Hydroxypropylcellulose-flurbiprofen conjugates: design, characterization, anti-inflammatory activity and enhanced bioavailability

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A B S T R A C T

Herein, we report novel macromolecular prodrugs (MPDs) of flurbiprofen (FLB) onto a cellulose ether, hydroxypropylcellulose (HPC). The FLB was activated with a powerful acylation reagent carbonyldiimadazole (CDI) in N,N0-dimethylacetamide (DMAc) solvent at room temperature. Imidazolide of FLB generated in situ reacts at 80°C for 24 h with pre-dissolved HPC to prepare HPC-FLB conjugates. The resultant MPDs of FLB showed moderate to high degree of substitution (DS: 0.35–1.3) with good yield (70–82%). Structures were thoroughly characterized using FTIR, UV and NMR spectroscopic analyses. The pharmacokinetic studies showed that the t1/2 and tmax values of FLB from HPC-FLB conjugate were increased substantially as compare to standard FLB indicates enhanced bioavailability of drug after conjugate formation. Remarked anti-inflammatory activity of the HPC-FLB conjugate was also observed.

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1. Introduction

Flurbiprofen (2-(3-fluoro-4-phenylphenyl)propionic acid) is a propionic acid derivative and non-steroidal anti-inflammatory drug commonly used treat pain (Maroof et al., 2015), inflammation and rheumatoid arthritis (Rovensky and Micekova, 2000; Boulos et al., 2005). FLB also shows some adverse effects on humans, i.e., nausea, abdominal pain, ulceration (Halen et al., 2009) gastrointestinal irritation (Gabriel et al., 1991) and hemorrhage (Salduz and Özder, 2019).

Such side effects of carboxylic acid containing non-steroidal anti-inflammatory drugs (NSAIDs) can be minimized by derivatizing carboxylic acid groups to their derivatives (i.e., prodrugs) which can be hydrolyzed preferably in the colon due to its pH and enzymes. This prodrug formation can reduce gastric irritancy caused by acid containing drugs (Halen et al., 2006) as well as such prodrugs if based on polymers can give sustained and intestine targeted drug delivery (Hussain et al., 2017). Literature is also witnessing that drugs from such MPDs of NSAIDs and antibiotics are more bioavailable in sustained fashion (Amin et al., 2015; Abbas et al., 2016).

Some prodrugs of FLB had also been synthesized in order to reduce its side effects and to get better patient compliance via reduction in dose and dose frequency. Couple of prodrug strategies have been developed for FLB where some useful results were obtained. Prodrugs of FLB based on alkyl esters of amino acids showed reduced toxicity and better solubility without affecting its pharmacological activity (Gairola et al., 2005). Another prodrug FLB-glycine conjugate showed reduction in ulceration of GIT and toxicity (Philip et al., 2008). In another study, dextran-FLB conjugates have been reported (Shrivastava et al., 2009) but in this case the degree of substitution (DS) of FLB was very low and could not lead to viable formulation for humans’ oral dose. The only MPD of the FLB has been reported which was based on another cellulose

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derivative where tosyl chloride was used as acylating agent (Abbas et al., 2020) and this reaction requires necessary clean up procedure to remove acidic side products.

Therefore, our interest is to develop MPDs of FLB with relatively high DS using more efficient and environment friendly reaction (i.e., 1,1′-carbonyldiimidazole (CDI) method) where there is no chance of production of any toxic side products as well (Hussain et al., 2004). In these days there is a great urge for polysaccharides to be used to design MPDs of NSAIDs (Hussain et al., 2013) and amongst polysaccharides, hydroxypropyl cellulose HPC has gained much importance (Abbas et al., 2017; Hussain et al., 2015). It is because of the fact that in HPC more degree of drug substitution can be achieved due to its stereochemical structure as the hydroxyl groups of the polymer are projected outside the chains. From these achievements and investigations in the field of prodrug formation, it is evident that there is a huge ground for the employment of HPC in advanced drug delivery as a macromolecular carrier of drugs. So, we are interested to produce the MPDs of FLB on to HPC not only due to its structure but also due to its biodegradability, non-toxicity, biocompatibility and hydrophilicity. The resultant conjugates are expected to offer sustained release of FLB owing to enzymatic hydrolysis in vivo. It is also being thought that HPC-FLB conjugate will be more bioavailable in sustained fashion therefore interests are to study their pharmacokinetic profile in the rabbit model. Anti-inflammatory activity of FLB from the HPC-FLB conjugate is also topic of interest.

