

Synergistic Effect of Polymer-Drug Self-Assembly and Hydrotropic Complexation on the Delivery of Ibuprofen

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ABSTRACT

Drug-loaded polymeric nanoconjugate is a valuable drug delivery strategy to enhance the effectiveness of poorly soluble drugs. This study investigates the synergistic effect of polymer-drug self-assembly and hydrotropic complexation, on conjugation efficiency and *in vitro* dissolution kinetics of ibuprofen. Ternary Ibuprofen-DEAE-Dextran-Nicotinamide nanoconjugates were prepared by hydrotropic solubilization and characterized via particle size measurement, zeta potential, conjugation efficiency, Scanning Electron Microscopy (SEM), Fourier Transform InfraRed (FTIR), Differential Scanning Calorimetry (DSC), Thermogravimetric Analysis (TGA), dissolution and drug release kinetics. The formulation of ibuprofen-DEAE-Dextran conjugate reduced the size of ibuprofen (2.87 μm) significantly to 77.92 nm (272-fold) at 0.1% (2.0×10^{-3} mM) DEAE-Dextran concentration. The zeta potential values were relatively low (1.24 to +13.87 mV) indicating low repulsion stabilization. Conjugation efficiency increased to a maximum of 95.68% and particle size of nanoconjugates was in the range 77.92 ± 1.61 to 994.27 ± 91.85 nm. The surface morphologies were spherical. FTIR revealed the formation of an amide via electrostatic, hydrophobic and hydrogen bonding interaction between solubilized ibuprofen and the cationic polymer, DEAE-Dextran. DSC analysis showed that the nanoconjugates exhibited new broad and diffuse peaks. The TGA thermograms exhibited two steps degradation profile. Marked enhancement of drug release was achieved by this method. The mechanism of release was non-Fickian diffusion for lower concentrations of DEAE-Dextran, while super case II was exhibited by higher concentrations. This work shows the formulation of amorphous ibuprofen-DEAE-Dextran nanoconjugates via a combination of polymer-drug self-assembly and hydrotropic solubilization with the potential of improving the delivery of poorly soluble ibuprofen.

Key Words: Ibuprofen, hydrotropic solubilization, nicotinamide, DEAE-Dextran, nanoconjugate

INTRODUCTION

Several new compounds that are being discovered by innovative research and development are highly hydrophobic and poorly soluble. Low solubility poses a myriad of challenges in drug development and this include severely hampering the bioavailability of orally administered dosage formulations

and development of parenteral formulations. Strong organic solvents have been used to improve the solubility of poorly soluble drugs which are unacceptable in practical use¹. In our earlier work, we used a low energy and green process via the drug-polyelectrolyte technique to overcome the low aqueous solubility of ibuprofen².

This time, the use of hydrotrope, specifically nicotinamide, as a solubilizing method to improve the solubility of ibuprofen in combination with the polymer-drug self-assembly technique would be utilized. Hydrotropy is a method used to increase the aqueous solubility of poorly soluble drugs via the addition of a second solute (the hydrotrope)^{3,4}. Nicotinamide aggregates via self-assembly is distinct from the surfactant self-assembly since hydrotropes form planar or open-layer structures distinct from spheroids formed by surfactants^{5,6}. Hydrotropy is superior to other solubilization methods such as surfactant or micellar solubilization⁷. Kim and his co-workers reported that nicotinamide achieves a solubility enhancement of less than 500-fold⁸. In line with using the green process devoid of use of solubilizing toxic solvents in our earlier studies, nicotinamide would be used for its solubilizing property advantage. In this study, nicotinamide was used as the hydrotropic agent in addition to the ibuprofen-polyion nanoconjugate.

Ibuprofen, a Biopharmaceutics Classification System (BCS) class II drug with low solubility and high permeability requires a high loading dose to be effective. There are ongoing research efforts to improve its solubility and ultimately the drug release potentials. In previous studies, we employed different methods to enhance the solubility of ibuprofen^{2,9}. In this study, combination of polymer-drug self-assembly and hydrotropic complexation was explored to form ternary nanoconjugate with enhanced conjugation efficiency and release profiles. Hydrotropic complexation has been reported to result in high water solubility while maintaining hydrophobicity¹⁰. Nicotinamide a non-ionic aromatic hydrotrope was therefore used in addition to the ibuprofen-DEAE-Dextran

nanoconjugate to enhance the solubility and dissolution of ibuprofen. The research intention is to enhance the conjugation efficiency and dissolution properties of ibuprofen by the combined advantages of hydrotropic solubilization and the solubilizing effect of the polymeric carrier.

MATERIALS

Ibuprofen was purchased from Fagron, UK while DEAE-Dextran hydrochloride (molecular weight 500,000 g/mol) and nicotinamide were purchased from Sigma-Aldrich, UK. They were all used as received without further modification. Analytical grade sodium hydroxide was used.

METHODS

Preparation of Ibuprofen-DEAE-Dextran nanoconjugates by hydrotropic solubilization

The concentrations of ibuprofen, DEAE-Dextran and Ibuprofen-DEAE-Dextran ratio are presented in Table 1. Ibuprofen weighing 200 mg was dissolved in 10 mL of 10% w/v nicotinamide solution, made up to 50 mL with 0.1% pluronic solution and heated up to 60 °C on a hot plate (Jenway 1000 hotplate and stirrer, UK). It was added drop-wisely into equal volume of the varying concentrations of DEAE-Dextran in 0.1% w/v pluronic solution at the same temperature under continuous magnetic stirring for 10 min (Jenway 1000 hotplate and stirrer). The pH of the drug polymer complex mixture was adjusted to pH 6.0 (Mettler Toledo pH meter) with 1 M NaOH¹¹. The Ibuprofen-DEAE-Dextran nanoconjugate prepared were dialysed and labelled as IbNic-control, IbD1Nic, IbD2Nic, IbD3Nic, IbD4Nic and IbD5Nic respectively. The nanosuspension formed was kept at room temperature prior to analysis.

