Department of Pharmaceutics[1], The National Center for Natural Products Research[2], School of Pharmacy, The University of Mississippi, USA

Compatibility studies of promethazine hydrochloride with tablet excipients by means of thermal and non-thermal methods

S. Thumma[1], M. A. Repka[1, 2]

Received September 15, 2008, accepted October 2, 2008

Dr. Michael A. Repka, D.D.S., Ph.D., Chair and Associate Professor of Pharmaceutics, Department of Pharmaceutics, School of Pharmacy, The University of Mississippi, University, MS 38677, USA
marepka@olemiss.edu

Pharmazie 64: 183–189 (2009) *doi: 10.1691/ph.2009.8268*

The compatibility of promethazine hydrochloride (PMZ) with various tableting excipients has been investigated by isothermal stress testing (IST) and differential scanning calorimetry (DSC). DSC thermograms of PMZ and each of the excipients investigated were compared with their corresponding physical mixtures (1 : 1) for evaluation. Furthermore, Fourier transform infrared spectroscopy (FTIR) data was used to corroborate the results of DSC and IST. A preliminary sustained release tablet formulation of the drug, prepared using compatible excipients, was stored under accelerated storage conditions (40 °C/75% RH) and analyzed for stability, drug release and bioadhesion characteristics for up to 3 months. Based on DSC results alone, drug-excipient interactions were observed with Pearlitol® SD200, lactose monohydrate and zinc stearate. Chromatographic analysis of the stressed binary mixture (stored at 55 °C for 3 weeks) containing PMZ-lactose monohydrate showed brown discoloration indicating potential interaction. However, stressed physical mixtures of PMZ-Pearlitol® SD200 and PMZ-zinc stearate indicated compatibility as opposed to the thermal analysis. The tablet formulation was found to be very stable after 3 months of storage at accelerated stability conditions. Also, the release profiles and bioadhesive properties were found to be unaltered. Thus, both thermal and non-thermal methods were utilized to successfully evaluate the compatibility of excipients with PMZ and the tablet formulation was found to be stable.

1. Introduction

Compatibility of an active component with excipients is one of the key factors which influence the stability of a formulation, because excipients can interact both chemically and physically with the drug (Fassihi and Persicaner 1987). Chemical interactions can result in the degradation of a medicament and thus reduce the fraction available for absorption. On the other hand, solubility and dissolution rate, uniformity of dose or ease of administration are affected by physical interactions (Crowley and Martini 2001). Assessment of possible incompatibilities between a drug and various excipients at an early stage therefore helps in development of a stable dosage form.

Incompatibilities between a drug and an excipient can occur due to various reasons. Insoluble products can be formed via charged interactions between counter ions produced by soluble and ionizable excipients in solution and ionizable drug substances. Also hydrogen-donating reactions can occur between actives containing hydrogen-donating functional groups and excipients. Incompatibility of famotidine and lansoprazole with the carbonyl group of polyvinylpyrrolidone (PVP) is an example of such an interaction (Indrayanto et al. 1994; Tabata et al. 1992). Physical adsorption of an excipient onto a drug's surface can initiate chemical breakdown. The catalytic degradation of nitrazepam in tablet dosage forms is an example (Czaja and Mielck 1982). The direct interaction of an excipient with an active pharmaceutical ingredient (API) and its subsequent degradation in most of the cases is catalyzed by water and favored by an increase in temperature. Many excipients contain an appreciable level of bound water which when released during process operations, such as grinding, degrade moisture sensitive drugs with which they are formulated (Sims et al. 2003). Interaction between impurities/residues found in excipients and drug substances is another common source of incompatibilities. Peroxide impurities in povidone (binder) and crospovidone (disintegrant) have been identified as a source of degradation of an oestrogen receptor modulator, raloxifene (Hartauer et al. 2000).

The assimilation of real-time stability and compatibility data is time-consuming and therefore it is desirable to obtain fast and reliable information about the possible interactions employing a suitable method. There is no universally accepted protocol for testing drug-excipient compatibility to date. Isothermal stress testing and thermal analysis of pharmaceutical substances are methods commonly used for this purpose. Differential scanning calorimetry (DSC) has been widely used as a rapid thermal method for assessing incompatibility between formulation components, since this method is fast, versatile and re-

quires only milligrams of sample (Araujo et al. 2003; Botha and Loetter 1990; Lin and Han 1992; Malan et al. 1997; Verma and Garg 2005).

Although a valuable technique, interpretation of DSC data can often be misleading. In most of the cases, interactions observed at accelerated temperatures may not occur at normal storage conditions (Van Dooren and Duphar 1983). Also, a solid-solid interaction does not necessarily indicate incompatibility, but might be beneficial in some cases (Bettinetti et al. 1988). When two substances are mixed, the purity of each is reduced in the mixture and DSC might not be able to discern a solid-solid interaction that is weak or non-existent (Holgado et al. 1995).

In isothermal stress testing (IST), the binary mixtures of the drug and excipients in the presence or absence of moisture are exposed to high temperatures and drug content determined by a suitable analytical technique (mostly by HPLC). Other non-thermal methods that have been used to assess the drug/excipient interactions include infrared spectroscopy (IR) (Balestrieri et al. 1996; Marini et al. 2003; Verma and Garg 2005), dissolution studies (Katakam et al. 1995) and x-ray diffractometry (XRD) (Joshi et al. 2002; Suryanarayanan and Herman 1991).

