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# Selection of excipients for extended release formulations of glipizide through drug–excipient compatibility testing

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**Abstract**

For the development of extended release formulations of glipizide, techniques of thermal and isothermal stress testing (IST) were used to assess the compatibility of glipizide with selected excipients. Initially, differential scanning calorimeter (DSC) was used to evaluate the compatibility. IR spectrum of drug–excipient mixture was also compared with that of pure drug and excipient. Compatibility of excipients defined in the prototype formula was tested using IST. Based on the DSC results alone, magnesium stearate, meglumine, TRIS buffer, and lactose, were found to exhibit interaction with glipizide. Stressed binary mixtures (stored at 50 °C for 3 weeks) of glipizide and meglumine showed yellow coloration indicating potential incompatibility. Based on the results of DSC, IR, and/or HPLC, excipients defined in the prototype formula were found to be compatible with glipizide. The optimized formulation developed using the compatible excipients were found to be stable after 3 months of accelerated stability studies (40 °C and 75% RH). Overall, compatibility of excipients with glipizide was successfully evaluated using the combination of thermal and IST methods and the formulations developed using the compatible excipients was found to be stable.


*Keywords:* Extended release; Stability; Incompatibility; Drug–excipient interaction; Glipizide; Dissolution

## 1. Introduction

Incompatibility between drugs and excipients can alter stability and bioavailability of drugs, thereby, affecting its safety and/or efficacy. Study of drug–excipient compatibility is an important process in the development of a stable solid dosage form. Drug–excipient compatibility testing at an early stage helps in the selection of excipients that increases the probability of developing a stable dosage form.

Despite the importance of drug–excipient compatibility testing, there is no universally accepted protocol for this purpose. The term thermal analysis refers to a group of techniques in which physical property of a substance and/or reaction products is measured as a function of temperature whilst the substance is subjected to a controlled temperature program. Differential scanning calorimeter (DSC) technique involves the application of a heating or a cooling signal to a sample and a reference. When the substance undergoes a thermal event, the difference in the heat flow to a sample and to a reference is monitored against time or temperature while the temperature is programmed in a specified atmosphere. As a result, energy associated with various thermal events (e.g., melting, glass transition temperature, crystallization, etc.) can be evaluated [1]. This method has been extensively reported in the literature for testing compatibility of excipients with number of drugs [2–7]. Use of DSC has been proposed as a rapid method for evaluating the physico-chemical

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interaction between two components. However, caution need to be exercised in the interpretation of DSC results. This is because of high temperature conditions required and the lack of moisture in conducting the experiments. Moreover, evaluation of DSC thermograms can be difficult and the conclusions based on the DSC results alone can be often misleading [4,6].

Another method that is commonly employed for evaluating the drug–excipient compatibility is isothermal stress testing (IST). The method involves storing the drug–excipient blends with or without moisture at high temperature and determining the drug content [4,8,9]. DSC can be used in combination with IST to evaluate compatibility of drugs with the selected excipients.

As part of an ongoing project on the development of extended release formulations of glipizide, techniques of thermal analysis and IST were utilized for drug–excipient compatibility testing. Glipizide, an oral hypoglycemic agent, is one of the most commonly prescribed drugs for the treatment of patients with type II diabetes mellitus [10]. It is a weakly acidic drug having a p$K_a$ of 5.9. Chemically, it belongs to the category of sulfonylureas. Initially, DSC was used for evaluating the compatibility of glipizide with selected excipients. In suspected cases of incompatibility, IR spectrum of pure drug was compared with that of drug–excipient mixture and pure excipient. Excipients found to be compatible were used for different formulation trials. Those excipients that were defined in the prototype formula were tested using IST. Finally, the developed formulations were evaluated after 3 months of storage at accelerated stability conditions (40 °C and 75% RH).

## 2. Experimental

### 2.1. Materials

Glipizide was received as gift sample from USV Limited, India and characterized using glipizide chemical reference substance (CRS) purchased from European Pharmacopoeia Commission Secretariat, France. Following chemicals and excipients were purchased from commercial sources and used as such Cellulose acetate (Fluka, Switzerland), colloidal silicon dioxide (Aerosil-200, Degussa, Germany), lactose (Meggle, Germany), mannitol (Pearlitol SD-200, Roquette, France), microcrystalline cellulose (Avicel PH-102, FMC, USA), sodium chloride AR (Loba Chemie, India), polyvinyl pyrrolidone (Plasdone K-29/32, ISP, USA), HPMC (Methocel E-15, Dow, USA), PEG-4000 (SD Fine Chemicals, India), meglumine (Sigma, USA), TRIS buffer GR (Loba Chemie, India), talc (Panacea Biotec, India), magnesium stearate (Mallinckrodt, USA), and methanol HPLC grade (Ranbaxy, India). Acetonitrile HPLC grade (JT Baker, Mexico) and potassium dihydrogen orthophosphate GR (Loba Chemie, India) were used for preparing mobile phase for HPLC analysis. Water used throughout the HPLC analysis was prepared by reverse-osmosis (Ultra Pure water system, ELGA, UK).

Table 1
Peak temperature and enthalpy values of glipizide in various drug–excipient mixtures

| Sample | Ratio (drug–excipient) | $T_{peak}$ (°C) | $\Delta H_{f\,corr}$ (J/g)[a] |
|---|---|---|---|
| Glipizide | – | 216.35 | 114.49 |
| Glipizide + cellulose acetate | 1:1 | 217.35 | 126.87 |
| Glipizide + colloidal silicon dioxide | 4:1 | 214.22 | 84.79 |
| Glipizide + lactose | 1:5 | [b] | [b] |
| Glipizide + MCC | 1:5 | 215.68 | 86.93 |
| Glipizide + magnesium stearate | 1:1 | [b] | [b] |
| Glipizide + mannitol | 1:5 | 187.00 | 115.48 |
| Glipizide + sodium chloride | 1:1 | 213.86 | 59.98 |
| Glipizide + HPMC | 1:1 | 216.18 | 107.09 |
| Glipizide + PEG-4000 | 1:1 | 205.35 | 43.77 |
| Glipizide + PVP | 1:1 | 207.57 | 67.26 |
| Glipizide + meglumine | 1:1 | [b] | [b] |
| Glipizide + TRIS buffer | 1:1 | [b] | [b] |
| Glipizide + talc | 1:1 | 215.49 | 108.27 |

[a] $\Delta H_{f\,corr} = \frac{\Delta H_{f\,obs}}{\%\,drug\,in\,sample} \times 100$; from reference [3].
[b] No distinguishable drug peak visible.

### 2.2. Differential scanning calorimetry

A differential scanning calorimeter (DSC 821[e], Mettler Toledo, Switzerland) was used for thermal analysis of drug and mixtures of drug and excipients. Excipients that were expected to be used in the development of formulation (diluents, osmotic agent, lubricant, coating polymers, alkalinizing agent) and the maximum expected ratio were selected for the present study. Individual samples (drug and excipients) as well as physical mixtures of drug and selected excipients (all passed through 60-mesh sieve) were weighed directly in the pierced DSC aluminum pan (Table 1) and scanned in the temperature range of 25–300 °C under an atmosphere of dry nitrogen. Heating rate of 10 °C/min was used and thermograms obtained were observed for any interaction.