2. Materials and methods

2.1. Materials

HPC (DS 3.00, MS 3.46, Mw 1.16 × 105) was procured from Nanjing Yeshun Industry and International Trading Co. Ltd, Jiangsu, China and dried at 110 °C for 5 h before use. Analytical grade methanol, ethanol, propanol, hexane and N,N-dimethylacetamide (DMAc), diethylther and 1,1′-carbonyldiimidazole (CDI) all were used as received from Sigma Aldrich. HCl and NaOH (Merck) were used for hydrolysis of drug and preparation of standard solutions for UV/Vis spectroscopy, respectively.

2.2. Measurements

FT-IR spectra of the conjugates were recorded on an IR-prestige-21 (Shimadzu, Japan) spectrometer. KBr pellet method was used to record the spectra of samples. Structures of the conjugates were determined using 1H NMR (400 MHz) in DMSO d6. To get a pharmacokinetics profile of the prodrug, an HPLC method was developed. The HPLC system (Agilent Technologies 1200 Series, Germany) was set up with UV–Vis detector (G1315B DAD), pump (G1311A) and degasser (G1322A). Shim-Pack columns (ODS 5 μm, 4.6 × 250 mm) were used for elution.

2.3. Synthesis of HPC-FLB conjugate 1, a typical example

Flurbiprofen (0.67 g, 2.75 mmol) was dissolved in DMAc (20 mL) then CDI (0.44 g, 2.75 mmol) was added and reaction mixture was stirred at for 24 h. HPC (1.0 g, 2.75 mmol) was dissolved in DMAc (20 mL) under stirring (80 °C, 1.5 h). The reaction mixture, i.e., FLB/CDI and HPC were mixed and reaction was then carried out at 80 °C for 24 h along with continuous stirring under nitrogen environment. After cooling of reaction mixture at room temperature, the product HPC-FLB conjugate 1 was separated from the reaction mixture by precipitation in diethyl ether (250 mL). Washing of the precipitates was also carried out with diethyl ether (100 mL) thrice followed by drying it in a vacuum oven at 50 °C for 24 h.

HPC-FLB conjugate 1; Yield: 70%; DS: 0.35 by UV/Vis spectrophotometer; FTIR (Kbr): 3485 ν(OH), 1714 ν(COester), 1448 ν(CH2) cm⁻¹. HPC-FLB conjugate 2; Yield: 79%; DS: 0.78 by UV/Vis spectrophotometer; FTIR (KBr): 3309ν(OH), 1714 ν(COester), 1462 ν(CH2) cm⁻¹. HPC-FLB conjugate 3; Yield: 82%; DS: 1.3; FTIR (KBr): 3498ν(OH), 1720 ν(CO Ester), 1452 ν(CH2) cm⁻¹; 1H NMR (DMSO d6): δ (ppm) = 1.37 (H-24), 3.21–3.40 (other AGU-H-1-8), 1.01 (H-9), 7.01–7.64 (aromatic-Hs).

2.4. HPLC/UV method development

An efficient and rapid reverse phase (RP) HPLC/UV method was developed and validated to calculate the drug contents of HPC-FLB conjugates. HPLC instrument used in this study, contained a UV–visible detector and column employed was reverse phase C18 (Genesis, USA; 5 μm × 4.6 mm × 250 mm). Mobile phase was acetonitrile:water (50:50 ν/ν) under isocratic conditions and filtered through 0.45 μm nylon filter before use. Flow rate was fixed at 1 mL min⁻¹ and samples were detected at λmax 248 nm with sample injection volume 20 μL throughout the study.

FLB (100 mg) was dissolved in 100 mL (1 mg/mL) of mobile phase. Then 10 mL from this solution was taken and diluted to 100 mL with mobile phase. This solution was further diluted to form solution of various concentrations, which were used for the formation of standard curve. Prior to packing into HPLC vials, all standard solutions of drugs and prodrugs were filtered using nylon syringe filter (0.45 μ) and sonicated before analysis. An isocratic mode was used for all chromatographic separations.

2.4.1. Validation

For the validation of HPLC/UV method, ICH guidelines were followed to study pharmacokinetic profile of FLB and MPDs. Different validation parameters which were studied are summarized below.

2.4.1.1. Linearity, precision and accuracy

Linearity of the method of HPLC was evaluated using ten solutions of varying concentrations (1–50 μg/mL) of FLB (standard). Calibration curve was developed for standard. Applying linear regression method, r² value was determined and linearity was assessed. For the determination of precision and accuracy, different solutions of standard of known concentration (quality control samples) were analyzed on HPLC. Three quality control samples were prepared by adding a known amount of standard. Low quality control sample, the middle quality control sample and the upper quality control sample. The concentrations of these samples represent the whole standard curve. Each quality control sample was analyzed ten times and their mean was calculated.

