Novel HPC-Ibuprofen Conjugates: Synthesis, Characterization, Thermal Analysis and Degradation Kinetics

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Summary: Naturally occurring hydrophilic polysaccharides are nowadays attracting the vigil eye of researchers working in areas of drug design and development. Amongst them, hydrophilic biopolymer hydroxypropylcellulose (HPC) is of particular interest. Its unique geometry allows the attachment of drug molecules with higher covalent loading as the hydroxyls are projected outside the polymer chains. The HPC-Ibuprofen conjugates as macromolecular prodrugs were therefore synthesized employing homogenous and one pot reaction methodology using *p*-toluenesulfonyl chloride. Present strategy appeared effective to synthesize conjugates with high yield (77-81%). Acid-base titration after saponification and ^{1}H-NMR spectroscopic analyses have revealed high degree of drug substitution (DS 0.88-1.40) on to HPC. Uni-modal absorptions were observed in gel permeation chromatograms which indicated no significant degradation of polymer. Macromolecular prodrugs with different DS of ibuprofen were synthesized, purified, characterized and found soluble in organic solvents. From thermogravimetric analysis, initial, maximum and final degradation temperatures of the conjugates were calculated and compared for relative thermal stability. Thermal degradation kinetics was also studied and results have indicated that degradation of conjugates follows about first order kinetics as calculated by Kissinger model. The energy of activation was also found moderate 92.38, 99.34 and 87.34 kJ/mol as calculated using Friedman, Broido and Chang models. It was found that these novel prodrugs of ibuprofen were thermally stable therefore these may have potential pharmaceutical applications.

Keywords: Hydroxypropylcellulose, Ibuprofen, Macromolecular prodrugs, Polysaccharides, Thermal analysis

Introduction

Ibuprofen (*RS*)-2-(4-(2-methylpropyl) phenyl) propanoic acid) belongs to propanoic acid derivatives class of non-steroidal anti-inflammatory drugs (NSAIDs). Ibuprofen is a famous drug is being used worldwide due to its efficacy and patient compliance. However, prolong use of ibuprofen drug is causative of nausea, stomach pain, vomiting and GIT disorders [1, 2]. Hence, macromolecular prodrugs (HPC-ibuprofen conjugates) can minimize side effects of ibuprofen because such conjugates are acid resistant, bypass stomach and release drug in intestine.

Hydroxypropylcellulose (HPC) is an important polysaccharide being used in prodrug design and applications. It has a number of valuable properties in this regard, such as, hydrophilicity, neutral nature, biocompatibility, biodegradability and cost-effectiveness. Therefore, HPC has perhaps all properties which are prerequisite for any drug carrier [3-6]. Several studies have shown the potential of hydroxypropylmethylcellulose (HPMC) and HPC in pharmaceutical and biomedical sciences [7-12]. Additionally, some related cellulose ether derivative based macromolecular prodrug design showed nanoassemblies in solution along with improved pharmacokinetic profile and thermal stability [13, 14]. A well-designed pathway for water-soluble polysaccharide based prodrugs [15, 16] is the covalent linkage of the drug onto the polymer by ester linkage using soft reaction conditions. *p*-toluenesulfonyl chloride is an efficient and widely used reagent for such conversions and better than the conventional reagents like acid chlorides and acid anhydrides [17, 18] which may impart toxic side products and impurities in prodrugs.

In this study, we report on homogenous and one pot synthesis of novel macromolecular prodrugs of ibuprofen using a hydrophilic polysaccharide HPC. Effects of increasing molar ratio on to the DS are also being reported. Further, we are focused on thermogravimetric analysis and degradation kinetics of newly synthesized prodrugs to access their thermal behavior.

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Results and Discussion

Macromolecular prodrugs of ibuprofen were synthesized homogeneously. Ibuprofen was *in situ* activated with *p*-toluenesulfonyl chloride (Tos-Cl) in *N,N*-dimethylacetamide (DMAc) containing pre-dissolved HPC [19]. Imidazole was added for neutralization of acidic side-products. This one pot synthesis preceded for 24 h at 80°C to yield HPC-ibuprofen conjugates with high DS. Scheme for the synthesis of ibuprofen prodrugs is outlined in Fig. 1. The HPC-Ibuprofen conjugates produced were soluble in acetone, DMSO, DMF and DMAc. The conditions and results are accumulated in Table-1.

