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Preformulation studies on grewia gum as a formulation excipient

Elijah I. Nep · Barbara R. Conway

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Abstract Grewia gum is a naturally occurring polysaccharide which has potential as a pharmaceutical excipient. Differential scanning calorimetry and Fourier transform infrared (FT-IR) spectroscopy techniques were used to examine the thermal and molecular behaviours, respectively, of mixtures of grewia gum with cimetidine, ibuprofen or standard excipients, to assess potential interactions. No disappearance or broadening of the melting endotherm was seen with cimetidine or ibuprofen. Similarly, there was no interaction between grewia gum and the standard excipients tested. The results obtained using thermal analyses were supported by FT-IR analysis of the material mixtures. Grewia gum is an inert natural polymer which can be used alone or in combination with other excipients in the formulation of pharmaceutical dosage forms.

Keywords Cimetidine · Ibuprofen · Grewia gum · Excipients · DSC · FT-IR

E. I. Nep · B. R. Conway
Life and Health Sciences, Aston University, Aston Triangle, Birmingham B4 7ET, UK

Present Address:
E. I. Nep (✉)
Department of Pharmaceutics and Pharmaceutical Technology, University of Jos, Jos, Nigeria
e-mail: nepeli2000@yahoo.com

B. R. Conway
Pharmacy, School of Applied Sciences, University of Huddersfield, Huddersfield HD1 3DH, UK

Introduction

Natural polymers can be usefully employed in the formulation of solid, liquid, and semi-solid dosage forms and has particular application, alongside synthetic polymers, in the design of modified release drug delivery systems. In addition to their biocompatibility and biodegradability, natural polymers may be considered particularly economically attractive providing an abundant supply of raw material that may be cultivated or harvested in a sustainable manner. However, substances from plant origin also pose several potential challenges and may exist in structurally complex mixtures, which may differ according to the location of the plants as well as other variables such as the season [1].

Before or during the development of solid dosage forms, large scale development trials are normally preceded by the assessment of possible interactions between a drug and different excipients used in the formulation [2, 3]. Although, excipients are required to be medically inert, physical and chemical interactions with APIs are commonplace [4]. The screening of a novel excipient for possible incompatibilities is therefore an absolute requirement.

A number of techniques have been used for screening of drug–excipient mixtures for interactions or incompatibilities to include isothermal stress testing and thermal analysis [4, 5]. Thermal analysis has the advantage over conventional isothermal stress testing in that long term storage of physical mixtures and chromatographic analysis are not required and only a few milligrams of sample is needed [4, 6–8]. However, the technique has been criticized as being inconclusive as moisture stress testing is usually not included and the temperature and heating rates used are not characteristic of normal storage conditions resulting in difficulty of interpretation and extrapolation of

results [4, 9, 10]. Consequently, differential scanning calorimetry (DSC) should be used in conjunction with other techniques. Furthermore, although DSC technique has been proven to be a reliable indicator of major interactions, the method only detects interactions but gives no indication of the extent of interaction or incompatibility [4]. Combining DSC technique with a technique such as Fourier transform infrared (FT-IR) spectroscopic analysis allows for detail understanding, elucidation, and interpretation of potential interactions at the molecular level. This enables a better picture of the nature and extent of the interaction to be elucidated.

Grewia gum is a polysaccharide gum obtained by extraction from the inner stem bark of the savannah shrub *Grewia mollis* (Fam. Tiliaceae). The gum has been characterised [11, 12] and its rheological [13], bioadhesive [14], binding, and mechanical properties of the tablets [15, 16] and films [17] have been evaluated. However, no study has been done on the potential interactions or incompatibility of the gum with APIs and/or standard excipients that could be used along with grewia gum in a tablet formulation.