2.4.1.2. Limit of detection (LOD), lower limit of quantification (LLOQ) and stability study

Standard solution in mobile phase was diluted to calculate LOD and LLOQ of each method to the response equal to twice times of the signal-to-noise ratio. The lower limit of quantitation was the lowest concentration of drug at which its peak can be identified and discrete with suitable precision and accuracy. Stability study was carried out for the evaluation of the time period that encompasses the duration of sample preparation to the analytical run time. That was about 30 min and the study was extended to the 72 h to assess stability.

2.4.1.3. Specificity and determination of plasma concentration by HPLC

Six different samples were used to check the specificity of the method. Serum was diluted with mobile phase and analyzed by HPLC after filtration using nylon syringe filter. Concentration
of drug in serum sample was calculated by its comparison with standard curve.

2.5. Pharmacokinetic studies

2.5.1. Participants and study design

For pharmacokinetics studies of drug and prodrug, 12 healthy male rabbits (=1.5 kg each) were used and divided in two groups. One is standard group which received standard (FLB) and other is treatment group which received HPC-FLB conjugate. Animals were kept under fasting condition for 12 h prior to drug administration. Standard drug and sample were administered by oral route by suspending in CMC. An oral dose of 2.58 mg/kg of standard FLB and 6.45 mg/kg of HPC-FLB conjugate (=2.58 mg/kg of FLB) was given and animals were allowed to take water after 1 h of drug administration, but had no access to food. Study procedures where animal models are used has been approved by the Institutional Research Ethics Committee of The University of Lahore. The studies on animal models were in accord with the directions of the National Institute of Health's Guidelines for the Care and Use of Laboratory Animals (NIH Publications No. 8023, revised 1978).

2.5.2. Specimen collection

After drug administration blood samples (1 mL each) were collected at 0, 0.25, 0.5, 1, 1.5, 2, 2.5, 4, 8, 12, and 24 h from the juggling vein from each animal using heparinized disposable syringes. Blood was taken in blood tubes containing anticoagulant EDTA, to prevent clotting.

2.5.3. Plasma sample preparation

Blood samples were immediately centrifuged at 3000 g for 3 min to separate plasma. Plasma was obtained as clear supernatant and was stored in a freezer at −5 °C. Then to separate proteins present in the plasma, acetonitrile (1 mL) was added in each plasma sample and again centrifuged to obtain serum that was then filtered with nylon filters and stored at −5 °C until used.

2.5.4. Pharmacokinetic parameters

Plasma concentration of the standard (FLB) was plotted vs time and AUC (area under the curve) was calculated using a widely accepted linear trapezoidal method. Different valuable kinetic parameters like peak drug concentration (C_{max}), half-life of drug (t_{1/2}), volume of distribution (Vd) and clearance (Cl), were determined from AUC.

2.5.5. Statistical analysis

Graphpad Prism 5.0 (GraphPad Software Inc., La Jolla, CA, USA) was used to statistically analyze the pharmacokinetics data. Results were expressed as mean ± SD.

2.6. In vitro drug release studies

For the evaluation of release behavior of HPC-FLB conjugate, in vitro drug release study was carried out in simulated gastric and intestinal fluids. For this study, Dissolution Apparatus II (Pharma Test, PT-DT70, Germany) was used.

Dissolution medium was prepared according to the standard procedure given in USP- 37. Simulated gastric fluid (SGF) of pH 1.2 and intestinal fluid (SIF) of pH 6.8 were prepared according to a standard procedure given in USP-30 NF 25. The standard solution of FLB of 2, 5, 10, 15, 20, 25 and 30 μg/mL were prepared and standard curve was generated. Likewise, the HPC-FLB conjugate (50 mg, contain 20 mg of FLB) was accurately weighed on an analytical balance and placed in the dissolution medium to evaluate in vitro release of drug from conjugate.

The dissolution media (900 mL) was placed in the vessel of Dissolution Apparatus II and allowed to equilibrate it to 37 ± 0.5 °C. HPC-FLB conjugate (50 mg) was placed in the media (apparatus speed was 50 rpm). Dissolution was first carried out in SGF (2 h), after that dissolution medium was filtered and residue, obtained on the filter paper was then transferred to SIF and drug release was observed for further 10 h in SIF. Aliquot of sample (5 mL) was withdrawn at specified time intervals and equal volume of same dissolution media was replenished to maintain the volume of media to 900 mL. Filtered samples with nylon syringe filters (0.45 μm) were then analyzed by UV–visible spectrophotometer at λ_{max} 248 nm. The experiment was repeated six times and their mean was calculated. By comparison with standard curve, conc. was determined. Cumulative % drug release was calculated and a graph was generated between time (h) and % drug release, which represented the release behavior of drug from HPC-FLB conjugate 3.