Table 1 Composition of ibuprofen-DEAE-Dextran nicotinamide nanoconjugates

Formulation	Drug-Polymer Ratio	Ibuprofen (%w/v)	DEAE-Dextran (%w/v)
IbNic-control	1:0	0.2	-
IbD1Nic	1:0.5	0.2	0.1
IbD2Nic	1:1	0.2	0.2
IbD3Nic	1:2	0.2	0.4
IbD4Nic	1:4	0.2	0.8
IbD5Nic	1:8	0.2	1.6

Determination of particle size and zeta potential of nanoconjugates

The mean particle size and zeta potential of the nanoconjugates were determined by ZetaPlus Zeta Potential Analyser (Brookhaven Instruments Corporation). Samples were diluted appropriately with distilled water and injected into the sample cell. Particle size measurements were carried out at a scaling angle of 90° and a temperature of 25 °C. Apparent z-average hydrodynamic diameter and polydispersity index (PI) were obtained. Zeta potential was determined by measuring the electrophoretic mobility of the dispersed particles in a charged field. Zeta potential measurements were done in aqueous solutions at 25 °C and the electric field strength was about 14.95 V/cm. All measurements of individual samples were a mean of six determinations for particle size and 10 runs for zeta potential.

Drug conjugation capacity/efficiency

Conjugation efficiency (equation 1) is the mass percentage of ibuprofen that forms the ibuprofen complex relative to the initial amount of ibuprofen added. The amount of ibuprofen that forms the ibuprofen complex was calculated as the difference between the amount of ibuprofen added and the amount of non-conjugated ibuprofen in the supernatant after centrifugation. The ibuprofen concentration was measured by UV (ThermoFischer Evolution 60 UV Spectrophotometer, UK) after passing it through 0.45 µm filter (Sartorius, Germany) at 264 nm wavelength¹². All measurements were an average of six determinations.

$$\text{Conjugation efficiency} = \frac{M_0 - M_i}{M_0} * 100\% \quad (1)$$

Where M_0 is the initial amount of ibuprofen added and M_i is the amount of non-conjugated ibuprofen in the supernatant after centrifugation.

Morphology and size: Scanning electron microscopy (SEM)

The surface characteristics of the reference compound and nanoconjugates were examined by Carl Zeiss SEM EVO High Definition 15 Scanning Electron Microscope (Carl Zeiss, Germany) using variable pressure technology

at low voltages with beam deceleration and high definition backscattered electron (BSE) imaging. The samples were mounted on double sided carbon tabs that were previously secured to aluminium stubs and then analysed at different magnifications and a pressure of 10 Pa. The accelerating voltage was 10 KV with probe current of 400 pA. The particle sizes of the reference compounds and the nanoconjugate images were determined using the SmartTiff software.

Fourier transform infra-red (FTIR)

FTIR was conducted using Perkin-Elmer Precisely Spectrum One FTIR Spectrometer and a Universal ATR Sampling Accessory (Perkin Elmer, USA). The samples were mounted directly on the diamond surface and the arm was placed over it by applying enough pressure in the range of 100 to 120 units. The spectrum was recorded in the wavelength region of 4000 to 650 cm^{-1} . All spectra were then collected at an average of 16 scans at a resolution of 4 cm^{-1} . All measurements were taken in replicates of four determinations.

Differential scanning calorimetry (DSC)

DSC was performed using Perkin Elmer Precisely Jade DSC machine with a Perkin Elmer Intracooler SP cooling Accessory (Perkin Elmer, USA) to study the thermal behaviour of the pure ibuprofen, DEAE-Dextran, physical mixtures and ibuprofen nanoconjugates. The sample sizes in the range of 8 to 10 mg were heated in hermetically sealed aluminium pans under nitrogen flow (40mL/min) using a scanning rate of 20 °C/min from -50 to 300 °C. Empty aluminium pan was used as a reference. Indium was used as the standard reference material to calibrate the DSC instrument. All measurements were an average of four determinations and expressed as mean $\pm$ S.D.

Thermogravimetric analysis (TGA)

TGA was performed using Perkin Elmer Pyris 1 Thermogravimetric Analyser (Perkin Elmer, USA) to monitor the mass of the pure starting materials and nanoconjugates as a function of temperature or time as the sample specimen is subjected to a controlled temperature program at atmospheric pressure. The weight of the empty reference pan placed in the crucible was zeroed and then removed. Samples of known weight in the range of 18 to 25 mg were placed

in aluminium pans and measurements performed at a scanning rate of 10 °C/min in the range of 25 to 500 °C. All measurements were an average of four determinations and expressed as mean $\pm$ S.D.

