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Characterization and relevance of physicochemical interactions among components of a novel multiparticulate formulation for colonic delivery

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Abstract

The primary objective of this study was to investigate potential interactions among a model drug (azathioprine; AZA), polymers and a divalent metal ion, which were utilized in the development of a novel multiparticulate formulation for colonic delivery. The approach involved preparation of beads by ionotropic gelation of deacylated gellan gum (DGG) in the presence of Ca^{2+} ions, followed by coating with Eudragit®S-100. Various possible physicochemical interactions among formulation components were characterized by DSC, FT-IR, XRPD, ^{1}H-NMR, and an isothermal stress test. Results of isothermal stress testing indicated that there was no significant interaction of AZA with DGG and Eudragit® S-100. However, results of DSC and XRPD studies suggested that there could be interactions between AZA and DGG, and ionotropic gelation can affect the physical state of AZA, which may have implications for drug release characteristics and, physical and chemical stability. The results of FT-IR studies were suggestive of interactions of DGG with AZA and Eudragit® S-100, and provided evidence for interactions of AZA and DGG with Ca^{2+} ions. The electrostatic interaction of DGG with Ca^{2+} was also supported by results of DSC studies while that between AZA and Ca^{2+} was confirmed by ^{1}H-NMR studies. This study, to our knowledge, is first reported investigation in which the unique thermal property of gellan gum gels, and possible interactions between a drug and counter ions of an ionotropic agent have been demonstrated through bead characterization studies. The formation of AZA–Ca^{2+} complex could have an impact on drug release kinetics, product stability and clinical efficacy for treatment of inflammatory bowel diseases or other diseases, which merit further investigation.

Keywords: Drug–polymer interactions; Incompatibility; Azathioprine; Ionotropic gelation; Polysaccharide beads

1. Introduction

Recently, there has been an increasing interest in the use of delayed-release formulation of azathioprine (AZA) for the treatment of inflammatory bowel diseases such as ulcerative colitis and Crohn's disease (Sandborn, 1998). However, there is an increasing evidence to suggest that multiparticulate colonic formulations offer several biopharmaceutic and clinical advantages for topical therapy of these diseases (Singh, 2007), which prompted us to develop a novel formulation of AZA for colon-specific delivery. The formulation was composed of enteric-coated beads, which were made by a series of formulation processes as described in Fig. 1. First, beads were made by ionotropic gelation of deacylated gellan gum (DGG) in the presence of Ca^{2+} ions. The beads were then coated with an aqueous solution of methacrylic acid copolymer Type B (Eudragit® S-100) (Singh et al., 2004).

The primary objective of this study was to evaluate the physicochemical interactions between AZA and utilized polymers (DGG and Eudragit® S-100). The chemical structures of the drug and polymers are shown in Fig. 2. DGG is a linear heteropolysaccharide made up of a tetramer repeat unit consisting of β-D-glucose, β-D-glucuronic acid and α-L-rhamnose residues in the molar ratio of 2:1:1 (Singh and Kim, 2005). Eudragit® S-100 is an anionic copolymer of methacrylic acid and methyl methacrylate in which the ratio of the free carboxylic groups to ester groups is approximately 1:2 (Röhm GmbH & Co., 2004).

Apart from drug–polymer interactions, another potential liability associated with development of solid dosage forms, in general, is that manufacturing processes may induce phase

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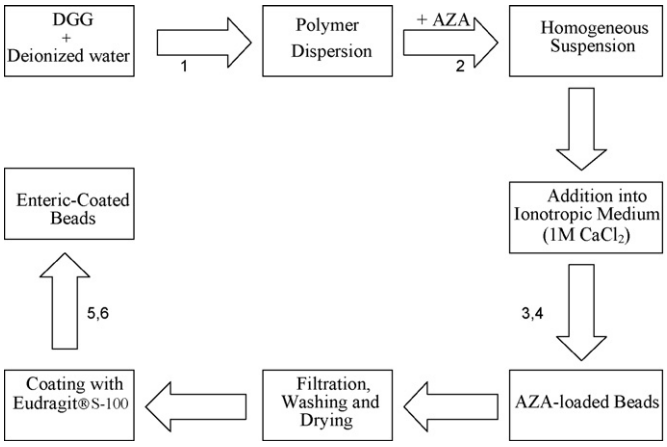

Fig. 1. Schematics of the formulation processes and various possible physicochemical interactions: 1, DGG/water interaction (hydrogen bonding); 2, AZA/DGG interaction; 3, AZA/Ca^{2+} interaction; 4, DGG/Ca^{2+} interaction; 5, AZA/Eudragit® S-100 interaction; 6, DGG/Eudragit® S-100 interaction.

transition or polymorphic changes in the drug. This could in turn impact the product stability and bioavailability (Zhang et al., 2004). For particulate delivery systems, the information pertaining to the physical state of the drug is important because kinetics of drug release can be influenced by the physical state of the drug in the microparticles (Baker, 1987). From controlled delivery point of view, the information related to physical state characterization of utilized polymers in formulations seems equally important, which are virtually non-existent in the literature. Accordingly, another objective of the present study was to evaluate the effects of formulation processes (ionotropic gelation and coating) on the physical states of AZA and DGG. These studies were rationalized primarily due to possible interactions of AZA and DGG with calcium ions, which are likely to occur during formulation of beads. Although the electrostatic interactions between DGG and various divalent cations including Ca^{2+} are well recognized (Singh and Kim, 2005), the possible interaction between a drug and counter ions of an ionotropic medium has never been addressed through bead characterization studies.

