Journal of Advances and Scholarly Researches in Allied Education
Vol. 16, Issue No. 6, May-2019, ISSN 2230-7540

Dextran Conjugation of Non–Steroidal Anti-Inflammatory Drug (Etodolac): A Colon Targeting Approach

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Abstract – Because of the presence of a free carboxylic group, etodolac, a non-steroidal anti-inflammatory medication extensively used in arthritis, has been linked to stomach ulcers and irritation. The current study describes the production of an etodolac mutual amide prodrug by masking the free carboxylic group with glucosamine, a dietary supplement used to treat arthritis. The structure of the synthesised prodrug was confirmed and characterised using elemental and spectroscopic analyses, melting point, and migration parameters (Rf and RM) determined using thin layer chromatography and high-performance liquid chromatography, respectively. Prodrug in vitro reversion studies show a high incidence of colon pH reversal. Animals were used for in vivo pharmacological testing. In comparison to etodolac, the prodrug has good analgesic, anti-inflammatory, and anti-arthritic properties. Ulcerogeniticity analysis was used to examine the prodrug's potential for harm. As a result, the prodrug has been shown to be more effective than etodolac and to have less gastrointestinal adverse effects.

Key Words – Mutual Prodrug, Etodolac, Dextran, Chemical and Pharmacological Characterization

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INTRODUCTION

For local therapy of a range of bowel disorders such as (ulcerative colitis, Crohn's disease), amebiasis, colonic cancer, local treatment of local colonic pathologies, and systemic administration of protein and peptide medicines, targeted drug delivery to the colon is extremely desirable [1]. The colon specific drug delivery system (CSDDS) should be able to safeguard the medication en route to the colon (i.e., drug release and absorption should not occur in the stomach or small intestine, and the bioactive agent should not be destroyed), as well as allowing drug release solely in the colon [2].

Although the oral route is the most convenient and favoured [3], alternative methods for colon-specific medication administration may be employed as well. Rectal administration is the quickest way to transfer medications to the colon. Rectal administration, on the other hand, makes it harder to reach the proximal region of the colon. Rectal administration might also be unpleasant for the patient, resulting in lower compliance [4]. Intrarectal drug preparation is available in the form of liquids, foam, and suppositories. The intrarectal method is utilised to transfer topically active drugs to the large intestine as well as for systemic dosage [5]. For the treatment of ulcerative colitis, corticosteroids such as hydrocortisone and prednisolone are given through the rectum. Although these medications are absorbed into the large intestine, their effectiveness is thought to be mostly related to topical administration. The amount of medicine that reaches the colon is determined by the formulation, the extent of retrograde spreading, and the retention duration. Foam and suppositories have been shown to be mostly retained in the rectum and sigmoid colon, but enema solutions have a large spreading capability. Because of the colon's high water absorption capacity, the contents are viscous and mixing is inefficient, limiting the access of most medications to the absorptive membrane. The human colon is home to around 400 different bacteria species, with a density of up to 1010 bacteria per gramme of intestinal contents. Azole reduction and enzymatic cleavage are two responses carried out by these gut florae. These metabolic mechanisms may be involved in the metabolism of a variety of medicines, and they might potentially be used to transfer peptide-based macromolecules like insulin to the colon by oral administration [6].

Non-steroidal anti-inflammatory medications (NSAIDs) are a family of pharmaceuticals that, in