Promethazine hydrochloride (PMZ) is a histamine H_1-receptor antagonist used in a variety of clinical conditions, primarily for the prevention and treatment of nausea and vomiting and for motion sickness. To our knowledge, most of the work on the PMZ has focused on the analysis of the drug in biological samples and in pharmaceutical preparations (Lara et al. 2006; Stavchansky et al. 1983; Zhang et al. 2005) with very little emphasis on formulation development (Attama and Ezeamama 2005; Reynolds et al. 2002). Also, there is no literature on the compatibility studies of drug with excipients commonly used in solid pharmaceutical dosage forms. Commercially PMZ is available in the tablet, syrup, injection and suppository dosage forms. The drug is readily absorbed (~90%) when administered orally. Drawbacks of oral administration are extensive first pass metabolism and side effects associated with frequent dosing necessitated by its short biological half life. For prophylaxis of nausea and vomiting, as during surgery and the postoperative period, and for treating motion sickness, the drug has to be administered frequently (3–4 h interval as needed). Hence, a sustained release delivery system is needed to enhance the patient compliance, reduce the frequency of dosing and the side effects associated with it. Also, when PMZ cannot be tolerated orally, injections and suppositories are the only options. However, each of these routes has their own disadvantages. Injectables carry the inherent problem of being invasive and require professional assistance, and therefore in many cases preclude self medication. Suppository formulations have never been widely accepted in the United States and are not patient friendly.

In the present study, techniques of thermal analysis and IST were used to assess the compatibility of promethazine hydrochloride (PMZ) with a number of excipients commonly used in solid pharmaceutical dosage forms. FTIR data was used to corroborate the results of DSC and IST. Furthermore, a preliminary sustained release tablet formulation for transmucosal delivery of PMZ was prepared utilizing the excipients found compatible with PMZ. This formulation was evaluated for stability, bioadhesive properties and drug release characteristics after 3 months at accelerated storage conditions (40 °C/75% RH).

2. Investigations, results and discussion

2.1. Differential Scanning Calorimetry

The principle of DSC is based on measuring the difference in the amount of heat required to increase the temperature of a sample (when it undergoes a thermal event) and reference as a function of temperature. The appearance, shift or disappearance of peaks and/or variations in the corresponding enthalpy values serve as indicators for assessing the possible incompatibilities between the formulation components by DSC (Botha and Loetter 1990). The thermograms of drug and each of the investigated excipients were compared with their respective binary mixtures (Figs. 1–5).

The DSC scan of PMZ showed a sharp endothermic peak at 236.04 °C corresponding to its melting point. In most of the binary mixtures, the drug peak appeared broader and shallower and occurred at a slightly lower temperature. These minor changes could be attributed to the mixing process which lowers the purity of each component in the mixture and does not necessarily indicate incompatibility (Botha and Loetter 1990). Table 1 shows a summary of peak transition temperature (T_{peak}) and heat of fusion/enthalpy (ΔH_f) values of PMZ in various physical mixtures.

The thermograms of PMZ mixtures containing Methocel® K100M, Carbopol® 971p, microcrystalline cellulose (MCC) and sodium starch glycolate (Explotab®) (Figs. 1A, 1B, 2A and 2B, respectively) exhibited all of the thermal features of the individual components. A broad endothermic peak between 40 and 100 °C was observed for cellulose polymers (Methocel® K100M and MCC), which can be attributed to volatilization of adsorbed water (Botha and Loetter 1990). Therefore PMZ was found to

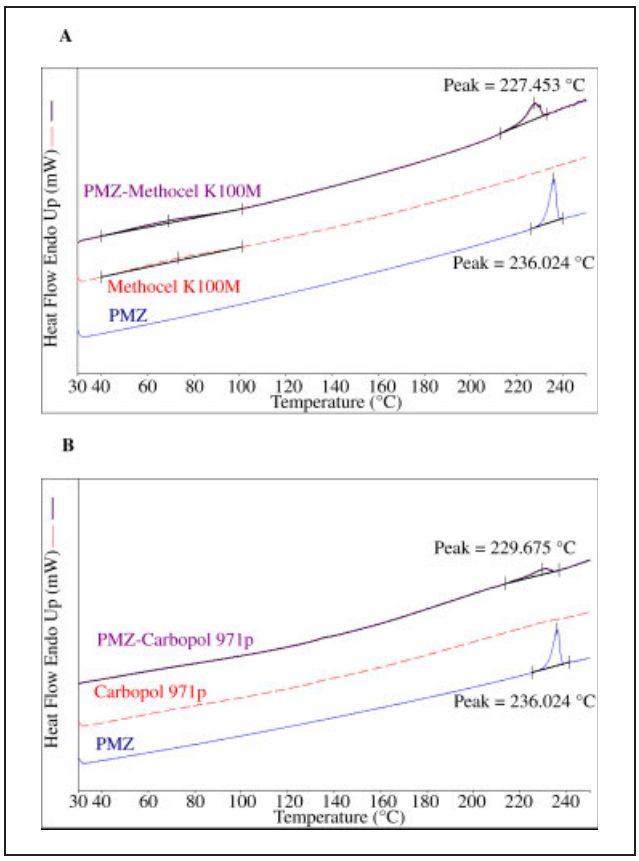

Fig. 1: DSC thermograms of (A) PMZ, Methocel® K100M and PMZ-Methocel® K100M physical mixture; (B) PMZ, Carbopol® 971p and PMZ-Carbopol® 971p physical mixture