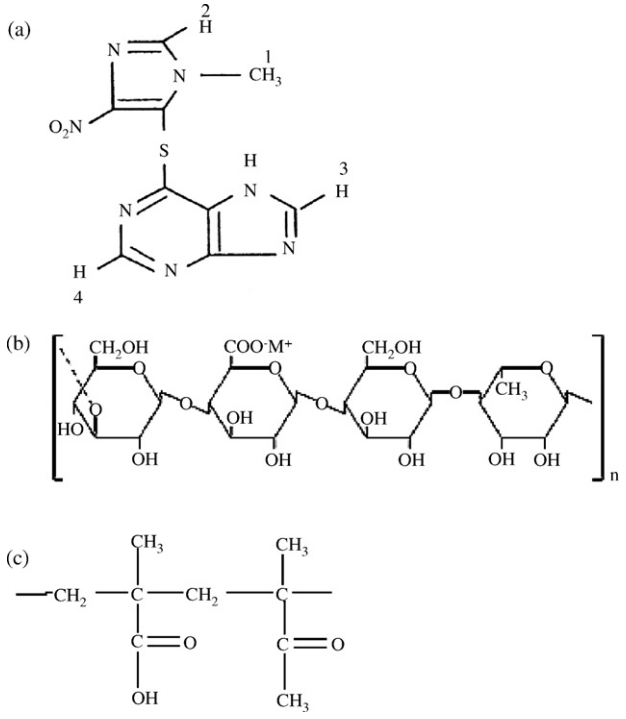

Fig. 2. Chemical structures of (a) azathioprine (adapted from Tanaka et al., 1991), (b) deacylated gellan gum (M^+ represents metal ions) and (c) Eudragit® S-100 (adapted from Röhm GmbH & Co., 2004).

Various possible physicochemical interactions among formulation components are briefly represented in Fig. 1. These interactions were probed by differential scanning calorimetry (DSC), Fourier-transform infrared (FT-IR) spectroscopy, X-ray powder diffractometry (XRPD), proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy, and an isothermal stress testing method. With certain limitations, each of these techniques is capable of indicating whether there is a change in the physical form of drug and polymers after formulation, and if any physicochemical interactions occur between drug and formulation components. All studies reported in this investigation involved physicochemical characterization of the drug and polymers in pure forms, formulations, and physical mixtures of drug and polymers in ratios similar to that of final formulation.

The characterization of interactions among drug, counter ions and polymers is important because it may have formulation implications. Several investigators have elucidated the roles and mechanisms of drug–polymer interactions which are relevant for drug release kinetics, product stability and polymorphic transformation of drugs (Hsiue et al., 1998; Jansen et al., 1998; Katzhendler et al., 1998; Lorenzo-Lamosa et al., 1998; Puttipipatkhachorn et al., 2001; Wong et al., 2002; Takka, 2003). The investigation of interaction between AZA and Ca^{2+} ions also seems clinically relevant in the light of growing number of examples demonstrating that complexation with metal ions could improve the pharmacological properties of several drugs including AZA (Dubler, 1996).

2. Experimental

2.1. Materials

Deacylated gellan gum (Gelrite®, Lot #18H09431), azathioprine (Lot #120K1401), deuterated dimethyl sulfoxide (DMSO-d_6) (Lot #08106TG) and *N*,*N*-dimethlyformamide (Lot #59H52311) were purchased from Sigma Aldrich Company (MO, USA). Anhydrous calcium chloride (Lot #F69167B09) was purchased from Amend Drug and Chemical Co. Inc. (NJ, USA). Eudragit® S-100 (Lot #1200105002) was supplied as gift sample from Röhm America Inc. (NJ, USA). All other chemicals were of analytical grade.

2.2. Isothermal stress testing

As relevant, binary mixtures of AZA with DGG and Eudragit® S-100 were prepared in ratios of 1:9 and 1:1, respectively, using mortar and pestle. Fifty milligrams of pure AZA and AZA–polymer mixtures were then dispensed in 5 ml screw-capped glass vials and stored in ovens (THELCO® laboratory

incubator, Precision Scientific Inc.) at 25, 35, and 45 °C. Samples were analyzed initially and then at specific intervals (weeks 1, 2, and 4) by a HPLC method (Singh et al., 2004). Prior to analysis, the contents were dissolved in dimethylformamide and filtered through 0.2 μ-Millipore filter. Both DGG and Eudragit® S-100 were not found to interfere with analysis of AZA. The assay values of various storage samples of AZA–polymer blends were compared with corresponding values of pure AZA samples using Student's *t*-test. The level of significance was considered at $p < 0.05$.