Possible drug–excipient interactions include eutectic formation, solid–solid reactions, solid–liquid reactions, and solid–gas reactions involving hydrolysis by evolved water vapour [4]. In this study, FT-IR and/or thermal analysis using DSC was employed to study any interactions between grewia polysaccharide gum and the active pharmaceutical ingredients, cimetidine and ibuprofen. FT-IR spectroscopy provides a useful tool for the evaluation of drug–polymer interaction studies, and incompatibility between the drug and excipient can be predicted by changes in the functional peaks (characteristic wave numbers) [18]. It was used as a complimentary technique to assist in the interpretation of the DSC results as the DSC alone does not yield direct chemical information [8]. A combination of DSC and FT-IR techniques will therefore provide more detailed information on interactions between drug and excipient than any of the techniques used alone.

Incompatibilities involving magnesium stearate have been described as frequent [4]. Consequently, likely interactions between grewia gum and some standard excipients used in the formulation of tablets were also investigated. This was done by comparing the results obtained for the controls with physical mixtures of the drug and polymer, or excipient and polymer [3, 19]. If the drug and the polymer interact, then the functional groups in the FT-IR spectra would show band shifts and broadening compared to the spectra for the pure drug and polymer [20]. When the FT-IR spectra or DSC traces of the physical mixtures are a summation of the characteristic traces obtained with the individual components of the physical mixtures, this indicates that there was no chemical interaction of the drug with polymer in physical mixes [8, 9, 20, 21].

Materials and methods

Materials

Ibuprofen and cimetidine were gifts from GSK. Ethyl cellulose (Ethocel®—standard 100FP Premium) and hydroxypropyl methylcellulose (Methocel®—K100 premium LVCR) were gifts from Colorcon, England. Metolose (Metolose®—90SH-100SR, viscosity-100 mPa s, substitution type-2208) was a gift from Shin Etsu Chem. Co Ltd., Japan. Colloidal silicon dioxide (Aerosil 200®) was a gift from Evonik, UK. Carboxy methylcellulose (CMC) (Blanose®—Type 7M1F-PHARM) was a gift from Aqualon, UK. Lactose monohydrate USP (Pharmatose®, grade DCL14) was a free gift from DMV-International, UK. Microcrystalline cellulose (Avicel®) was a gift from FMC BioPolymer, UK. Grewia polysaccharide gum (air-dried) was extracted from the crude bark in our laboratory as previously reported [12]. All other materials were procured from Sigma-Aldrich, UK.

FT-IR spectroscopic analysis

Small amounts of the API (cimetidine or ibuprofen), grewia gum, or the standard excipients were individually blended with KBr (1:10) and compressed into discs on an IR press to serve as controls. Also equal amounts of grewia gum and cimetidine or ibuprofen, or grewia gum and standard excipient were blended and compressed on an IR press. The resultant discs were then scanned on a Mattson Galaxy 3020 FT-IR spectrophotometer (Unicam, England).

DSC analysis

DSC (Diamond DSC Perkin Elmer, USA) was used to study the interaction of grewia polysaccharide gum with the APIs (cimetidine and ibuprofen) or with other excipients. About 3 mg of the pure drug or excipient was accurately weighed into the aluminium (4 mg) sample pan which was then sealed before scanning from 20 °C up to 200 °C at a rate of 10 °C/min under nitrogen atmosphere. Physical mixture of the drug and excipient or excipient and excipient (1:1) was also transferred into the sample pan, sealed, and scanned as detailed previously. All other interactions were studied between 20 and 200 °C except interactions with lactose monohydrate which were monitored up to 230 °C.

Results

FT-IR screening of grewia gum–ibuprofen interactions

The FT-IR absorption bands of grewia gum, ibuprofen, and their physical mixtures (1:1) are shown in Fig. 1. The absorption bands of grewia gum are typical for carbohydrates. The FT-IR spectrum for grewia gum has previously been reported [12]. Briefly, the broad band occurring at 3436 cm^{-1}, results from the presence of hydroxyl (*–OH*) groups. The peak obtained at 2930 cm^{-1} results from stretching modes of the *C–H* bonds of methyl groups (*–CH_3*). Absorption bands around 1618 and 1430 cm^{-1} may be attributed to carboxylate groups of the uronic acid residues [22]. Also absorption peaks at 1740 and 1258 cm^{-1} are typical of acetyl groups [23]. The wave numbers between 800 and 1200 cm^{-1} represent the finger print region for carbohydrates [24]. Characteristic absorption peaks were visible for ibuprofen at 1710 and 2955 cm^{-1} which are caused by the carbonyl stretching vibration and the hydroxyl stretching vibration, respectively. Interaction with ibuprofen primarily interferes with the position or intensity of these two peaks [25, 26].