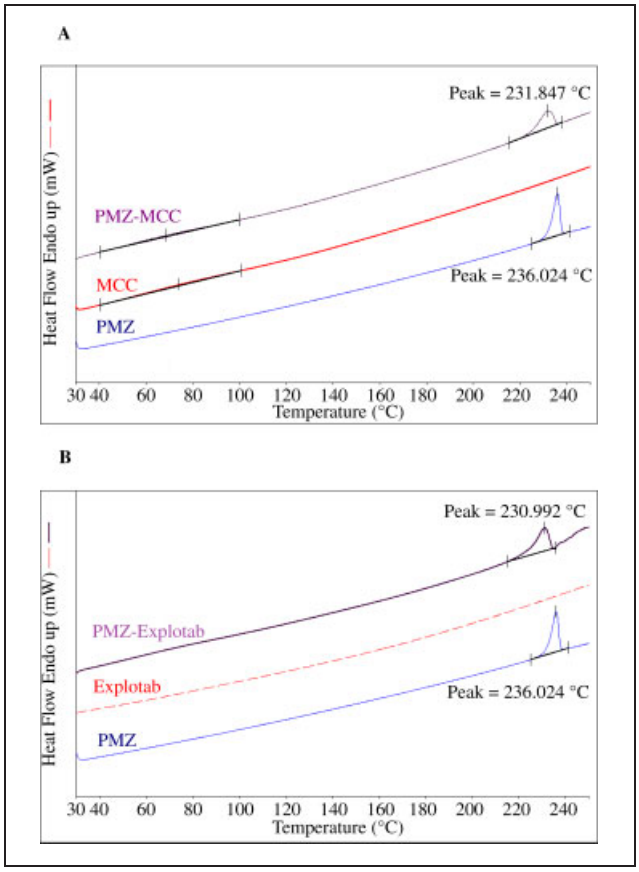

Fig. 2: DSC thermograms of (A) PMZ, microcrystalline cellulose (MCC) and PMZ-MCC physical mixture; (B) PMZ, Explotab® and PMZ-Explotab® physical mixture

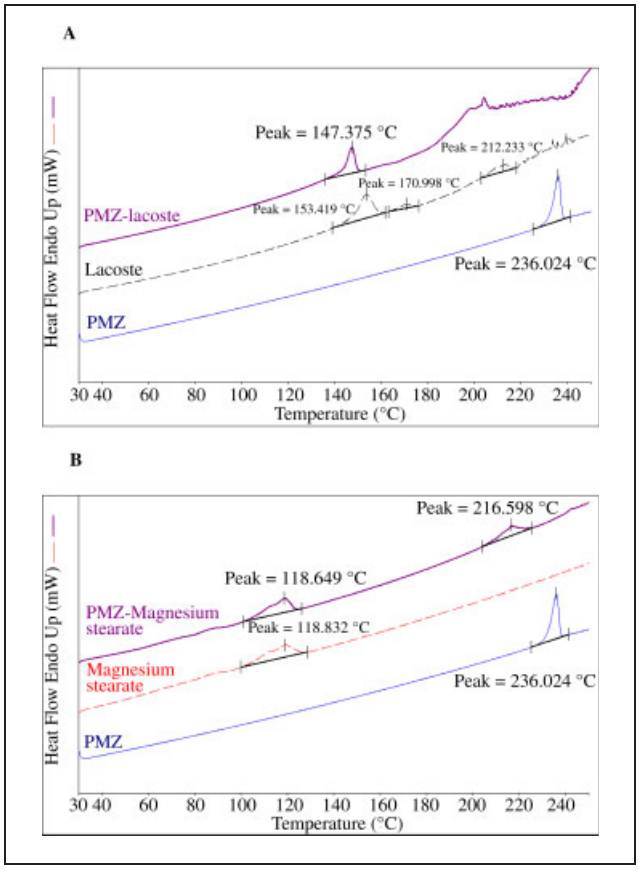

Fig. 4: DSC thermograms of (A) PMZ, lactose monohydrate and PMZ-lactose monohydrate physical mixture; (B) PMZ, magnesium stearate and PMZ-magnesium stearate physical mixture

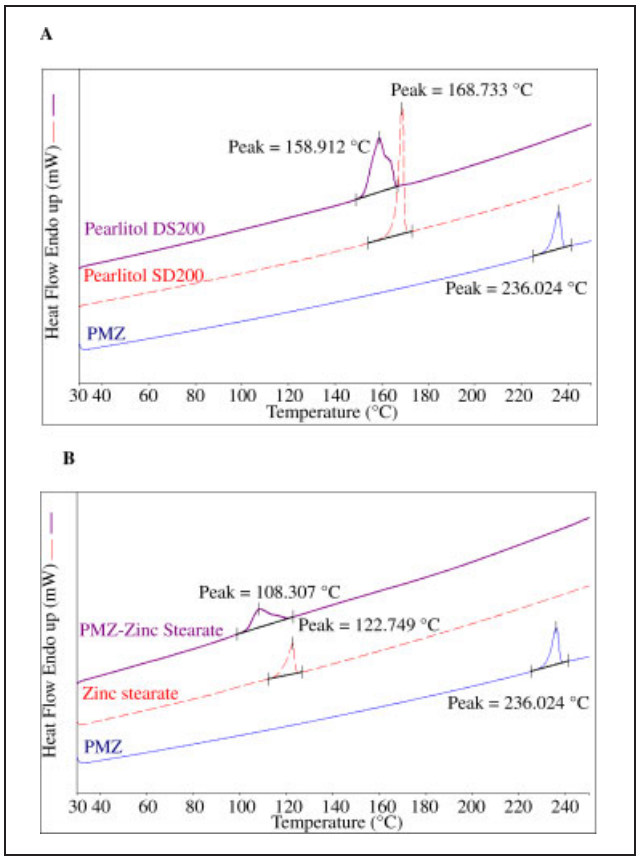

Fig. 3: DSC thermograms of (A) PMZ, Pearlitol® SD200 and PMZ-Pearlitol® SD200 physical mixture; (B) PMZ, zinc stearate and PMZ-zinc stearate physical mixture