addition to their anti-inflammatory properties, may also have analgesic and antipyretic properties [7]. NSAIDs work by inhibiting cyclooxygenase (COX) enzymes, which are responsible for the synthesis of prostanoids [6]. COX enzymes are classified as COX-1 (constitutive), COX-2 (inducible in inflammatory processes), and COX-3 (isozyme) [10]. To compete with the natural substrate, a medication must be extremely lipophilic and acidic like arachidonic acid [8]. Etodolac is an acetic acid derivative used to treat rheumatic illnesses and postoperative pain. It is rapidly metabolized in the liver and predominantly excreted via the kidney [4, 5]. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been linked to a variety of side effects, including renal dysfunction, cardiovascular adverse events, asthma triggering, and a considerable increase in clotting times [6,8]. Furthermore, NSAIDs have been shown to have negative effects on the gastrointestinal tract, including nausea, vomiting, and diarrhoea. The second mechanism involves prostaglandin E2 (PGE2) and prostacyclin (PGI2), which protect gastric mucosa by stimulating bicarbonate and mucin secretion and increasing mucosal blood flow [9]. The third mechanism involves prostaglandin E2 (PGE2) and prostacyclin (PGI2), which protect gastric mucosa by stimulating bicarbonate and mucin secretion and increasing mucosal blood flow. Prodrugs are converted enzymatically and/or chemically in vivo to release the active parent drug and achieve the desired pharmacological action [6-9]. This method is extensively employed in medicinal chemistry since it can enhance an existing drug's unfavourable characteristics while also decreasing its therapeutic efficacy. GIT irritation and bleeding can be reduced using ester prodrugs for NSAIDs with a carboxylic acid group. One method for preventing GIT irritation is to inhibit the acidic moiety by esterification without altering its therapeutic impact [10]. The goal of this study is to synthesize etodolac dextran conjugates and assess their potential for usage as a polymeric prodrug for oral drug administration. In addition, in vivo animal studies were carried out to analyse the drugs' pharmacological effects and gastrointestinal toxicity.

MATERIALS AND METHODS

Materials

Fleming Laboratories Limited in Telangana, India, generously donated etodolac. Fluka Biochemika in Switzerland provided differing molecular weights of dextran and N, N-carbonyldiimidazole (CDI). Hi-Media Laboratories Pvt. Ltd. in India sold Dextran. The other compounds were synthetic in nature. Sisco Laboratories in India provided the silica gel GF 254 for TLC. All additional solvents and chemicals were purchased from Qualinges fine chemicals in India and were of reagent grade. The melting points were determined using a melting point determination instrument manufactured by Sigma Instrument in India. The IR spectra were collected in the region of 4000 to 400 cm^{-1} using a Perkin Elmer FT-IR spectrometer.

Methods

Drug identification tests

Melting point determination

Melting point of Etd was determined by capillary fusion method, by using calibrated thermometer and melting point apparatus (Jindal, S.M. Scientific Instruments Pvt. Ltd., New Delhi) (Indian Pharmacopoeia 1996) [6].

UV spectrophotometric study

100 mg Etd was dissolved in 0.1 M sodium hydroxide solution and diluted to 100 ml with the same alkaline solution, then 1 ml of this solution was diluted to 100 ml with the same alkaline solution. Using a Shimadzu UV double beam spectrophotometer (Shimadzu 1700, Tokyo, Japan), this solution (0.001 percent w/v) was scanned for absorption maxima (max) in the range of 226 to 255 nm (Indian Pharmacopoeia 1996) [11].

FTIR Spectrophotometeric Study

IR spectroscopic studies gives the information of the any functional groups which are present in unknown substance. For this study we determined functional group by using Perkin Elmer's FTIR spectrometer. All formulations were scanned in the wavelength region of 4000-400 cm^{-1} [11].

Synthesis of Dextran Prodrug

Etd-dex prodrugs were made by activating the carboxylic group with N, N–carbonyl diimidazole and then condensing it with dextran in situ to produce Etd acylimidazole (Figure 1). Thin layer chromatography was used to monitor the reaction's progress, using n-hexane, water, ethyl acetate, and glacial acetic acid (30: 10: 10: 2.5) as the stationary phase and n-hexane, water, ethyl acetate, and glacial acetic acid as the mobile phase. Due to the moisture sensitivity of N, N–carbonyl diimidazole, dry solvents were utilised throughout the experiment, and anhydrous conditions were maintained [12,13].