DSC screening of grewia gum–ibuprofen interactions

Thermograms for grewia gum, ibuprofen, and the physical mixtures are shown in Fig. 2. The trace for ibuprofen showed a sharp melting endothermic peak at about 78.46 °C with a linear onset temperature of 75.72 °C, whilst the corresponding values for grewia/ibuprofen physical mixture were 76.63 and 75.00 °C, respectively. The peak was maintained following heating with grewia gum and did not show any evidence of degradation over this temperature range.

FT-IR screening of grewia gum–cimetidine interactions

The FT-IR absorption spectrum (Fig. 3) recorded for cimetidine has a double broad band at 3240 cm^{-1} assigned to *vibrational* (*NH*) of the associated *NH* group. The absorption bands have been assigned as shown in Table 1 [27].

Grewia gum gives characteristic absorption bands typical of carbohydrates as detailed previously. The spectrum is shown in Fig. 1. Also Fig. 3 shows the spectra of grewia gum and cimetidine and the physical mixture of cimetidine and grewia gum (1:1). The spectrum of the physical mixture was a summation of the peaks of the individual absorption peaks of the components of the physical mixture.

DSC screening of grewia gum–cimetidine interactions

The DSC trace for cimetidine showed a sharp melting endothermic peak at about 142 °C with a linear onset temperature of about 140 °C as shown in Fig. 4. The DSC traces for grewia gum show no peaks. The physical mixture of the gum with cimetidine showed no shift in the melting endotherm for cimetidine.

FT-IR screening of grewia gum–standard excipient interactions

The FT-IR spectra of lactose monohydrate, colloidal silicon dioxide, and grewia gum were compared with the physical mixtures (1:1) of grewia gum and lactose

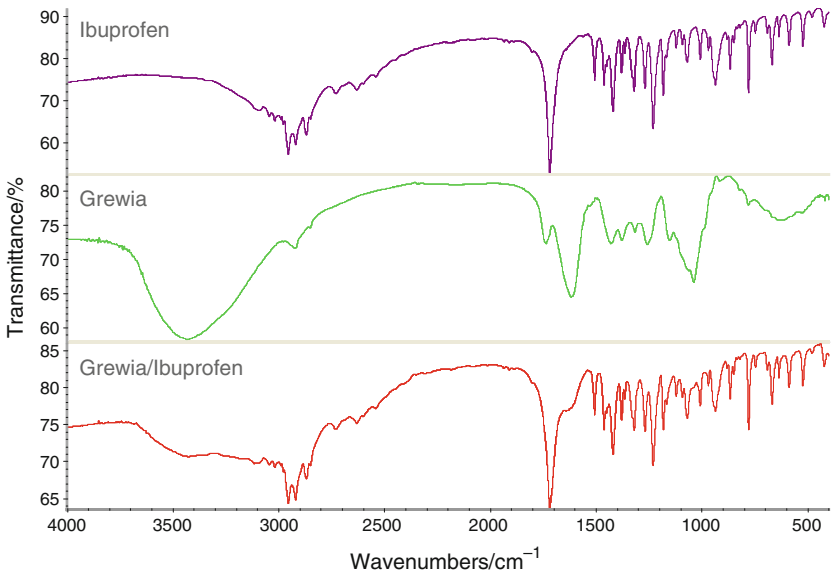

Fig. 1 FT-IR spectra of ibuprofen, grewia gum, and ibuprofen/grewia gum physical mixture (1:1)

