 and -CH of hydroxypropyl moiety are overlapped with AGU signals.

In drug design and development, the stability of newly developed drug conjugates is an important factor to attain longer shelf life of drug. While preparing the polysaccharide-NSAID conjugates, generally increased stability of the drug is targeted. Therefore, thermal analysis is carried out to observe the difference in stability between the pure drug and polymer-drug conjugates thereof. Thermogravimetric and differential thermogravimetric (TG/DTG) curves were obtained at heating rate of 10°C/min under nitrogen environment up to 800°C. The overlay TG and DTG curves of HPC, mefenamic acid and HPC-mefenamic acid conjugate **2** are represented in Fig. 4 and Fig. 5, respectively.

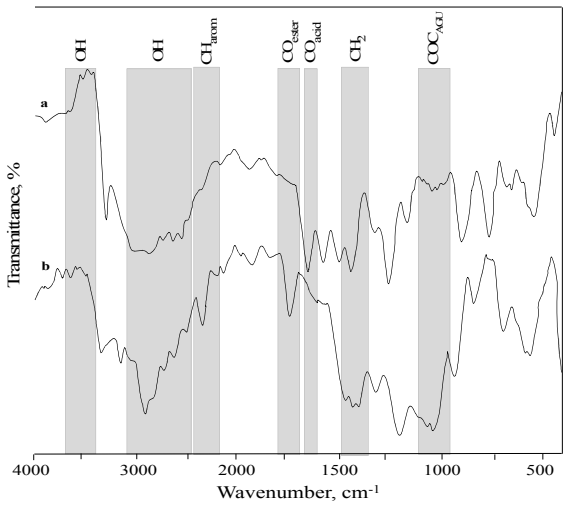

Fig. 2: Overlay FTIR (KBr) spectrum of **a)** mefenamic acid and **b)** HPC-mefenamic acid conjugate **2** (DS 0.80) indicating ester CO absorptions at 1738 cm^{-1}.

The thermogravimetric analysis of HPC, mefenamic acid and HPC-mefenamic acid conjugate **2** has revealed a significant thermal stability imparted to drug after its conjugate formation (Fig. 5). Thermal decomposition of HPC-mefenamic acid conjugate **2** starts at 231°C (Tdi) and ends at 343°C with thermal decomposition maxima (Tdm) at 314°C which is significantly higher than the thermal degradation temperatures of unmodified drug. The details of the degradation data is given in Table-2.

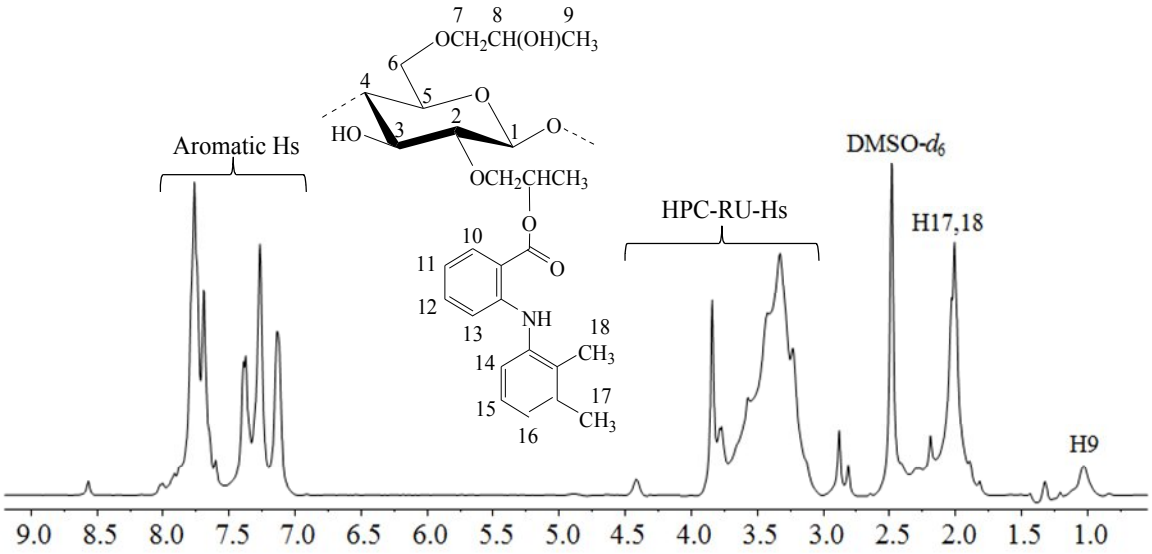

Fig. 3: ^{1}H-NMR (400MHz, NS 32, d_6-DMSO) spectrum of HPC-mefenamic acid conjugate 2 (DS 0.80).