Dissolution and drug release studies

Calibration curve (not shown) was constructed by using pure ibuprofen reference standard (secondary standard) dissolved in buffer solution (pH 7.4) within the concentration range 1.56 and 50 $\mu\text{g/mL}$ (7.56 to 242.39 mM). The correlation was linear ($r^2 = 0.9953$) and the measurements at six levels of concentration were reproducible with limit of quantification (LOQ = 10 $\times$ standard error of the intercept/slope) of 0.37 $\mu\text{g/mL}$ (1.79 mM). The concentrations of ibuprofen were derived from this calibration curve. Thereafter the dissolution profile of the ibuprofen-loaded nanoconjugates was studied using the USP dissolution method¹³. 90 mL of the ibuprofen-DEAE-Dextran nanoconjugates containing 1 mg/mL ibuprofen was put in a dialysis tubing (Visking Medicell Ltd London UK with diameter 18/32" and exclusion size 12000 to 14000 Da). Both ends were tied. The dialysis tubing was suspended in 900 mL of PBS pH 7.4, rotated at 50 rpm and maintained at 37 ± 0.5 °C using Pharma Test PT DT7 USP Apparatus II Dissolution Test Instrument - paddle method (Pharma Test Ltd, Germany). At pre-determined time intervals 10, 20, 30, 60 min, 1, 2, 4, 6 and 24 h, 5 mL aliquots were withdrawn and replaced with 5 mL PBS pH 7.4. Drug concentrations were quantified using UV (ThermoFischer Evolution 60 UV-Visible Spectrophotometer, UK) after filtering through 0.45 μm filter (Sartorius, Germany) at 264 nm. All measurements were an average of four determinations and expressed as mean $\pm$ S.D. A calibration curve was produced using a series of dilution of reference standard ibuprofen in PBS pH 7.4 and analysed by UV at 264 nm. The calibration curve was linear at concentrations between 1.56 and 50 $\mu\text{g/mL}$ with R^2 value of 0.99. The absorbance values obtained from the drug release of the nanoconjugates were correlated with the calibration curve and the amount of ibuprofen released was determined.

Drug release kinetics

Data obtained from *in vitro* release studies were fitted to various kinetic equations. The

kinetic models used are zero order, first order and Higuchi equation.

The zero-order rate equation (2) describes the systems where the drug release rate is independent of its concentration¹³. The cumulative % drug release vs. time plot is made.

$$C = K_0 t \quad (2)$$

Where k_0 is zero order rate constant expressed in units of concentration/time and t is the time.

The first order rate equation (3) describes the release from the systems where release rate is concentration dependent¹⁴. The log cumulative % drug release vs. time plot is made.

$$\log C = \log C_0 - Kt/2.303 \quad (3)$$

Where C_0 is the initial concentration of drug and K is first order constant.

Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion: equation (4)¹⁵. The cumulative % drug release vs. square root of time is made.

$$Q = Kt^{1/2} \quad (4)$$

Where Q is the cumulative amount of drug released and K , is the constant and it reflects the design variables of the system.

Korsemeyer *et al.* derived a simple relationship which described drug release from a polymeric system: equation (5). To find out the mechanism of drug release, first 60 % drug release data was fitted in Korsemeyer-Peppas model:

$$M_t/M_\infty = Kt^n \quad (5)$$

Where M_t/M_∞ is a fraction of drug released at time t , K is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms¹⁶. The log cumulative % drug release vs. log time plot is made. The criterion for selecting the appropriate model is the highest R^2 value which indicates linearity of dissolution data¹⁷.

Similarity factors

The similarity fit factor denoted f_2 was used to compare the dissolution profiles of the drug–

polymer conjugates (test) and ibuprofen control (reference). The similarity f_2 factor is defined by equation (6) proposed by Moore and Flanner¹⁸:

$$f_2 = 50 \log \left\{ \left(1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right)^{-0.5} \times 100 \right\} \quad (6)$$

Where n is the number of dissolution sample times, and R_t and T_t are the individual or mean percent dissolved at each time point, t , for the reference and test dissolution profiles, respectively. The f_2 value greater than 50 suggests that the two profiles are similar. The f_2 value of 100 suggests that the test and the reference profiles are identical and as the value becomes smaller the dissimilarity between release profiles increases¹⁹.

Statistical analysis

Quantitative data are presented as mean $\pm$ standard deviation. The significance of the differences between means was assessed using Analysis of Variance (ANOVA) and Post hoc Tukey Test with a statistical significance level set at $p < 0.05$ using IBM SPSS (Statistical Package for Social Science) 20.

RESULTS AND DISCUSSION

Hydrotropic complexation was carried out to solubilize ibuprofen using 10% w/v nicotinamide. The research intention is to enhance the solubility of ibuprofen by the combined advantage of hydrotropic solubilization and the solubilization effect of the polymeric carrier. Hydrotropic agents have been reported to enhance the aqueous solubility of various poorly water-soluble compounds due to the presence of large amount of additives such as sodium benzoate, sodium-o-hydroxy benzoate, sodium-p-hydroxy benzoate, sodium salicylate, urea, nicotinamide, sodium citrate and sodium

acetate²⁰. They also increase the number of hydrogen bridges in the water clusters making the water more hydrophobic, therefore a better solvent for the poorly soluble drug or due to change in solvent character known as hydrotrope solubilization phenomenon²¹. Ahuja and his co-workers prepared urea with nicotinamide as hydrotrope in varied proportions by hydrotropy solid dispersion method to enhance the dissolution of rofecoxib²².

Particle size, polydispersity index and zeta potential

The particle size of processed ibuprofen without polymer which served as the control was 2.87 μm as earlier reported in our studies²³. Hydrotropic complexation with nicotinamide also produced nanoconjugates at all concentrations of DEAE-Dextran used. The nanoconjugate sizes ranged from 77.92 to 994.27 nm and the size increased with increase in DEAE-Dextran concentrations (shown in Figure 1) with the solubility enhancement of about 272-fold (77.92 nm). Sanghvi *et al.*²⁴ have reported the use of nicotinamide as potent solubility enhancing agent for poorly soluble drugs. They reported significant improvement in solubility up to 4000-fold (Benzophenyl urea derivative) with 20% nicotinamide however the effect on particle size was not investigated. The only NSAID on the list of the drugs they investigated was ketoprofen with solubility enhancement of 12-fold. The concentration of nicotinamide used in this study was based on the preliminary study which showed that the critical micelle concentration (cmc) of nicotinamide is 10% w/v, it was opined that higher concentrations could lead to self-association which could interfere with the conjugation process.