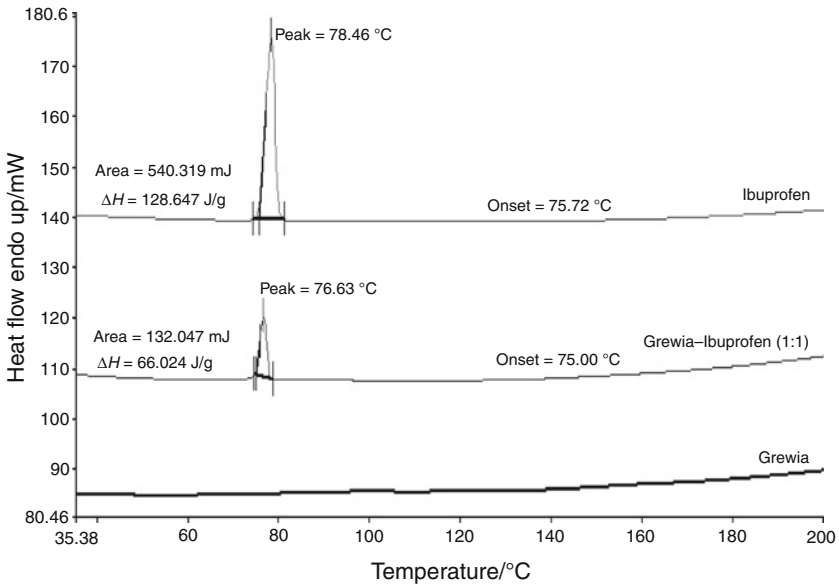

Fig. 2 DSC traces of ibuprofen, grewia polysaccharide gum, and the physical mixture at 20–200 °C and scan rate of 10 °C/min under nitrogen atmosphere

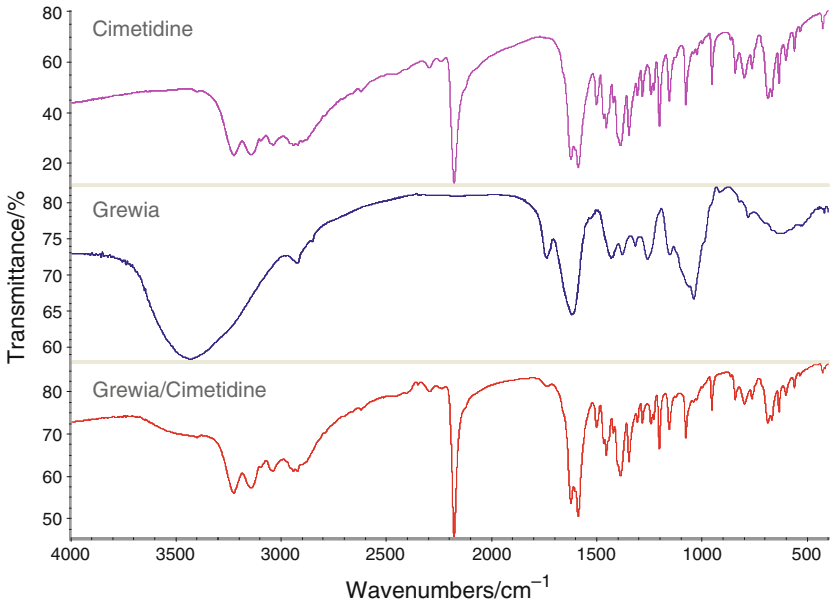

Fig. 3 FT-IR spectra of cimetidine, grewia gum, and cimetidine/grewia gum physical mixture (1:1)

Table 1 Assignment of FT-IR absorption bands for cimetidine

Wave number/cm^{-1}	Functional groups	Intensity
3226–3147	ν(N–H)	Broad, strong
2187	ν(C≡N)	Medium, strong
1622	ν(C=N)	Broad, strong
1586	ν_{asym}(C=N–C=C)	Medium, strong
1506	σ(N–SH)	Medium
1456	ν_{sym}(C=N–C=C)	Strong
697–668	ν(C–S)	Broad, strong

monohydrate, or colloidal silicon dioxide in Fig. 5. The absorption bands for lactose monohydrate were observed at 3600–3200 cm^{-1} which characterized the stretching vibrations of *C–O–H* bonds of lactose alcohol groups existing either free or bonded [28]. Two sharp bands at 3000–2800 cm^{-1} have been assigned to the stretching vibrations of two types of *C–H* bonds [29]: those that were within the constituents of lactose (glucose and galactose units), and those of the methyl alcohol function outside the glucose and galactose units. The stretching vibrations of water from crystallization of *OH* bonds and of water adsorbed to the surface of the lactose under analysis are a weak peak visible at 1600–1700 cm^{-1} [28]. The bands observed at 1500–1200 cm^{-1} also characterize the bending vibrations of *C–H* bonds [29]. All bands occurring between 1040 and 1160 cm^{-1} have been attributed to the asymmetrical stretching vibrations of *C–O–C* ether unit bonds