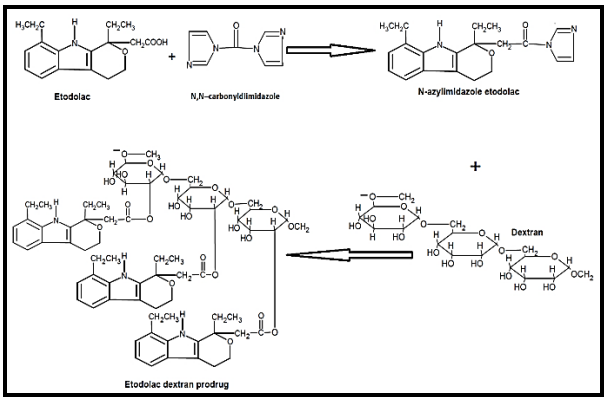

Figure 1. Synthesis of Etd-dex Prodrug

Characterization of ETD and ETD-DEX Pro-drug

Melting Point Determination

By utilising a calibrated thermometer and melting point equipment (Jindal, S.M. Scientific Instruments Pvt. Ltd., New Delhi), the melting points of Etd and Etd-dex prodrugs were determined [12].

Thin Layer Chromatography (TLC)

TLC of Etd and Etd-dex prodrug was performed with Silica Gel GF_{254} used as stationary phase. Sample spots of 5 µl of compound solution were loaded at 1.5 cm intervals. The compounds were allowed to develop by an ascending technique in TLC jar, under conditions of equilibrium using a mobile phase of methanol: water (3:1 v/v). The plates were dried and the developed spots were localized under ultra violet cabinet at short wave length 254 nm. The R_f value were determined for the compound as the average of three readings [13].

R_M Value Determination

R_M value was determined by reversed phase TLC. Silica gel GF_{254} TLC plates were soaked for 5 h in acetone containing 3% n-octanol and left to dry overnight. Sample spots of 5 µl of compound solution were loaded at 1.5 cm intervals. The compounds were allowed to develop by an ascending technique in a chromatographic chamber under conditions of equilibrium using a mobile phase of methanol: water: chloroform (14:5:1 v/v) [14]. The plates were dried and the developed spots were localized under ultra violet cabinet at short wave length 225 nm. The R_f value was determined for the compound as the average of three readings and the corresponding R_M values were calculated using the formula:

$$RM = \log(1/Rf - 1)$$

Scanning Electron Microscopy (SEM)

Morphology of Etd and Etd-dex prodrug was characterized by SEM using HITACHI S 3400 N (Japan) at Birbal sahni institute of palaeobotany, university road, Lucknow. Gold coating of Etd and Etd-dex prodrug, were done for sample processing &mounting. Then gold palladium coating and then sample examination & photography was done [15].

Preformulation studies of Etd and Etd-Dex prodrug

Preparation of calibration curve of Etd in phosphate buffer pH 6.8

Calibration curve of Etd was prepared in phosphate buffer pH 6.8. Appropriate aliquots from the stock solution of Etd (100 µg/ml) were used to prepare three sets of dilution consisting of different concentrations of Etd (2-18 µg/ml), Aliquots of the stock solution of (100 µg/ml) were pipetted out into a series of 10 ml volumetric flask and diluted with phosphate buffer pH 6.8 to get final concentrations in the range of 2-18 µg/ml. The absorbance of the resultant solutions was measured at suitable λ_{max} values using UV spectrophotometer [16].

***In Vitro* reversion of Etd-Dex prodrug at different pH and in colonic environment**

Preparation of calibration curve of Etd in n-butanol

Calibration curve of Etd was prepared in *n*-butanol. Appropriate aliquots from the stock solution of Etd (100 µg/ml) were used to prepare three sets of dilution consisting of different concentrations of, 2-18 µg/ml. Aliquots of the stock solution of Etd (100 µg/ml) were pipette out into a series of 10 ml volumetric flask and diluted with *n*-butanol to get final concentrations in the range of 2-18 µg/ml. The absorbance of the resultant solutions was measured at suitable λ_{max} values using UV spectrophotometer [6].