2.3. Differential scanning calorimetry

Samples of AZA, DGG, physical mixture (1:9) of AZA and DGG, and selected formulations were characterized using a DSC 7 PC-Series (Perkin-Elmer Corp., Norwalk, CT, USA). These formulations were placebo beads, AZA-loaded (uncoated) beads, and enteric-coated beads. Samples (1.0–4.0 mg) were scanned in hermetically sealed aluminum pans (Perkin-Elmer Inc., CT, USA) over the temperature range between 30 and 300 °C at a scanning rate of 5 °C/min. All samples were held at 30 °C for 1 min before scanning. An empty sealed aluminum pan was used as a reference. Nitrogen was used for purging the sample holders at a flow rate of 20 ml/min. All tests were performed in duplicate.

2.4. X-ray powder diffractometry

These studies were performed with samples of AZA, DGG, physical mixture of AZA and DGG (1:9), and crushed powder of AZA-loaded (uncoated) beads. Samples were filled into an aluminum sample holder and exposed to Cu Kα radiation (40 kV × 40 mA) in a wide-angle X-ray powder diffractometer (Philips PW3040, Philips Analytical, Eindhoven, The Netherlands). Each sample was scanned in a continuous mode with the diffraction angle, 2θ, increasing from $5 < 2\theta < 45°$.

2.5. Fourier-transform infrared spectroscopy

Infrared spectra were recorded on a Perkin-Elmer FT-IR System, Model: Spectrum BX (Perkin-Elmer, USA). Pellets were prepared from a finely ground mixture of test sample (1–2 mg) and dried KBr (200–300 mg) using a Quick Press and a 7 mm die set (Perkin-Elmer, USA). The various samples analyzed were: (a) AZA, (b) AZA-loaded (uncoated) beads, (c) DGG, (d) Eudragit® S-100 and (e) enteric-coated beads. The samples were scanned between 4000 and 450 cm^{-1} at an interval of 1.0 cm^{-1}.

2.6. Proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy

One-dimensional ^{1}H-NMR studies were performed on samples of AZA, DGG and AZA-loaded (uncoated) beads. Approximately 50 mg of samples were dissolved in 0.5 ml of DMSO-d_6 and filtered through glass wool prior to analysis. The ^{1}H-NMR spectra were recorded on a Bruker 400 Ultrashield spectrometer at 27 °C (300 K). Chemical shifts were determined relative to tetramethylsilane and are reported in parts per million (ppm). The parameters were as follows: operating frequency = 400 MHz; pulse length = 6.5 μs.

3. Results and discussion

3.1. Isothermal stress testing

The protocol of isothermal stress testing typically involves stressing drug–excipient blends in sealed containers at temperature above that used for accelerated testing (e.g., 50 °C, 60 °C, etc.), with or without added moisture, and analyzing the drug and/or its degradation products (Gu et al., 1990). In the present study, binary mixtures of AZA and polymers were stored at various temperatures (in 10 °C increments) without any added moisture. Samples of pure AZA stored at similar conditions served as controls.

The results are summarized in Table 1, which show that there is no degradation of AZA in the pure drug and in drug–polymer mixtures. The assay values for drug–polymer mixtures were not different ($p > 0.05$) from their corresponding pure drug samples, suggesting that there was no significant interaction of AZA with DGG and Eudragit® S-100.

The analysis of binary mixtures at initial and other time points also indicated the homogeneity of dispensed powder mixtures. The %relative standard deviation (R.S.D.) values for initial and stressed samples (data shown for last time point only) were ≤2.5%.

3.2. Differential scanning calorimetry

Fig. 3 shows the physical state characteristics of AZA and DGG in their pure forms, in a physical mixture and in selected formulations. The thermogram of pure AZA showed a sharp endothermic peak at 253 °C corresponding to its melting transition point, followed by an immediate exotherm indicating drug degradation (curve B). The enthalpy (ΔH) values for endo and exothermic peaks were 25.284 and −158.991 J/g, respectively.

In case of pure DGG, an exothermic peak was observed suggesting that polymer undergoes thermal degradation. An exothermic peak also appeared in the thermogram of the physical mixture of AZA and DGG; however it was slightly shifted to a lower temperature (241.6 °C) when compared with exothermic peaks of AZA or DGG. In addition, the endotherm of AZA did not appear in the thermogram of the physical mixture (curve C).

Table 1
Solid-state compatibility of AZA with DGG and Eudragit® S-100 at 25, 35, and 45 °C after 4 weeks

Samples	25 °C	35 °C	45 °C
Pure AZA	99.38 ± 2.47	99.53 ± 1.33	99.02 ± 1.68
AZA:DGG (1:9)	96.90 ± 0.49	99.68 ± 1.22	99.78 ± 2.39
AZA:Eudragit® S-100 (1:1)	99.75 ± 2.31	99.95 ± 1.92	99.68 ± 0.63

Results are shown as %AZA remaining and each value represents mean ± S.D. of six determinations.