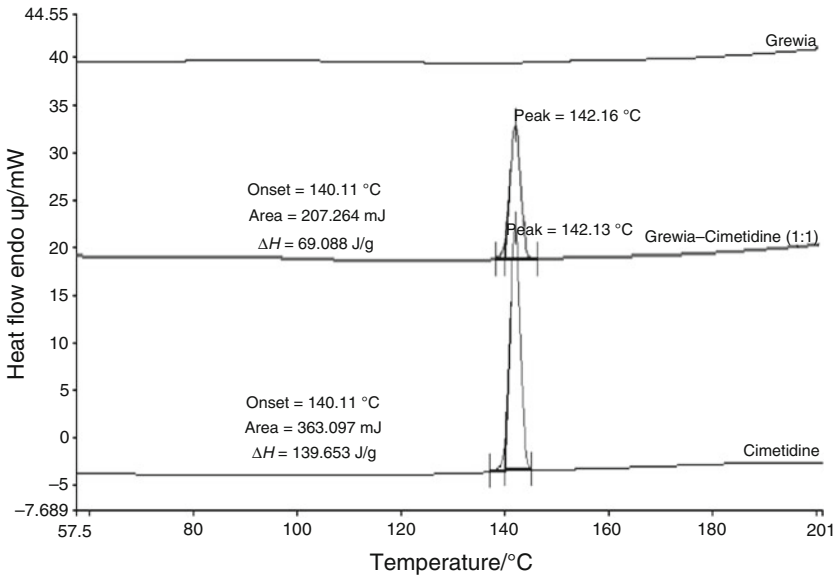

Fig. 4 DSC traces for cimetidine, grewia gum, and cimetidine/grewia gum physical mixture (1:1) under nitrogen atmosphere and a scan rate of 10 °C/min up to 200 °C

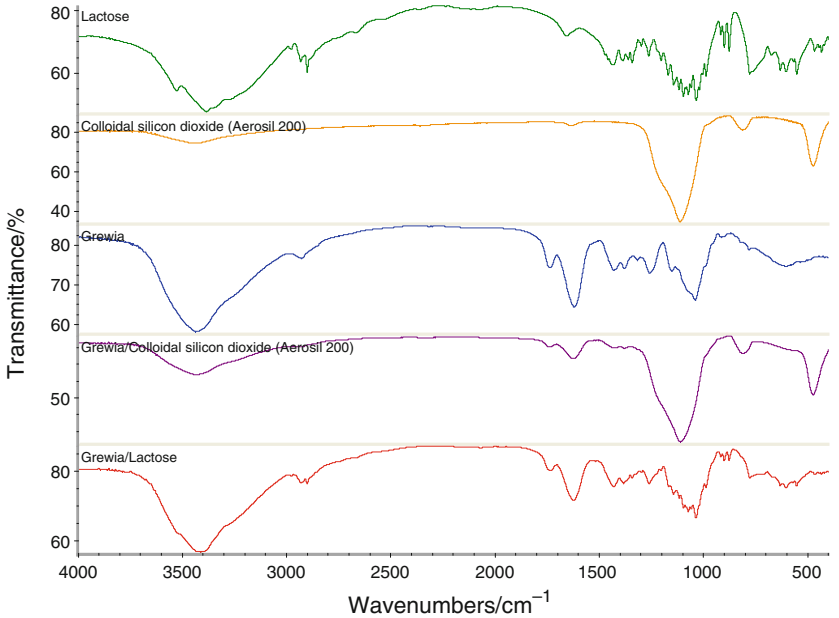

Fig. 5 FT-IR spectra of lactose, colloidal silicon dioxide, grewia, and the physical mixtures of grewia/colloidal silicon dioxide (1:1) or grewia/lactose monohydrate (1:1)

(glucose and galactose) [29]. From 730 to 960 cm^{-1} vibrations of the entire lactose molecule appeared. These bands are observed in all sugars [28]. A physical mixture of lactose and grewia gum (Fig. 5) gave absorption peaks which are a summation of the absorption bands from individual excipients.

