Research Article

Enhancement of the *in-vitro* Controlled-Release of Nimesulide from Alginate-based Matrix Devices

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ABSTRACT

The goal of this paper is to develop an alginate-based matrix device to control the release rate of a very poorly soluble drug such as nimesulide for 12h. The molecular weight and degree of substitution of the polymer were determined by capillary viscometry and conductimetry, respectively. The compaction behavior was determined using the Heckel and Leuenberger analyses. The intrinsic dissolution was conducted on an Apparatus II dissolutor using a pH 6.8 phosphate buffer. Matrixes containing 100 mg of nimesulide and different levels of sodium alginate and electrolytes or surfactants were made on a single punch tablet machine. Matrixes containing benzalconium chloride at levels >300mg improved the solubility and the release profile of nimesulide. Conversely, sorbitan laurate, sodium lauryl sulfate and electrolytes such as sodium chloride failed to improve the release rate of nimesulide from the hydrophilic matrix. The release characteristics of nimesulide from these matrixes were best described by the Korschmeyer-Peppas model. The alginate-based system containing benzalconium chloride has a potential to improve and control the release characteristics of nimesulide within 12h.

Keywords: Nimesulide, Sodium alginate, Surfactant, Electrolytes, Modified release.

INTRODUCTION

Nimesulide is an anti-inflammatory non-steroidal drug (NSAID), which is used in the treatment of articular inflammatory conditions associated with rheumatoid arthritis. It has a better therapeutic index, less gastro-lessivity and better tolerability with respect to other NSAIDs due to its sulfanilide moiety[1] However, it has to be administered twice a day due to its short half-life (1.8-4.7 h) increasing the incidence of gastric side effects. The usual oral dose in adults ranges from 100 to 200 mg[2]. For this reason, a modified release system is needed to achieve an optimal therapy, improve patient compliance and safety, reducing dose dumping, plasma fluctuations and the incidence of side effects. Due to its poor solubility, few approaches have been attempted to develop a controlled release nimesulide. One study employs coacervation to encapsulate nimesulide and tizanidine with a release extent of 10 h, but encapsulation efficiencies below 91%.[3] Another study reports the production of PLA microspheres with nimesulide using the solvent-evaporation method rendering an encapsulation efficiency of 70%.[4] A solid dispersion and complexation with β-cyclodextrins has also been attempted to increase slightly its solubility.[5,6] However, these products exhibit safety and scale-up issues due to the disposition of residual solvents. Therefore, it is imperative to look for alternative devices such as hydrophilic matrixes including sodium alginate to control the release of nimesulide for 12h.

A hydrophilic matrix is composed of a hydrophilic polymer, an active ingredient and other excipients homogeneously distributed in a three dimensional network. Several factors affect the drug release from a hydrophilic swelling matrix. These factors include drug solubility, polymer swelling and erosion, drug dissolution/diffusion characteristics, distribution of drug within the polymer matrix, proportion and geometry of the system and the viscoelastic properties of the polymer and porosity of the matrix. In swelling ionic polymers the swelling behavior depends on the number of intermolecular bonds per volume of polymer and on the ionic strength of the release medium.[7]

Sodium alginate is a linear anionic copolymer derived from the β-D(1→4)-mannuronic (M) and α (1→4)-L-guluronic (G) acids. It is composed of homopolymeric blocks of consecutive G or M-residues (poly G and poly M, respectively) and heteropolymeric blocks of alternating M and G (MGMGM) chains.[8]

On the other hand, alginic acid forms gelling networks via complexation particularly with calcium. This phenomenon is known as ionotropic nucleation where pairs of helical chains are packed with the calcium ions located between them.[9] This is explained by the "zigzag" structure of polyguluronic acid (GG-blocks), whose carboxylate and hydroxyl functional groups (negative charged regions) can form coordination sites to accommodate the Ca^{2+} ion, through dimerization of the polyguluronate sequences. However, this Ca-alginate complex suffer from a poor stability in simulated gastric fluid (SGF), simulated intestinal fluid (SIF) and 0.1 M NaCl solution leading to uncontrolled release of drugs. For this reason, it is worthwhile to consider sodium alginate as an alternative modified release carrier for drugs.[10] Sodium alginate is ideal to modulate drug control release since it is insoluble in the gastric fluid preventing the release of the drug in the stomach. Therefore, drug release occurs only after

reaching the pH region of the intestinal tract, in which sodium alginate is converted into a viscous soluble eroding gel.