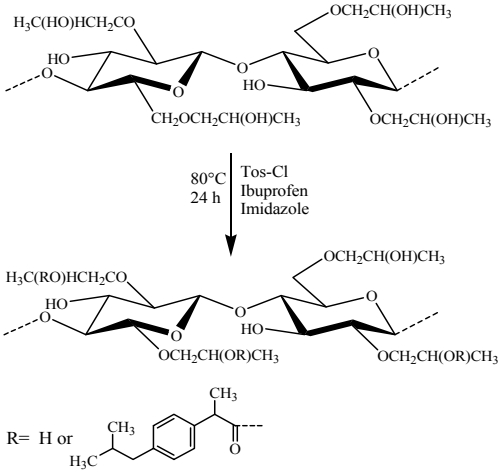

Fig. 1: Synthesis scheme of HPC-Ibuprofen conjugates.

The HPC-Ibuprofen conjugates (**1-3**) were synthesized by applying different mole ratios of the reactants and resultant conjugates were purified by re-precipitation method. Diethyl ether was used for washing the precipitates of HPC-Ibuprofen conjugates. The reactants and acidic side products were ether soluble hence removed by washing along with vigorous stirring. The residues were re-precipitated twice from DMF into diethyl ether to ensure the purity of the macromolecular prodrugs obtained.

The HPC-Ibuprofen conjugates **1-3** were characterized with the help of spectroscopic and chromatographic analyses. The DS of covalent drug loading on to polymer HPC was determined by standard titration method (acid-base) after saponification. Titrations were carried out thrice and mean values are therefore reported (see Table-1). Attachment of ibuprofen on to HPC was confirmed by carrying out FTIR spectroscopy. Fabrication of HPC-Ibuprofen conjugates were also verified by ^{1}H-NMR spectroscopy. Thermogravimetric analysis (TGA) and derivatives TG (DTG) were used to characterize the HPC-Ibuprofen conjugates for their thermal behavior. Characterization of products and their relevant spectra are given in coming sections.

The FTIR spectra of HPC-Ibuprofen conjugates (i.e., prodrugs) **1-3** showed characteristic ester absorptions in the range of 1729-1738 cm^{-1}. Other characteristic stretching bands of aromatic CH_2 group appeared at 2844-3093 cm^{-1} merged with signals of hydroxyl groups. The CH_2 scissoring vibrations were seen in the range of 1445-1452 cm^{-1} for conjugates **1-3**. The typical spectrum of HPC-Ibuprofen conjugates **3** is shown in Fig. 2. So, FTIR spectra have confirmed success of HPC-Ibuprofen conjugates formation as distinct ester peak appeared at 1730 cm^{-1} for sample **3**.

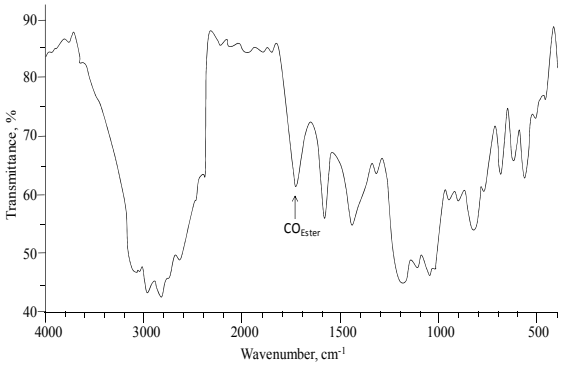

Fig. 2: FTIR (KBr) spectrum of HPC-Ibuprofen conjugate **3** (DS 1.40).

Table-1: The conditions and results for the reaction of *in situ* activated ibuprofen with hydroxypropylcellulose (2 g) at 80°C for 24 h.

