International Journal of Pharmaceutics 422 (2012) 91–100

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Tannate complexes of antihistaminic drug: Sustained release and taste masking approaches☆

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ARTICLE INFO

Article history:
Received 30 July 2011
Received in revised form
24 September 2011
Accepted 17 October 2011
Available online 21 October 2011

Keywords:
Brompheniramine maleate
Tannic acid
Complex
Solid-state NMR
Electronic tongue
Bitter taste

ABSTRACT

The aim of this investigation was to evaluate the complexation potential of brompheniramine maleate (BPM) and tannic acid (TA) for sustained release and taste masking effects. The complexes (1:1–1:7 TA to BPM ratio) were prepared by the solvent evaporation method using methanol, phosphate buffer pH 6.8 or 0.1 N HCl as common solvents. The complexes were characterized microscopically by scanning electron microscopy (SEM), chemically by Fourier transform infrared (FTIR) and solid-state NMR (SSNMR), thermally by differential scanning calorimetry (DSC), for crystallinity by powder X-ray powder diffraction (PXRD), for organoleptic evaluation by electronic tongue (e-tongue), and for solubility in 0.1 N HCl and phosphate buffer pH 6.8. The dissolution studies were carried out using the USP II method at 50 rpm in 500 ml of dissolution media (0.1 N HCl or phosphate buffer pH 6.8). SEM images revealed that the morphology of complexes were completely different from the individual components, and all complexes had the same morphological characteristics, irrespective of the solvent used for their preparation, pH or ratio of BPM and TA. The FTIR spectra showed the presence of chemical interactions between the TA and BPM. DSC, PXRD and SSNMR indicated that the drug lost its crystalline nature by formation of the complex. Complexation has significantly reduced the solubility of BPM and sustained the drug release up to 24 h in phosphate buffer pH 6.8 media. The bitter taste of the BPM was completely masked which was indicated by Euclidean distance values which was far from the drug but near to its placebo in the complexes in all ratios studied. The taste masked complexes can be potentially developed as suitable dosage forms for pediatric use. In summary, complexation of BPM and TA effectively sustained the dissolution and masked the bitter taste of drug for the development of suitable dosage forms for pediatric use.

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1. Introduction

Brompheniramine (BP), 3-(4-bromophenyl)-N,N-dimethyl-3-pyridin-2-yl-propan-1-amine is an alkylamine class antihistamine. The commercial preparation contain its maleate salt due to its higher solubility and ease of handling compared to drug base which is liquid at room temperature (Sperber and Papa, 1951, 1954; Walter, 1962). It is a first-generation antihistamine and available over the counter for the treatment of the symptoms of the common cold and allergic rhinitis, such as runny nose, itchy eyes, watery eyes, and sneezing (Betts, 1996). Brompheniramine works by acting as an antagonist of histamine H_1 receptors. It also functions as a moderately effective anticholinergic agent and antimuscarinic agent similar to other common antihistamines such as diphenhydramine (Passalacqua et al., 2002). Its usual adult and pediatric doses are 6–8 mg and 2–4 mg every 4–6 h, respectively (Brompheniramine maleate material safety data sheet, 2011). Patient compliance could be improved by administration in a sustained and/or controlled release formulation, as it would reduce the frequency of administration, adverse effects and treatment cost. Pharmaceutical technologies reported to sustain and/or control the drug release are solid dispersion with water insoluble polymers e.g. Eudragit (Pignatello et al., 2002), ethylcellulose (Ghaly et al., 1993), novel dosage forms such as floating dosage forms (Hu et al., 2010), osmotically controlled delivery systems (Verma et al., 2000), colloidal drug delivery system (Slowing et al., 2008), complexation with cyclodextrins (diethyl-β-cyclodextrin, triethyl-β-cyclodextrin, triacetyl-β-cyclodextrin, tributanoyl-β-cyclodextrin etc.) (Sinha et al., 2002) and tannic acid (TA) (Burgalassi et al., 1996). However, no investigators have reported the complex of brompheniramine maleate (BPM) and TA for sustained release effect in published literature.

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0378-5173/$ – see front matter. Published by Elsevier B.V.
doi:10.1016/j.ijpharm.2011.10.033

BPM is a bitter molecule and may have crucial impact on the palatability of its formulations (Brompheniramine maleate MSDS http://datasheets.scbt.com/sc-210967.pdf). The palatability and compliance specifically for children are interconnected since unpatability ensued in no compliance. This has implication in adherence to dosage regimen and therapeutic outcome. The bitterness of drug can be masked or suppressed by pharmaceutical technologies such as coating with water-insoluble polymers, e.g., Eudragit or ethyl cellulose (Cerea et al., 2004), complexation (Rahman et al., 2010), solid dispersion (Khan et al., 2007), and using sweetener and/or flavor (Strickley et al., 2008).

TA ($C_{76}H_{52}O_{46}$), a hydrolyzable tannin, has numerous industrial, medicinal and food additive applications. It is a naturally occurring compound with a central sugar molecule substituted with five digallic acid moieties (Aelenei et al., 2009; Herrera-Becerra et al., 2010). TA is also used as a drug for the treatment of burns for its astringent, haemostatic and antibacterial activities (Garlea et al., 2010). It is also mentioned in Code of Federal Regulation 21 as one of the inactive ingredient of many over the counter drug products (Code of Federal Regulation 21 – Food and Drug Administration). Recently TA and TA-mimicking dendrimers have been shown to be a potential elastin and collagen stabilizing agent (Kasyanov et al., 2006). TA acts as a cross-linking agent in the formation of nano- and microsystems due to its ability to interact with amino group to form complexes and/or salts through ionic, hydrogen bonding and/or hydrophobic interactions (Hagerman and Butler, 1981). Its use has been reported in the formation of microparticles of capsaicin (Xing et al., 2004) and allyl isothiocyanate (Zhang et al., 2011), production of iron oxide nanoparticles (Herrera-Becerra et al., 2010), micellar delivery of doxorubicin (Kim et al., 2009), production of nanosystems of bovine serum albumin (Shutava and Lvov, 2006) and doxycycline delivery with collagen (Albu et al., 2010). It is also used as a salt and/or complex former to sustain the drug release. Lidocaine (Burgalassi et al., 1996), amphetamine, morphine, atropine, prophenpyridamine (Cavallito and Jewell, 1958), diethylcarbamazine (Baveja et al., 1985), chlorpheniramine (Cavallito et al., 1963; Leflein and D'Addio, 2003), phenylephrine (Cavallito et al., 1963; Bogner and Walsh, 1964), heroine, hydromorphone, L-α acetylmethadol (Brands et al., 1980), carbetapentane (Leflein and D'Addio, 2003) and diphenhydramine (Redkar et al., 2006; Nandgude et al., 2008) have been reported as a tannate complex and/or salt for sustained release action. Another pharmaceutical application of TA is its ability to suppress or mask the bitter taste of a drug molecule by the formation of its tannate salt and/or complex. Tannate salt and/or complex has been reported to mask the bitter taste of berberine (Chauhan et al., 1970) and propanolamine (Daharwal et al., 2005).