Colloidal silicon dioxide (Aerosil 200®) showed a prominent characteristic peak at 1110 cm^{-1} (Fig. 5) due to *Si–O* linkage (15). The absorption band at 3600–3200 cm^{-1} may be due to *OH* stretching vibrations from moisture adsorbed on the surface of the excipient. A physical mixture of the excipient with grewia gum gave a resultant absorption band that is a summation of the individual absorption bands of the two excipients.

The FT-IR spectra for magnesium stearate, microcrystalline cellulose, grewia gum, and their physical mixtures (1:1) are shown in Fig. 6. The twin peaks at 1577 and 1466 cm^{-1} in magnesium stearate are attributed to asymmetric carboxylate (*COO−*) stretching vibration and symmetric carboxylate stretching vibration, respectively, whilst the peaks at 2917 and 2850 cm^{-1} are attributed to the *C–H* stretching vibration [30]. The broad band at about 3452 cm^{-1} is due to *OH* stretching vibrations of the associated water molecule. The physical mixture of magnesium stearate with grewia gum (1:1) showed the characteristic absorption peaks of magnesium stearate and grewia gum and appears to be a summation of the individual absorption peaks. The pure microcrystalline

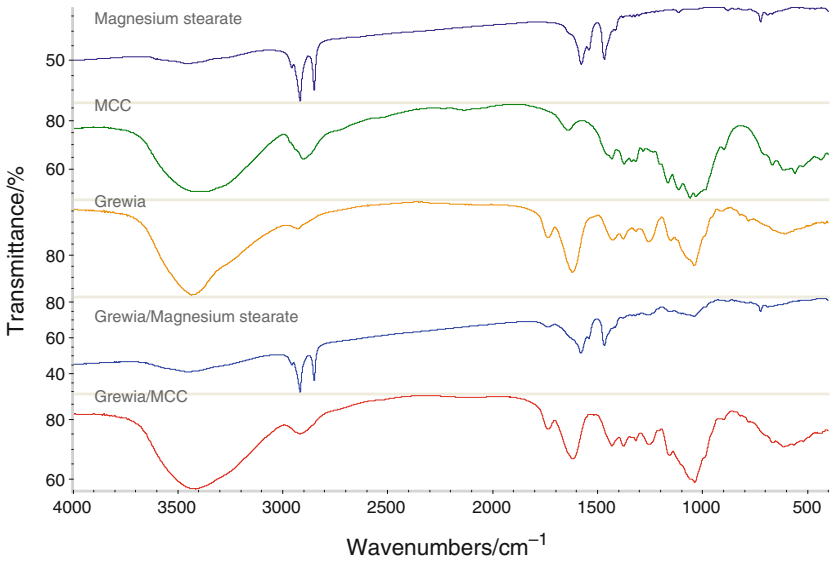

Fig. 6 FT-IR spectra of magnesium stearate, microcrystalline cellulose (MCC), grewia, and the physical mixtures of grewia/magnesium stearate (1:1) or grewia/microcrystalline cellulose (1:1)