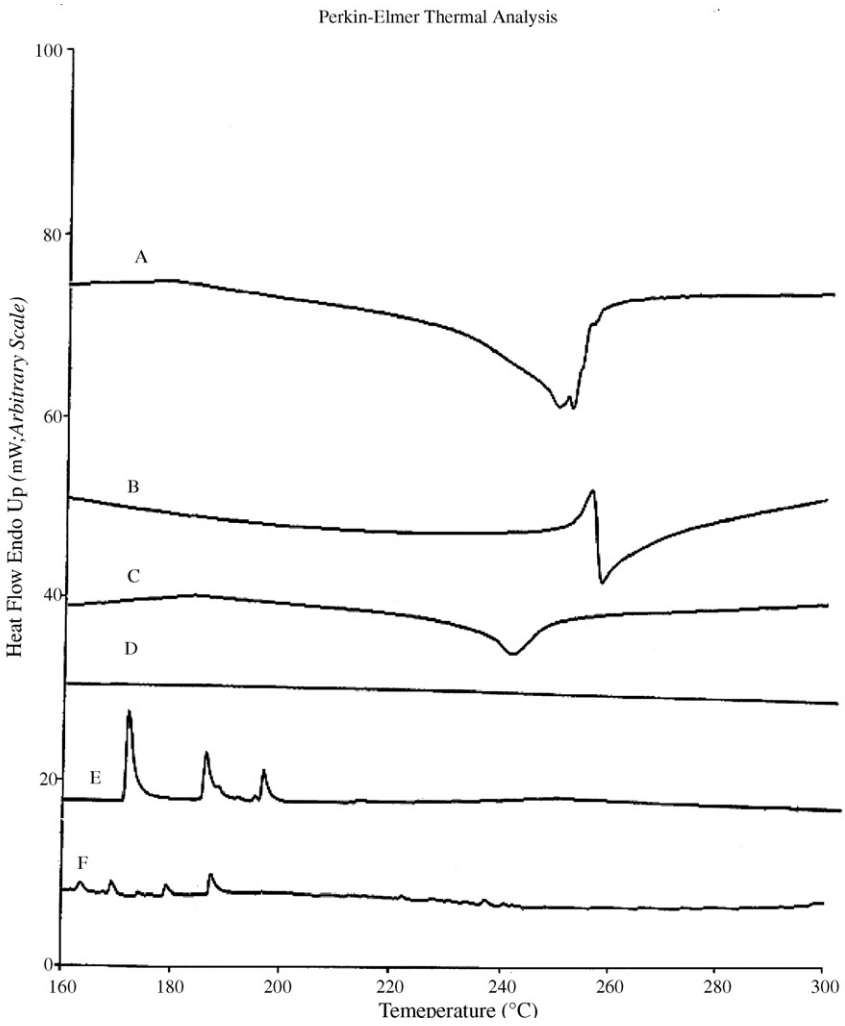

Fig. 3. DSC thermograms of (A) pure DGG powder, (B) pure AZA powder, (C) physical mixture of AZA and DGG (10% drug), (D) AZA-loaded beads coated with Eudragit® S-100 (8.6% drug), (E) placebo gellan beads and (F) AZA-loaded (uncoated) beads (9.5% drug).

These changes in peak characteristics of AZA and DGG could be attributed to change in purity of individual components (because of 'dilution effect') and/or a physical interaction between AZA and DGG. The absence of AZA endotherm in the thermogram of the physical mixture may be due to dissolution of the crystalline drug in the polymer at high temperatures during heating in DSC measurements.

The thermogram of placebo beads revealed interesting results. The exothermic peak of DGG disappeared and instead small endothermic peaks appeared (curve E), which had melting temperatures between 170 and 185 °C. This indicates that a portion of the polymer converts from amorphous to crystalline form during formation of the gel beads. This transition is attributed to the formation of the gel architecture which consists of crystalline regions, called junction zones, and some amorphous regions. Physicochemical studies suggest that in presence of Ca^{2+} ions, junction zones of the gellan gels are formed due to aggregation of double helices, which is promoted by carboxylate–Ca^{2+}–carboxylate interactions (Chandrasekaran and Thailambal, 1990). The intensity of peaks diminished after AZA was incorporated into beads and their endotherm temperatures were slightly shifted (curve F). These changes suggest that the crystallinity of the crosslinked polymer decreases after entrapment of AZA within its network.

The appearance of the multiple endothermic peaks in the DSC heating curves for placebo and AZA-loaded beads represents a unique thermal property of gellan gum gels which has never been reported in the solid ('beads') state. From a molecular point of view, an explanation for this thermal behavior could be based on the findings of Miyoshi et al. (1996). These authors also observed multiple endothermic peaks during DSC studies of gellan gum gels containing divalent cations, and attributed to "unzipping" of zipper like hydrogen-bonded junction zones upon heating to 120 °C. These small peaks are therefore not due to plurality of beads taken as a sample.