In vitro reversion of Etd-dex prodrug to Etd at different pH and in colonic environment

The reversion of Etd-dex prodrug was examined at 37 ± 0.5^{0}C in HCl buffer pH 1.2, phthalate buffer pH 4.0, phosphate buffer pH 6.8, phosphate buffer pH 6.8, phosphate buffer pH 6.8, and phosphate buffer pH 6.8 containing fresh rat faecal content (20 % w/v). By modifying the ionic strength (µ=0.5) of each buffer with a predetermined quantity of potassium chloride, the ionic strength was kept constant. The reaction was started by keeping the Etd-dex prodrug concentration at 100 µg/ml in glass vials. The vials were kept in a water bath at 37 ± 0.5^{0}C for different time intervals. For analysis 5 ml solution was withdrawn from the vials at different time intervals and was shaken with equal amount of *n*-butanol so as to extract free Etd reverted from Etd-dex prodrug. The concentration

of Etd was directly estimated from the *n*-butanol layer on UV spectrophotometer at 315.5 nm [15].

Ulcerogenicity study

The ulcerogenic activity was determined by Rainsford cold stress method which is an acute study model and is used to determine ulcerogenic potency of a drug at ten times higher dose. Albino rats weighing 150-200 g were fasted overnight prior to administration of the compounds, water was given at libitum. The animals were randomly distributed in three groups namely control, drug and prodrug, of six animals each. Control group received 1% w/v carboxy methyl cellulose (CMC) orally. The drug (Etd) and prodrug (Etd-dex) were administered orally, as fine particles suspended in 1% w/v CMC. The mice were stressed by exposure to cold after receiving 5 ml of the aqueous medication solutions orally (-15oC for 1 h). To guarantee equal cold exposure, the animals were housed in separate polypropylene cages. The animals were scarified by cervical dislocation after 2 hours of medication treatment. With a magnifying lens, the stomach and duodenal portions were opened along the larger curvature and the number of lesions were counted. Microimage process software (DA1-180M v 2.01) and an Olympus SP 350 camera were used to assess the size of ulcers (Olympus, Tokyo, Japan). Scoring for the ulcers was done as 0 for normal colored stomach, 0.5 for red coloration, 1 for spot ulcers, 1.5 for hemorrhagic streaks, 2 for ulcers ≥3 but ≤ 5, 3 for ulcers ≥5 [16].

STABILITY STUDIES

A three-month accelerating condition stability test was carried out after preparation by which Etd-dex was kept in an oven at a temperature of 40 ± 1 °C and a relative humidity of 75%. Percentage drug remaining, liquefaction, discoloration, etc. were determined at the end of one, two and three months, respectively.

PHARMACOLOGICAL EVALUATION

Induction of inflammation

The rats were deprived of food for 24 hours before being infected with colitis, but they had unlimited access to water. A little ether anaesthetic was administered to the rats. The tip of a rubber cannula (o.d., 2mm) was introduced rectally into the colon 8 cm proximal to the anus, around the splenic flexture. The rubber cannula was used to inject 2,4,6-trinitrobenzene sulphonic acid (TNBS) into the colon (15 mg/0.3 ml each rat) diluted in 50 percent (v/v) aqueous ethanol.

Evaluation of induced colitis

Rats weighing 150 to 175 g were split into 13 four-person groups, each with a control and standard group. They had to fast for 48 hours before taking the medicine (water ad libitum). The Etd-dex prodrug was given orally as an aqueous solution or suspension (10-30 mg/kg). The dosages were determined using a rat model of the drug's anti-inflammatory action. The animals were murdered seven hours after receiving the medicine. Specimens from the stomach were taken and put on filter paper that had been soaked in saline. By flipping the specimens over the index finger, the presence or absence of stomach pain was determined. For each stomach sample, the number of ulcers was counted and the severity was recorded using the following scores: 0.0= no ulcer, 1.0= superficial ulcers, 2.0= significant ulcers, and 3.0= perforation. By subtracting the mean score of each treatment group from the mean score of the control group, the severity index of stomach damage was determined (level of significance is $P< 0.01$ with regard to control).