The focus of present study was to investigate the complexation approach of TA with BPM for sustained release action and taste masking by evaluating their physicochemical and organoleptic properties.

2. Materials and methods

2.1. Materials

BPM and TA were purchased from Fisher Co. (Norcross, GA, USA) and Acros Organics, USA (Morris Plains, NJ, USA), respectively. Methanol, tetrahydrofuran, potassium hydrogen phosphate and sodium hydroxide were obtained from Fisher Scientific Co. (Norcross, GA, USA). Size '3′ hard gelatin capsules shell was generously gifted by Capsugel, Greenwood, MA, USA. All other chemicals and reagents were of analytical grade.

2.2. Methods

2.2.1. Preparation of complexes

Complexes were prepared by the solvent evaporation method (Rahman et al., 2010). Briefly, TA (0.05 M) and BPM (0.35 M) stock solutions were prepared in methanol, phosphate buffer pH 6.8 (50 mM) or 0.1 N HCl. The drug and complexing agent solutions were mixed in different proportion to make 1:1 (SD-1) to 1:7 (SD-7) TA to BPM molar ratios complexes. Complexes precipitated as soon as the solutions of BPM and TA in phosphate buffer and 0.1 N HCl was mixed. The amounts precipitated in acidic condition were less than those at neutral pH. The complexes were retrieved by evaporating methanol at room temperature for 24 h while water was removed by heating at 40 °C for 6 h and further vacuum drying at 30 °C for 24 h. The complexes were crushed and passed through sieve #60 and kept in closed containers for further characterization studies.

Physical mixtures were also prepared by triturating the drug and TA using a mortar and pastel (1:1 (PM-1), 1:4 (PM-4) and 1:7 (PM-7) molar ratios of TA and BPM) followed by passing through sieve #60.

2.2.2. Fourier transform infrared spectroscopy

Chemical characterization was done using Fourier transform infrared (FTIR) spectroscopy equipped with an attenuated total reflectance accessory (Thermo Nicolet Nexus 670 FTIR, GMI Inc., Ramsey, MN, USA). Spectra were collected in transmittance mode with 50 scans and 4.0 points of resolution. OMNIC ESP software (version 5.1) was used to capture and analyze the spectra.

2.2.3. Differential scanning calorimetry

Thermal properties of BPM, TA, their physical mixtures and complexes were also investigated by differential scanning calorimetry (DSC). DSC thermograms were collected with a DSC Q2000 (TA Instruments Co., New Castle, DE, USA). The sample equivalent to 1–2 mg was hermetically sealed in an aluminum pan. The temperature ramping rate was 10 °C/min up to 250 °C. This temperature range covered the melting point of both components. The nitrogen gas was flowing at a pressure of 20 psi to provide inert atmosphere during the measurement and prevent oxidation reaction.

2.2.4. Powder X-ray diffraction

The crystallinity was determined by PXRD and performed using a benchtop X-ray diffractometer (MD-10 mini diffractometer, MTI Corporation, Richmond, CA, USA) with Cu K 2α rays (λ = 1.54056 Å), a voltage of 25 kV and a current of 30 mA, in flat plate $\theta/2\theta$ geometry, over the 2θ ranges 15–75°. Diffraction patterns were recorded for 20 min.

2.2.5. Solid-state nuclear magnetic resonance spectroscopy

^{13}C solid-state NMR (SSNMR) experiments were performed at 75 MHz on a Varian VNMR 400 spectrometer (Agilent, formerly Varian Inc., Palo Alto, CA) using a Varian T3 narrow-bore double-resonance probe fitted with a 4-mm PENCIL™ module. All solid-state experiments included ramped-amplitude cross polarization (CP) (Metz et al., 1994; Pines et al., 1973) magic-angle spinning (MAS) (Andrew et al., 1959) at a rate of 5 kHz, and SPINAL64 decoupling (Fung et al., 2000) at a field strength of ~72 kHz. Spectral acquisitions included total suppression of spinning sidebands (TOSS) (Dixon et al., 1982) and samples were externally referenced with 3-methylglutaric acid (Barich et al., 2006). Pulse delays of at least 1.5 times the ^{1}H T_1 (obtained via inversion-recovery) were used. All spectral acquisitions took place at ambient temperature.

2.2.6. Scanning electron microscopy

The powder morphology of BPM, TA and complexes were visualized by scanning electron microscopy (SEM, JSM-6390 LV, JEOL, Tokyo, Japan) at a working distance of 20 mm and an accelerated voltage of 5 kV. Samples were gold coated with a sputter coater (Desk V, Denton Vacuum, NJ, USA) before SEM observation under high vacuum of 45 mTorr and high voltage of 30 mV.

2.2.7. Solubility studies

Solubilities of the complexes and BPM were determined in phosphate buffer pH 6.8 and 0.1 N HCl. An excess amount of BPM and complexes were suspended in 5 ml of media and vortexed for 30 s. The samples were continuously shaken in a horizontal shaker at 120 rpm and 25 °C for 72 h. The equilibrium time for maximum solubilization was determined based on our preliminary investigations. The samples were filtered through a 0.45 μm nylon filter, diluted with mobile phase and injected into the HPLC system for the quantitation of solubilized drug. Experiments were performed in triplicate. The HPLC method was developed and validated as per ICH guidelines (International Conference of Harmonization, 2005). An HP 1050 (Agilent technologies, CA, USA) HPLC was fitted with quaternary pumps, autosampler, and UV detector set at a wavelength of 210 nm, and column temperature was maintained at 26 °C. The HPLC stationary phase was composed of a reverse phase Luna C18 (2), 4.6 × 254 mm (5 μm packing) column and a C18, 4.6 × 12.5 mm (5 μm packing) Luna C18 (2) guard column (Phenomenex Torrance, CA, USA). The composition of the mobile phase was phosphate buffer pH 5.0 (20 mM):methanol:tetrahydrofuran (46:50:04) and pumped isocratically at a flow rate of 1 ml/min.

2.2.8. Dissolution studies

The complexes and physical mixtures equivalent to 12 mg of BPM were filled into hard gelatin capsules (size #3). The dissolution experiment was performed using the USP II paddle method at 37 °C and 50 rpm in 500 ml phosphate buffer (0.2 M) or 0.1 N HCl media, respectively. The dissolution experiment was run for 24 h and 2 h in phosphate buffer pH 6.8 and 0.1 N HCl media, respectively. The amount of drug dissolved at different time intervals was determined by the above-mentioned HPLC method. Studies were performed in triplicate.