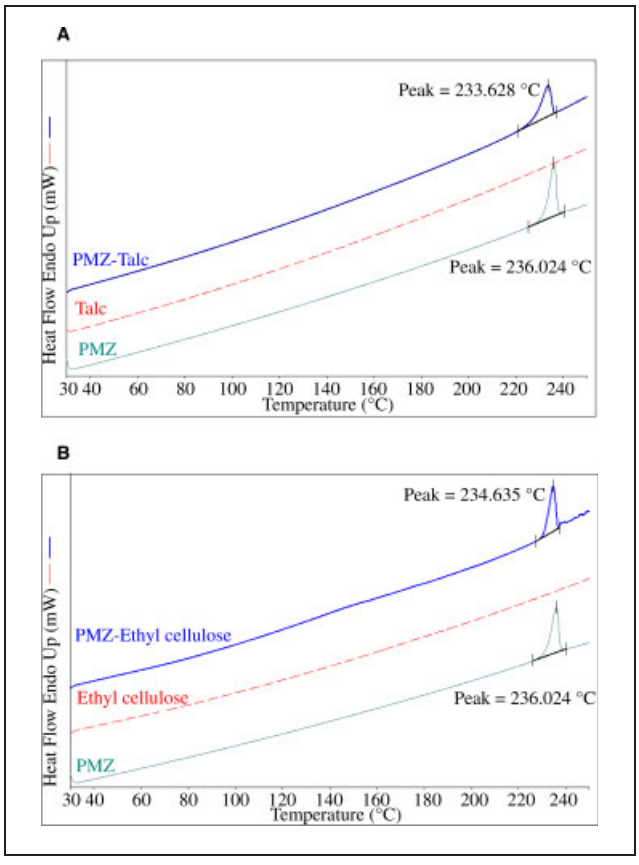

Fig. 5: DSC thermograms of (A) PMZ, talc and PMZ-talc physical mixture; (B) PMZ, ethylcellulose and PMZ-ethylcellulose physical mixture

Table 1: Summary of the results of DSC and IST of PMZ in various drug excipient mixtures

Sample	DSC		IST
	T_{peak} (°C)	ΔH_f (J/g)	% drug remaining
PMZ	236.02	102.72	99.21 ± 1.45
PMZ + Methocel® K100M	227.45	74.22	102.12 ± 2.31
PMZ + Carbopol® 971p	229.48	81.98	105.62 ± 4.72
PMZ + Pearlitol® SD200	[a]	[a]	98.58 ± 4.19
PMZ + lactose monohydrate	[a]	[a]	*
PMZ + MCC	231.85	86.54	97.84 ± 1.34
PMZ + Explotab®	230.99	104.04	99.24 ± 2.12
PMZ + magnesium stearate	216.59	62.54	98.69 ± 2.84
PMZ + zinc stearate	[a]	[a]	98.12 ± 3.27

T_{peak} and ΔH_f represent peak temperature and enthalpy values of PMZ in various drug-excipient mixtures
[a] Drug peak missing
* Brown color formation in the drug-excipient binary mixture after 3 weeks of storage at 55 °C

be compatible with Methocel® K100M, Carbopol® 971p, MCC and Explotab®.

The DSC thermograms of Pearlitol® SD200 (Fig. 3A) and zinc stearate (Fig. 3B) showed sharp endothermic peaks at 168.73 and 122.74 °C, respectively, which broadened and shifted to a lower temperature in their physical mixtures. The drug peak was completely missing in the DSC trace of both the physical mixtures indicating that PMZ might be interacting with these excipients (Van Dooren and Duphar 1983).

Lactose showed endothermic peaks at 153.41, 170.99 and 212.23 °C corresponding to the dehydration of bound water, crystalline transition and melting point, respectively (Araujo et al. 2003) (Fig. 4A). The melting event is immediately followed by the degradation of lactose. The physical mixture containing lactose showed complete absence of the drug during the thermal event. Furthermore, the degradation of lactose immediately following its melting was also observed in the physical mixture. The absence of a melting endotherm of the drug in the physical mixture and its possible interaction with degradation products of lactose provides a probability that these two components are incompatible. However, a definite conclusion cannot not be made on the compatibility of the two components based on DSC data alone.

The DSC thermogram of magnesium stearate showed an endotherm, although not very sharp, at 118.83 °C (Figure 4B). The thermogram of the physical mixture containing magnesium stearate exhibited a broadened PMZ peak, which shifted to a lower temperature (216.69 °C). There were no additional thermal effects observed in the physical mixture indicating that magnesium stearate is compatible with PMZ.

The DSC thermograms of talc (Fig. 5A) and ethylcellulose (Fig. 5B) did not exhibit any peaks in the temperature range of 25–250 °C. The physical mixtures containing talc and ethylcellulose showed characteristic endothermic peaks of the drug suggesting that these excipients are also compatible with PMZ.