This paper discusses the effect of sodium alginate on the release properties of nimesulide which is a very water insoluble drug. Thus, hydrophilic matrixes composed of sodium alginate, nimesulide, surfactants and electrolytes were prepared by a wetting method followed by tableting to achieve a 12 h controlled release dosage form. This provides a lower but controlled drug concentration over an extended period of time (12 h). The resulting dissolution profiles and release kinetics of the matrices were also assessed.

MATERIALS AND METHODS

Chemicals and Reagents

Nimesulide (lot 241300493002) was donated by Laproff Laboratories (Medellin, Columbia). Sodium alginate (lot 2366-500) was purchased from Danisco ingredients (Copenhagen, Denmark). Benzalconium chloride (lot, 10309) was obtained from Protokimica (Medellin, Columbia). Sodium lauryl sulfate (lot 128K0039) and sorbitan laurate (Span® 20, lot 094K0089) were obtained from Sigma-Aldrich (St. Lois, USA).

Fourier Transforms Infrared Characterization (FT-IR)

The analysis was conducted on a Perkin-Elmer spectrophotometer (Perkin Elmer, CA, USA) equipped with the Spectra software (Spectrum BX, vs. 5.3.1, CA, USA). Spectra were obtained between 400 and 4000 cm^{-1} and the resolution, interval length and number of scans employed were 16, 2.0 and 16 cm^{-1}, respectively.

Differential Scanning Calorimetry Analysis (DSC)

Samples were analyzed between 20 to 480 °C to investigate the occurrence of enthalpy variations, resulting from physical or chemical changes. The thermograms were obtained on a Differential Calorimeter (DSC 200, NETZSCH-Feinmahltechnik GmbH, Germany) under a dynamic air atmosphere. Approximately, 3 mg of sample was heated at 10 °C/min at a heat flow of 10 mL/min in the capped aluminum pan.

Intrinsic Viscosity and Molecular Weight Analyses

It was determined by capillary viscometry dissolving sodium alginate in 0.1 M sodium chloride solution to render final concentrations of 0.2, 0.4 and 1 w/v%. Samples were sonicated for 1h before testing. A Canon-Fenske capillary viscometer was immersed in a water bath, equipped with a temperature controller set at 20 °C. Approximately, 8 mL of solution was employed per sample and the elution times measured.

The intrinsic viscosity [η] and the viscosity average molecular weight were obtained from equations 1 and 2, respectively:

$$\left[\frac{\left(\frac{t}{to}\right)-1}{C}\right] = [\eta] + kC \qquad (1)$$

$$[\eta] = 1.228\text{x}10^{-5} * M_w{}^{0.963} \qquad (2)$$

where, t and to are the efflux times of the alginate solution and the solvent, respectively. Five measurements were made for each solution and the resulting averages were used to calculate the relative viscosities.

Degree of Substitution (DS)

It was determined by a back acid-base conductometric titration of the corresponding free carboxylate groups with respect to the pure alginic acid. Approximately, 0.1g of sample was dissolved in 100 mL of 0.1M of NaOH. Subsequently, it was back titrated with 0.35 M HCl. The degree of substitution was calculated from the following equation:

$$DS = \frac{\#\ of\ COOH\ moles\ in\ sodium\ alginate}{\#\ of\ COOH\ moles\ in\ unsubstituted\ alginic\ acid} \qquad (3)$$

Where, the # of COOH groups = number of moles of NaOH – moles of titrated HCl.