2.2.9. Taste masking efficiency

α-Astree liquid and taste analyzer (e-Tongue) was used for organoleptic evaluation of complexes. The system consists of seven potentiometric sensors designated as JB, BA, BB, HA, ZZ, CA and GA by the manufacturer (Alpha MOS, Toulouse, France), an Ag/AgCl reference electrode (Metrohm Ltd., USA), a mechanical stirrer (Metrohm Ltd., USA), a 48-position sample changer and 802 swing head for sampling (Metrohm Ltd., USA), an interface electronic module for signal amplification and analog to digital conversion (Alpha MOS, Toulouse, France) and AlphaSoft software for data collection and analysis (Alpha MOS, Toulouse, France). The samples were prepared by dissolving the complex equivalent to 4 mg/5 ml BPM in artificial saliva (pH 5.5) (Kwokal et al., 2003) to simulate the commercially available suspension. BPM and corresponding placebo containing only TA samples were also prepared. The sensors were conditioned, calibrated and diagnosed by running the standard samples provided by the Alpha MOS. Nine measurements were made for each sample, signal was collected for 120 s, and the last 20 s of the signal were used for data analysis. After each formulation analysis, the sensors were washed with deionized water. A reference standard, hydrochloric acid (0.01 M), was analyzed after each sample measurement to normalize the sensors' responses over measurements periods.

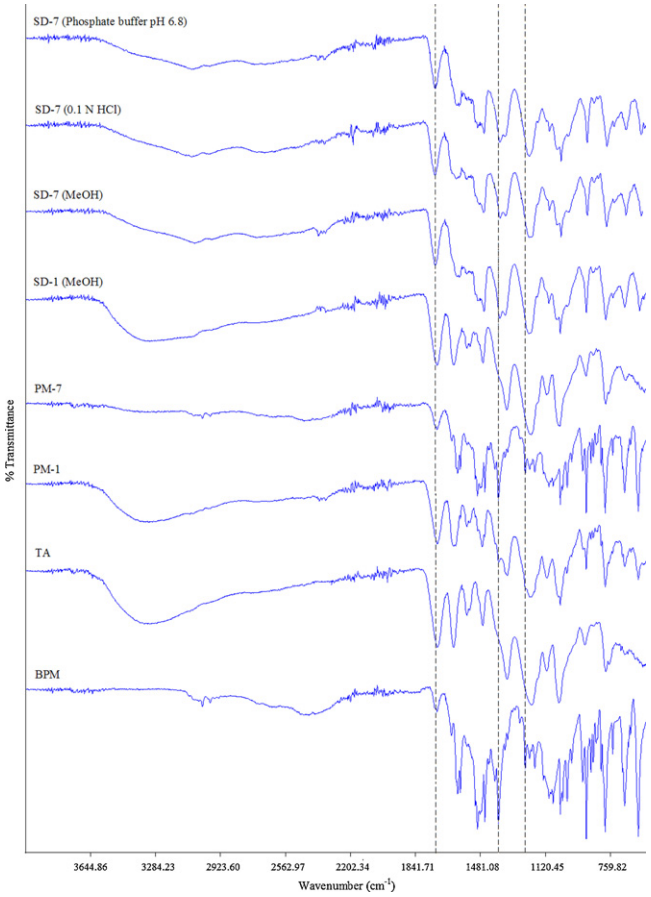

Fig. 1. Fourier transform infrared spectra of the BPM, TA, PM and complexes.

3. Results and discussion

3.1. Fourier transform infrared spectroscopy

The FTIR spectrum of BPM showed an aliphatic and aromatic C–N stretching vibration at 1205 and 1355 cm^{-1}, respectively, two peaks at 2966 and 3010 cm^{-1} due to alkane group stretching vibrations (Fig. 1) and a stretching vibration at 863 cm^{-1} due to bromobenezene. It also showed C=C stretching and bending vibrations at 1623 and 880–1006 cm^{-1}, respectively. The spectrum of TA showed C=O stretching at 1695 cm^{-1} and C–O stretching at 1018 cm^{-1}. Out-of-plane and in-plane bending vibration of O–H was detected at 752 and 1315 cm^{-1}, respectively, and its stretching vibration was at 3355 cm^{-1}. The physical mixture of BPM and TA showed peaks corresponding to the individual components, indicating no chemical interaction existed between the components. Compared to the corresponding physical mixture at the same molar ratio, the FTIR spectra of complexes showed the absence of the characteristic peaks of BPM indicating a significant chemical interaction between BPM and TA. These interactions could be explained by the chemical nature of TA and BP base. BP is an amino group containing weakly basic molecule with pK_a 3.59 and 9.12 (Trissel, 2000). TA interacts strongly with amino group containing molecules through ionic, hydrophobic and/or hydrogen bonding (Hagerman and Butler, 1981). TA (pK_a 6, Robert and Guy, 1976) and maleic acid (pK_a 1.5 and 6.5, Pine et al., 1980) are weak acid. The interactions involved replacement of maleic acid with the TA molecule in the BP salt. This was confirmed by appearance of characteristic maleic acid carbonyl peak at 1705 cm^{-1} in the complexes (Barra et al., 1999). The peak was intense and sharp in it unlike BPM which appears as a small broad peak. It

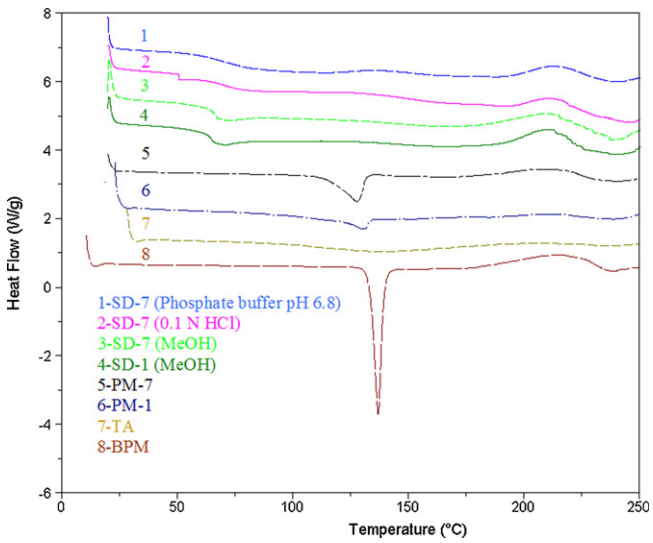

Fig. 2. Differential scanning calorimetry thermograms of the BPM, TA, PM and complexes.

indicated that maleic acid dissociated from brompheniramine and exist as a separate entity in the complex. Furthermore, chemical interactions were evident from shift in the aromatic C–N stretching vibration of BPM from 1355 cm^{-1} to 1347 cm^{-1} and disappearance of aliphatic C–N stretching vibration which were present in BPM and their physical mixture at 1205 cm^{-1}. However the aromatic C–N stretching band intensity was very weak in the complexes compared to parent BPM. Similarly, the –OH stretching vibration of TA broadens, indicating possible hydrogen bonding between TA and brompheniramine. Furthermore, the spectra of all molar ratios studied showed identical spectra irrespective of solvents and pH indicating no effect of solvent and pH on the FTIR spectra of the complexes.