### 2.3. IR spectroscopy

IR spectra of drug and drug–excipient blends were recorded on an IR spectrophotometer (Impact-410, Nicolet, USA) in the range of 4000–500 $cm^{-1}$ using potassium bromide discs.

### 2.4. Isothermal stress testing

Based on the DSC results and initial formulation studies, list of excipients and the expected range to be used in the formulation was narrowed down. For IST studies, drug and different excipients (Table 2) were weighed directly in 4 ml glass vials ($n = 2$) and mixed on a vortex mixer for 2 min. In each of the vials, 10% w/w water was added and the drug–excipient

Table 2
Results of analysis of IST samples after 3 weeks of storage at stressed conditions

| Sample | Ratio (drug–excipient) | % Remaining |
|---|---|---|
| Glipizide | – | 97.03 |
| Glipizide + cellulose acetate | 1:4 | 96.47 |
| Glipizide + magnesium stearate | 3:2 | 101.94 |
| Glipizide + mannitol | 0.5:4.5 | 105.74 |
| Glipizide + sodium chloride | 0.5:4.5 | 106.25 |
| Glipizide + meglumine | 0.25:4.75 | [a] |
| Glipizide + TRIS buffer | 0.25:4.75 | 97.43 |
| Glipizide + PVP | 1:1 | 104.12 |

[a] Yellow color formation in the drug–excipient blend after 3 weeks of storage at stressed conditions.

blend was further mixed with a glass capillary (both the ends of which were heat sealed). To prevent any loss of material, capillary was broken and left inside the vial. Each vial was sealed using a teflon-lined screw cap and stored at 50 °C (Hot air oven, Universal, Narang Scientific, India). These samples were periodically examined for any unusual color change. After 3 weeks of storage at the above conditions, samples were quantitatively analyzed using HPLC. Drug–excipient blends without added water and stored in refrigerator served as controls.

For sample preparation, 2 ml of methanol was added into each vial. The mixture was vortexed and transferred to 100 ml volumetric flask. Vials were rinsed twice with methanol and the volume made up. The samples were centrifuged and the supernatant filtered through 0.45-μm nylon membrane filters. After appropriate dilutions, samples were analyzed using HPLC and drug content determined from the calibration curve prepared within the expected range.

For the analysis of drug–excipient mixtures, Shimadzu HPLC system equipped with LC-10 AT VP pump, DGU-14 AM on-line degasser, SIL-10 AD VP autoinjector, CTO-10 AS VP column oven, and SPD-10 AVP UV-VIS detector was utilized. For peak purity testing, SPD-M 10 A VP PDA detector was used. Shimadzu CLASS-VP software (Version 5.03) was used for data acquisition and mathematical calculations. Chromatographic separation of glipizide was performed on a $C_{18}$ Spherisorb column (4.6 mm × 250 mm; 5 μm particle size; Waters, USA). Mobile phase used was Acetonitrile-phosphate buffer (25 mM, pH 3.5), in the ratio of 40:60 v/v at a flow rate of 1 ml/min. Temperature of the column oven was maintained at 25 °C. Standard solutions and drug–excipient samples (20 μl) were injected and analyzed at 225 nm using a UV detector. For peak purity testing, PDA detector in the range of 200–800 nm was used.

### 2.5. Formulation development and stability studies

The details of the formulation development can be found elsewhere [11]. In brief, core tablets of glipizide (Table 3) were prepared by wet granulation using single stroke tablet-punching machine (CMS-25, Cadmach, India) fitted with 10 mm standard concave punches. Glipizide and all the excipients were mixed and passed through 30-mesh sieve. The blend was mixed for 10 min and PVP (Plasdone K 29/32) was added. The mixture was granulated with ethanol and the resulting wet mass passed through 18-mesh sieve. The granules were dried at 50 °C (approximately for 10 min) to get an LOD value between 0.9 and 1.1%, after which they were passed through 22-mesh sieve. These sized granules were then blended with magnesium stearate (60-mesh passed) and compressed into tablets having an average weight of 360 mg. The core tablets were then coated in an automated perforated coating pan (GAC-250, Ganscoater, India) with a coating solution shown in Table 4. Sufficient coating solution was applied until desired weight gain (12 ± 0.5%) was obtained. The tablets were dried in an oven for 16 h at 50 °C before being stored or evaluated.

Table 3
Composition of core tablets of glipizide

| Ingredients | % w/w |
|---|---|
| Glipizide | 2.78 |
| TRIS buffer | 48.61 |
| Sodium chloride | 9.72 |
| Mannitol | 29.89 |
| PVP | 5.00 |
| Magnesium stearate | 1.50 |
| Talc | 2.00 |
| Colloidal silicon dioxide | 0.50 |

The optimized formulation of glipizide (GLOP-IV/A) was packed in strips of 0.04 mm thick aluminum foil laminated with PVC coating and stored in ICH certified stability chambers (WTC Binder, Germany) maintained at 40 °C and 75% RH. The samples were withdrawn periodically and subjected to assay and dissolution studies.

For assay, one accurately weighed tablet ($n = 5$) was dissolved in 100 ml of methanol. The samples were sonicated (Ultra sonic water bath, 3510, Branson, USA) for 30 min, after which they were filtered through 0.45-μm nylon membrane filter. The filtered solutions, after appropriate dilution with methanol, were analyzed by a validated UV spectroscopic method [12] at 276 nm (Lambda 20 UV–vis spectrophotometer, Perkin-Elmer, USA).

Drug release testing of the formulations ($n = 6$) was carried out using USP-I dissolution apparatus (TDT-06P, Electrolab, India) at 100 rpm. Simulated Intestinal Fluid, pH 6.8 (1000 ml) maintained at 37 ± 0.5 °C was used as dissolution medium. The samples (10 ml) were withdrawn at predetermined time and replaced with an equivalent amount of

Table 4
Coating composition for the core tablets of glipizide

| Ingredients | % w/w |
|---|---|
| Cellulose acetate | 2.58 |
| PVP | 0.64 |
| Triacetin | 0.26 |
| PEG-400 | 0.52 |
| Methanol | 24.00 |
| Dichloromethane | 72.00 |

fresh medium. The samples were filtered through a 0.45-μm nylon membrane filter and analyzed spectrophotometrically at 276 nm. The cumulative percent drug release was plotted against time to determine the release profile.

Release profiles of formulation stored at accelerated stability conditions were compared using model independent pair-wise approach, which included the calculation of "difference factor", $f_1$ and "similarity factor", $f_2$. These fit factors directly compare the difference between the percent drug released for a reference and a test product [13]. The difference factor ($f_1$) measures the percent error between the two curves over all time points and is calculated as follows:

$$f_1 = \frac{\sum_{j=1}^{n} |R_j - T_j|}{\sum_{j=1}^{n} R_j} \times 100 \quad (1)$$

where $n$ is the number of sampling points, $R_j$ and $T_j$ are the percent dissolved of the reference and test products at each time point $j$. The two release profiles are considered to be similar, if $f_1$ value is lower than 15 (between 0 and 15).