2.7. Evaluation of anti-inflammatory activity

Albino Wister rats were divided into 3 groups (n = 5, male). Group 1: Control (CMC + carrageenan), Group 2: Standard (Standard FLB + carrageenan) and Group 3: Treatment (HPC-FLB conjugate + carrageenan).

Diameter of the paw of the rats in all groups was determined using Vernier caliper before giving any treatment or anti-inflammatory agent. After this, rats in the first group were administered with 3 mL solution of carboxymethylcellulose (CMC), rats in the group 2 received standard (FLB) and rats in the group 3 received HPC-FLB conjugate orally using an oral cannula. Conjuigate and standard were administered by suspending them in 1% solution of CMC. Dose of standard was 2 mg/Kg, whereas dose of HPC-FLB conjugate was 5 mg/Kg (equivalent weight containing 2 mg/Kg of FLB).

Carrageenan induced rat paw edema model was used to evaluate anti-inflammatory activity of drug and prodrug. After about 1 h of drug administration, inflammation was induced by sub planter injection of 0.1 mL of freshly prepared 1% carrageenan solution in normal saline in the left hind paw of the rats. Paw diameter was measured by digital Vernier caliper for 24 h at different time intervals. Percentage inhibition of edema was then calculated.

Results of anti-inflammatory activity are expressed as mean ± S.E.M. For the statistical analysis of results, one-way ANOVA and Student's t-test were used. Results were found statistically highly significant (p < 0.05) when compared to control.

3. Results and discussions

3.1. Synthesis and characterization of HPC-FLB conjugates

HPC-FLB conjugates were synthesized homogeneously in DMAc. The carboxylic acid groups of FLB were activated with an efficient acylating reagent CDI to obtain imidazolide of FLB. For this purpose, CDI and FLB were mixed in DMAc solvent and stirred at room temperature for 24 h. The pre-dissolved HPC polymer in DMAc was allowed to react with in situ activated drug, i.e., imidazolide of FLB at 80 °C for 24 h. The reaction is schemed out in Fig. 1. Three samples of HPC-FLB conjugates with different molar ratios were synthesized and characterized. All products were thoroughly washed with ethanol as un-reacted drug and all other impurities were soluble in ethanol. The DS of all samples was calculated three times by using UV/Vis spectrophotometer. The products obtained were soluble in organic solvents like DMSO, DMF, and DMAc. All the conjugates 1–3 were insoluble in water due to
their hydrophobic nature and sufficiently high drug contents onto polymer backbone.

Degree of substitution of HPC-FLB conjugates were determined using UV/Vis spectroscopic technique. Amount of drug loaded per HPC repeating unit was calculated in term of mg of drug per 100 mg of conjugate and DS was expressed as number of substituted drug moieties per repeating unit of polymer. Conjugates 1–3 showed DS of FLB in the range of 0.35–1.3 indicating significant potential of synthesized prodrugs which may offer viable amount of FLB for the development of oral formulation. Different reaction conditions and results are summarized in Table 1.

Table 1
The conditions and results for reaction of HPC (1 g) with FLB after in situ activation with CDI at 80 °C for 24 h.

| Sample | Molar ratioa | DC  | DSb | Yield | Solubility         |
|--------|--------------|-----|-----|-------|--------------------|
| 1      | 1:1:1        | 18  | 0.35| 70%   | DMAc, DMF, DMSO    |
| 2      | 1:2:2        | 33  | 0.78| 79%   | DMAc, DMF, DMSO    |
| 3      | 1:3:3        | 45  | 1.3 | 82%   | DMAc, DMF, DMSO    |

aHPC: CDI: FLB; bThe DS was determined from DC (by using UV/Vis data)

Fig. 1. Synthesis of HPC-FLB conjugates applying in situ activation of FLB with CDI.

Fig. 2. FTIR spectra of FLB, HPC and HPC-FLB conjugate 3.
FTIR spectra of HPC-FLB conjugates 1–3 showed absorbance of ester moiety (COester) at 1714–1737 cm⁻¹, aromatic C–H group was appeared at 2779–2937 cm⁻¹ and still free hydroxyl groups (–OH) were observed at 3309–3498 cm⁻¹. The polymer C–O peaks were detectable in the range of 1066–1074 cm⁻¹. The FTIR spectrum indicated successful conversion as presence of new ester signals was clearly observed in spectra. The CH₂ groups were detected at 1448–1462 cm⁻¹ for different conjugates. The typical overlay spectra of HPC-FLB conjugate 3, FLB and HPC are shown in Fig. 2. The FTIR spectrum of HPC-FLB conjugate 3 showed ester absorption at 1720 cm⁻¹ confirming the covalent loading of drug to HPC. The aromatic C–H group are detectable at 2779 cm⁻¹ and remaining free hydroxyl groups (–OH) appeared at 3498 cm⁻¹. The polymer C–O–C peak is also evident in the spectrum at 1066 cm⁻¹.