Sample	Molar Ratio[a]	DS[b]	DS[c]	Yield (g / %)	Solubility
1	**1:1:1:2**	**0.83**	**0.88**	**2.3/77**	**Acetone, DMF, DMSO, DMAc, THF**
2	**1:2:2:4**	**1.00**	**1.02**	**2.4/76**	**Acetone, DMF, DMSO, DMAc**
3	**1:3:3:6**	**1.33**	**1.40**	**2.9/81**	**Acetone, DMF, DMSO, DMAc**

[a]HPC repeating unit **:** *p*-Toluenesulfonyl chloride**:** Ibuprofen **:** Imidazole; [b]The DS was determined by acid-base titration after saponification; [c]The DS was determined by ^{1}H-NMR spectroscopy.

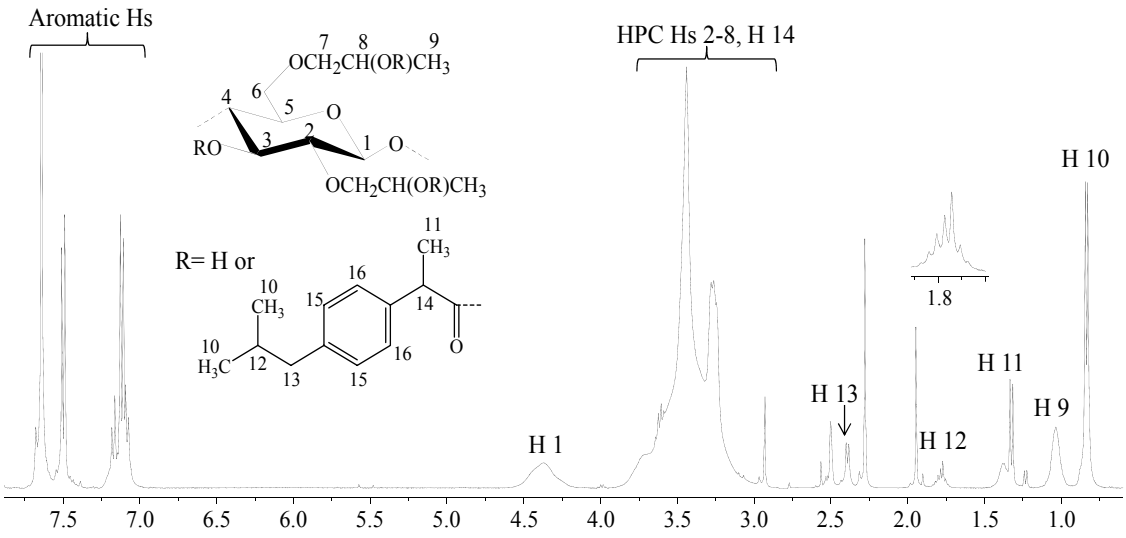

Fig. 3: The ^{1}H-NMR (400 MHz, DMSO-d_6, NS 16) spectrum of HPC-Ibuprofen conjugate **3** (DS 1.40).

The HPC-Ibuprofen conjugates **1-3** were carefully characterized by ^{1}H-NMR (400 MHz, DMSO-d_6) spectroscopy. From spectra it is therefore inferred that ibuprofen was attached to HPC as the aromatic Hs are found at δ 7.10-7.65, 7.08-7.65 and 7.13-7.64 ppm for samples **1-3**, respectively. Protons of HPC polymer repeating unit were detectable at δ 3.14-4.40, 3.15-4.39 and 3.17-4.37 ppm for sample **1**, **2** and **3**, respectively. Fig. 3 depicts a representative ^{1}H-NMR spectrum of sample **3** (DS 1.40). The CH_3 signals of HP moiety onto HPC polymer appeared at δ 1.03 ppm. The -CH_2 and -CH protons of HP moiety were found overlapped with repeating unit of HPC. The protons of both methyl groups (H-10) were seen at 0.84 ppm while another methyl group of drug (H-11) appeared at 1.33 ppm. The CH (H-12) in drug was recognized by its typical septet signal centered at 1.77 ppm. The CH_2 of drug (H-13) was assigned for 2.40 ppm. The ^{1}H-NMR spectroscopic analysis therefore showed successful synthesis of HPC-Ibuprofen conjugates due to presence of all related signals. DS was calculated from ^{1}H-NMR spectra by the comparison of signal intensities and found to be 0.88, 1.02 and 1.40 for sample **1-3**, respectively. DS obtained from ^{1}H-NMR spectra were found comparable with DS values calculated using acid base titration after saponification and results are gathered in Table-1.