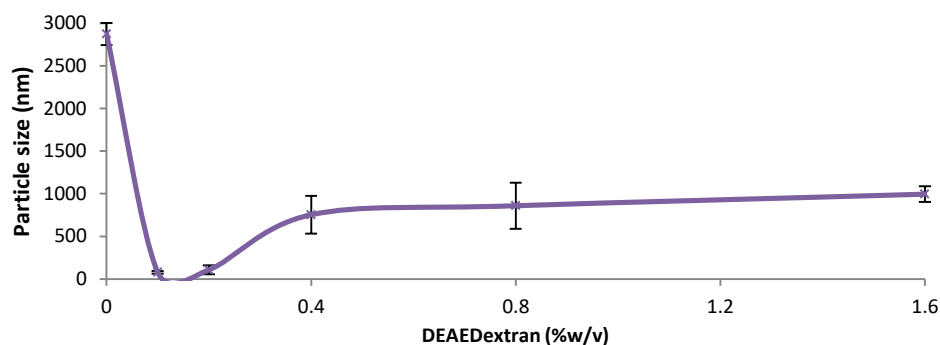


Figure 1: Effect of DEAE-Dextran concentration on particle sizes of the drug-polymer conjugates.

The polydispersity index (PDI) of ibuprofen control was 0.67 (Table 2) which indicated a broad and non-homogeneous size distribution. The PDI of IbDNic nanoconjugates ranged from 0.23 to 0.55 which indicated a net medium homogeneous size distribution. This suggests that the nanoconjugates exhibited

semi homogenous size distribution which may translate to medium stabilization of the particles formed. However, a PDI of 0.23 at DEAE-Dextran concentration of 3.2×10^{-2} mM suggested narrow particle size distribution and high homogeneity.

Table 2: Particle size, polydispersity index and zeta potential of ibuprofen-DEAE-Dextran nanoconjugates. Each value represents mean $\pm$ SD (n = 6).

Formulation	Ibuprofen (%w/v)	DEAE-Dextran (%w/v)	Particle size (nm)	Polydispersity Index	Zeta Potential (mV)
IbNic-control	0.2	-	2872.12 $\pm$ 128.9	0.67 $\pm$ 0.08	-7.251 $\pm$ 1.3
IbD1Nic	0.2	0.1	77.92 $\pm$ 1.61	0.48 $\pm$ 0.03	1.24 $\pm$ 0.42
IbD2Nic	0.2	0.2	107.75 $\pm$ 5.28	0.56 $\pm$ 0.09	2.23 $\pm$ 0.59
IbD3Nic	0.2	0.4	753.12 $\pm$ 22.19	0.50 $\pm$ 0.09	4.95 $\pm$ 0.26
IbD4Nic	0.2	0.8	858.47 $\pm$ 27.21	0.55 $\pm$ 0.13	13.87 $\pm$ 0.23
IbD5Nic	0.2	1.6	994.27 $\pm$ 91.85	0.23 $\pm$ 0.02	2.84 $\pm$ 0.18

The zeta potential of the ibuprofen/DEAE-Dextran nanoconjugates increased from -7.251 mV in the control batch to steady maximum value of +13.87 mV as presented in Table 2. The negative zeta potential in the ibuprofen control indicates electrostatic repulsion between ibuprofen molecules and therefore higher physical stability of the colloidal suspension in the absence of DEAE-Dextran. The positive values of zeta potentials suggest surface modification of the nanoparticles by the cationic DEAE-Dextran. It was noted that zeta potential in the hydrotropic complexation

technique tended to reduce towards neutrality after attaining the maximum value (Figure 2) probably because of aggregation of the nanoconjugates which may occur when the particles overcome the energy barrier of electrostatic repulsion and approach each other to form bigger aggregates. The values of zeta potential observed in this study were relatively low (1.24 to +13.87 mV) indicating low repulsion stabilization probably because stabilization of the nanoconjugates is by steric effect rather than electrostatic repulsion as reported by Plakkot *et al*²⁵.

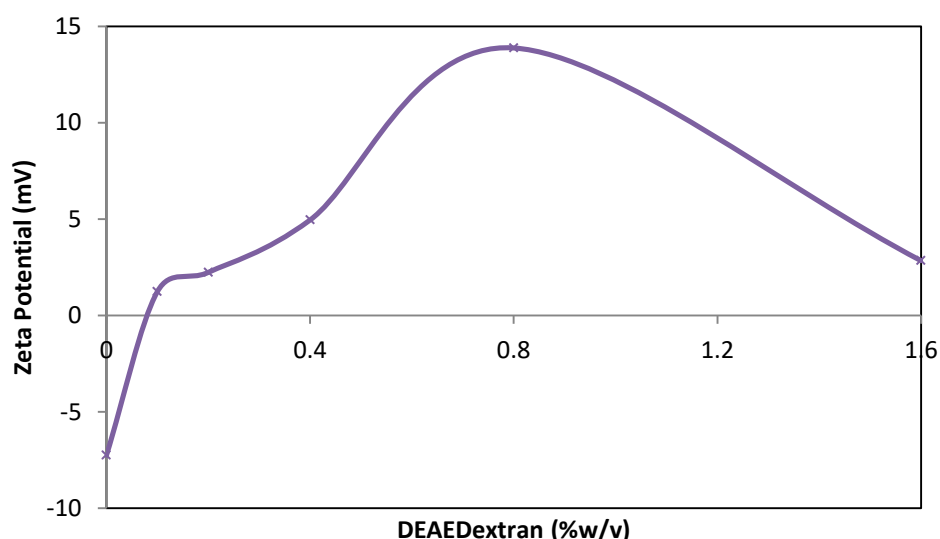


Figure 2: Effect of DEAE-Dextran on zeta potential measurements of drug-polymer conjugates.