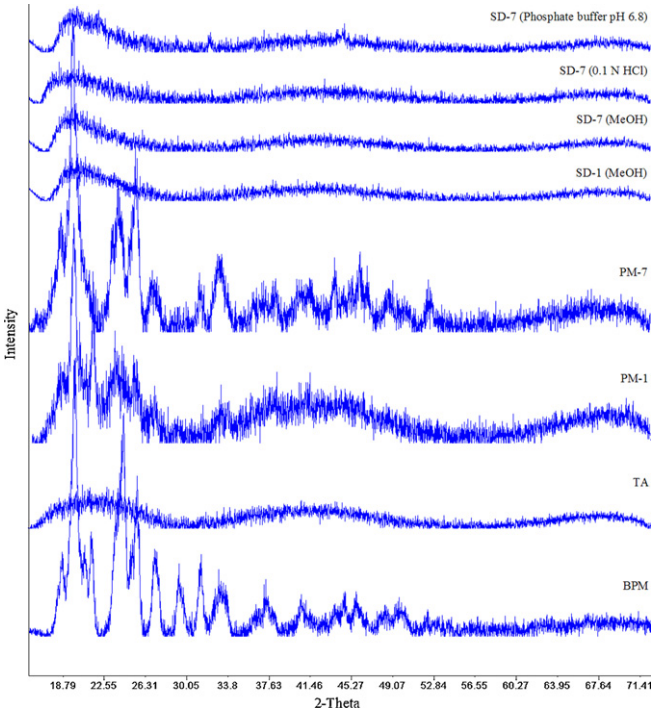

Fig. 3. Powder X-ray diffractograms of the BPM, TA, PM and complexes.

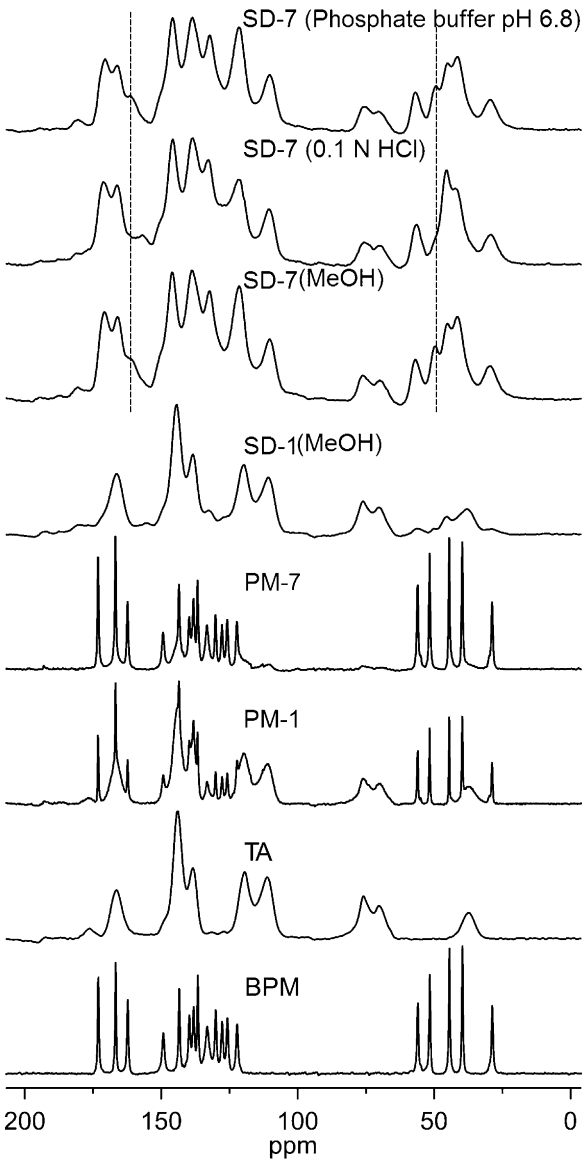

Fig. 4. ^{13}C SSNMR spectra of the BPM, TA, PM and complexes.

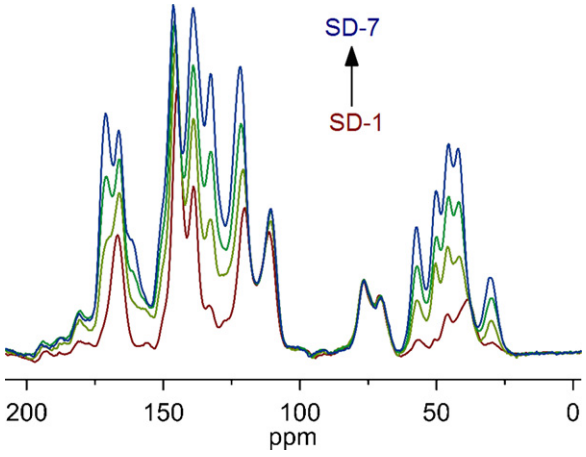

Fig. 5. ^{13}C SSNMR spectra of SD-1, SD-3, SD-5 and SD-7 prepared by drying from methanol. Spectra are scaled to the same relative amount of TA.