The activity of myeloperoxidase (MPO) was measured using the distal colon (4 cm) as previously described. One unit of myeloperoxidase activity is defined as the capacity to breakdown 1mol of peroxide per minute at 25^0C.

RESULTS AND DISCUSSIONS

Drug identification tests

Melting point of Etd-dex conjugate thesis was found to be 110^0C which was within the limits of the literature value of 144^0 -150^0 c (Indian Pharmacopoeia 1996), indicating that the sample was Etd. 0.001% w/v Etd solution in 0.1M NaOH was scanned for absorption maxima (λ_{max}) in the range of 223 to 225 nm, Etd showed experimental absorption maxima of 223.5 nm and specific absorbance of 800, which corresponded to the literature value (Indian Pharmacopoeia 2010), indicating the sample as Etd.

FT-IR spectrophotometeric study

FT-IR spectrum of Etd-dex conjugate showed absorption band at 2969 cm^{-1} (N-H stretching of amide), 1738 cm^{-1} (C=O stretching of ester), 1650 cm^{-1} (C=O stretching of amide), 1535 cm^{-1} (N-H bending of amide), 1261 cm^{-1} (C- N stretching), 1032 cm^{-1} (C-O stretching of ester), are the characteristic peaks of ester and amides and confirmed the presence of ester group and formation of amide bond of Etd-dex conjugate. FT-IR spectrum of Etd (figure 2) showed absorption band at 3300-2500 cm^{-1} (O-H stretching of COOH group), 1406 cm^{-1} (O-H bending of COOH group), 1361 cm^{-1} (C-O bending of COOH group), those confirmed the acidic nature of Etd.

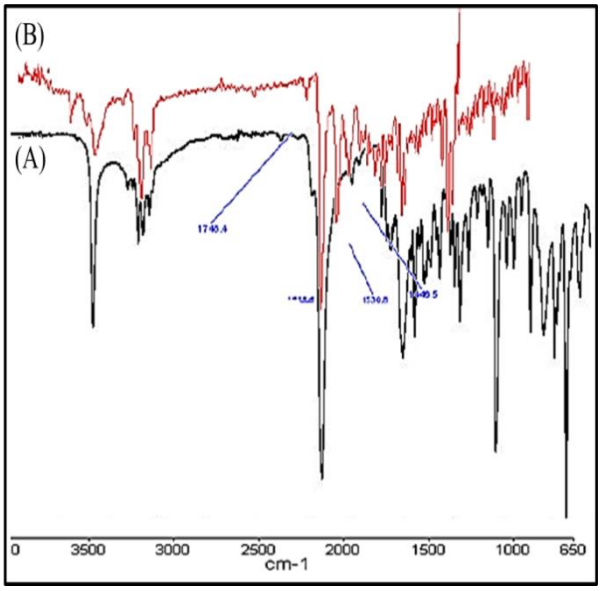

Figure 2. FT-IR spectrum of (A) ETD and (B) ETD-DEX conjugate

Characterization of ETD and ETD-DEX prodrug

Melting point of Etd and Etd-dex prodrug, determined by capillary fusion method were found to be 144-150 ^{0}C and 110 ^{0}C respectively. Difference in the melting points of Etd and Etd-dex prodrug suggested prodrug formation.

Thin layer chromatography of Etd and Etd-dex prodrug was done according to the method described under section 2.2.3.2. The R_f value was determined for the compounds as the average of three readings. The R_f value of Etd and Etd-dex prodrug were found to be 0.56 ± 0.02 and 0.60 respectively, the new R_f value confirmed the synthesis of Etd-dex prodrug with single spot, confirming purity of Etd and Etd-dex prodrug.