¹H NMR (400 MHz, DMSO d₆) spectrum of HPC-FLB conjugate 3 (Fig. 3) showed signals of aromatic proton of FLB in the range of δ 7.09–7.64 (H-13, H-16, H-17, H-19, H-23) ppm. Methyl protons of drug were recorded at δ 1.37 (H 24) ppm while the protons of HPC polymer backbone/anhydroglucose unit (AGU) were recorded in the range δ 3.21–3.40 (H 1–8) ppm. Signal at δ 1.01 ppm was recognized to methyl at hydroxypropyl moiety of HPC (H-9). Broad signals also also indicating the polymer nature of the conjugate. Solution of HPC-FLB conjugate was analyzed on UV–visible spectrophotometer and its absorbance was compared with standard (FLB) curve. UV data of HPC-FLB conjugate revealed that 100 mg of HPC-FLB conjugate contained 40 mg of FLB which is a very high proportion of FLB drug in conjugate.

3.2. Pharmacokinetic studies

Pharmacokinetic study was carried out in rabbit models. Pharmacokinetic parameters i.e. AUC, Cmax, Tmax, Cl, Ke and t1/2 were calculated. The Tmax of HPC-FLB conjugate 3 was high as compare to standard, furthermore t1/2 of test compound was also found to
be greater than standard drug. Levels of FLB in plasma remained high for a significant period of time which improves its bioavailability from drug conjugate due to sustained release of drug from the conjugate in the body. $C_{\text{max}}$ was found to be 31.03 $\mu$g/mL for HPC-FLB conjugate 3 with $T_{\text{max}}$ 4 h. While $C_{\text{max}}$ for the standard drug was 37.3 $\mu$g/mL with $T_{\text{max}}$ 1 h. Results of the pharmacokinetic study are expressed in Table 2 and Fig. 4 whereas the results of validation of HPC/UV method are expressed in Table 3. HPLC spectra of FLB, FLB in plasma and HPC-FLB conjugate in plasma are shown in supplementary data (see Figs. S1–S3).

3.3. In vitro drug release study

In vitro drug release study was carried out in SGF (2 h) and SIF (10 h). Results have indicated that in SGF, only 9% drug release was release which is negligible and may be from tablet surface whereas in SIF, 57.15% drug was released from HPC-FLB conjugate in 12 h (Fig. 5) but in sustained fashion.

3.4. Anti-inflammatory activity of HPC-FLB conjugate

Anti-inflammatory activity of HPC-FLB conjugate 3 and FLB (standard) was assessed in rats model using carrageenan induced paw edema. Results of HPC-FLB conjugate 3 (treatment group) were found highly significant when compared to the control and standard groups (Fig. 6). HPC-FLB was orally administered to albino Wistar rats and paw diameter (cm) was measured at specific time intervals. Significant reduction of edema was evident at 3rd, 4th, 5th and 6th h after the administration of drug. Maximum inhibition of edema by HPC-FLB conjugate was observed around 4th h, whereas anti-inflammatory activity of standard FLB was maximum within first 2 h then reduced. From these results, it is obvious that HPC-FLB conjugate has more anti-inflammatory potential/control on inflammation as compared to the FLB.

4. Conclusions

Macromolecular prodrugs (MPDs) of FLB were synthesized using CDI reagent under mild reaction conditions. This method led to high degree of drug substitution on to polymer HPC. Pharmacokinetic studies of HPC-FLB conjugate showed enhanced bioavailability of FLB also in sustained fashion. In vitro drug release also witnessed the FLB release from conjugates was sustained in SIF. In SGF, release of FLB was nominal hence such prodrugs we designed are better candidates to reduce gastric irritancy. HPC-FLB conjugates when subjected to anti-inflammatory assay showed improved control on inflammation rather than FLB itself. Such macromolecular prodrugs (MPDs) of FLB could be a model study to develop MPDs of different NSAIDs. Such MPDs may lead to the development of prodrugs that can alleviate NSAID associated gastric irritancy along with the improved pharmacokinetic profile.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsps.2020.06.009.

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