Drug conjugation efficiency

The efficiency of attaching drugs to the polymer carrier is very important for the success of polymer therapeutics. It is desirable to achieve higher conjugation efficiency for clinical applications. The conjugation efficiency of IbDNic conjugates was in the range of 95.48 to 95.68%. This was higher than the findings of Jiang *et al.* which stated a maximum entrapment efficiency of 72.20% for ibuprofen-DEAE-Dextran complex¹¹. It appeared that the concentration of DEAE-Dextran did not affect the conjugation efficiency. The conjugation efficiency was

relatively constant, thus independent of DEAE-Dextran concentration.

Morphology and size – Scanning electron microscopy

The surface morphology of IbDNic conjugates were single and spherical in Figure A to 3E while the control in Figure 3F were rectangular in shape. The particle sizes increased with increasing concentration of DEAE-Dextran in the range of 77.52 to 162.7 nm as measured on the images. The values of the particle sizes were smaller when compared to the particle size analyzer measurements.

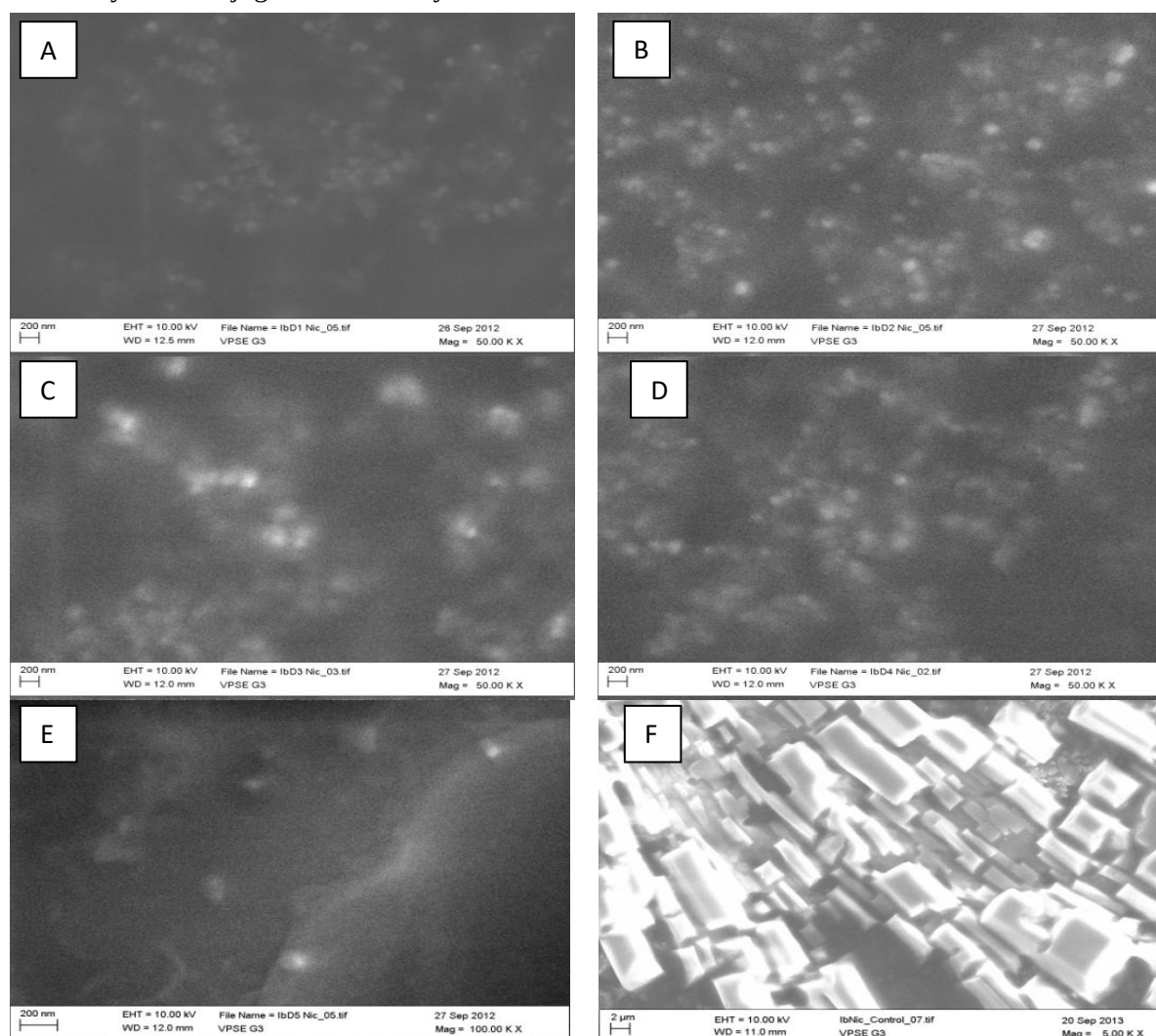


Figure 3 Scanning electron micrographs of ibuprofen-DEAE-Dextran nicotinamide nanoconjugates (A) IbD1Nic, (B) IbD2Nic, (C) IbD3Nic, (D) IbD4Nic, (E) IbD5Nic and (F) IbNic-control.