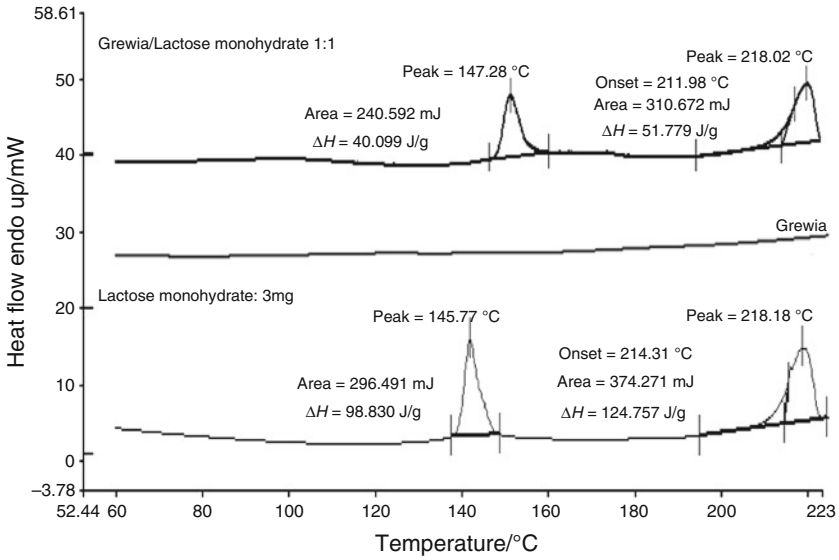

Fig. 7 DSC traces of lactose monohydrate and physical mixture of and grewia/lactose monohydrate, at 10 °C/min up to 225 °C under nitrogen atmosphere

cellulose spectrum shows several bands characteristic of cellulose structure, 3400 cm^{-1} [hydroxyl (OH) stretching vibrations], 2900 cm^{-1} (*CH* stretching), 1432 cm^{-1} (CH_2 stretching), and 1140–1400 cm^{-1} (*CH*, CH_2, and *C–O* stretching). The peak at 1640 cm^{-1} is attributed to the presence of water [31]. Physical mixture of the microcrystalline cellulose with grewia gum (1:1) showed no evidence of interaction. The spectrum of the mixture is only a summation of the absorption bands from the individual components.

DSC screening of grewia gum–standard excipient interactions

The DSC endotherm for lactose monohydrate showed a strong dehydration endotherm with a peak maximum temperature of about 145.7 °C, followed by the lactose melting point endotherm with an onset of about 213 °C and peak of 218.2 °C (Fig. 7). A physical mixture of grewia gum with lactose monohydrate (Fig. 7) showed little effect on the melting point onset and peak temperatures.

The DSC traces of magnesium stearate showed two endothermic events occurring at about 80–110 °C and a second at 110–130 °C (Fig. 8). The DSC scans of grewia gum and colloidal silicon dioxide or microcrystalline cellulose (fig not shown), show no melting point peaks. The observed trace of the physical mixtures of grewia gum with colloidal silicon dioxide or microcrystalline cellulose represent a summation of the data from the individual components of the physical mixture and did not result in any endothermic event outside that shown by the individual excipients.

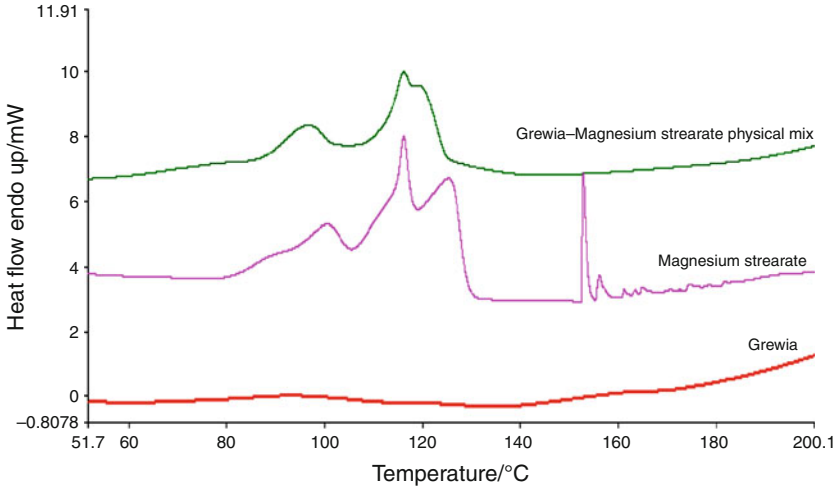

Fig. 8 DSC traces of magnesium stearate and physical mixture of grewia/magnesium stearate at 10 °C/min under nitrogen atmosphere