The melting endotherm of AZA was absent in the thermograms of uncoated and enteric-coated beads, indicating that drug was dispersed as amorphous ("dissolved") form in the polymer matrix of gellan gum. This phase transition may be attributed to a physical interaction between AZA and gellan gum. The absence of exothermic peaks in placebo and uncoated beads suggest that formulation process ("ionotropic gelation") could

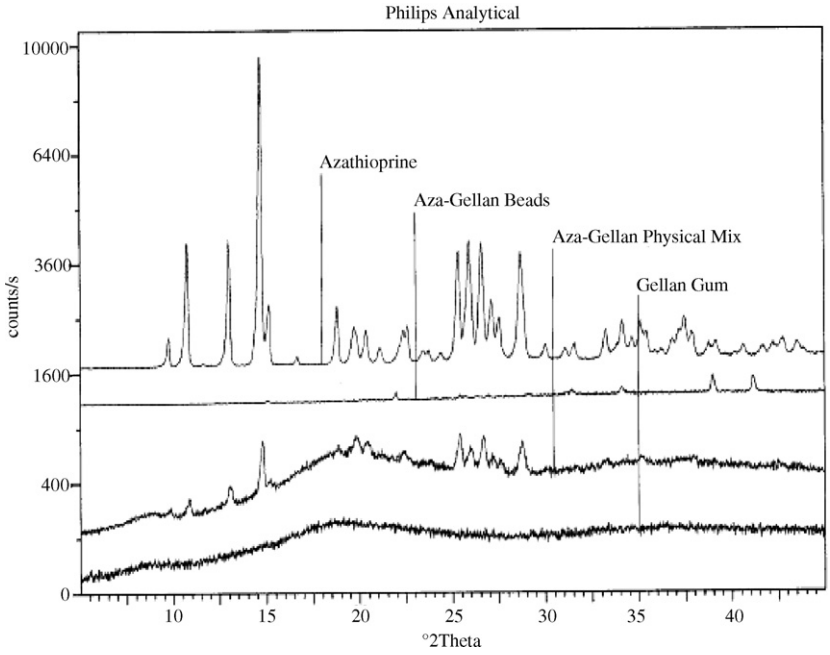

Fig. 4. X-ray powder diffractograms of pure AZA and DGG, physical mixture of AZA and DGG (1:9) and AZA-loaded beads.

prevent the thermal decomposition of AZA and DGG, which may have implications for product stability.

3.3. X-ray powder diffractometry

Conventional analytical techniques such as HPLC although provides the total drug content in the microparticulate systems, it cannot distinguish the drug dissolved in the matrix from that which is dispersed as crystals in the matrix (Dash et al., 2002). In this regard, XRPD is the most preferred technique.

Fig. 4 shows the diffraction patterns of AZA, DGG, physical mixture of AZA and DGG (1:9), and AZA-loaded beads. The diffractograms of pure AZA and DGG indicate their crystalline and amorphous nature, respectively. In the physical mixture, the crystalline peaks of AZA were present, although with reduced intensity as expected. On the other hand, in the AZA-loaded beads, the peaks of AZA were absent which in turn suggest that AZA is converted from crystalline to amorphous (or "nanocrystalline") state upon bead formulation. That is, a substantial fraction of AZA is present as dissolved form in the polymer matrix. As both amorphous and nanocrystalline forms of AZA are not stable, they will tend to revert to the more thermodynamically stable crystalline form. However, gellan beads incorporating AZA inside its three-dimensional network could serve as stabilizing agent hindering the recrystallization.

The physical stability of AZA in amorphous form is desirable because it is poorly soluble in water (208.41 μg/ml at 25 °C; Singh and Kim, 2005). In the light of a recent investigation (Konno and Taylor, 2006), it is reasonable to speculate that stabilizing effect of gellan gum could be related to reduced nucleation rate of AZA caused by drug–polymer interaction. However, AZA–Ca^{2+} interaction might also contribute to the physical stability of AZA in beads. The presence of these interactions could therefore result in higher kinetic barrier to crystallization and a decrease in the molecular mobility of AZA in the polymer matrix, which is expected to be lower because of stronger affinity of DGG and AZA for Ca^{2+} ions. These mechanisms have been suggested for stabilizing effects of several other polymers such as polyvinylpyrrolidone, polyacrylic acid, hydroxypropylmethylcellulose, hydroxypropylmethylcellulose acetate succinate which inhibit the crystallization tendency of amorphous drugs (Miyazaki et al., 2004, 2006; Aso and Yoshioka, 2006; Konno and Taylor, 2006). Nevertheless, the presence of drug–polymer interaction has also been reported to prevent polymorphic changes in the drug when encapsulated in alginate beads (Wong et al., 2002).

The diffractogram of AZA-loaded beads showed the emergence of small peaks at 2θ values of 39 and 41.5° which were not observed in case of pure AZA or physical mixture. These peaks were however observed during run of a blank sample holder therefore, confirming that these peaks originated due to aluminum. Overall, XRPD results are similar to those of DSC with regard to the physical state of AZA in pure and formulated (beads) forms, and are suggestive of a physicochemical interaction between AZA and DGG.