The similarity factor ($f_2$) is a logarithmic transformation of the sum of squared error of differences between the test $T_j$ and the reference products $R_j$ over all time points. It was calculated using the following equation:

$$f_2 = 50 \log \left\{ \left[ 1 + \left(\frac{1}{n}\right) \sum_{j=1}^{n} w_j |R_j - T_j|^2 \right]^{-0.5} \times 100 \right\} \quad (2)$$

where $w_j$ is an optional weight factor and other terms are as defined earlier. The two dissolution profiles are considered to be similar, if $f_2$ value is more than 50 (between 50 and 100). For the calculation of $f_1$ and $f_2$ values, only one data point was taken into consideration after 85% of the drug was released.

## 3. Results and discussion

### 3.1. Drug–excipient compatibility testing

Selected DSC scans of drug and drug–excipient mixtures are shown in Figs. 1–13. The thermal behavior of pure drug, respective excipient, and the combination of drug and excipient is compared in the DSC thermograms. Peak transition temperature ($T_{peak}$) and heat of fusion or enthalpy ($\Delta H_f$) of glipizide in various excipient mixtures is summarized in Table 1.

The DSC trace of glipizide showed a sharp endothermic peak at 216.35 °C. In majority of the cases, melting endotherm of drug was well preserved with slight changes in terms of broadening or shifting towards the lower temperature. It has been reported that the quantity of material used, especially in drug–excipient mixtures, affects the peak shape and enthalpy [4,5]. Thus, these minor changes in the melting endotherm of drug could be due to the mixing of drug and excipient, which lowers the purity of each component in the mixture and may not necessarily indicate potential incompatibility [7,14–16].

The IR spectrum of test material is shown in Fig. 14 and the following characteristic bands were observed [12] 1689 (–C=O, amide), 1651 (–C=O, urea), 1528 (Ar–CH, stretching), 1443 (Ar–CH, bending), and 1333 and 1159 $cm^{-1}$ ($-SO_2NH$).

The DSC scan of microcrystalline cellulose (MCC) showed a broad endotherm at 63.29 °C (starting from 28.98 °C and ending at 104.76 °C), which may be attributed to the loss of adsorbed water [5,15]. The thermogram of glipizide–MCC mixture showed an endothermic peak of drug at 215.68 °C, indicating that there was no interaction (Fig. 1). Characteristic bands of glipizide were well retained in the IR spectrum of glipizide–MCC mixture without any new bands, indicating that there was no change in the structure of drug. On the basis of above results, it was concluded that glipizide is compatible with MCC.

The DSC scan of lactose showed endothermic peaks at 148.50 °C (corresponding to dehydration of bound water), 172.10 °C (crystalline transition), 215.09 °C (melting point), and a small peak at 221.02 °C [1]. The DSC thermogram of glipizide in the presence of lactose is shown in Fig. 2. Melting endothermic peak of glipizide was missing in glipizide–lactose mixture, which suggested incompatibility. Initially, during formulation development, attempts were made to use lactose as diluent. When ready for compression blend (containing glipizide, meglumine/TRIS buffer, and lactose) was tested for loss on drying (LOD), yellow color formation in the blend was observed, indicating that there was incompatibility. This yellow coloration might have occurred because of interaction between amine group of meglumine/TRIS buffer and lactose. Since solubility modifier (meglumine/TRIS buffer) was required to improve the solubility of glipizide, it was felt that presence of lactose in the formulation might pose long-term stability problem and hence, it was not pursued further.

A sharp melting endotherm was observed at 166.45 °C in the DSC trace of mannitol (Fig. 3). In case of glipizide–mannitol mixture, there was broadening of melting endotherm of mannitol (at 168.53 °C). The drug peak appeared at 187.00 °C with a little change in $\Delta H_f$ value. The IR spectrum of glipizide–mannitol mixture showed the presence of characteristic bands of glipizide. Thus, any change in the structure of glipizide was ruled out and it was concluded that there is no chemical incompatibility between glipizide and mannitol.

In the DSC scan of sodium chloride, no peak was observed in the temperature range of 25–300 °C (Fig. 4). The melting endotherm of glipizide was well retained in the DSC trace of glipizide–sodium chloride mixture (213.86 °C). In IR spectrum of glipizide–sodium chloride mixture, bands corresponding to glipizide were observed without any new bands. It was concluded that glipizide is compatible with sodium chloride.

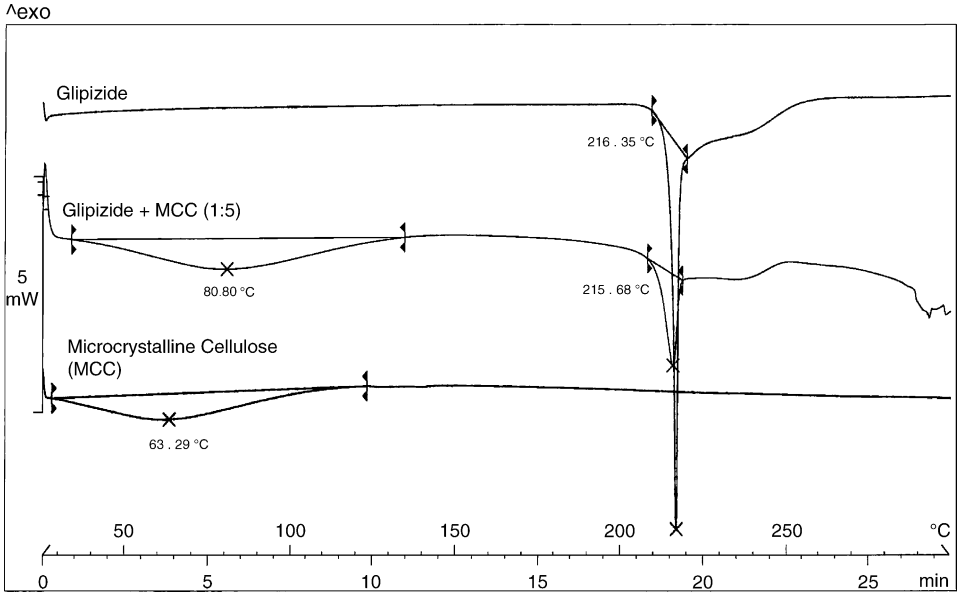


Fig. 1. DSC thermogram of glipizide with MCC.

A sharp endothermic peak at 130.32 °C was observed in the DSC thermogram of meglumine, which broadened and shifted to lower temperature (122.81 °C) in glipizide and meglumine mixture (Fig. 5). Drug peak was completely missing in the DSC trace of mixture, which indicated incompatibility. During formulation development, initial trials were taken with meglumine. Later on, it was observed that there was sticking problem in the tablets when meglumine was used. Therefore, no attempts were made further to characterize the type of interaction between glipizide and meglumine and eventually, it was not used in the formulation.