2.2. Fourier Transform Infrared Spectroscopy

FTIR was performed on the drug/excipient mixtures that showed incompatibility during the DSC studies after subjecting them to isothermal stress (55 °C for 3 weeks). The IR spectrum of PMZ (Fig. 6A) shows the following characteristic bands, 2378 (NH^+ stretching), 1591 (aromatic C=C stretching), 1457 (CH_3 and CH_2 bending), 1378 (CH_3 bending) and 1334 (C−N stretching of tertiary amine). The IR spectra of physical mixtures containing Pearlitol® SD200, lactose monohydrate and zinc stearate are shown in Figs. 6B, 6C and 6D, respectively. An interaction between the hydroxyl group (band at ∼3383) of lactose and protonated nitrogen (band at 2378) of PMZ might lead to an incompatibility between the two. Since both of the groups were found intact in the FTIR spectra of the physical mixture containing lactose, incompatibility between the two components is improbable. Also the presence of all of the characteristic bands corresponding to PMZ with out any new bands further indicates compatibility. Similar results were found in the case of physical mixture containing Pearlitol® SD200 (hydroxyl group and protonated nitrogen were found intact) indicating compatibility. In the case of the physical mixture containing zinc stearate, an interaction can occur between the protonated nitrogen of PMZ (band at 2378) and COO^- group (∼2900) of the excipient. The FTIR spectra of the physical mixture showed the presence of both of the interacting groups, clearly indicating that both of the components are compatible with each other.

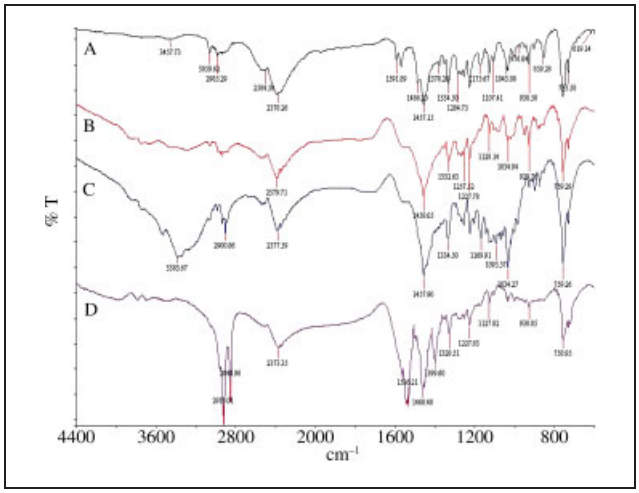

Fig. 6: FTIR spectrum of (A) promethazine hydrochloride, (B) promethazine hydrochloride-Pearlitol® SD200 (1 : 1) physical mixture, (C) promethazine hydrochloride-lactose monohydrate (1 : 1) physical mixture and (D) promethazine hydrochloride-zinc stearate (1 : 1) physical mixture

2.3. Isothermal Stress Testing

Isothermal stress testing (IST) utilizing HPLC was performed on all of the drug-excipient mixtures investigated to substantiate the DSC data. The results of HPLC analysis are presented in Table 1. Chromatograms of the binary mixtures were compared with that of the pure drug for assessing the compatibility. Physical mixtures of PMZ with Methocel® K100M, Carbopol® 971p, MCC, Explotab® and magnesium stearate all exhibited very slight changes in drug content after being subjected to IST. Also, the retention time (RT) and peak shape of the drug were unaltered corroborating the results of thermal analysis. DSC of the physical mixture containing Pearlitol® SD200 indicated incompatibility. However, no significant degradation of drug was observed in the HPLC analysis of the stressed PMZ-Pearlitol® SD200 binary mixture as opposed to DSC data. No discoloration was noticed after 3 weeks, further indicating its compatibility with PMZ. However, the physical mixture containing lactose exhib-

ited a brown color after 3 weeks of storage at stressed conditions substantiating the DSC result. The browning of the physical mixture may be attributed to a Maillard reaction (Duvall et al. 1965). Lactose is known to undergo a non-enzymatic browning reaction (generally known as the Maillard reaction) with amines. Although the reaction is believed to occur mainly in primary amines, an interaction between the protonated nitrogen of PMZ and free lactose is possible. Thermal analysis of the physical mixture containing zinc stearate indicated incompatibility based on the disappearance of the drug's endothermic peak. Chromatographic analysis of the stressed PMZ-zinc stearate mixture however, showed no significant drug degradation indicating its compatibility with PMZ.

2.4. Evaluation of preliminary sustained release tablet formulation

A preliminary sustained release tablet formulation (composition shown in Table 2) was prepared for oral transmucosal delivery of PMZ, utilizing only those excipients that were found compatible by all of the three methods employed. Methocel® K100M and MCC were used as a sustained release polymer and directly compressible excipient (filler and binder), respectively. Magnesium stearate and talc served as a lubricant and glidant, respectively. Oral mucosal delivery necessitates the use of mucoadhesive polymers in these dosage forms since they should ideally adhere to the mucosa and withstand salivation, muscular movement, and swallowing for a predetermined period of time. Carbopol® 971p was therefore incorporated as a bioadhesive polymer based on our previous work.