R_M value represents lipophilicity of compound, higher the R_M value, higher will be the lipophilicity of the compound. R_M value was determined by reversed phase TLC according to the method described under section 2.2.3.3. The R_M value of Etd and Etd-dex prodrug were found to be -0.122±.006 and -0.116±.0084 respectively, this confirmed the synthesis of Etd-dex prodrug. The result also indicates higher lipophilic character of Etd-dex prodrug when compared to Etd and should traverse the lipoidal membrane at a faster rate than Etd.

SEM of Etd (figure 3) and Etd-dex prodrug shows change in morphology of the drug and prodrug. Difference in the morphology of Etd and Etd-dex prodrug confirming the product formation.

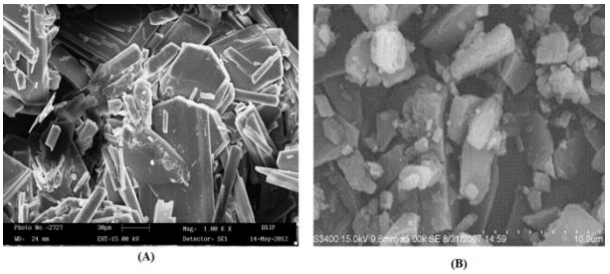

Figure 3. Scanning electron microscopy of Etd and Etd-dex prodrug

Preparation of calibration curve of Etd-dex conjugate in phosphate buffer pH 6.8

Absorption maxima was found 226 nm and absorbance values (mean of 3 determinations ±SD) of the dilutions prepared in the concentration range of 2-16 µg/ml in phosphate buffer pH 6.8. The data was plotted without standard deviation and the calibration curve (figure 4) obtained followed Beer's–Lambert law with r^2 value 0.9984.

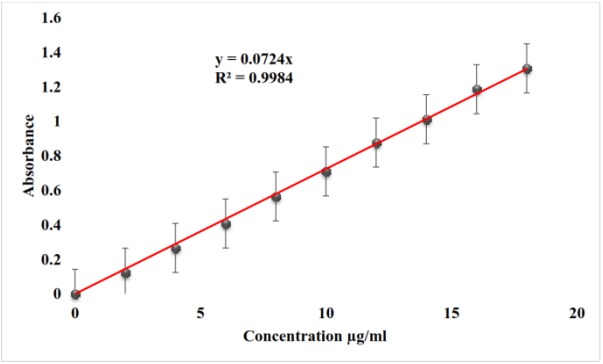

Figure 4. Calibration curve of Etd in phosphate buffer pH 6.8

***In vitro* reversion study of Etd-dex in conjugate at different pH and in presense of fresh rat fecal content**

PREPARATION OF CALIBRATION CURVE OF IN *n*-BUTANOL

Absorption maxima was found 315.5 nm and absorbance values (mean of 3 determinations) of the dilutions prepared in the concentration range of 2-16 microg/ml in n-butanol. The data was plotted without standard deviation and the calibration curve (figure 5) obtained followed Beer's–Lambert law with r^2 value 0.9986.