Powder Properties

The true density (ρ_{true}) was measured on ~2 g of sample employing a Helium pycnometer (AccupycII 1340, Micromeritics, USA). Flow rate was determined on ~20 g of powder by recording the time taken to pass freely through a glass funnel (13.1 mm diameter). Moisture content was determined on a Shimadzu infrared moisture analyzer (MOC63U, MA, USA) loaded with ~0.5 g of sample and operated at 110 °C for 10 min. Likewise, powder compressibility and the particle size distribution were obtained on 20 g of sample employing an AutoTap® and RoTap® sieve shaker for 10 minutes as reported previously.[11]

Tableting Properties

Biconvex compacts of ~200 mg were manufactured on an instrumented single station tablet press (Compac 060804, Indemec, Columbia) equipped with a 6.5-mm diameter flat-faced punches and die tooling at a dwell time of 1 s at compression pressures from 10 to 300 MPa. Compression forces were measured directly from a load cell (LCGD-10K, Omega Engineering, Inc, Stanford, CT). The weight, diameter and height of the resulting compacts were then measured and fitted to the Heckel and Leuenberger models as reported previously.[12]

Nimesulide Release Studies

Approximately, 100 mg of nimesulide, surfactant (50-400 mg) and sodium alginate (qs 2g) were blended on a mortar and pestle. The powder mixture was then wetted with ~1 mL of distilled water and dried on a convection oven for 2h at 60 °C. The dry mixtures were then compressed in an instrumented single station tablet press (Compac 060804, Indemec, Columbia) at ~37 MPa to form cylindrical matrices. The release studies were conducted on an Erweka (DT6-K, Erweka GmbH, Milford, CT) Type 2 apparatus operated at 37 °C and 50 rpm for 12h. A 900 mL of phosphate buffer pH 6.8 was used as a

release medium. Aliquots of 2 mL each, were taken, filtrated and diluted (100 µL/2 mL) before measurement. The concentration of nimesulide was found by UV analysis (HACH DR500, HACXH Company, Loveland, CO) at 386 nm. A calibration curve was built at 2, 4, 6 and 10 µg/mL concentrations.

Statistical Analysis

The drug release studies data were fitted to the model by conducting a non-linear regression and the least square analyses. These were conducted using the Statgraphics® software centurion XV (Statpoint Technologies, Inc).

RESULTS AND METHODS

FT-IR and DSC Characterization

The FT-IR spectroscopy represents a fingerprint of a material with absorption bands, which corresponds to the frequencies of vibrations between the bonds of the atoms forming a material. Due to the different combination of atoms each material has a unique infrared spectrum and hence, this technique is useful for qualitative analysis. The FT-IR spectrum of sodium alginate is shown in Figure 1. It showed vibrational bands at 3418 cm^{-1} due to the OH inter and intramolecular hydrogen bonding. Since sodium alginate has two equivalent CO bonds, which have an intermediary force between C=O and CO, the carboxylate ion shows two characteristic bands, one of which is intense, from the axially asymmetric deformation of C=O bond at 1633 cm^{-1}. The other one is weaker, and observed around 1385 cm^{-1} and is attributed to the axial symmetrical deformation of the C-O bonding. Further, in the fingerprint region it exhibits a band around 834 cm^{-1} assigned to the mannuronic acid sequences.

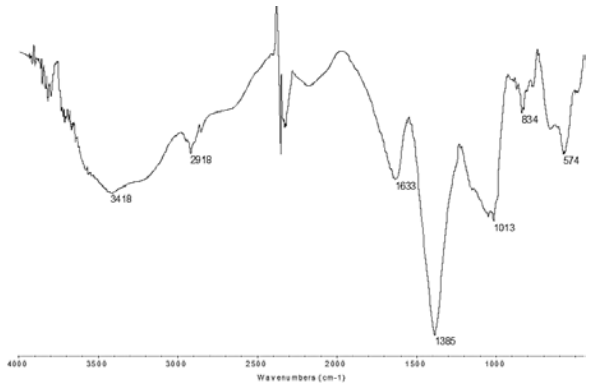

Figure 1: FT-IR spectrum of sodium alginate

The DSC curve of sodium alginate is shown in Figure 2. This type of thermal analysis is based on the enthalpy change of a given sample, resulting in a physical change (i.e., sublimation, evaporation, or condensation) or chemical change (i.e., degradation, decomposition, oxidation, etc) as a function of time or temperature. Kinetic parameters such as energy of activation (Ea), melting point, lifetime, etc could be obtained from these tests. The DSC curve showed two phases of decomposition under air atmosphere. Dehydration occurred in the first step (20-180 °C) losing around 13% of weight. This temperature range is wide due to the hydroxyl and carboxyl groups responsible for the strong interaction with water molecules.[13] The absorbed water molecules have different properties and are classified as freezing water (shown as an endothermic event at 60 °C), freezing bound water and non-freezing bound water according to their increasing strength. The last two types of water are released slowly only at temperatures higher than 100 °C and did not show any major thermal event. On the other hand, decomposition of the complexes formed between 180 °C and 400 °C took place losing ~67% of the initial weight. In this range, three events took placed at 250, 319 and 366 °C corresponding to the exothermic decomposition into low molecular weight carbohydrates, sodium oxalate and sodium carbonate, respectively. It is reported that thermal decomposition of alginates occurs via formation of sodium oxalate as intermediate fragments, resulting in sodium oxide at temperatures higher than 600 °C.[14]