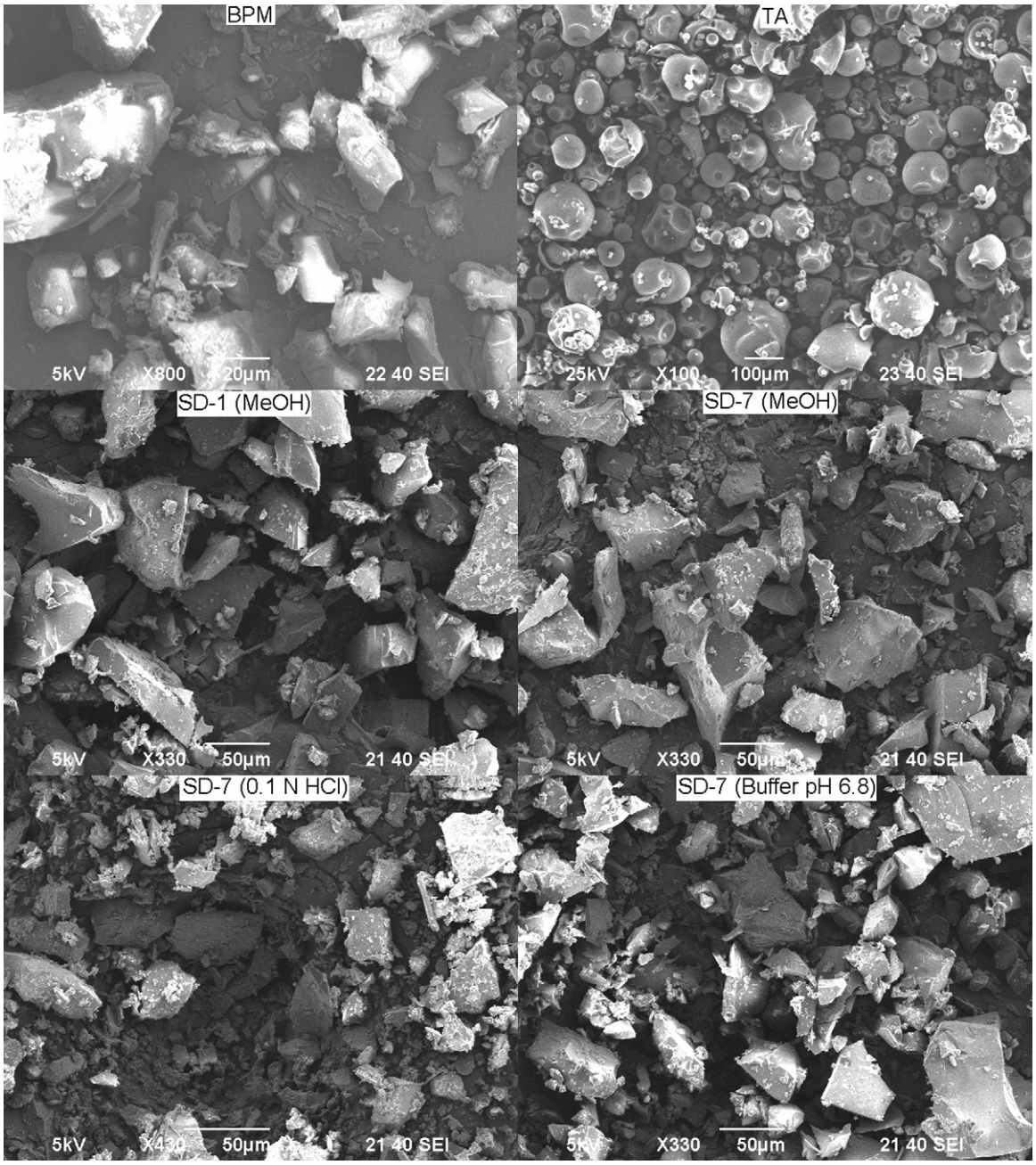

Fig. 6. Scanning electron microscope photomicrographs of the BPM, TA, PM and complexes.

3.2. Differential scanning calorimetry

The DSC thermogram of BPM showed a melting endotherm at 137.1 °C indicated the crystallinity of BPM used in the study (Fig. 2). The DSC thermogram of TA did not show any endotherm indicating its amorphicity. The equimolar physical mixture of BPM and TA showed broader endothermic peak at lower temperature (134.4 °C) which was probably due to the interaction of TA with the melt of BPM. The complexes also showed no endotherm indicating its amorphous nature. Thus, the drug lost its crystalline nature during the complex formation. However, a weak endotherm was observed in the complexes (all molar ratios) at 75 °C that was not observed in the thermogram of individual components. This endotherm might indicate the formation of new solid phase due to drug complexation with TA through ionic, hydrophobic and/or hydrogen-bond interactions. All molar ratios prepared using different solvents and pH showed flat endotherm indicating no effect of solvent and pH on the thermal properties of complexes.

3.3. Powder X-ray diffraction

Fig. 3 shows the powder diffraction patterns of the samples. BPM showed sharp peaks at 2θ value of 19.02, 20.2, 21.7, 24.5, 25.85, 27.4, 29.65 and 31.70° indicating the crystallinity of the drug raw material. The TA showed halo diffractogram devoid of any reflection peaks indicating its amorphous nature. The physical mixtures showed the characteristics peaks of BPM, although less intense due to drug solid dilution by TA in the samples. The complexes at all the molar ratios prepared in different solvent and pH showed same halo diffractogram similar to TA and did not show the characteristic peaks of the drug. The complex formation caused a change in physical state of the drug from crystalline to amorphous nature. In

addition, the absence of any new peaks in the diffractograms of the complexes might indicate that the new solid state observed in the corresponding DSC thermograms was amorphous in nature with the characteristic phase transition at 75 °C.

3.4. Solid-state nuclear magnetic resonance spectroscopy

Fig. 4 shows ^{13}C SSNMR spectra of bulk BPM and TA, as well as physical mixtures (PM-1 and PM-7). The spectrum of raw BPM contains sharp, crystalline peaks whereas the spectrum of raw TA consisted of broad, amorphous chemical shift peaks. These observations are consistent with the DSC and PXRD observations of the crystalline and amorphous natures of BPM and TA, respectively. The spectra of the physical mixtures showed overlapping peaks that corresponded to the individual components, indicating a lack of interactions between the TA and BPM.

^{13}C SSNMR spectra of complexes prepared from solution (MeOH, 0.1 N HCl, or pH 6.8 phosphate buffer) showed broad amorphous peaks and are completely different from their individual components. This was indicated by the change in the values of chemical shift suggesting strong chemical interaction between TA and BP and the formation of new solid phase. Comparing the spectra of complexes prepared from 0.1 N HCl versus those from pH 6.8 or methanol demonstrated differences among these solution-prepared samples. The most apparent differences existed near ~160 and 45 ppm, where the locations of peaks differed. This was likely the result of differences in the ionization state of the maleic acid (pK_as of 1.5 and 6.5) and BP (pK_as of 3.59 and 9.12) under the different preparation conditions.

The complexes prepared from methanol were further analyzed by SSNMR as a function of TA:BPM. Fig. 5 shows a spectral overlay of complexes SD-1, SD-3, SD-5 and SD-7 prepared from methanol. The spectra were all scaled vertically so that the TA signal contribution was the same in each sample. This meant that the displayed peak-intensity changes arose from the increasing levels of BPM in each sample. The figure clearly showed a progressive increase in the broad, amorphous peaks as the ratio of TA:BPM increases from SD-1 to SD-7. No abrupt changes, such as a significant change in peak location or the appearance of new peaks, were observed in the spectra as the TA:BPM ratio increased. This suggested that the TA and BPM existed in a single amorphous phase in the complexes. They were interacting at all the ratio studied, even at high loading levels of BPM, since the appearance of a separate BPM-rich phase would be expected to produce new peaks. The existence of a single phase is supported by ^{1}H T_1 values, which were the same for all peaks in the spectra of SD-1 through SD-7.