3.4. FT-IR spectroscopy

FT-IR studies were performed to characterize various interactions at the molecular level. The FT-IR spectra of AZA, polymers and formulations are shown in Fig. 5. In case of pure DGG, characteristics peaks are observed due to H–bonded O–H stretch vibration of hydroxyl groups (3400 cm^{-1}), C–H stretch vibration of CH_2 group (2908 cm^{-1}), asymmetric carboxylate anion stretching (1610 cm^{-1}), symmetric carboxylate anion stretching (1418 cm^{-1}) and C–O stretching (1032 cm^{-1}).

AZA exhibited major bands due to stretchings of N–H group (3109, 2988 and 2810 cm^{-1}) and purine ring (1580 cm^{-1}),

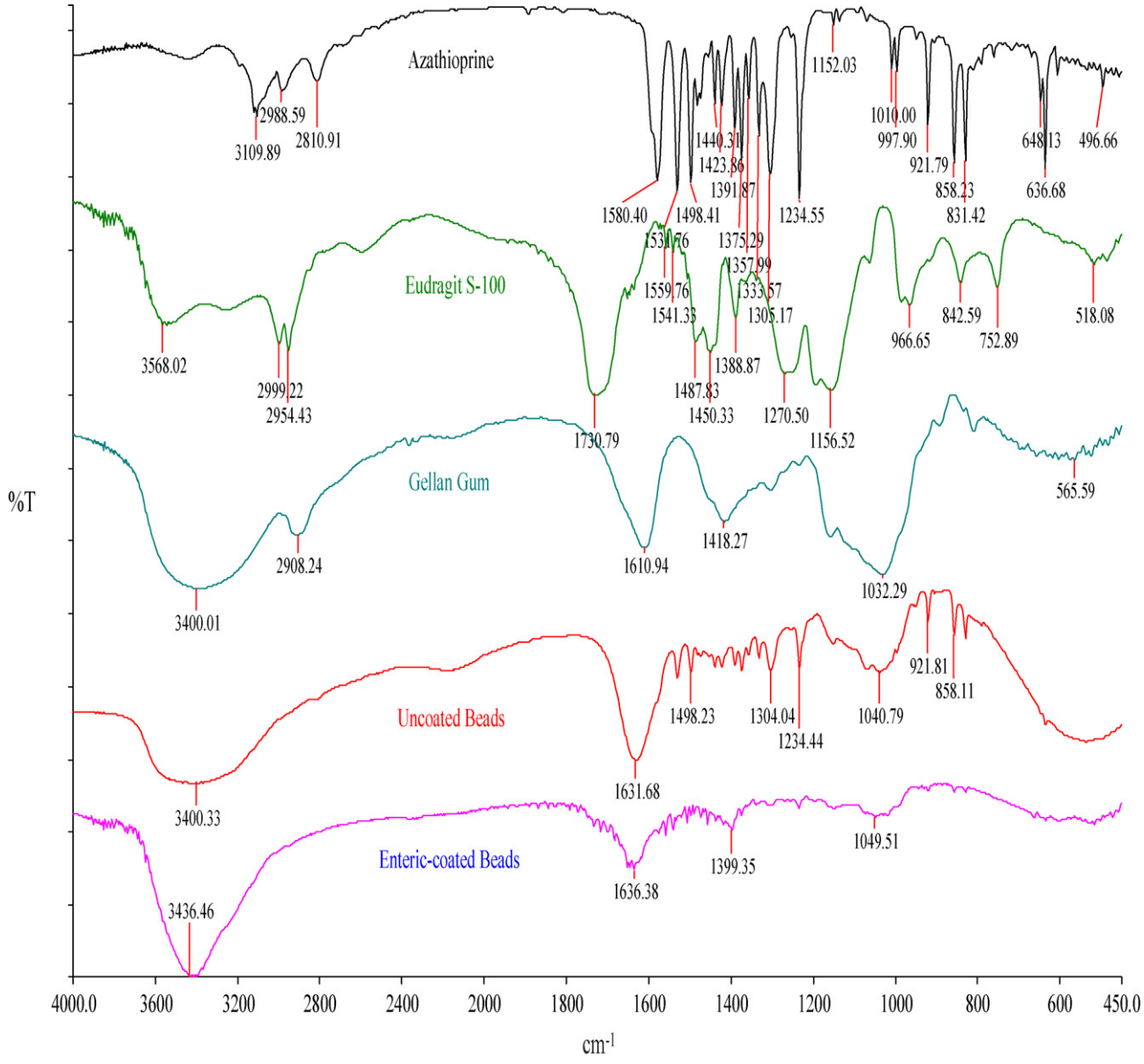

Fig. 5. FT-IR spectra of pure AZA, DGG, Eudragit® S-100 and formulations.

as reported previously (Chifotides et al., 1994a). The FT-IR spectrum of Eudragit® S-100 shows carbonyl C=O stretch (1730 cm^{-1}) due to presence of esterified carboxylic groups of methacrylic acid, along with further ester vibrations at 1270 and 1156 cm^{-1}. Absorption peaks between 2500 and 3500 cm^{-1} are attributed to the presence of hydroxyl groups and water (Cilurzo et al., 2003) and are superimposed by CH_x vibrations between 2900 and 3000 cm^{-1}. Further CH_x vibrations were observed at 1487, 1450 and 1388 cm^{-1}. These FT-IR data are consistent with findings of previous studies (Cilurzo et al., 2003; Röhm GmbH & Co., 2004).