The results of stability, drug release and bioadhesion characteristics of the preliminary tablets exposed to accelerated stability conditions (40 °C/75% RH) are presented in Table 3. The tablets were found to be very stable after 3 months at tested conditions. The drug content remained unchanged after 1 month (98.34 ± 3.21) and 3 months (105.12 ± 4.21) as compared to zero time (99.21 ± 1.45). No remarkable changes in the physical appearance such as discoloration were observed. In addition, there were no changes in the release rate of the drug during storage as illustrated in Fig. 7. Tablets stored for 1 month and 3 months allowed the release of 88.13 and 95.24% PMZ, respectively after 12 h as compared to 93.87% drug released from those unexposed to accelerated conditions at the same interval. Furthermore, tablets stored at 1 month and 3 months demonstrated an f2 value of 69.21 and 77.87, respectively, indicating similarity of the release profiles. Generally, f_2 values greater than 50 (between 50 and 100) ensure similarity in dissolution profiles (Costa and Sousa Lobo 2001). The bioadhesive properties (PAF and AUC) demonstrated little change with time. Since the bioadhesion remained unchanged during the storage period, it is believed that the preliminary tablet formulation will function effectively as a mucoadhesive dosage form.

Table 2: Composition of preliminary sustained release tablet formulation of promethazine hydrochloride

Drug/ Excipient	% w/w
Promethazine hydrochloride	12.5
Methocel® K100M	37.5
Carbopol® 971p	3.0
Microcrystalline cellulose	45.0
Magnesium stearate	1.0
Talc	1.0

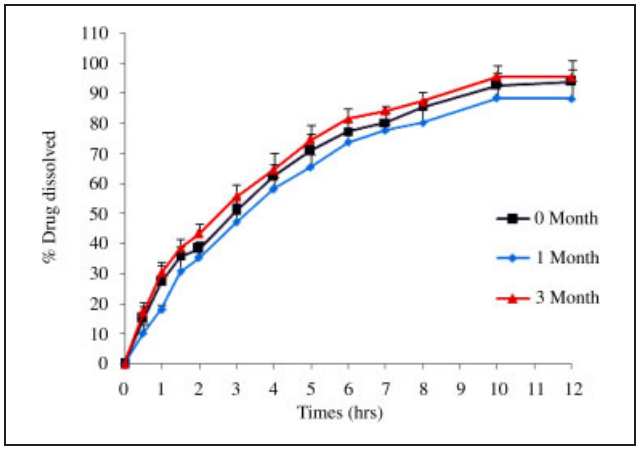

Fig. 7: Dissolution profile of a preliminary PMZ sustained release tablet formulation (n = 3) after 3 months of storage at accelerated stability conditions (40 °C/75% RH)

3. Experimental

3.1. Materials

Promethazine hydrochloride was obtained from Hawkins, Inc., (Minneapolis, MN). Hypromellose (Methocel® K100M) was generously donated by the Dow Chemical Company (Midland, MI) and Carbopol® 971p was purchased from Noveon, Inc., (Cleveland, OH). Pearlitol® SD200 (spray dried mannitol) was obtained from Signet Chemical Corp., (Mumbai, India). Lactose monohydrate, zinc stearate, magnesium stearate, potassium phosphate dibasic and talc were obtained from Fischer Chemicals (Fair Lawn, NJ). Microcrystalline cellulose (MCC) and sodium starch glycolate (Explotab®) were purchased from Spectrum Chemical, Inc., (Gardena, CA). Methanol and acetonitrile (both HPLC grade) used for analysis were obtained from Fischer Chemicals (Fair Lawn, NJ).

3.2. Differential Scanning Calorimetry

A Perkin-Elmer Pyris 1 DSC was used for thermal analysis of the drug-excipient mixtures. Data analysis was performed using Pyris Manager™ software. The samples were initially subjected to a heat-cool cycle to remove the thermal history of the samples (by heating to 100 °C and holding for 10 min followed by cooling). A second heat cycle was initiated wherein approximately 4 mg of either drug or excipient, or 8 mg of the

Table 3: Results of promethazine hydrochloride preliminary tablet formulation evaluation after 3 months of storage at accelerated stability conditions

Study	Parameter	Time (month)		
		0	1	3
Stability	% PMZ remaining[a]	99.21 ± 1.45	98.34 ± 3.21	105.12 ± 4.21
Bioadhesion	PAF (N)[a]	2.43 ± 0.61	2.32 ± 0.78	2.59 ± 0.34
	AUC (N.mm)[a]	0.72 ± 0.11	0.61 ± 0.06	0.80 ± 0.10
Drug release	f_2 value[b]	–	69.21	77.87

[a] Values are expressed as mean ± standard deviation
[b] PMZ sample unexposed to accelerated conditions (initial sample) was treated as the reference to calculate f_2 values

drug/excipient mixture 1: 1 (w/w), were analyzed in sealed aluminum pans under nitrogen flow (20 mL/min), at a heating rate of 10 °C/min, over a temperature range of 30 to 250 C. An empty sealed pan was used as reference. The 1 : 1 weight ratio was chosen because it maximizes the likelihood of observing any interaction. The thermograms were interpreted according to the guidelines of Van Dooren and Duphar (1983) and Smith (1982).

3.3. Isothermal Stress Testing

Accurately weighed amounts of drug and excipient (1 : 1) were placed in glass vials and mixed on a vortex mixer for 2 min. 10 % w/w water was added to each of the vials, mixed further and sealed tightly using a Teflon-lined screw cap. The samples were prepared in triplicate, stored at 55 °C for 3 weeks and examined weekly for color changes. The samples were quantitatively analyzed using HPLC for the content of active drug remaining at the end of 3 weeks. Drug-excipient blends without added water served as controls. The total content of the vials were used for analysis to prevent sampling errors.