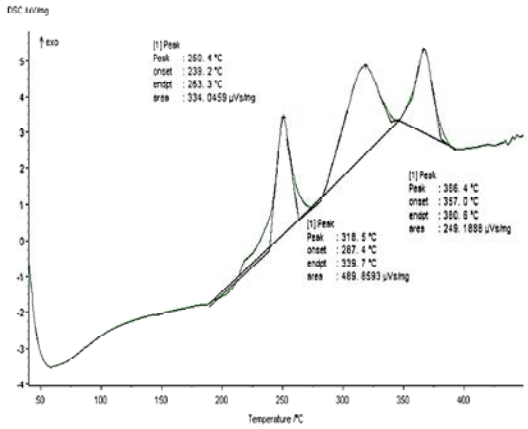

Figure 2: Differential Scanning Calorimetry of sodium alginate

The physical properties of sodium alginate are listed on Table 1. The intrinsic viscosity [η], of sodium alginate was 0.149 dL/g rendering an average molecular weight of 17.4 kD indicating that this polymer is able to produce gels of a good strength.[15] The degree of substitution indicates that 95% of all carboxyl groups from manuronic and guluronic acids are in the carboxylate sodium salt form.

The particle size of sodium alginate was 208 µm and it is considered as moderately fine according to the US Pharmacopoeia. This is the result of the extraction process from seaweeds especially from the milling and drying processes. The particle size of sodium alginate was larger than those of widely known commercial excipients such as lactose, microcrystalline cellulose and starch which ranged from 50 to 180 µm. For this reason, this material had a larger bulk and tap densities and better flow rates than the aforementioned excipients. The high equilibrium moisture content is due to the presence of many carboxylate and hydroxyl moieties which are able to form hydrogen bonds with incoming water molecules from the environment. On the other hand,

compressibility, which is expressed as the relative volume reduction of a material in response to the applied pressure was ~17% indicating a good ability for blending with a drug for making tablets.

Table 1: Physical properties of sodium alginate and nimesulide

Property	Sodium alginate	Nimesulide
Molecular weight (kDa)	17.4	308.31
Bulk density (g/cm^3)	0.68 ±0.01	0.34
Tap density (g/cm^3)	0.82 ±0.01	0.54
Moisture content (%)	13.64	0.1
True density (g/cm^3)	1.56± 00	1.463
Mean particle size (µm)	207.7±22.6	12.3
Flow rate (g/s)	23.6±1.6	0.3
Compressibility (%)	16.6 ±0.2	48.7
pH (25 °C)	6.58	N.A.
Degree of substitution	0.95	N.A.
Hydrodynamic volume	1.4	N.A.
Swelling value (mL/g) at	1.0±0.2	0
Tablet swelling (%) at	74	0.3
Intrinsic viscosity (dL/g)	0.149	N.A.
Py (MPa^{-1})a	91.2	64.4
D_A[b]	0.53	0.71
D_0[c]	0.43	0.23
D_B[d]	0.09	0.47
Tmax (MPa)[e]	1.23	1.48
γ (MPa^{-1})[f]	0.0053	0.085
AUC_g (MPa)^2	163	266

[a] Yield pressure, Py=1/slope

[b] Total powder packing al low pressures, $Da=1-e^{-intercept}$

[c] Initial rearrangement as a result of die filling, $D_0=\rho_{bulk}/\rho_{true}$

[d] Particle rearrangement, $D_b=D_A-D_0$

[e] Theoretical maximum tensile strength

[f] Compression susceptibility

[g] Compactibility found from the area under the tensile strength curve

Tableting Properties

Table 1 lists the tableting parameters for sodium alginate and nimesulide obtained from the Heckel and Leuenberger models, respectively. The yield pressure (P_y) is related to the type of deformation upon compression. Results indicate that sodium alginate was more fragmenting than nimesulide. Further, sodium alginate presented the largest total powder densification due to die filling (D_0), whereas, nimesulide showed the largest powder rearrangement behavior (D_B) due to its small particle size.