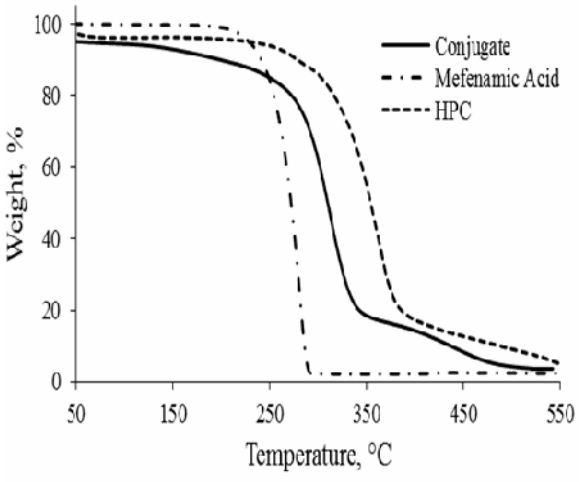

Fig. 4: Overlay TG curves of HPC, mefenamic acid and HPC-mefenamic acid conjugate **2.**

Thermal kinetic parameters of degradation of HPC, mefenamic acid and HPC-mefenamic acid conjugate **2** were evaluated by using Friedman, Broido and Chang kinetic models. The results of thermal kinetics are summarized in Table-3. The activation energy (*Ea*) of thermal degradation of HPC-mefenamic acid conjugate **2** was found in good agreement when calculated from Friedman, Broido and Chang models, *i.e*., 142.80, 143.24 and 142.70 kJ/mol, respectively. Whereas, 17.77% weight loss occurs after major degradation which may correspond to the furfural formation in polymer degradation and is not taken into account in present work. It is also evident from the results of thermal kinetics that the HPC-mefenamic acid conjugate has comparable *Ea* values to the pure drug. The degradation of HPC-mefenamic acid conjugate followed first order kinetics as calculated form Chang model.

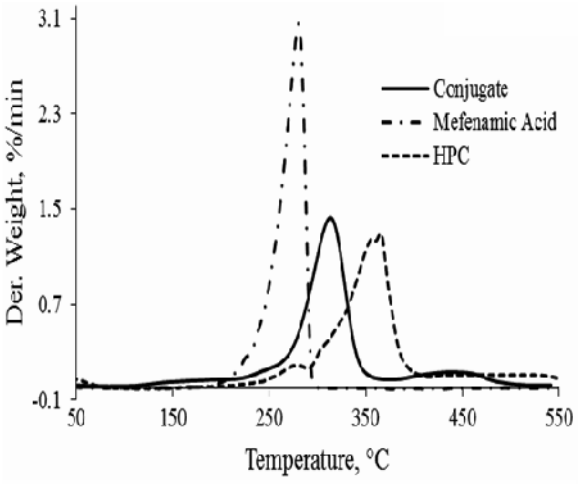

Fig. 5: Overlay DTG curves of HPC, mefenamic acid and HPC-mefenamic acid conjugate **2.**

Table-2: Thermal degradation temperatures drawn from TG/DTG curves of HPC polymer, mefenamic acid and HPC-mefenamic acid conjugate recorded at the onset of 10°C/min.

Sample	Tdi (°C)	Tdm (°C)	Tdf (°C)	Weight loss (%) at Tdf	Char yield Wt.
HPC	242	369	413	84.12	4.21 % at 563°C
Mefenamic acid	210	280	296	97.79	2.16 % at 300°C
Conjugate 2	231	314	343	82.23	2.37 % at 499°C

Table-3: Thermal degradation kinetics of HPC polymer, mefenamic acid and HPC-mefenamic acid conjugate recorded at the onset of 10°C/min.

Sample	Method	R^2	*n*	*M*	*Ea* (KJ/mol)	ln*Z*	$Z(S^{-1})$
HPC	Friedman	0.998	-	-9414	78.27	15.11	3.65×10^{6}
	Broido	0.999	-	-10521	87.48	17.09	2.64×10^{7}
	Chang	0.997	1	-10129	84.23	15.84	7.57×10^{6}
Mefenamic acid	Friedmcn	0.998	-	-15564	129.41	29.88	9.47×10^{12}
	Broido	0.999	-	-18156	150.96	32.90	1.94×10^{14}
	Chang	0.998	1	-17827	148.22	34.13	6.64×10^{14}
Conjugate 2	Friedman	0.999	-	-17175	142.80	28.66	2.79×10^{12}
	Broido	0.999	-	-17228	143.24	27.76	1.14×10^{12}
	Chang	0.997	1	-17163	142.70	28.77	3.12×10^{12}

Conclusion

Mefenamic acid prodrugs were fabricated with a neutral and non-ionic semisynthetic derivative of cellulose, *i.e*., hydroxypropylcellulose (HPC) by using homogeneous reaction methodology. HPC proved itself as a potential candidate for high covalent loading of drugs as higher DS was obtained while making mefenamic acid prodrugs. The macromolecular prodrugs, *i.e*., HPC-mefenamic acid conjugates synthesized were soluble in organic solvents. The products obtained have acid resistant HPC polymer backbone therefore it will be possible to keep the stomach safe from the harmful effects of such acidic drug, *e.g*., mefenamic acid, after converting it to macromolecular prodrug as HPC-mefenamic acid conjugates. Esterified drugs will be released at basic pH of colon more preferably. Additionally, mefenamic acid became thermally stable after esterification with HPC as HPC-mefenamic acid conjugates which is important factor in order to increase the shelf life of prodrug.

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