A Waters HPLC-UV system (Waters Corp, Milford, MA) and a Luna 3μ C-8 (2), 150 × 4.60 mm column (Phenomenex, Torrance, CA), were used at a detection wavelength of 249 nm. The mobile phase consisted of acetonitrile-25mM dibasic potassium phosphate (50 : 50, vol./vol., adjusted to pH 7.0 with orthophosphoric acid). The analyte was detected using a Waters 2917 detector. The flow was maintained at 1.0 mL/min, with PMZ and degradants eluting within 15 min. The temperature of the column was maintained at 25 °C. A calibration curve was constructed for the drug using a series of standard solutions of known concentrations, and the area under the peak was employed to determine the concentration of PMZ in the sample solutions.

3.4. Fourier Transform Infrared Spectroscopy (FTIR)

FTIR of drug and drug-excipient blends subjected to isothermal stress (55 °C for 3 weeks) were recorded using a Perking Elmer FTIR instrument (Paragon 500). Pellets of samples, prepared by grinding and dispersing the powder in micronized IR grade KBr powder using an agate mortar and pestle were scanned over a wave number range of 4000–600 cm^{-1}. The spectrum was recorded utilizing Spectrum™ v5.0.2 software.

3.5. Preparation and evaluation of preliminary sustained release tablet formulation

The composition the sustained release tablet formulation of PMZ prepared by a direct compression method is shown in Table 2. Promethazine hydrochloride, Methocel® K100M, Carbopol® 971p, and microcrystalline cellulose, were passed through a 40-mesh screen to deagglomerate the powder materials. The powder mixtures were blended for 15 min using a V-blender, lubricated with 1% magnesium stearate for 3 min and tableted using a single punch-tableting machine (STD model RDD3, Ridhi, Ahmedabad, India) equipped with 6 mm punches. Tablets (adjusted to contain 12.5 mg of the drug) weighing 100 mg each were compressed at 156 Mpa pressure with a dwell time of 10 s. The prepared tablets were packed in strips of 0.04 mm thick aluminum foil, laminated with a PVC coating and stored at 40 °C and 75% RH. They were analyzed at pre-determined time intervals for up to 3 months to determine the amount of PMZ remaining via HPLC. Simultaneously, bioadhesion and dissolution studies were performed on the samples at each of the time intervals.

To determine the PMZ remaining after storage at aforementioned conditions, each tablet (n = 20) was weighed individually and powdered. A quantity of powder equivalent to 10 mg of the drug was dissolved in 10 ml methanol in a volumetric flask, shaken on a vortex mixer for 2 min and centrifuged for 15 min at 4000 rpm. Subsequently, the clear supernatant was diluted appropriately with methanol and assayed.

Dissolution studies (n = 3) were performed utilizing a Hanson SR8-Plus dissolution test system according to USP 31 apparatus I, basket-rack assembly. A 900 ml volume of 0.05 M phosphate buffer (pH 6.8) maintained at 37 ± 0.5 °C was used as the dissolution medium. Rotational speed of the baskets was 100 rpm. Samples (2 ml) were collected at pre-determined time intervals (0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10 and 12 h) and replaced with an equivalent amount of fresh medium. The samples were filtered through 0.45 μm nylon membrane filters and analyzed by HPLC. The cumulative percent drug release was plotted against time to determine the release profiles.

Dissolution profile comparisons were made on the tablets stored at accelerated conditions using a model independent pair-wise approach. Similarity factor (f2) was used to compare the difference between the percent drug released from a reference and a test product (Costa and Sousa Lobo 2001). The PMZ tablet formulation unexposed to accelerated conditions (initial sample) was treated as the reference product. For dissolution profiles to be considered similar, f_2 values should be close to 100.

3.6. Bioadhesion measurements

Bioadhesion measurements were performed utilizing a Texture Analyzer (TA.XT2i, Texture Technologies Corp., Scarsdale, NY/Stable Micro Systems, Godalming, Surrey, UK) equipped with Texture Expert™ software. Each tablet (n = 6) was wetted with nanopure water for 60 s and placed on a slotted die-cut fixture (TA-303 Indexable Adhesive Test Rig) on the base of the Texture Analyzer. Rabbit buccal mucosa was attached to a 7 mm diameter, circular steel probe using a cyanoacrylate adhesive. The Texture Expert™ software was programmed such that the probe approached the tablet at a predetermined rate of 1 mm/s, applied a force of 3.5 N for 60 s, and then withdrew at a speed of 0.5 mm/s. These parameters were chosen based on previous studies (Repka and McGinity 2000, 2001a, b). During the withdrawal phase of the probe, the Texture Expert™ software recorded the force deflection profiles. The maximum force required to detach the tablet on the lower base die from the upper probe, known as the peak adhesive force (PAF) and the area under the curve (AUC), representing the work of adhesion, were determined by the generated profiles.

Acknowledgements: The authors would like to thank the Department of Pharmaceutics, University College of Pharmaceutical Sciences, Warangal, India for their help and support with tableting equipment.

References

Araujo AAS, Storpirtis S, Mercuri LP, Carvalho FMS, dos Santos Filho M, Matos JR (2003) Thermal analysis of the antiretroviral zidovudine (AZT) and evaluation of the compatibility with excipients used in solid dosage forms. Int J Pharm 260: 303–314.

Attama AA, Ezeamama UF (2005) Systematic delivery of chloroquine and promethazine using pH-sensitive polymers. Drug Deliv 12: 103–107.

Balestrieri F, Magri AD, Magri AL, Marini D, Sacchini A (1996) Application of differential scanning calorimetry to the study of drug-excipient compatibility. Thermochim Acta 285: 337–345.

Bettinetti GP, Mura P, Liguori A, Bramanti G, Giordano F (1988) Solubilization and interaction of naproxen with polyvinylpyrrolidone in aqueous solution and in the solid state. Farmaco Ed Prat 43: 331–343.