Gel permeation chromatography (GPC) was carried out for the assessment of polymer degradation during reaction. From GPC results, it is inferred that present synthesis strategy and reaction conditions did not cause significant degradation of the polymer chains in HPC-Ibuprofen conjugates as uni-modal absorptions were only seen in spectra. For instance, GPC spectrum of HPC-Ibuprofen conjugate **2** is shown in Fig. 4.

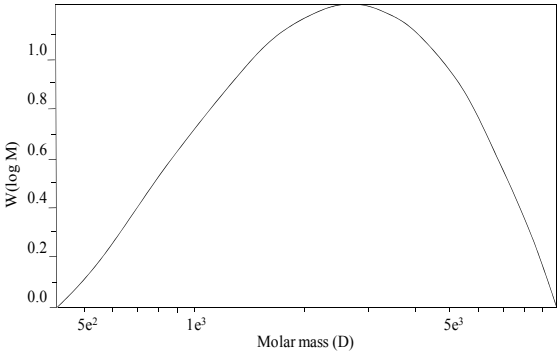

Fig. 4: The GPC analysis of HPC-Ibuprofen conjugate **2** (DS 1.02) indicating uni-modal absorption.

Shelf-life of prodrugs or drugs can be increased by acquiring stability of drug in macromolecular prodrug conjugates. Polysaccharide based prodrugs generally attain higher thermal stability in case of NSAIDs conjugates [4]. Therefore, thermal analysis of pure drug ibuprofen, HPC polymer and HPC-Ibuprofen conjugates were recorded. The overlay TG and DTG curves of ibuprofen, HPC and HPC-Ibuprofen conjugate **3** are depicted in Fig. 5 and 6, respectively while thermal degradation data obtained from these graphs are summarized in Table-2.

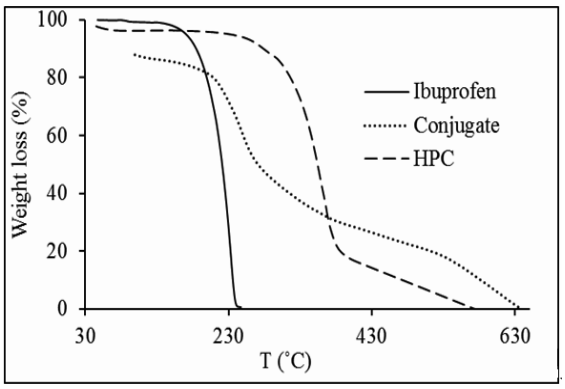

Fig. 5: Overlay TG curves of HPC, ibuprofen and HPC-ibuprofen conjugate **3** (DS 1.40).

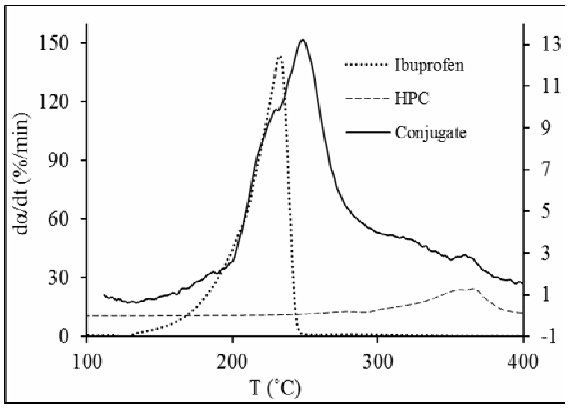

Fig. 6: Overlay DTG curves showing comparative degradation patterns of ibuprofen, HPC and their conjugate **3** (DS 1.40).

Table-2: Results of Thermogravimetric analysis for HPC, ibuprofen and HPC-Ibuprofen conjugate **3** (DS 1.40).