Fourier Transform Infrared Spectroscopy

Ibuprofen/DEAE-Dextran nanoconjugates prepared by hydrotropic complexation technique exhibited three peaks at 3327 to

3312 cm^{-1} ; 2149 to 2090 cm^{-1} and 1635 cm^{-1} corresponding to hydrogen bonding, transition metal carbonyls (2100 to 1800 cm^{-1}) and

amide respectively (Figure 4). The disappearance of the carbonyl peak also suggests its involvement in electrostatic

interaction with the DEAE-Dextran. The hydrogen bonding and formation of amide was evident in the spectra.

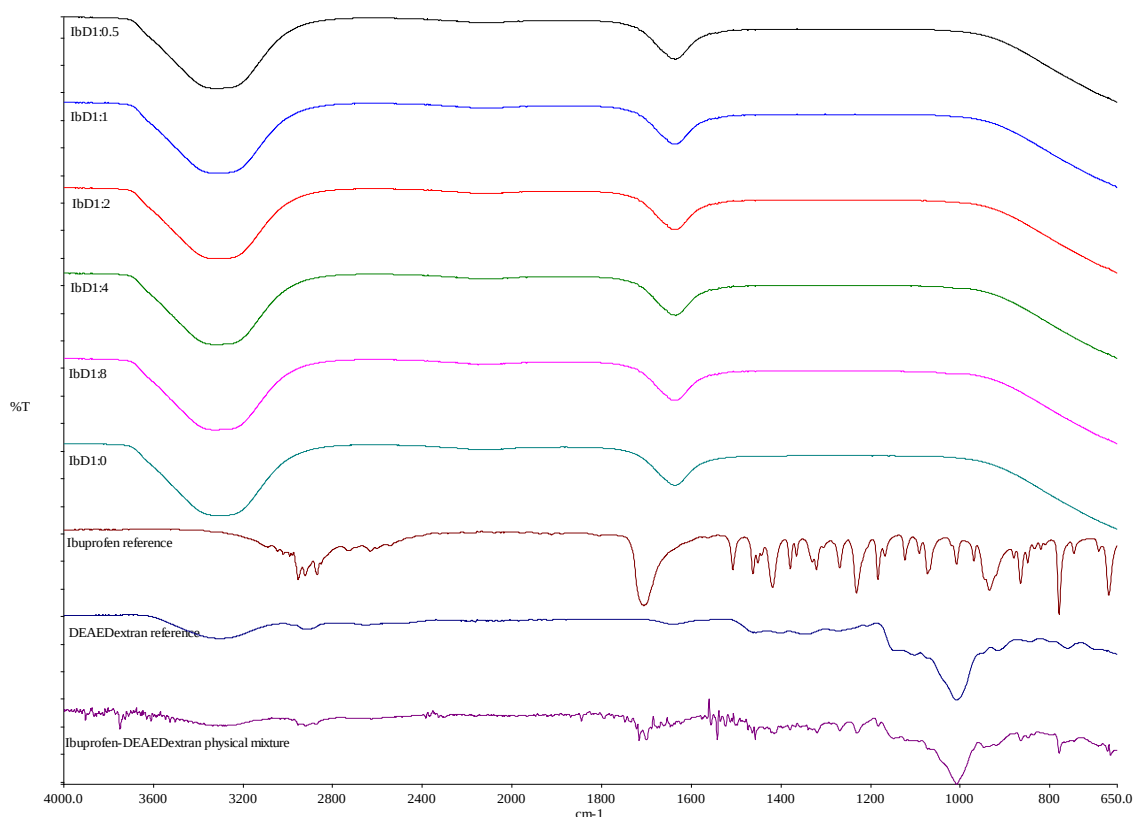


Figure 4 The FTIR spectra of ibuprofen-DEAE-Dextran nicotinamide nanoconjugates, ibuprofen control, ibuprofen-reference, DEAE-Dextran-reference and ibuprofen-DEAE-Dextran physical mixture.

Differential scanning calorimetry (DSC)

The DSC thermograms of the nanoconjugates obtained from the hydrotropic complexation technique exhibited three peaks at ibuprofen/DEAE-Dextran weight ratios 1:0.5; 1:1 and 1:4 while other weight ratios studied exhibited only two peaks as presented in Figure 5. The first peak exhibited two minima values of 7.34 °C and 3.62 °C at ibuprofen/DEAE-Dextran weight ratio 1:0.5 and 1:2 respectively suggesting formation of multiple complexes. The second peak which was assigned to melting point of ibuprofen decreased to a minimum value of 64.67 °C at ibuprofen/DEAE-Dextran ratio of 1:0.5 beyond which it increased steadily. It was opined that lower concentration of DEAE-

Dextran was required for complexation in this technique and the lower melting peak for ibuprofen indicates the amorphous state of the nanoconjugates formed. The absence of ibuprofen peaks at weight ratios 1:2 and 1:8 may indicate the formation of eutectic mixture as well as formation of multiple complexes. The melting point of nicotinamide was reported to be in the range of 128 to 131 °C²⁶. The third peak did not vary significantly with increase in concentration of DEAE-Dextran. The thermal decomposition peak of ibuprofen at 237.51 °C disappeared in all the IbDNic nanoconjugates however the ibuprofen melting peak exhibited higher values indicating isothermal stability of the nanoconjugates.