The DSC trace of TRIS buffer showed two endothermic peaks at 139.14 (probably due to evaporation of adsorbed moisture) and 172.73 °C (melting point of TRIS buffer), followed by a wave-like endotherm at 300 °C, which probably is due to decomposition of TRIS buffer (Fig. 6). In the thermogram of glipizide and TRIS buffer mixture, the peak of TRIS buffer shifted to lower temperature (135.60 °C). Also, the drug peak was missing and a broad endothermic peak was observed at 296.16 °C. DSC results points towards some incompatibility between glipizide and TRIS buffer. However, IR spectrum of glipizide–TRIS buffer mixture showed the presence of characteristic bands corresponding to glipizide. There was no appearance of new bands in the IR spectrum. Hence, there was strong evidence of unchanged drug structure and lack of chemical interac-

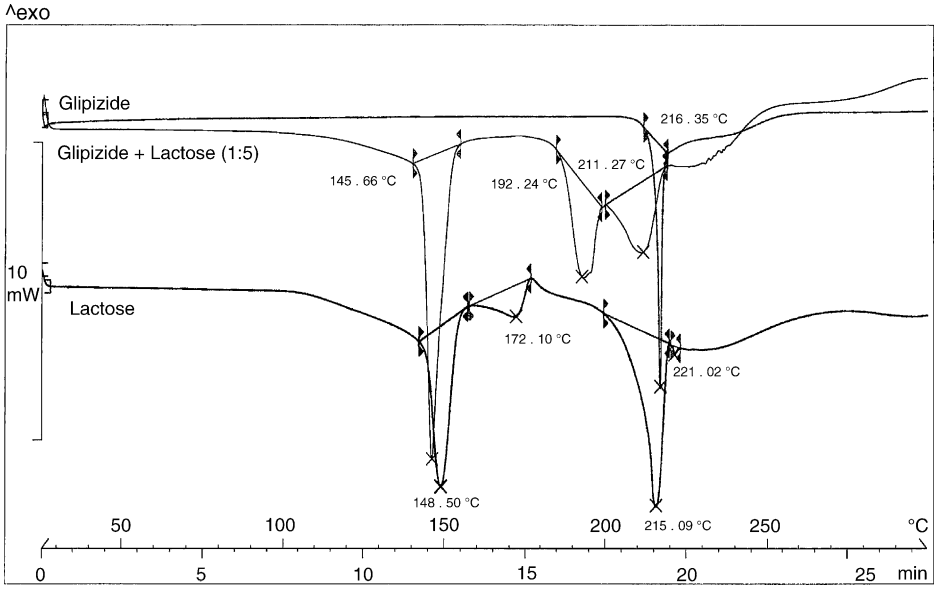


Fig. 2. DSC thermogram of glipizide with lactose.

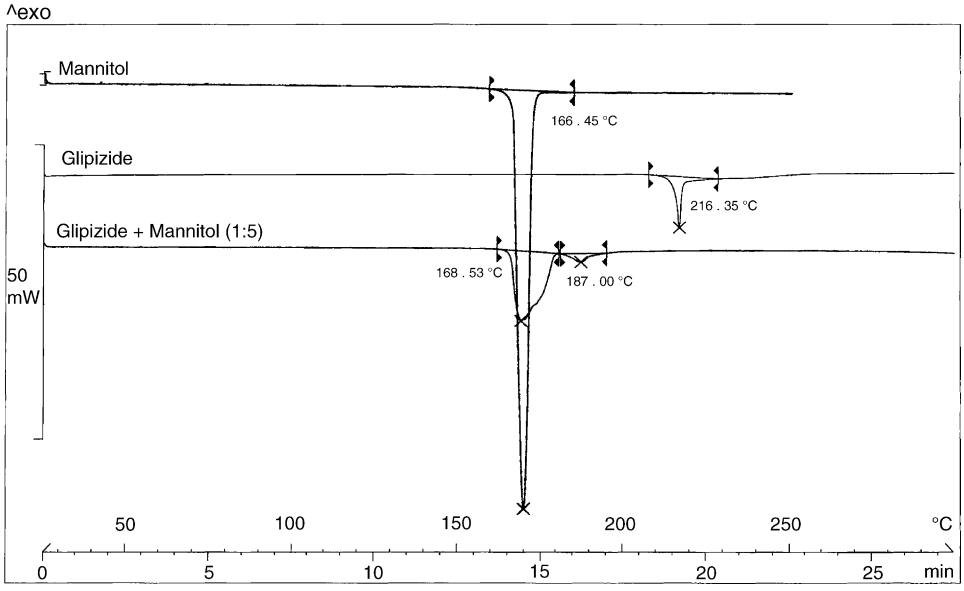


Fig. 3. DSC thermogram of glipizide with mannitol.

tion between the two. Thus, it was concluded that there is no chemical incompatibility between glipizide and TRIS buffer.

In the DSC scans of colloidal silicon dioxide (CSD) and talc, no peaks were observed in the range of 25–300 °C (Figs. 7 and 8). Endothermic peak of glipizide was well preserved at 214.22 and 215.49 °C in the DSC traces of glipizide–CSD and glipizide–talc mixtures, respectively. Also, the bands corresponding to glipizide were present in the IR spectrum of both the mixtures, confirming that there was no change in the structure of glipizide. It was concluded that glipizide is compatible with both CSD and talc.

In DSC trace of magnesium stearate, an endothermic peak was observed at 121.11 °C (Fig. 9). A small peak was also present at 203.83 °C, which might be due to palmitate impurity [5,6]. The DSC scan of glipizide–magnesium stearate showed several endothermic peaks that could not be correlated directly either with magnesium stearate or glipizide. The DSC trace of glipizide–magnesium stearate mixture suggests that there may be some incompatibility, which might be physical in nature. However, IR spectrum of glipizide–magnesium stearate mixture showed the presence of bands corresponding to glipizide. No extra bands were present in the IR spectrum, which confirmed that there is no chemical interaction between the two.

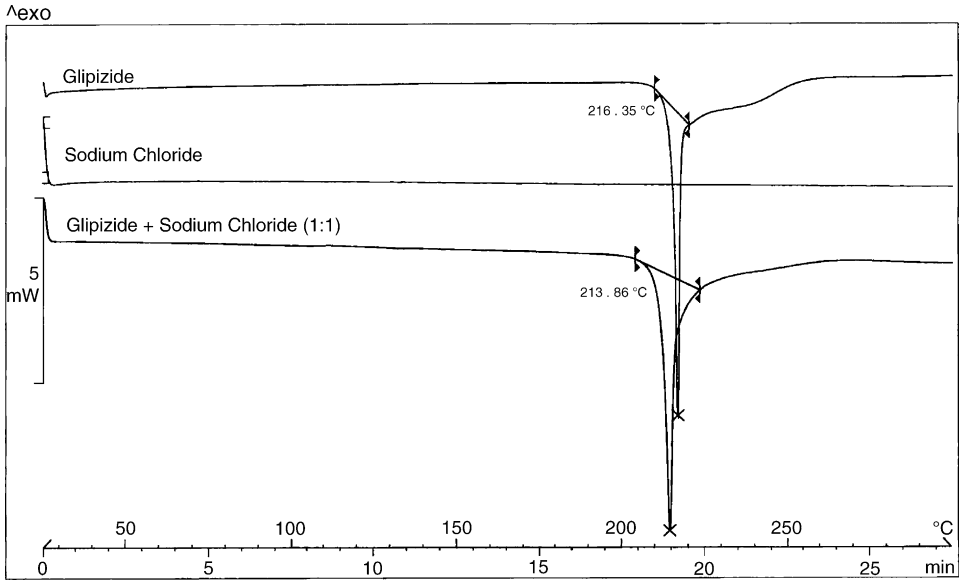


Fig. 4. DSC thermogram of glipizide with sodium chloride.