Sample	Tdi	Tdm	Tdf	Weight loss (%) at Tdf	Char yield Wt (%)
HPC	**240**	**365**	**396**	**99.85**	**0.05 % at 563°C**
Ibuprofen	**135**	**233**	**245**	**95.39**	**1.06 % at 259°C**
Conjugate 3	**160**	**246**	**292**	**95.73**	**1.53 % at 400°C**

Tdi, Tdm, Tdf = Initial, maximum, final thermal decomposition temperatures in °C.

Single step degradation of ibuprofen was observed that started at 135°C (Tdi) and ended at 245°C (Tdf) while maximum decomposition (Tdm) was observed at 233°C. Although analysis was performed up to 800°C but TG and DTG curves got parallel at temperature 277°C and no further change in mass was observed in the thermogram of pure ibuprofen. Thermal analysis revealed that Tdm for ibuprofen, HPC and HPC-Ibuprofen conjugates **3** were found at 233, 365 and 246°C, respectively. It was concluded from data that ibuprofen got extra thermal stability after prodrug formation (sample **3**). Prodrug of ibuprofen becomes 13°C more stable than pure drug regarding Tdm. It is also important to note that degradation of HPC-ibuprofen conjugates start 25°C (Tdi 160°C) later than pure ibuprofen drug (Tdi 135°C). Nevertheless, thermal results have indicated that thermally more stable prodrugs of ibuprofen based on HPC were successfully fabricated showing potential for higher shelf life due to extra thermal stability.

Friedman, Chang, Broido and Kissinger models were used to calculate kinetic parameters of thermal degradation of ibuprofen, HPC and HPC-Ibuprofen conjugate **3**, e.g., energy of activation *(Ea)*, correlation factor *(R^2),* slope *(m),* order of reactions (*n*) and frequency factor *(Z).* Plots of Friedman, Chang and Broido were drawn using TG and DTG curves. Kinetic parameters obtained from these graphs are summarized in Table-3. The *Ea* values of HPC-Ibuprofen conjugate **3** were found comparable, i.e., 92.38, 99.34 and 87.34 kJ/mol as calculated from Friedman, Broido and Chang models, respectively for first and major degradation step 1. In second step, less than 5% degradation was observed that may correspond to furfural formation from polysaccharide (HPC) material. Comparable *Ea* values of HPC-Ibuprofen conjugates and drug are indicative of stability of ibuprofen in HPC-Ibuprofen conjugates. The *n* was calculated by Kissinger model and it was found that degradation of HPC-Ibuprofen conjugate follows first order kinetics.

Table-3: Comparative kinetic parameters calculated using different kinetic models for ibuprofen and HPC-Ibuprofen conjugate **3** (DS 1.40).

Sample	Method	R^2	*n*	*m*	*Ea (KJ/mol)*	*lnZ*	*Z (s^{-1})*
Ibuprofen	**Friedman**	**0.999**		**-9158**	**76.14**	**23.14**	**1.86×10^{8}**
	Broido	**0.999**		**-13604**	**113.11**	**27.11**	**9.89×10^{9}**
	Chang	**0.999**		**-10822**	**89.98**	**26.88**	**7.86×10^{9}**
	Kissinger		**1**				
HPC-Ibuprofen conjugate 3	**Friedman**	**0.997**		**-11111**	**92.38**	**18.57**	**1.9×10^{6}**
	Broido	**0.998**		**-11948**	**99.34**	**21.89**	**5.3×10^{7}**
	Chang	**0.999**		**-10505**	**87.34**	**23.4**	**2.4×10^{8}**
	Kissinger		**1**				

R^2 = correlation factor; *n* = order of reaction; *M* = slope, *E*a = Energy of activation; *Z* = shape index.

Experimental

Reagents and Chemicals

Hydroxypropylcellulose (MS 3.46, 60% HP moieties; Nanjing Yeshun Industry & International Trading Co. Ltd, Jiangsu China-Mainland) was dried at 110°C for 5 h to remove moisture contents. Analytical reagent grade organic solvents and other chemicals (Fluka) were used as obtained. The HCl and NaOH ampule (1 mol/L) of Merck were used for acid-base titration. Ibuprofen (gifted by Candid Pharmaceuticals, Sialkot, Pakistan) was of US pharmacopoeia (USP) standard.