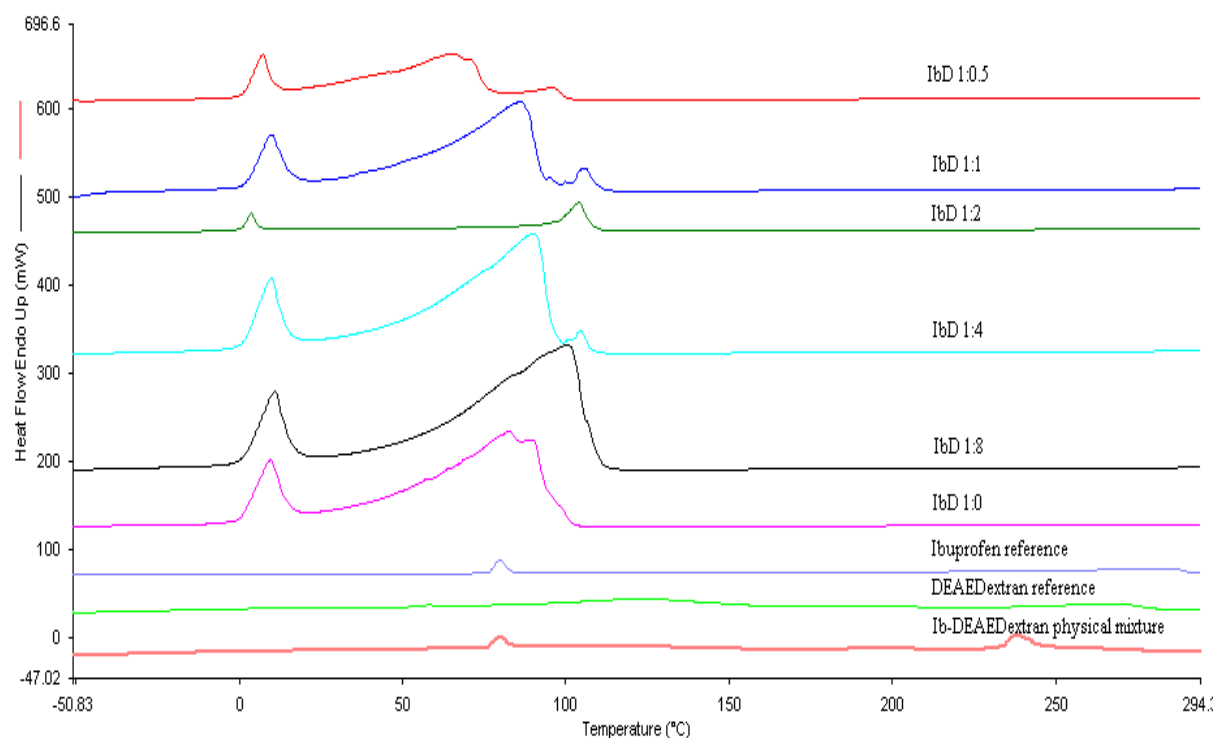


Figure 1 DSC thermograms of ibuprofen-DEAE-Dextran nicotinamide nanoconjugates, ibuprofen control, pure ibuprofen, DEAE-Dextran and physical mixture of ibuprofen and DEAE-Dextran.

Thermogravimetric analysis (TGA)

The TGA thermograms of nanoconjugates obtained from the hydrotropic complexation technique are presented in Figure 6. The IbDNic nanoconjugates showed one step of weight loss at temperatures below 150 °C

which indicated weight loss due to free water in the conjugates²⁷. The step of inflection decreased with increasing concentration of DEAE-Dextran. The decomposition step was absent suggesting isothermal stability of the nanoconjugates.

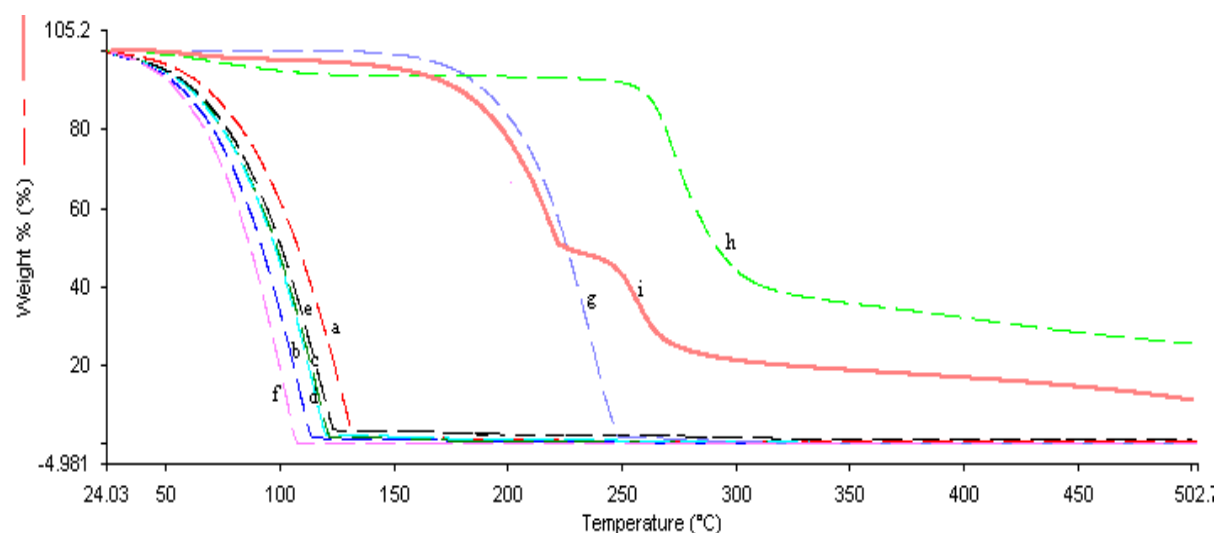


Figure 6 TGA thermograms of ibuprofen-DEAE-Dextran conjugates (a) IbD1Nic, (b) IbD2Nic, (c) IbD3Nic, (d) IbD4Nic, (e) IbD5Nic, (f) IbNic-control, (g) ibuprofen-reference, (h) DEAE-Dextran-reference and (i) ibuprofen-DEAE-Dextran physical mixture.