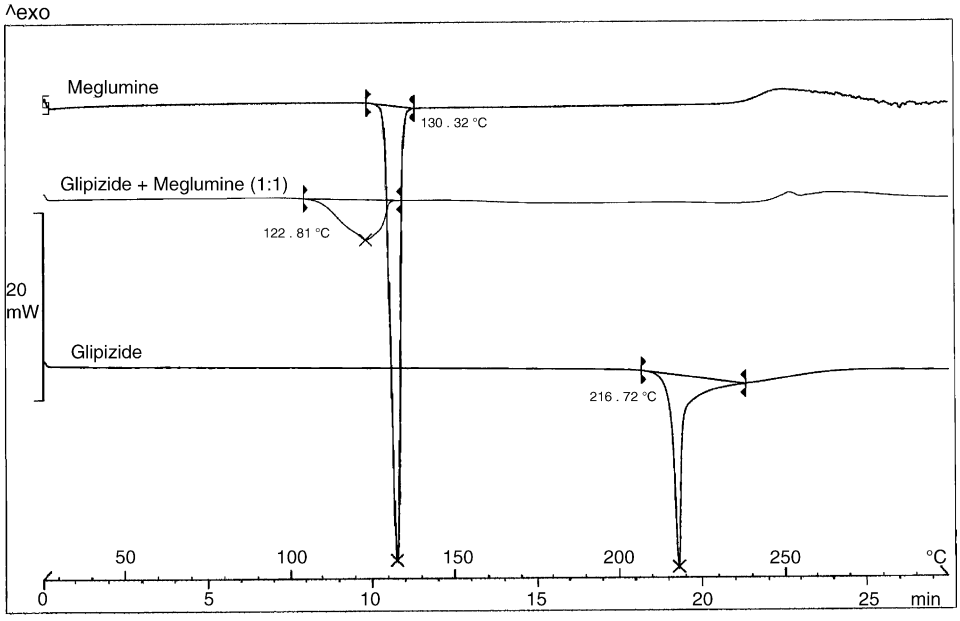


Fig. 5. DSC thermogram of glipizide with meglumine.

The DSC trace of cellulose acetate showed a broad endotherm at 66.79 °C, probably because of evaporation of adsorbed moisture (Fig. 10). Another endotherm was observed at 229.28 °C, which corresponded to its melting point. DSC thermogram of glipizide and cellulose acetate mixture showed the features of both glipizide and cellulose acetate, with drug's melting endotherm present at 217.35 °C. IR spectrum of glipizide–cellulose acetate mixture showed the presence of characteristic bands of glipizide confirming that there was no change in the drug structure. Therefore, based on above results, it was concluded that glipizide is compatible with cellulose acetate.

In the DSC thermogram of HPMC, a broad endothermic peak at 65.96 °C, due to evaporation of adsorbed moisture, was observed (Fig. 11). The melting endotherm of drug was present at 216.18 °C in the DSC trace of glipizide–HPMC mixture, which ruled out any incidence of incompatibility. Also, the IR spectrum of mixture of glipizide and HPMC showed the presence of characteristic bands of glipizide and there were no new bands. Thus, it was concluded that glipizide is compatible with HPMC.

DSC trace of PEG-4000 showed a sharp endothermic peak at 62.11 °C, retained well in glipizide and PEG-4000 (62.84 °C). Endothermic peak of drug was broadened and

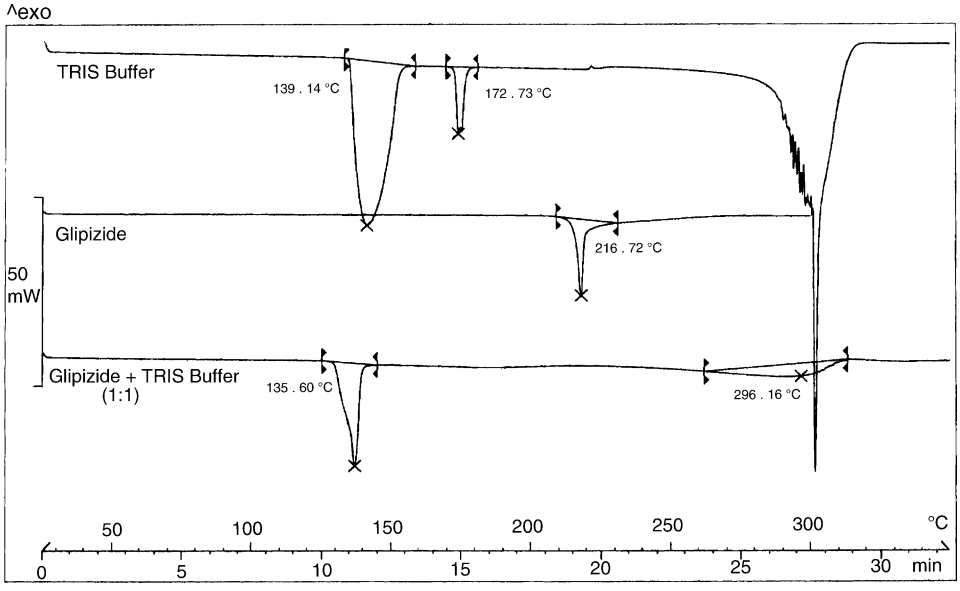


Fig. 6. DSC thermogram of glipizide with TRIS buffer.

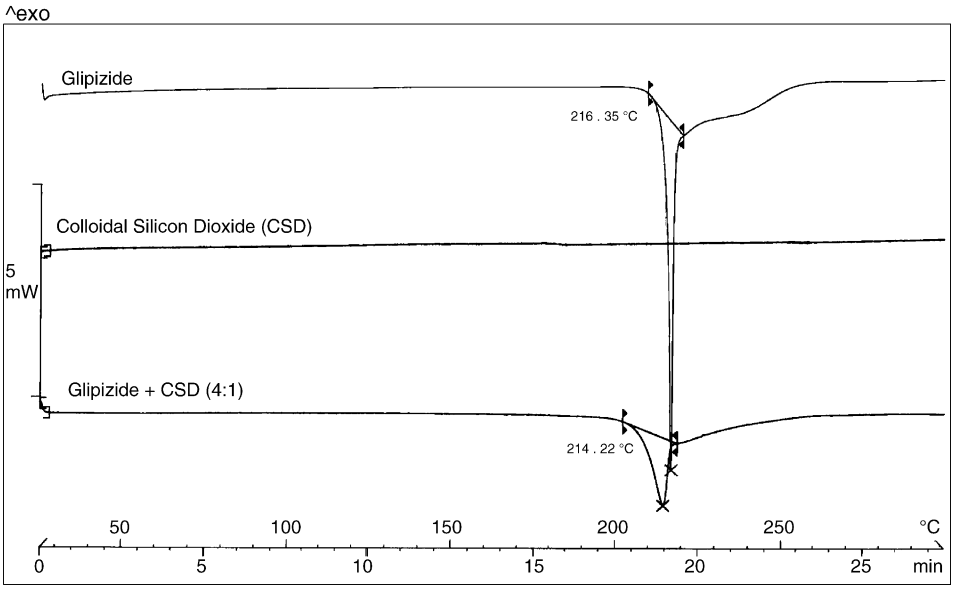


Fig. 7. DSC thermogram of glipizide with colloidal silicon dioxide.

shifted to lower temperature (205.35 °C) in the thermogram of glipizide and PEG-4000 mixture (Fig. 12). This could be because of melting of PEG-4000 and partial dissolution of drug in the molten excipient, because of which there was a shift in the drug peak and reduction in $\Delta H_f$ [5,6]. However, after analyzing the IR spectrum, all the characteristic bands of glipizide were observed and it was concluded that glipizide is compatible with PEG-4000.