Measurements

The FTIR (KBr) spectra were measured on IR-Prestige 21 (Shimadzu, Japan) using KBr pellet technique where pellets were dried under vacuum before taking spectra in order to remove traces of moisture or entrapped solvent if any. The ^{1}H-NMR (400 MHz) spectra of the HPC-Ibuprofen conjugates were acquired in DMSO-d_6 and all spectra were recorded with 16 numbers of scans. Agilent Technology 1200 (Germany) series equipment was used for GPC analyses of HPC-Ibuprofen conjugates **1-3**. The instrument was equipped with pump (PU-980), refractive index detector (RI 930), degasser (DG -980-50) and UV detector (UV-975 at 254 nm). The polymer standards columns were used for the size exclusion chromatography using DMF solvent at a flow rate of 0.5-1.0 cm^3/min at 40-45°C. The GPC equipment was calibrated with polystyrene standards. Thermal analyses of the HPC-Ibuprofen conjugates were carried out using TA Instrument equipped with a thermo-balance (SDT Q600 USA). To record simultaneous thermal analysis, temperature was varied at the rate of 10°C/min from ambient to 800°C. The thermal data were analyzed by MS Excel® 2010 and Universal Analysis 2000 software v 4.2E.

Dissolution of the HPC

For typical preparation HPC (2 g) was dissolved in DMAc (30 mL) by heating for 30 min at 80°C to obtain clear solution.

Synthesis of HPC-Ibuprofen Conjugates; a Typical Example (Sample **3**)

Ibuprofen (3.40 g, 16.5 mmol) was added to the solution of HPC (2 g, 5.5 mmol) in DMAc containing imidazole (2.25 g, 33.0 mmol). *In situ* activating agent, *p*-toluenesulfonyl chloride (3.16 g, 16.5 mmol) was added in parts to the reaction mixture. Reaction was preceded at 80°C for 24 h under nitrogen. The reaction mixture was precipitated in diethyl ether (300 mL) and washed three times to remove un-reacted drug and by products. The precipitates of HPC-Ibuprofen conjugates were dried at 40°C for 24 h.

DS: 1.33 by acid base titration after saponification and 1.40 by ^{1}H-NMR spectroscopy; Yield: 2.90 g (81%); FTIR (KBr): 3090 ν(OH), 1730 ν(CO_{Ester}), 1445 ν(CH_2) cm^{-1}; ^{1}H-NMR (DMSO-d_6, δ ppm): 1.03 (H-9), 0.84 (H-10), 1.33 (H-11), 1.77 (H-12), 2.40 (H-13), 3.17-3.90 (HPC repeating unit-H-2-8), 4.37 (H-1), 1.03 (H-9), 7.13-7.64 (aromatic-Hs). Same procedure was adopted for all of samples and analytical data of rest of the products is given below.

Analytical Data for Synthesis of HPC-Ibuprofen Conjugates, (Sample **1**)

DS: 0.83 by acid base titration after saponification and 0.88 by ^{1}H-NMR spectroscopy; Yield: 2.3 g (77%). FTIR (KBr): 3039 ν(OH), 1738 ν(CO_{Ester}), 1452 ν(CH_2) cm^{-1}; ^{1}H-NMR (DMSO-d_6, δ ppm): 1.03 (H-9), 0.85 (H-10), 1.32 (H-11), 1.76 (H-12), 2.42 (H-13), 3.14-4.40 (other AGU-H-1-5), 7.10-7.65 (aromatic-Hs).

Analytical Data for Synthesis of HPC-Ibuprofen Conjugates, (Sample **2**)

DS: 1.0 by acid base titration after saponification; 1.02 by ^{1}H-NMR spectroscopy; Yield: 2.4 g (76%); FTIR (KBr): 3263-3500 ν(OH), 1729 ν(CO_{Ester}), 1448 ν(CH_2) cm^{-1}; ^{1}H-NMR (DMSO-d_6, δ ppm): 1.02 (H-9), 0.84 (H-10), 1.32 (H-11), 1.76 (H-12), 2.41 (H-13), 3.15-4.39 (other AGU-H-1-5), 7.08-7.65 (aromatic-Hs).