In case of drug-loaded (uncoated) beads, peaks due to stretching vibrations of N–H group and purine ring were lost. The disappearance of the three peaks owing to N–H stretching vibrations indicates the deprotonation of the N–H position of AZA upon coordination with Ca^{2+} ions, while the disappearance of the band at 1580 cm^{-1} upon metal coordination is a consequence of charge redistribution of the purine ring (Chifotides et al., 1994b). These major changes therefore suggest that AZA complexes with Ca^{2+} ions during ionotropic gelation, and is supported by findings of other investigators who observed similar spectral changes for complexes of AZA with other metal ions (Singh et al., 1991; Chifotides et al., 1994a). Other noticeable changes include absence of DGG peaks at 1418 and 2908 cm^{-1}, which are indicative of interaction between AZA and DGG. Shifts in DGG peaks related to asymmetric carboxylate group and C–O stretchings (observed at 1631 and 1040 cm^{-1}) may be attributed to the ionic interaction between carboxylic groups of DGG and Ca^{2+} during formulation of beads. The reduced intensity of AZA peaks in low frequency region (1531–831 cm^{-1}) could be attributed to change in purity, in general, although metal coordination at N–H position may also cause reduction

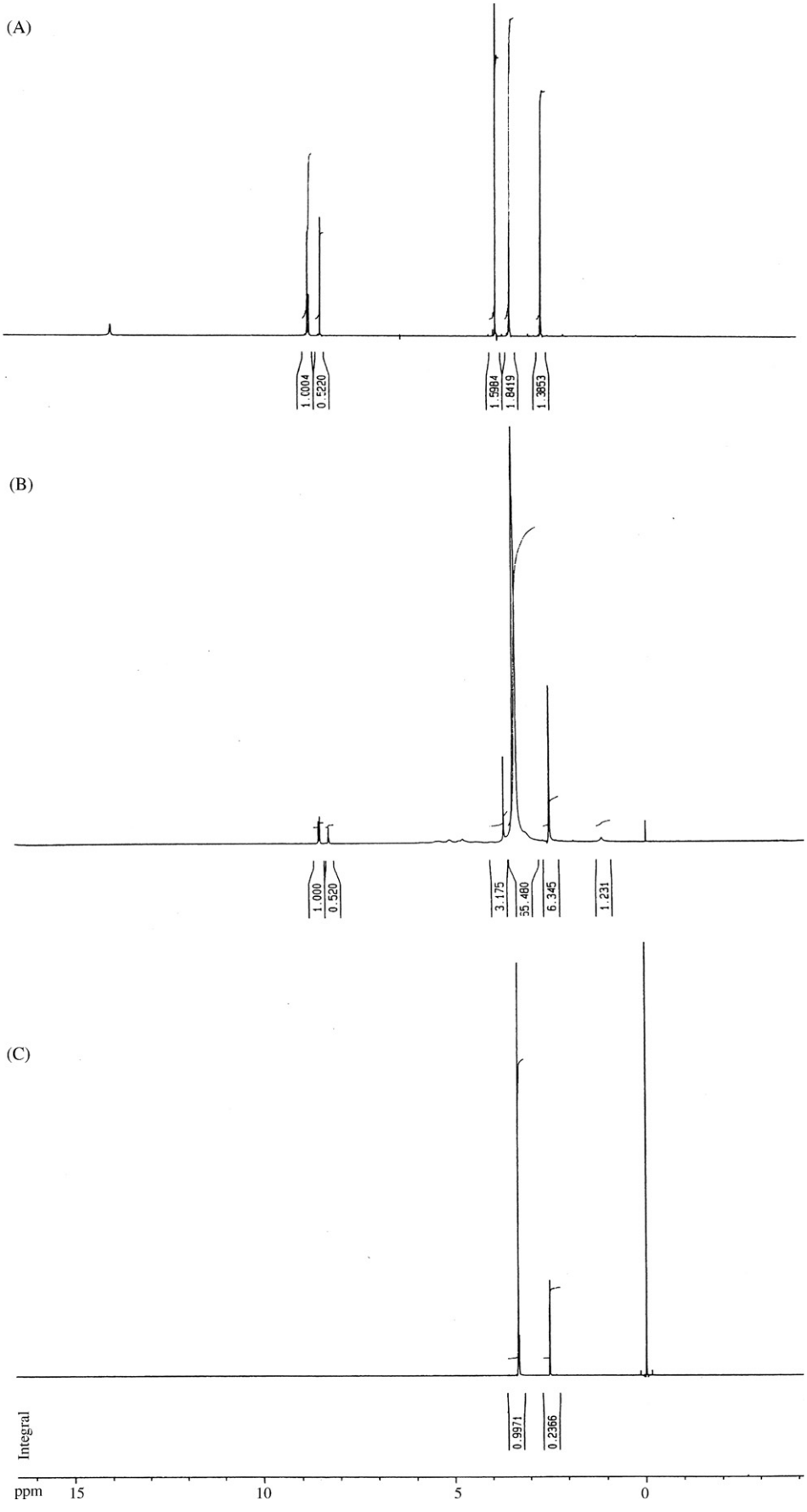

Fig. 6. The ^{1}H-NMR spectra of (A) pure AZA, (B) AZA-loaded beads and (C) DGG.