Pharmaceutical materials, by virtue of their response to applied forces, can be classified as elastic, plastic, or brittle. Since sodium alginate was considered more brittle than nimesulide, upon compression it breaks down into small particles, whereas in nimesulide sliding of crystal planes is more likely to occur. However, in both materials bonding was favored, but in nimesulide the increase in contact area between particles was better than sodium alginate and thus, nimesulide formed stronger compacts when a compression force was applied. Therefore, the stronger packing structure of nimesulide makes its crystalline regions to get closely packed and thus, the intermolecular forces, i.e., van de Waals forces increased, leading to a more ordered rearrangement within the particles resulting in a compact with a high tensile strength (T_{max}). As a result, nimesulide could withstand large deformations without breaking, whereas sodium alginate failed having a negligible deformation. For this reason, it is necessary to combine both materials and form a matrix so this polymer increases the release rate and decrease the matrix compactibility.

The compression susceptibility (γ) of sodium alginate was smaller than that of nimesulide. This proves that nimesulide required low compression forces to achieve a compact with a high tensile strength. For instance, nimesulide and sodium alginate required compression forces of ~110 and 280 MPa, respectively to form compacts of comparable tensile strength. As a result, compactibility of sodium alginate (brittle deforming material) was lower than that of nimesulide (plastic deforming material). As a result, sodium alginate required higher compression forces to achieve strong compacts.

Drug Release Studies

Figure 3 shows the intrinsic dissolution results of nimesulide pellets made at different compression pressures. The pH of a 3% w/v of sodium alginate was 6.58 and it is close to that of the dissolution media. Nimesulide is poorly soluble in water (0.01 mg/mL at 25 °C) and released ~20% of the dose within 12h. Therefore, in order to increase the amount of nimesulide released and control its *in-vitro* release profile sodium chloride was use to increase the ionic strength and modify the gelling properties of sodium alginate. However, sodium chloride only increased the release in the first 5 h and then it remained unchanged in respect to the polymer matrix without NaCl.

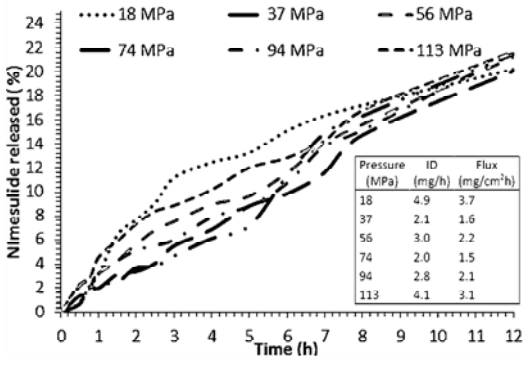

Figure 3: Intrinsic dissolution (ID) profiles of nimesulide matrixes in a pH 6.8 phosphate buffer

Nimesulide is a very poorly soluble drug (0.01 mg/mL). In fact, the intrinsic dissolution and the flux were too low in the first two hours and then decreased. Further, it is barely absorbed in the gastric region where the pH is too low.[16] For this reason, a modified release swelling matrix is desirable to release the drug in the gastrointestinal tract where it is more soluble. However, sodium alginate alone barely released ~45% of the drug within 12h and their matrixes did not disintegrate and showed a negligible swelling. This could be explained by the low molecular weight of sodium alginate might containing few G-blocks which renders a gel with a moderate strength and in this way contribute to the controlled release of nimesulide.