Drug release studies

The release of Ibuprofen from IbDNic conjugates was in the range of 86.53 to 99.72%, which was significantly higher ($p < 0.05$) than the release by ibuprofen control (30.72%) presented in Figure 7. The order of release of ibuprofen from IbDNic conjugates at 24 h is as follows: IbD1Nic > IbD2Nic > IbD4Nic > IbD5Nic > IbD3Nic > IbNic-control. Increasing concentration of DEAE-Dextran significantly increased ($p < 0.05$, $n = 20$) the release of ibuprofen from the

conjugate. Nicotinamide acts as water structure disruptors by increasing the solubility which destroys clusters of associated water molecules releasing water of solvation²⁸. It was opined that the structure disruptors (nicotinamide) prevented self aggregation of ibuprofen which led to increase in solubility of ibuprofen. In a similar study, Ahuja *et al.* reported that higher drug release of rofecoxib was observed with urea and nicotinamide systems via their ability to destroy water structure and complex formation²² supporting the findings in this study.

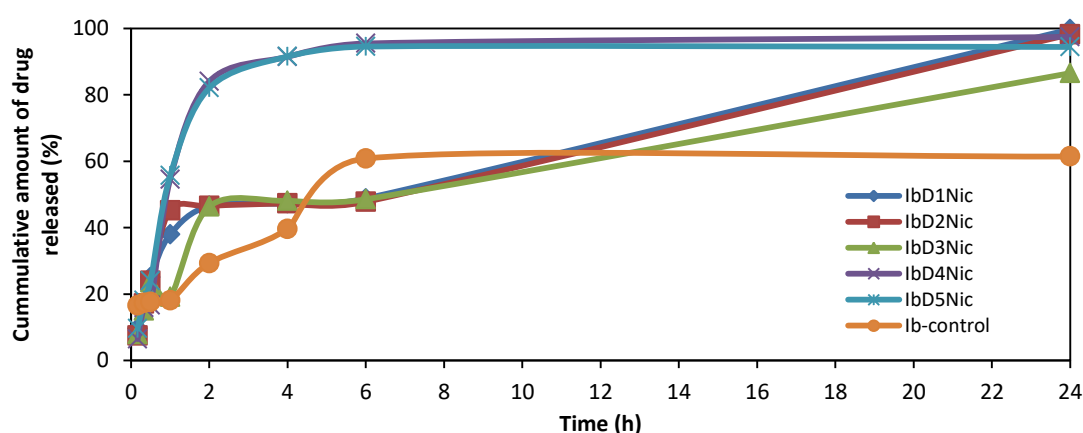


Figure 7 Release profile of ibuprofen from DEAE-Dextran nicotinamide nanoconjugates. Each data point represents mean $\pm$ SD ($n = 4$).

Drug release kinetics

The data were best fitted with the Higuchi kinetic models for IbD1Nic, IbD2Nic and IbD3Nic conjugates (lower concentrations of DEAE-Dextran) while IbD4Nic, IbD5Nic and ibuprofen control were best fitted with Korsemeyer-Peppas kinetic models. The n

values presented in Table 3 indicated that for IbD1Nic, IbD2Nic and IbD3Nic conjugates, the release mechanism was anomalous (non Fickian) diffusion where diffusion exponent (n) is $0.43 < n < 0.85$, while for IbD4Nic and IbD5Nic a Super Case II transport mechanism (where $n > 0.85$) was exhibited.

Table 3 Regression coefficient (r) values of different kinetic models and diffusion exponent (n) of Korsemeyer-Peppas models for the release of ibuprofen from DEAE-Dextran nicotinamide nanoconjugates.

Formulation	Zero order	First Order	Higuchi	Korsemeyer-Peppas	
	R^2	R^2	R^2	R^2	n
IbNic-control (IbD 1:0)	0.61	0.56	0.80	0.88	0.32
IbD1Nic (IbD 1:0.5)	0.86	0.53	0.94	0.86	0.44
IbD2Nic (IbD 1:1)	0.81	0.45	0.90	0.79	0.48
IbD3Nic (IbD 1:2)	0.79	0.51	0.92	0.88	0.49
IbD4Nic (IbD 1:4)	0.35	0.26	0.59	0.95	1.15
IbD5Nic (IbD 1:8)	0.34	0.27	0.58	0.99	0.98

Similarity factor

The f_2 similarity factor was used to compare the drug release profiles of processed ibuprofen control (reference) with ibuprofen-DEAE-Dextran nanoconjugates (tests) and the

CONCLUSION

Ibuprofen-polymer ternary nanoconjugates have been successfully prepared from ibuprofen, DEAE-Dextran and nicotinamide using the combination of polymer-drug self-assembly and hydrotropic techniques. The combined techniques were devoid of toxic solvents. The combined method showed great potential in improving the delivery of ibuprofen.

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