Table 2
^{1}H-NMR data for AZA and AZA-loaded bead formulation

Samples	Chemical shifts, δ (ppm)			
	CH_3 (position 1)	N–H	–CH (position 2)	–CH (position 3)
Pure AZA	3.69s	13.75s	8.25s	8.56d
AZA-loaded beads	3.70s	–	8.30s	8.55d

s: singlet; d: doublet.

in intensity of certain peaks (e.g., 1234 cm^{-1}) (Chifotides et al., 1994b).

The intensity of AZA peaks were further reduced in enteric-coated beads. In addition, peaks of Eudragit® S-100 due to vibrations of ester (1730, 1270 and 1156 cm^{-1}) and associated hydroxyl groups (2954 and 2999 cm^{-1}) were lost, and the peak due to hydroxyl group vibration (3400 cm^{-1}) of DGG shifted to a higher wave number. These changes suggest that an interaction occurred between DGG and Eudragit® S-100. Changes in the remainder of the spectrum were related to DGG peaks, which were essentially the same as noted in uncoated beads. The absence of any 'new' peak in spectra of uncoated and enteric-coated beads further suggests that formulation processes (ionotropic gelation and bead coating) do not suffer from any degradation.

3.5. ^{1}H-NMR spectroscopy

^{1}H-NMR has been previously used to study the complexation of AZA with several heavy metal ions such as Ag^+, Pt^{2+}, Pd^{2+}, Ru^{2+}, and Rh^{3+} (Chifotides et al., 1994b). The objective of the present study was to elucidate such possible interaction of AZA with Ca^{2+}, which is likely to occur during formulation of beads.

Fig. 6 shows the ^{1}H-NMR spectra of AZA (Fig. 6A), bead formulation (Fig. 6B) and DGG (Fig. 6C) in DMSO-d_6. For our ^{1}H-NMR studies, DMSO-d6 was selected as a suitable solvent since it promptly dissolves AZA as well as DGG. The ^{1}H-NMR data for AZA and AZA-loaded beads are summarized in Table 2. The spectrum of AZA shows one resonance at 3.69 ppm corresponding to methyl protons at position 1, and resonances of the aromatic protons at 8.25 and 8.56 ppm, corresponding to methine (–CH) groups at positions 2 and 3 (Fig. 2a), respectively. In addition, one resonance was observed at 13.75 ppm, which corresponds to imine (N–H) proton of the purine ring. Most of the resonances assigned in this study are in reasonable agreement with previously reported ^{1}H-NMR data of AZA (Tanaka et al., 1991; Chifotides et al., 1994b).

In case of DGG, the resonance was observed at 3.33 ppm, which is typically assigned to methyl protons of rhamnose residues. Furthermore, the absence of acetate signal in the spectrum, which is usually observed at 2.14 ppm (Jay et al., 1998), affirms the 'deacylated' nature of gellan gum.

In case of drug-loaded beads (Fig. 6B), the resonance due to N–H proton of AZA was not observed indicating that N-atom at this position is deprotonated (Chifotides et al., 1994b). In addition, a downfield shift of 0.05 ppm was noted for protons of methine group at position 2 (Table 2). These changes confirm that AZA complexes with Ca^{2+} during formulation of beads, which is consistent with results of FT-IR studies. The strong interaction between deprotonated AZA and Ca^{2+} ions is apparently facilitated by the pH of the ionotropic medium (pH 10.0). The pK_a values of AZA have been estimated to be <3.2 (pK_{a_1}) and 8.0 (pK_{a_2}) corresponding to imidazole and purine rings, respectively (Tanaka et al., 1991). At an alkaline pH of 10.0, the dissociation of NH on the purine ring would be complete (>99%). This is evident by the largest shift (13.75 ppm) observed for imine proton. The complexation behavior of AZA with Ca^{2+} ions is also supported by our solubility data (Singh and Kim, 2005) and mass spectrometry (unpublished results). The formation of AZA–Ca^{2+} complex may play a role in the stability of amorphous AZA, as discussed earlier. In addition, it could also improve the pharmacokinetics and pharmacological properties of AZA, which merit further investigation.

4. Conclusions

The existence of possible interactions among formulation components was demonstrated by various physicochemical methods. To authors' knowledge, this is first reported investigation on physicochemical interaction of AZA with polymers commonly used in solid controlled-release formulations. In addition, the potential interaction between a drug and counter ions has been demonstrated, which must be taken into consideration while utilizing ionotropic gelation as a formulation technology. The presence of these interactions could have a direct impact on drug release kinetics, product stability and clinical efficacy of AZA. Overall, the results obtained were in favor to support the development of a multiparticulate formulation of AZA based on the selected formulation approaches.

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