The presence of carboxyl and hydroxyl moieties in the polymer chain allows for a strong interaction with ions. The presence of the sodium cation increases the polymer hydration. Thus, the gelling ability of the matrix increases slightly when adding salts of monovalent cations because the polymer solution expands with increasing ionic strength. Once sodium ions are dumped into the medium, polymer hydration and swelling decreases due to the high concentration of Na^+ and K^+ ions in the medium. Thus, sodium may increase initially the hydration because these ions carried water onto the polymer. This is explained by the increased swelling of the polymer due to the high water affinity of sodium chloride releasing all its content into the medium within 5h. After 5h polymer swelling decreased and hence, nimesulide release rate was reduced. Conversely, the sodium chloride matrix failed to release more than 12% of nimesulide within 12 h since if formed hard compacts hindering the release via a diffusion mechanism. On the other hand, the increase in the viscosity of the medium is considered as negligible since the pH (6.8) did no change during the 12h of the study. It is known that in the gastric fluid solubility decreased due to the precipitation of free alginic acid at a pH below 3, and thus drug release of free alginic acid in this region is considered negligible.

The influence of a surfactant dispersed within the matrix on the nimesulide release profile was also assessed. Anionic surfactants such as sodium lauryl sulfate hindered the release due to the competing behavior with the anionic polymer for incoming water molecules resulting in a dehydration of the polymer. On the contrary, non-anionic and cationic surfactants such as sorbitan laurate and benzalconium chloride (BC) increased the release having the latter a better hydrating effect. BC also allowed for a better solubilization of the drug released in the media and fastened gelling/erosion of the polymer matrix.

Figure 4 shows the *in-vitro* release profiles of nimesulide from sodium alginate matrixes having different concentrations of BC. During the dissolution study sodium alginate absorbed water, swelled and concomitantly eroded partially depending on the BC level. The powder material was able to swell at 37 °C increasing its volume to a 74% within 12 h. However, in presence of BC swelling reached a 200% increase. These matrix tablets are considered hydrophilic due to the high water affinity of their components.

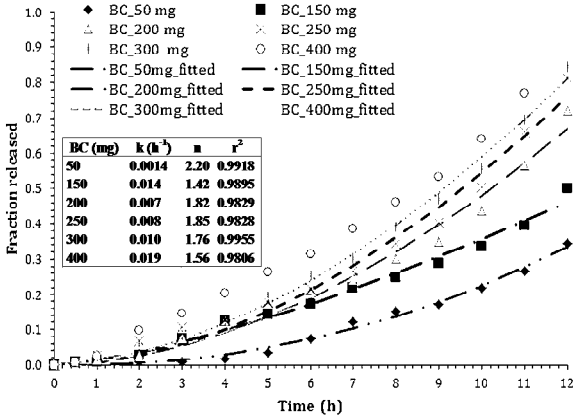

Figure 4: *In-vitro* nimesulide release profiles from sodium alginate matrixes containing different levels of benzalconium chloride

The enhancement and the achievement of a controlled release of nimesulide for 12 h obtained with the incorporation of cationic surfactants such as benzalconium chloride. In this case, a bifasic release took place. The first step for drug release was water penetration with a formation of a gellified outer layer characterized by a volume expansion where the drug was mainly released by diffusion. On the other hand, after 5h, erosion also took place increasing drug release and solubilization in the medium. This effect was more intense for matrixes containing high levels of BC.

The release models of Higuchi, Hixon and Crowell, and Korsmeyer-Peppas were used to analyze the *in-vitro* data and find the model that best represents the nimesulide release. The Korschmeyer-Peppas model was selected for the analysis due to the best fit to the experimental data:

$$F=k*t^n \qquad (4)$$

where, F is the fraction of drug released within the range of 0.1 to 0.60 at a time t, k is the release rate constant which incorporates structural and geometric factors. On the other hand, "n" is the exponent that characterizes the process of drug transport mechanism. If "n" is equal to 0.45; 0.45 < n < 0.89; and >0.89 the diffusion process is Fickian, non-fickian, and zero order, respectively for a cylindrical matrix. All data followed the Korschmeyer-Peppas model, where the release constant increased with increasing levels of benzalconium chloride. Further, all release profiles had a good fit to the Korschmeyer-Peppas model where all "n" values were larger than 0.89 indicating a zero order release.

The release mechanism was given once the polymer chains get in contact with the phosphate solution and the chains were reoriented and expanded to achieve a new equilibrium condition.

CONCLUSION

The alginate-based polymer was successfully employed to produce a hydrophilic matrix for the controlled release of a class II poorly soluble drug such as nimesulide.

A benzalconium chloride level of 400 mg was suitable to achieve a 90% drug release within 12h.

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