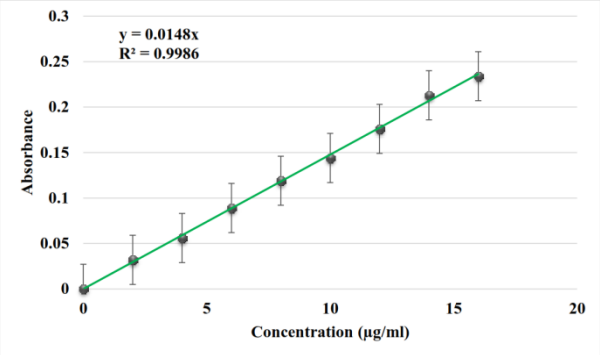

Figure 5. Calibration curve of Etd in *n*-butanol

***In vitro* reversion study of Etd-dex prodrug at different pH and in presense of fresh rat fecal content**

To follow in vitro kinetics, a reversed amount of Etd was utilised. Kinetic studies (Figure 6) revealed that prodrug reversion was nearly non-existent in the gastric (HCl buffer pH 1.2) and cecal (acid phthalate buffer pH 4.0) environments, and only 6.05 and 8.14 percent in the intestinal (phosphate buffer pH 6.8 and 6.8) environments, respectively, over the course of 8 hours, achieving the goal of passing the GIT without any free drug release. Reversion was tested in phosphate buffer pH 6.8 in the presence of 20% w/v fresh rat faeces to confirm the prodrug's intestinal breakdown. During a 48-hour period, the prodrug caused a 59.13 percent reversion of Etd in colonic conditions, according to first order kinetics. The accelerated hydrolysis of the prodrug in the presence of amidase enzyme, generated by colonic microflora, was responsible for the enhanced reversion in the presence of a colonic environment. According to in vitro reversion experiments, the prodrug may bypass the GIT and be converted to Etd in the colon.

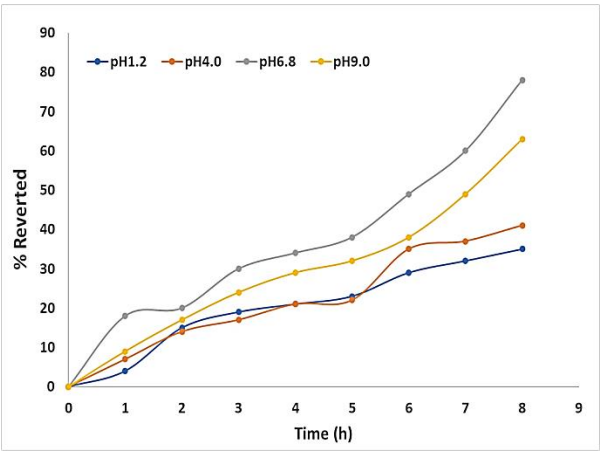

Figure 6. *In vitro* reversion study of Etd-dex prodrug at different pH in presence of fresh rat fecal content at pH 6.8

Ulcerogenicity Study

The ulcerogenic activity of all Etd-dex conjugates was shown to be much lower than that of the parent medication, according to the studies. Etodolac caused ulcers and gastrointestinal problems. Dextran conjugation mitigated the etodolac's gastrointestinal toxicity much more, according to the findings (Figure 7).

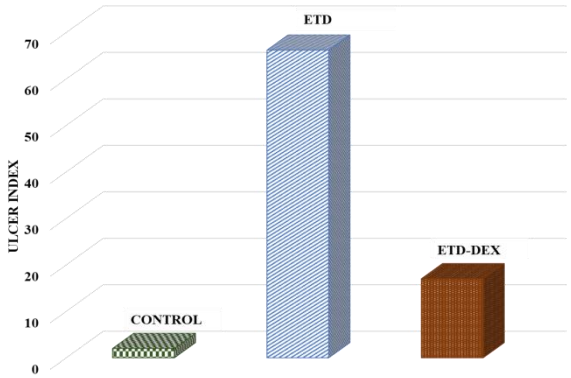

Figure 7. Comparative Ulcer Index of control, Etd and Etd-dextran prodrug

CONCLUSION

The Etd-dex prodrug was successfully synthesised, and spectrum analysis validated the structure. The pharmacological reaction of the prodrug was good. When compared to the parent medication, the prodrugs had higher anti-inflammatory activity and a lower ulcer index. In conclusion, the current research suggests that dextran may be successfully used as a promoter for carboxylic function compounds. Dextran may also be used as a polymeric carrier to achieve colon site specificity due to the presence of enzymes and an alkaline pH in the colon, as well as enhanced physiochemical characteristics and less gastrointestinal side effects, according to the study.

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