Determination of Degree of Substitution (DS)

Sample (100 mg) was dissolved in 1M aq.NaOH (50 mL) and stirred overnight at room temperature. The pH of the mixture was adjusted to 7 by adding 0.01M HCl. Then a known amount of 1M aq.NaOH was added to the solution and back titrated using 0.1M HCl to reach the pH 7 again. The formula used for determination of DS is given below;

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

where, M(Ru) is molar mass of repeating unit of polymer, n.NaOH is the number of moles of

NaOH after saponification, Mr(RCO) is molar mass of ester functionality and Ms is mass of sample taken.

Determination of DS by ^{1}H-NMR Spectroscopy

The DS of the ibuprofen onto HPC was calculated from ^{1}H-NMR spectrum as per ref. [20] by the comparison of spectral intensities of signals.

Thermal Analysis and Degradation Kinetics

From TG curves, DTG was drawn and Tdi, Tdm and Tdf were calculated in order to compare the thermal stability of each step in conjugate, drug and polymer. Regarding the degradation kinetics, Friedman [21], Broido [22] and Chang [23] models were used. Friedman model determines the degradation kinetics as per eq. 1.

Order (n) of thermal degradation reaction was calculated from Chang model as per eq. 2. The plot of ln[($d\alpha/dt$)/(1-α)n] versus 1/T gives a straight line. Energy of activation (Ea) and frequency factor (Z) were calculated from the slope of this straight line. The Ea and Z were also calculated from Broido kinetic model as per eq.3.

$$ln\left(\frac{d\alpha}{dt}\right) = lnZ + n\,ln(1-\alpha) - \frac{Ea}{RT} \qquad Eq.\ 1$$

$$ln\left[\frac{\frac{d\alpha}{dt}}{(1-\alpha)^n}\right] = lnZ - \frac{Ea}{RT} \qquad Eq.\ 2$$

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

where, in eq. 1-3, $d\alpha/dt$ 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; $1-\alpha$ is the weight of sample left at a certain temperature that is also taken from the TG curve; T is the absolute temperature recorded; w_0 is initial weight; w_∞ is final weight; $y = (w_t-w_\infty)/(w_0-w_\infty)$ and w_t is weight at a given time t.

Shape index S of the DTG curve was used to calculate the reaction order n using Kissinger's method [24]. Rising and falling inflection points of the DTG curves were used to evaluate the shape index S using eq. 4. The value of n was calculated as a function of S value using eq. 5 and eq. 6.

$$S = (d^2\propto/dt^2)L/(d^2\propto/dt^2)R \qquad Eq.\ 4$$

$$n = 1.88S (S \geq 0.45) \qquad Eq.\ 5$$

$$n = 1.26S^{0.5} (S \leq 0.45) \qquad Eq.\ 6$$

where, $d^2\alpha/dt^2$ is 2nd derivative of TG and its values are noted from 2DTG curve; R and L are the quantities at the right and left inflection points.

Conclusions

Chemically benign and facile organo-soluble HPC-Ibuprofen conjugates with high covalent drug loading are successfully synthesized under homogeneous reaction conditions. The synthesis protocols are monitored with various characterization techniques. These new HPC-Ibuprofen conjugates were found thermally more stable than pure ibuprofen. The DTG curve analysis indicated that maximum degradation temperature (Tdm 246°C) of HPC-Ibuprofen conjugates is higher than that of unmodified/pure ibuprofen (Tdm 233°C). Additionally, it is found that degradation rate of conjugate (12.3 %/min) is much lower than that of pure drug (143.6 %/min). These facts show that after conjugation, ibuprofen becomes more stable in the form of macromolecular prodrug, i.e., HPC-Ibuprofen conjugate. Therefore, these newly fabricated HPC-Ibuprofen conjugates could be useful prodrugs of ibuprofen for potential pharmaceutical and pharmacological applications.

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