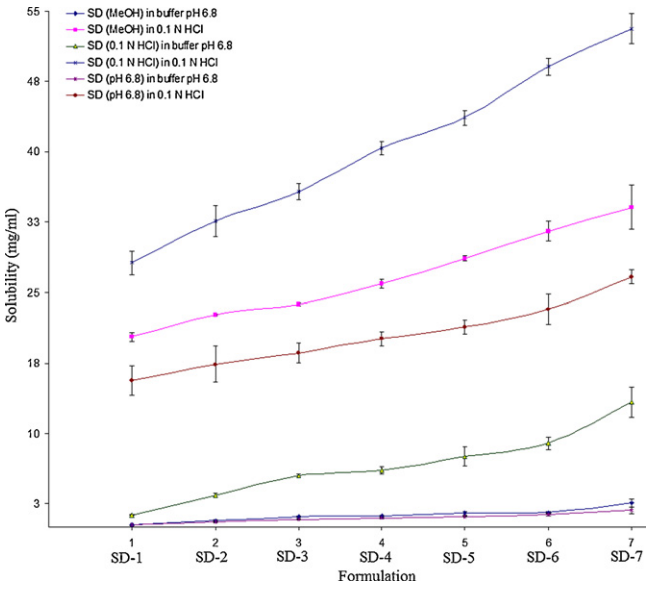

Fig. 7. Solubility profile of complexes in 0.1 N HCl and phosphate buffer pH 6.8.

In an effort to identify the peaks in the ^{13}C SSNMR spectra of amorphous samples, it was important to acquire the spectrum of amorphous BPM. Samples of BPM were lyophilized and cryomilled, since both of these preparation methods are commonly used to produce amorphous solids. The resulting materials were analyzed at room temperature by DSC and ^{13}C SSNMR. No evidence for the presence of amorphous material was observed in any of the samples. This suggested that either (i) the kinetics of crystallization is too rapid for complete amorphization of BPM to occur and/or (ii) amorphous BPM was unstable at room temperature, and the analysis at low temperatures would be necessary to observe the amorphous phase without significant crystallization. The drug existed in an amorphous state in the complexes and stable at room temperature. This further indicated that a significant chemical interaction existed between BPM and TA molecules to keep the material in a stable amorphous phase.

3.5. Scanning electron microscopy

The photomicrograph of TA showed irregular spherical particles and that of BPM showed broken crystals suggesting the crystalline nature of the drug (Fig. 6). The complexation of both ingredients showed only one type of broken particles that were

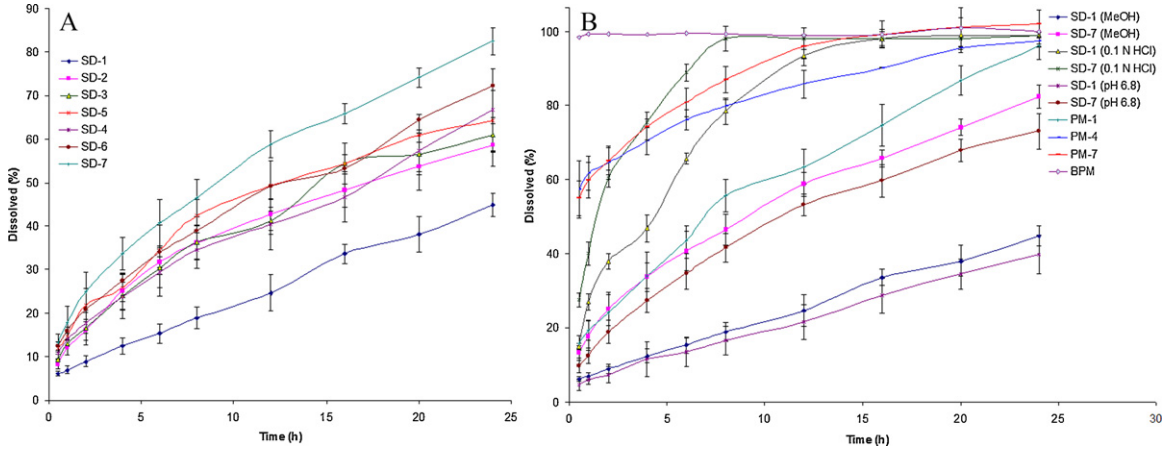

Fig. 8. Dissolution profiles of complexes (A) prepared in methanol and (B) prepared in 0.1 N HCl and phosphate buffer pH 6.8.

different in shape and texture than those for the starting raw materials, indicating homogeneity of the preparations. Photomicrographs of complex prepared in 0.1 N HCl and phosphate buffer also showed same type of solid phase as prepared in methanol, indicating insignificant effect of solvents and pH on the morphology of complex.

3.6. Solubility studies

Solubility profiles are shown in Fig. 7. The complex drastically decreased the solubility of BPM that was found to be 43.01 ± 1.25 and 73.99 ± 0.55 mg/ml in 0.1 N HCl and phosphate buffer pH 6.8, respectively. The solubility of complexes (SD-1 to SD-7) varied from 0.261 ± 0.003 to 2.563 ± 0.406 mg/ml, 1.275 ± 0.038 to 13.329 ± 1.570 mg/ml and 0.204 ± 0.017 to 1.760 ± 0.373 mg/ml in phosphate buffer pH 6.8 for complex prepared from methanol, 0.1 N HCl or phosphate buffer, respectively. Likewise, the solubilities of the complexes (SD-1 to SD-7) prepared from methanol, 0.1 N HCl, or phosphate buffer were 20.294 ± 0.482–34.082 ± 2.388 mg/ml, 28.148 ± 1.274–53.142 ± 1.659 mg/ml and 15.631 ± 1.581–26.666 ± 0.745 mg/ml, respectively, when tested in 0.1 N HCl. The high and low solubility of BP from the complexes in the acidic and neutral conditions, respectively, could be explained by chemical interaction between the drug and TA. The FTIR studies indicated potential chemical interactions between the components of complexes. Due to the weakly basic nature of the BP, the association between the BPM and TA is stronger in the neutral condition and therefore small amount of drug was solubilized in this condition. In general, basic molecule ionizes in the acid condition and thus more solubility is expected (Li et al., 1999). In contrast, the association was weaker between the complex components in the acidic condition due to the BP ionization. Another possibility was the replacement of TA in the complexes with hydrochloric acid which is the stronger acid and might have formed hydrochloride salt of BP. The higher solubility in the complexes prepared in the 0.1 N HCl was due to the formation of an acidic microenvironment which favor dissociation of TA and BPM. Similarly, the lower solubility in the complexes prepared in the buffer pH 6.8 was due to the neutral microenvironment which hindered the dissociation and hence retarded the solubilization.