In case of PVP, a broad endotherm was observed at 66.11 °C due to loss of adsorbed moisture (Fig. 13). The thermogram of glipizide and PVP mixture showed broadening and shifting of drug peak to lower temperature (207.57 °C). This kind of phenomenon may be due to simple mixing of drug and excipient, which lowers the purity of each compound [5]. Since, the characteristics bands of glipizide were present in the IR spectrum of mixture of glipizide and PVP, it was confirmed that there is no change in the drug structure and both glipizide and PVP are compatible with each other.

Based on the results of formulation trials, following excipients were defined in the prototype formula: sodium chloride, mannitol, TRIS buffer, PVP, cellulose acetate, and magnesium stearate. These excipients were tested using the tech-

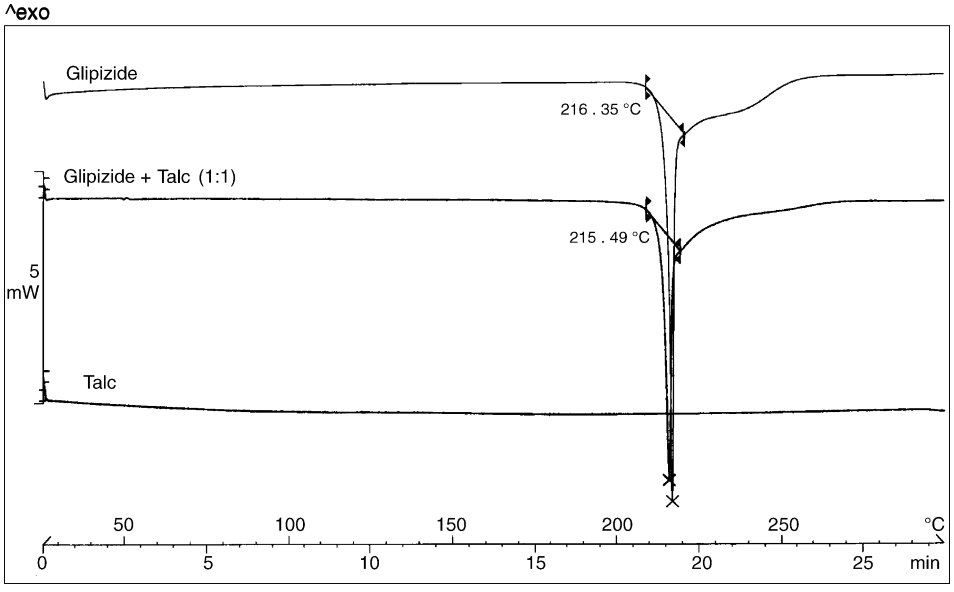


Fig. 8. DSC thermogram of glipizide with talc.

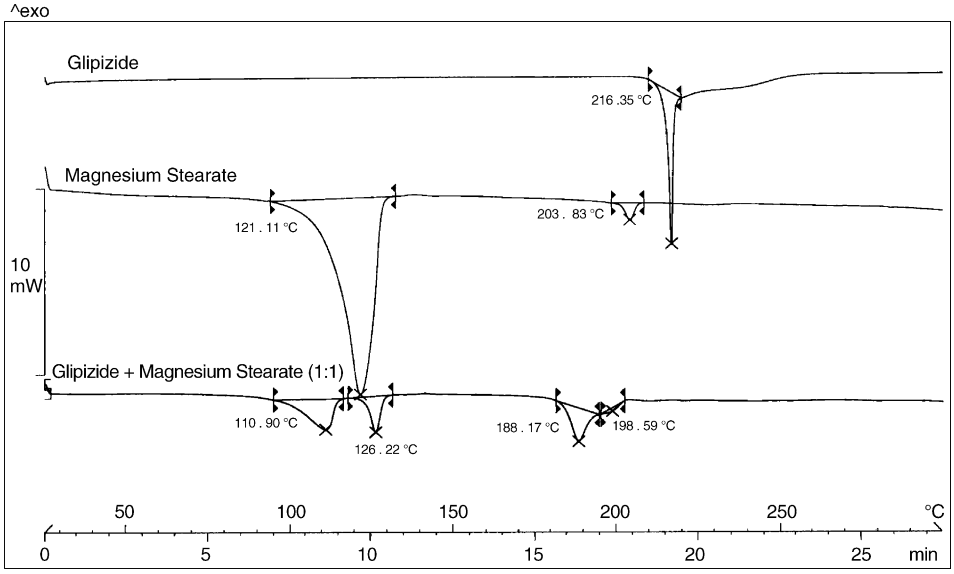


Fig. 9. DSC thermogram of glipizide with magnesium stearate.

nique of IST and the quantitative results are shown in Table 2. It can be seen from the table that there is little change in the drug content after storage of drug–excipient blends under stressed conditions.

Mannitol was used as a diluent and based on the results of DSC alone; it is difficult to conclude compatibility between the two. However, as seen from Table 2, there is little change in the drug content in IST samples after 3 weeks of storage at stressed conditions. When the HPLC chromatogram of glipizide–mannitol mixture was compared with that of pure glipizide, it was found that the retention time (RT) and peak shape of drug were unchanged. Therefore, it was concluded that both glipizide and mannitol are compatible with each other. In the developed formulations, sodium chloride was used as osmagent and there was little change in the drug content indicating that both sodium chloride and glipizide are compatible.

As glipizide is practically water-insoluble drug, meglumine and TRIS buffer were used as solubility modifiers. Both are alkalinizing agent that increases the microenvironmental pH of the core so as to increase solubility of glipizide, which is a weakly acidic drug. DSC results of glipizide and meglumine mixture indicated incompatibility. Mixture of glipizide and meglumine developed yellow coloration after 3 weeks

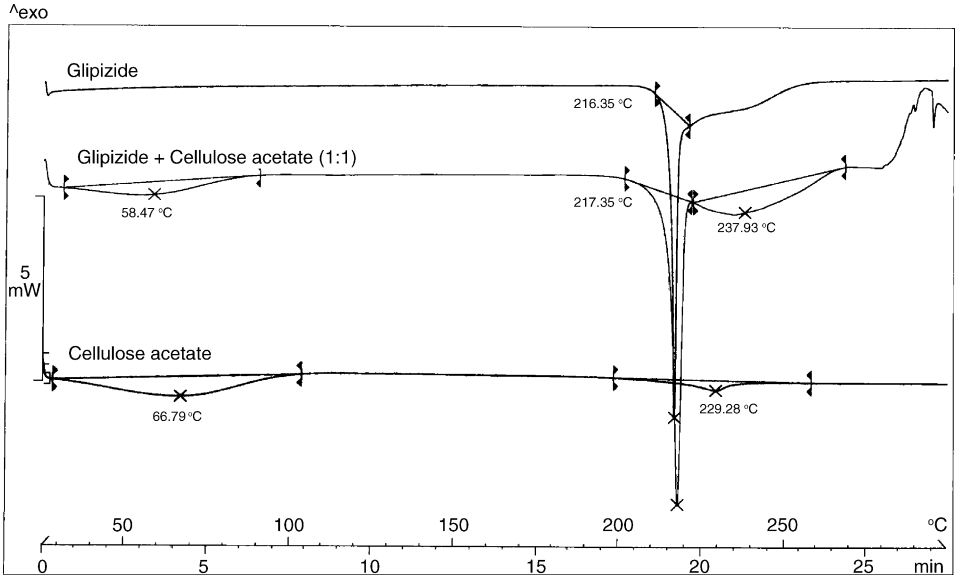


Fig. 10. DSC thermogram of glipizide with cellulose acetate.