Botha SA, Loetter AP (1990) Compatibility study between naproxen and tablet excipients using differential scanning calorimetry. Drug Dev Ind Pharm 16: 673–683.

Costa P, Sousa Lobo JM (2001) Modeling and comparison of dissolution profiles. EurJPharmSci 13: 123–133.

Crowley P, Martini L (2001) Drug-excipient interactions. Pharm Technol Eur 13: 26–28, 30–32, 34.

Czaja J, Mielck JB (1982) Solid-state degradation kinetics of nitrazepam in the presence of colloidal silica. Pharm Acta Helv 57: 144–153.

Duvall RN, Koshy KT, Pyles JW (1965) Comparison of reactivity of amphetamine, methamphetamine and dimethylamphetamine with lactose and related compounds. J Pharm Sci 54: 607–611.

Fassihi AR, Persicaner PHR (1987) Solid state interaction of bromazepam with poly(vinylpyrrolidone) in the presence of moisture. Int J Pharm 37: 167–170.

Hartauer KJ, Arbuthnot GN, Baertschi SW, Johnson RA, Luke WD, Pearson NG, Rickard EC, Tingle CA, Tsang PKS, Wiens RE (2000) Influence of peroxide impurities in povidone and crospovidone on the stability of raloxifene hydrochloride in tablets: identification and control of an oxidative degradation product. Pharm Dev Technol 5: 303–310.

Holgado MA, Fernandez-Hervas MJ, Rabasco AM, Fini A (1995) Characterization study of a diclofenac salt by means of SEM and fractal analysis. Int J Pharm 120: 157–167.

Indrayanto G, Mugihardjo, Handayani R (1994) Compatibility study between famotidine and some excipients using differential scanning calorimetry. Drug Dev Ind Pharm 20: 911–920.

Joshi BV, Patil VB, Pokharkar VB (2002) Compatibility studies between carbamazepine and tablet excipients using thermal and non-thermal methods. Drug Dev Ind Pharm 28: 687–694.

Katakam M, Bell LN, Banga AK (1995) Effect of surfactants on the physical stability of recombinant human growth hormone. J Pharm Sci 84: 713–716.

Lara FJ, Garcia-Campana AM, Gamiz-Gracia L, Bosque-Sendra JM (2006) Ales-Barrero F. Determination of phenothiazines in pharmaceutical formulations and human urine using capillary electrophoresis with chemiluminescence detection. Electrophoresis 27: 2348–2359.

Lin S, Han R (1992) Differential scanning calorimetry as a screening technique to determine the compatibility of salbutamol sulfate with excipients. Pharmazie 47: 266–268.

Malan C, de Villiers M, Lotter A (1997) Application of differential scanning calorimetry and high performance liquid chromatography to determine the effects of mixture composition and preparation during the evaluation of niclosamide-excipient compatibility. J Pharm Biomed Anal 15: 549–557.

Marini A, Berbenni V, Moioli S, Bruni G, Cofrancesco P, Margheritis C, Villa M (2003) Drug-excipient compatibility studies by physico-chemi-

cal techniques. The case of indomethacin. J Therm Anal Calorim 73: 529–545.
Repka M, McGinity J (2000) Influence of vitamin E TPGS on the properties of hydrophilic films produced by hot-melt extrusion. Int J Pharm 202: 63–70.
Repka M, McGinity J (2001a) Influence of chlorpheniramine maleate on topical hydroxypropylcellulose films produced by hot-melt extrusion. Pharm Dev Technol 6: 297–304.
Repka M, McGinity J (2001b) Bioadhesive properties of hydroxypropylcellulose topical films produced by hot-melt extrusion. J Control Release 70: 341–351.
Reynolds TD, Mitchell SA, Balwinski KM (2002) Investigation of the effect of tablet surface area/volume on drug release from hydroxypropylmethylcellulose controlled-release matrix tablets. Drug Dev Ind Pharm 28: 457–466.
Sims JL, Carreira JA, Carrier DJC, Simon R., Easton L, Hancock SA, Simcox CE (2003) A new approach to accelerated drug-excipient compatibility testing. Pharm Dev Technol 8: 119–126.
Smith A (1982) Use of thermal analysis in predicting drug-excipient interactions. Anal Proc 19: 559–561.
Stavchansky S, Wallace JE, Wu P (1983) Thermal and photolytic degradation studies of promethazine hydrochloride: a stability-indicating assay. J Pharm Sci 72: 546–548.
Suryanarayanan R, Herman CS (1991) Quantitative determination of the active ingredient in a multicomponent tablet formulation by powder x-ray diffractometry. Int J Pharm 77: 287–295.
Tabata T, Makino T, Kashihara T, Hirai S, Kitamori N, Toguchi H (1992) Stabilization of a new antiulcer drug (lansoprazole) in the solid dosage forms. Drug Dev Ind Pharm 18: 1437–1447.
Van Dooren AA, Duphar BV (1983) Design for drug-excipient interaction studies. Drug Dev Ind Pharm 9: 43–55.
Verma RK, Garg S (2005) Selection of excipients for extended release formulations of glipizide through drug-excipient compatibility testing. J Pharm Biomed Anal 38: 633–644.
Zhang Q, Zhan X, Li C, Lin T, Li L, Yin X, He N, Shi Y (2005) Determination of promethazine hydrochloride and its preparations by highly accurate nephelometric titration. Int J Pharm 302: 101–107.