3.7. Dissolution studies

Fig. 8A shows the dissolution profile of the complexes prepared in methanol. The entire drug dissolved from the complexes in less than 1 h in 0.1 N HCl at all the ratios of the complexes prepared by different solvents and pHs (data not shown). The dissociation of the complexes was promoted in the acidic media that could explain the immediate dissolution of the drug. However, the drug dissolution in the neutral condition (pH 6.8) was sustained for more than 24 h. This was probably due to the weaker driving forces to dissociate the complexes in the absence of the acidic microenvironment. The drug dissolution increased with the ratio of drug in the complexes and could be arranged with increasing drug amount as SD-1 < SD-2 < SD-3 < SD-4 < SD-5 < SD-6 < SD-7. Similar patterns of drug dissolution were shown by complexes prepared from 0.1 N HCl or phosphate buffer (pH 6.8). However, the percentage of drug dissolved was higher from the complex prepared in the 0.1 N HCl and lower from the complex prepared in phosphate buffer (Fig. 8B). This was possibly due to the precipitation of acidic chloride salt within the complex matrix during the drying step and hence created an acidic microenvironment during the dissolution to promote a faster drug dissolution, and vice versa in respect to the neutral phosphate salts. In the acidic and neutral condition the association was weaker and stronger between the components of complexes, respectively. Thus, the rank order of the dissolution of the drug from its complexes could be arranged as 0.1 N HCl > methanol > phosphate buffer. Furthermore, the dissolutions of the corresponding raw drug, physical mixture (1:1 and 1:7 TA:BPM) and complexes were compared. The extent of dissolution was higher in the physical mixture than the corresponding complexes albeit less than the raw drug in the neutral condition. This was due to the chemical interaction between BPM and TA in the physical mixture as soon as it contacted the dissolution media. As a result, a layer of corresponding hydrophobic complex precipitated was formed at the surfaces of the physical mixtures particles to retard the rate of drug dissolution.

3.8. Taste masking efficiency

Data of the last six replicates out of nine measurements for each sample and signal from 100 to 120 s of each replicate were

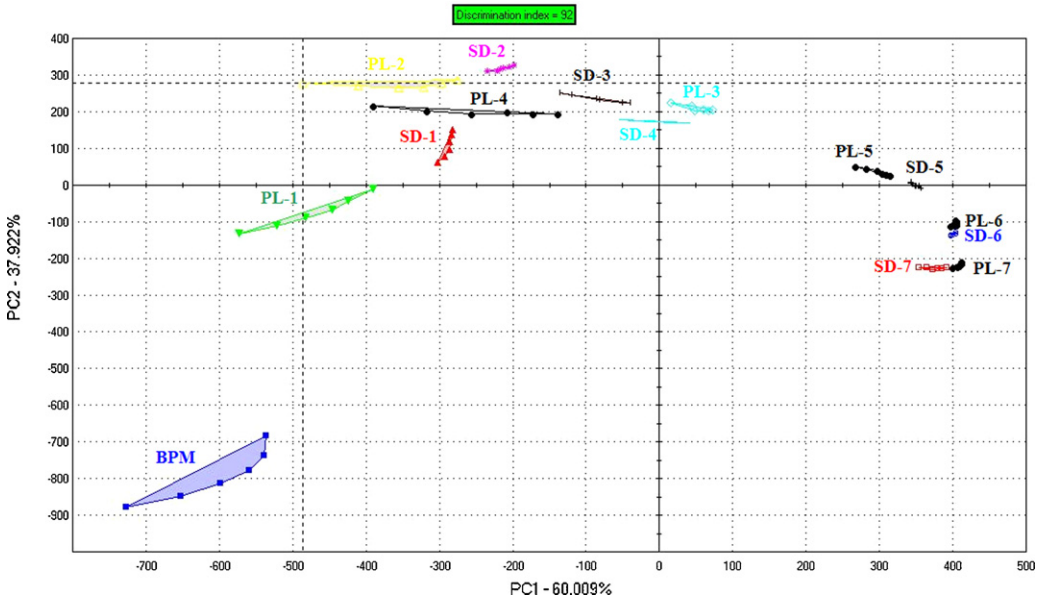

Fig. 9. PCA map of complexes prepared in methanol and their placebo.

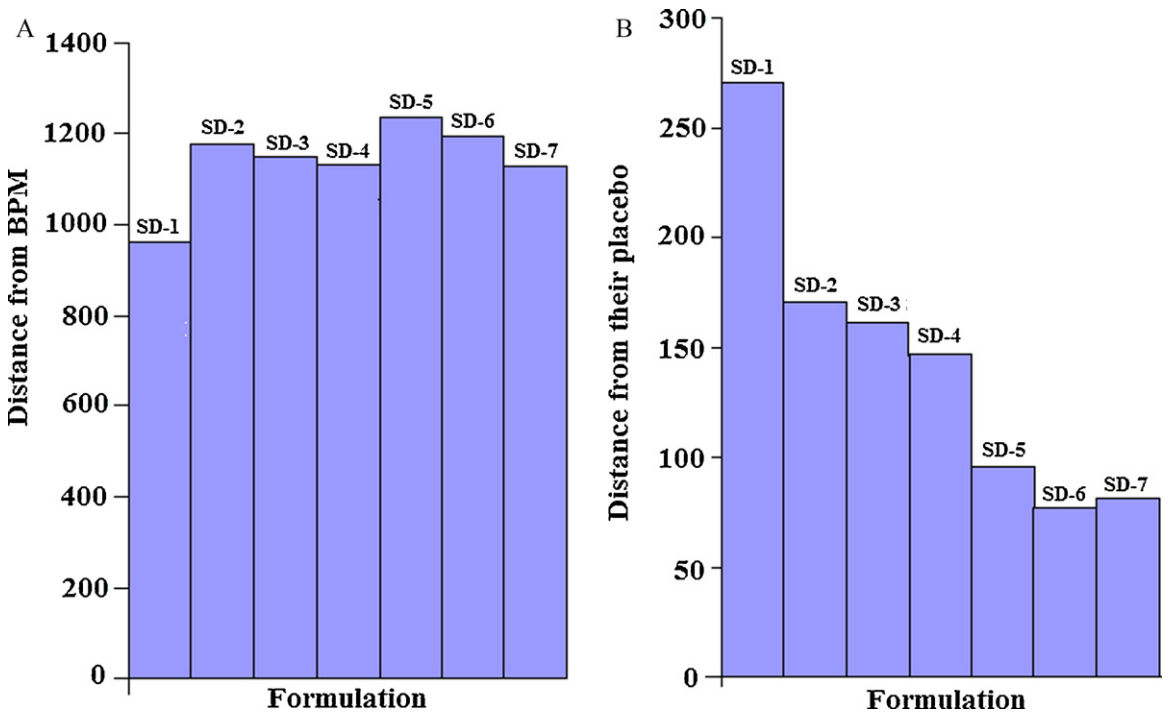

Fig. 10. Euclidean distance plot (A) complexes and their placebos against BPM and (B) complexes against their placebos.

used in multivariate statistical analysis. According to the manufacturer's recommendation, this was done to lessen the variations due to the nature of the sensors. Furthermore, the data of ZZ and AB sensors were excluded from the data analysis because of their lesser discriminative power compared to other sensors. The multivariate analyses used were principal component analysis (PCA) and discriminant functional analysis (DFA).