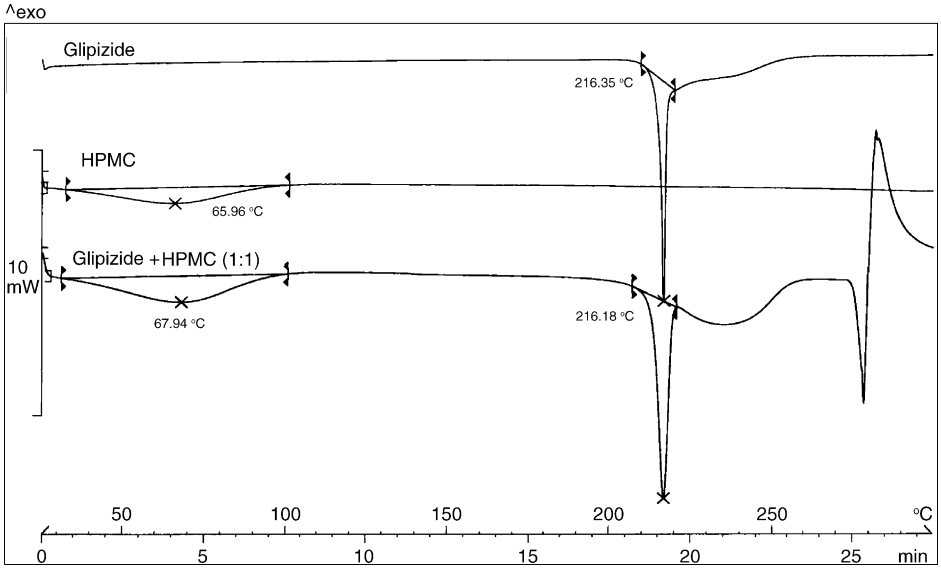


Fig. 11. DSC thermogram of glipizide with HPMC.

of storage at stressed conditions, indicating incompatibility between glipizide and meglumine. Initial formulation studies with meglumine also showed color change in the blend. Therefore, no attempts were made further to characterize the type of interaction between glipizide and meglumine and eventually, it was not used in the formulation.

DSC results of glipizide and TRIS buffer also indicated some incompatibility. However, there was no change in the chromatographic behavior of drug in its pure form and drug–excipient mixture. Also, quantitative results after 3 weeks of storage at stressed conditions ruled out any drug degradation. It was concluded that there is no chemical incompatibility between glipizide and TRIS buffer.

In case of glipizide–magnesium stearate mixture also, no definite conclusion could be drawn based on the DSC results alone. However, results of IST studies showed the drug content to be within limits concluding that both are compatible with each other.

In case of cellulose acetate, there was little change in the drug content further substantiating the results of DSC and IR studies that both glipizide and cellulose acetate are compatible with each other. Mixture of glipizide and PVP also showed little change in the drug content demonstrat-

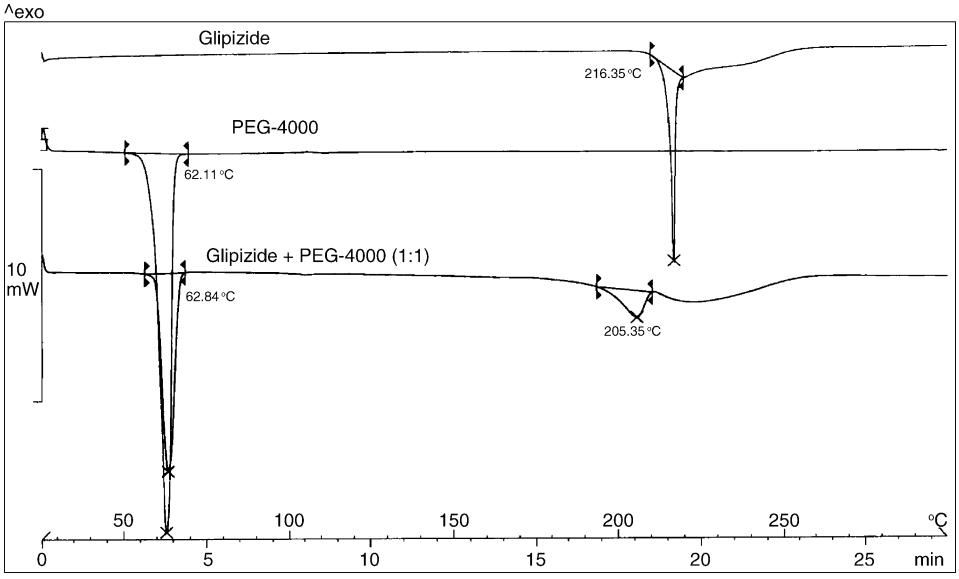


Fig. 12. DSC thermogram of glipizide with PEG-4000.

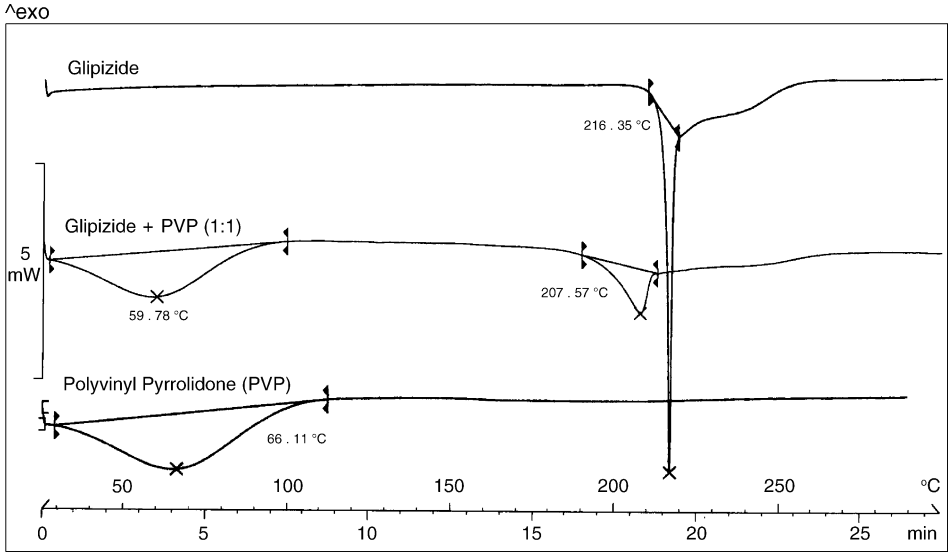


Fig. 13. DSC thermogram of glipizide with PVP.