Discussion

Grewia gum–API interactions

The results indicate that both cimetidine and ibuprofen maintained the crystal morphology and the melting endotherm was still visible when combined with grewia gum. The disappearance of the melting point endotherm is an indication of conversion of a crystalline material to an amorphous form [32, 33]. The physical mixing of grewia gum with ibuprofen or cimetidine did not interfere with the nature of the materials and indicated that no interactions occur between grewia gum and cimetidine, or ibuprofen. It has been reported that even miniscule amounts of impurity in a material will affect the colligative properties of that material [9]. The depression of the temperature at maximum peak height might therefore be expected. The linear melting point onset of cimetidine or ibuprofen remained the same even in the presence of grewia gum (Figs. 2, 4).

The FT-IR results also confirm that no interactions occurred between grewia gum and cimetidine, or ibuprofen. It has been reported that any interaction with ibuprofen primarily interferes with the position or intensity of the FT-IR absorption peaks at 1710 and 2955 cm^{-1} which are caused by the carbonyl stretching vibration and the hydroxyl stretching vibration, respectively [25, 26]. The results show that both peaks including the fingerprint region of the individual components of the physical mixture were not affected. The FT-IR spectra of the physical mixtures are a summation of the characteristic traces obtained with the individual components of the physical mixtures and indicate that there was no chemical interaction of the drug with polymer in physical mixes [20].

Grewia gum–standard excipient interactions

Lactose monohydrate has a linear onset temperature of 213 °C. The strong endothermic peak maximum of about 145.7 °C is due to dehydration of the water molecule associated with the lactose monohydrate [18]. A physical mixture of grewia gum with lactose monohydrate (Fig. 7) showed little effect on the melting point onset and peak temperatures. This result agrees with the FT-IR analysis which indicated that no interactions occur between grewia gum and lactose monohydrate.

Colloidal silicon dioxide (Aerosil 200®) is an anhydrous form of silicon dioxide with a melting point of 1610 °C [18] which is beyond the range for this experiment. Microcrystalline cellulose is made of microcrystals each containing a chain of over 200 glucose molecules [34]. The microcrystals are hinged together and surrounded by amorphous cellulose to form cellulose microfibril. Consequently both materials showed no endothermic peaks. The resultant trace after physical mixing with grewia gum was a summation of the individual traces. This indicates that no interaction occurred between grewia gum and colloidal silicon dioxide or microcrystalline cellulose (fig not shown).

The DSC traces of magnesium stearate showed two endothermic events occurring at about 80–110 °C and a second at 110–130 °C (Fig. 8). The first event is attributable to loss of water from the hydrated state of the magnesium stearate, whilst the second event suggests that melting of the material occurred at this point [10]. What appears to be a third endotherm at 147 °C may be attributable to onset of degradation of the material. After mixing the magnesium stearate with grewia gum (Fig. 8), the peak at 147 °C disappeared and does suggest a suppression of the degradation of magnesium stearate. This observation

does not agree with the FT-IR analysis which showed no obvious interactions between grewia gum and magnesium stearate. This variation may be attributable to the different temperatures used for analysis by the two techniques. Interactions with magnesium stearate are frequently reported [4]. Such interactions do not, however, always translate to an incompatibility [9].

Conclusions

Grewia gum does not interact with the APIs used in this study (cimetidine and ibuprofen) and may be a useful excipient in pharmaceutical formulation. Both DSC and FT-IR evaluation of the interaction between physical mixtures of grewia polysaccharide gum and other excipients used in the formulation of the tablets revealed no interaction between grewia gum and microcrystalline cellulose, colloidal silicon dioxide, or lactose monohydrate.

There is evidence to suggest that grewia gum may interact with magnesium stearate. This result was, however, not supported by the FT-IR analysis. Although, it is accepted that any changes in the DSC traces may be as a result of an interaction, such changes are not always due to incompatibilities [9, 21]. For industrial extrapolation, however, it may be necessary to consider an alternative to magnesium stearate as a lubricant in the formulation of dosage forms containing grewia gum as excipient.

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