PCA was performed using two principal components that allowed for clustering the data in a PCA map. Fig. 9 shows the PCA score graph for the complexes prepared from methanol. PC1 and PC2 could explain 60.01 and 37.92% of the variation in the data, respectively. The scattering of replicates of same-group data was very wide due to the nature of the sensors. The same drawback was detected and reported in the literature by Lorenz et al. (2009). The PCA map enabled the estimation of distance between the centers of gravity for the clusters of data samples (complexes and its placebos, and complexes and BPM, respectively). This distance is called the Euclidean distance, which is the distance between the centers of the cluster of one sample set to the center of the cluster of another sample set. The distance was used to assess the similarity between each pair of samples and the suppression of BPM bitterness. A discriminative index (DI), ranging from negative values to 100 is reported on a PCA map (Lorenz et al., 2009). The higher DI represented a better discrimination among the samples of the group. All the complexes and placebos were far distanced from the drug. The distances and DIs between BPM and complexes, and BPM and placebos were more

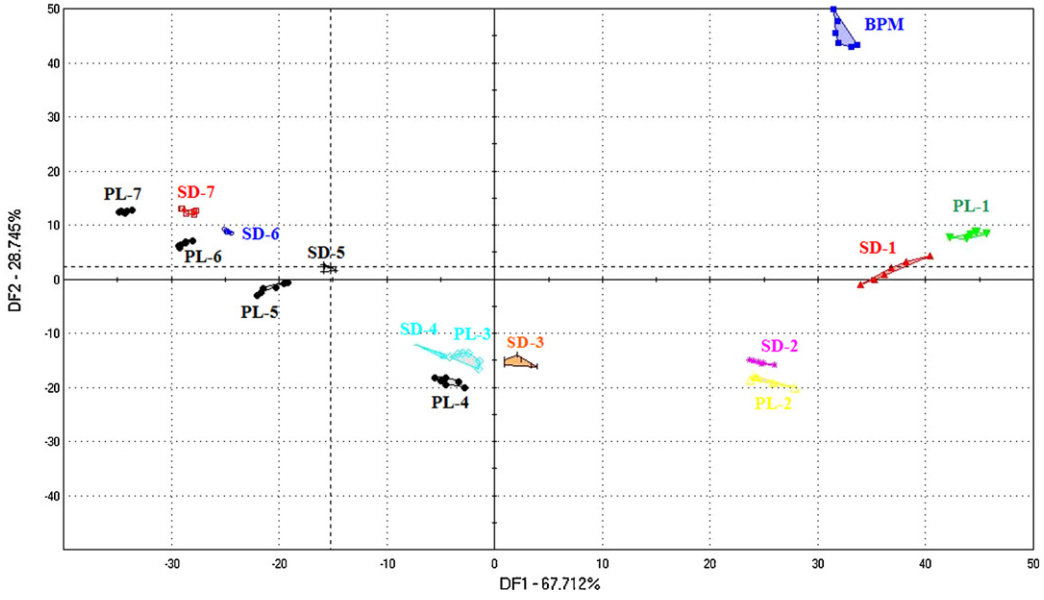

Fig. 11. Discriminant functional analysis plot of complexes and their placebos.

than 958 and 731, and 97.48 and 93.75%, respectively. Thus, the model was more discriminative toward formulations than placebos. The distances and DIs between formulations and their placebos were less than 271 and 83.33%, respectively (Fig. 10). This was suggestive of the less discrimination between formulations and their placebos. The distances and DIs between the complexes and either the drug or their placebos decreased up to formulation SD-5 afterward it became constant thus suggesting that the molar ratio of 1:5 of BPM and TA might be sufficient to mask the bitter taste of BPM.

Dimensionality of data can be reduced by another multivariate analysis tool, discriminant functional analysis (DFA). It is similar to PCA except a different algorithm is used in this computation. The DFA model assumes that similar samples (replicates) are clustered, while PCA considers each replicate individually (Lorenz et al., 2009). This principal could explain the reason for less scattering of replicates within the same data set. Unlike PCA, DFA can be used for prediction. A DFA score graph was constructed using two DFA components (Fig. 11). DFA1 and DFA2 represented 67.712 and 28.745% of the variability in the data. Complexes can be arranged in increasing value of DF1: SD1 > SD2 > SD3 > SD4> SD5 > SD6 > SD7, which correspond to the decrease in the ratios of TA to BPM. Thus DFA1 might represent BPM. Furthermore, all the formulations and their placebos were far distanced from the drug, thus indicating that the complexes effectively suppressed the bitter taste of the drug.

4. Conclusions

FTIR studies indicated chemical interaction between the BPM and TA. The drug lost its crystalline nature as confirmed by PXRD, DSC and SSNMR. The complex of BPM significantly decreased the solubility of the drug. The dissolution was immediate in acidic environment but it was sustained for 24 h at pH 6.8. Thus sustained release dosage forms could be developed from tannate complex in conjunction with other pharmaceutical technology such as coating with enteric polymer to prevent the drug release in acidic pH. Further, there are already developed and approved sustained release commercial dosage forms that release faster in the low pH stomach area and precipitated at high pH small intestinal area. This provides the advantage of reducing the frequency of administration. It was also successful in masking the bitter taste of BPM which will greatly improve therapeutic compliance in the pediatric patient population. TA is a GRAS (generally regarded as safe) category excipient and the use of TA in pharmaceutical products will not create any regulatory hurdles in their approval (Food and drug administration select committee on GRAS). This approach can be potentially applied to similar chemical entities for sustained release and taste masking application by complexation with TA. It also provides a new paradigm for the product development and possibly will generate intellectual property for the pharmaceutical industry.

Acknowledgements

The authors would like to thank the Oak Ridge Institute for Science and Education (ORISE) for supporting the post doctoral research program and Dr. Samy Raghu for assisting in running solution NMR experiment. This work was supported in part by a funding from National Institute of Health (IAA, Y1-HD-0052-01).

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