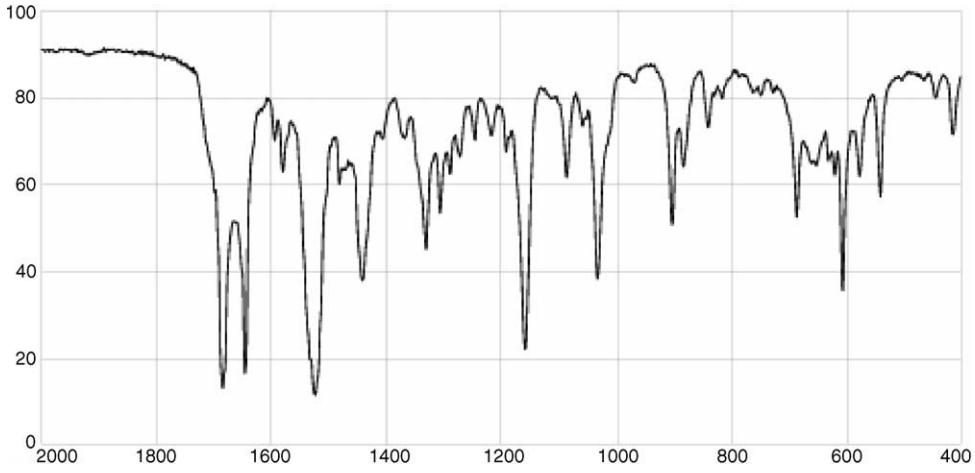


Fig. 14. IR spectrum of glipizide.

ing that both glipizide and PVP are compatible with each other.

### 3.2. Formulation development and stability studies

Excipients defined in the prototype formula were used for formulation development. Various core and membrane variables were varied to optimize the prototype formula [11]. The optimized formulation (GLOP-IV/A), packed in strips of 0.04 mm thick aluminum foil laminated with PVC, was evaluated after 3 months of storage at accelerated stability conditions (40 °C and 75% RH), results of which are shown in Table 5 and Fig. 15. It is evident that the formulation is having good stability in terms of both drug content and dissolution stability. There was little change in the drug content after 3 weeks of storage at accelerated stability conditions (Table 5). Drug peak was found to be pure, when tested using PDA detector. Release profile was similar after stability studies as shown by the $f_1$ (less than 15) and $f_2$ values (more than 50). Based on the results, it can be concluded that the formulations are stable after 3 months of storage at accelerated stability conditions.

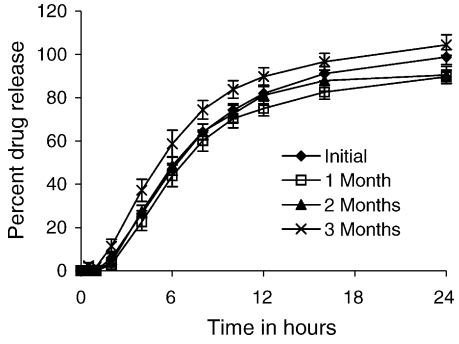


Fig. 15. Dissolution stability of optimized glipizide formulations after 3 months of storage at accelerated stability conditions. Key to symbols: initial (♦), 1 month (□), 2 months (▲), and 3 months stability sample (✕).

Table 5
Evaluation of GLOP-IV/A formulation in 0.04 mm thick aluminum foil after 3 months of storage at 40 °C and 75% RH

| Parameter | Initial | One month | Two months | Three months |
|---|---|---|---|---|
| Drug content (%)[a] | 104.60 ± 2.44 | 106.71 ± 2.90 | 101.35 ± 1.64 | 102.16 ± 2.07 |
| Hardness (kp)[a] | 25.72 ± 1.95 | 28.70 ± 2.30 | 28.86 ± 2.19 | 28.58 ± 2.13 |
| $f_1$ value[b] | – | 8.63 | 3.85 | 14.52 |
| $f_2$ value[b] | – | 61.62 | 72.73 | 54.50 |

[a] Values expressed as average ± standard deviation.
[b] Initial sample (0-month) was taken as reference to calculate $f_1$ and $f_2$ values.

## 4. Conclusions

The results confirmed that DSC could be used as a rapid method to evaluate the compatibility between drug and excipients. However, caution need to be exercised while interpreting the DSC results alone. Wherever possible, other techniques such as IR and quantitative analysis after storage under stressed conditions should be taken in conjunction with DSC results to reach any definite conclusion. In the present study, results of DSC along with IR and/or HPLC were successfully employed to assess the compatibility of glipizide with the excipients used in the development of extended release formulations.

No concrete evidence of interaction was observed between glipizide and majority of the excipients used in the development of *in house* formulations of glipizide. However, based on the DSC results alone, an interaction was suspected between glipizide and few of the excipients (lactose, meglumine, TRIS buffer, and magnesium stearate). However, based on the results of IR and/or HPLC analysis, any possible pharmaceutical incompatibility between glipizide and TRIS buffer and magnesium stearate was ruled out.

To use the results of this study, extended release formulations were developed using the excipients found to be compatible with glipizide. The optimized formulation, packed in strips of aluminum foil, was found to be stable after 3 months of accelerated stability studies, thus, validating the claims that the above methods were successfully used to assess the compatibility between glipizide and excipients.

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## References

[1] A.A.S. Araujo, S. Storpirtis, L.P. Mercuri, F.M.S. Carvalho, M.S. Filho, J.R. Matos, Int. J. Pharm. 260 (2003) 303–314.
[2] E.C.V. Tonder, A.P. Lotter, S.A. Botha, Drug Dev. Ind. Pharm. 16 (1990) 2125–2133.
[3] S. Venkataram, M. Khohlokwane, S.H. Wallis, Drug Dev. Ind. Pharm. 21 (1995) 847–855.
[4] R. Kandarapu, V. Grover, H.P.S. Chawla, S. Garg, S. T. P. Pharma Sci. 11 (2001) 449–457.
[5] P. Mura, A. Manderioli, G. Bramanti, S. Furlanetto, S. Pinzauti, Int. J. Pharm. 119 (1995) 71–79.
[6] P. Mura, M.T. Faucci, A. Manderioli, G. Bramanti, L. Ceccarelli, J. Pharm. Biomed. Anal. 18 (1998) 151–163.
[7] S.A. Botha, A.P. Lotter, Drug Dev. Ind. Pharm. 16 (1990) 673–683.
[8] A.T.M. Serajuddin, A.B. Thakur, R.N. Ghoshal, M.G. Fakes, S.A. Ranadive, K.R. Morris, S.A. Varia, J. Pharm. Sci. 88 (1999) 696–704.
[9] L. Gu, R.G. Strickley, L. Chi, Z.T. Chowhan, Pharm. Res. 7 (1990) 379–383.
[10] R.N. Brogden, R.C. Heel, G.E. Pakes, T.M. Speight, G.S. Avery, Drugs 18 (1979) 329–353.
[11] R.K. Verma, S. Garg, Eur. J. Pharm. Biopharm. 57 (2004) 513–525.
[12] R.K. Verma, Development and evaluation of novel osmotically controlled oral drug delivery systems for glipizide and isosorbide mononitrate, Ph.D. thesis, Department of Pharmaceutics, NIPER, SAS Nagar, India, 2002.
[13] J.W. Moore, H.H. Flanner, Pharm. Technol. 20 (1996) 64–74.
[14] A. Smith, Anal. Proc. 19 (1982) 559–561.
[15] T. Durig, A.R. Fassihi, Int. J. Pharm. 117 (1993) 161–170.
[16] C.E.P. Malan, M.M. Villers, A.P. Lotter, J. Pharm. Biomed. Anal. 15 (1997) 549–557.