CHAPTER-5
5. PREFORMULATION STUDY

5.1 Introduction

Historically, preformulation had its birth in the very early sixties. Prior to this time, many assays that were used to assess stability (e.g., those in official Pharmacopoeia) simply indicated the amount of drug that originally was incorporated into the dosage form. However, starting with the early sixties more and more stability-indicating assays were being introduced into pharmaceutical practices. But it was apparent that work had to be done prior to the point when formulation was initiated, and that was the beginning of the branch of the pharmaceutical sciences which, today is known as Preformulation.

Prior to nomination into product development, a drug should undergo a phase traditionally called preformulation. Preformulation is the physicochemical characterization of the solid and solution properties of compounds. Preformulation studies supplies information needed to define nature of the drug substance. This information is then used as the framework for the drugs combination with pharmaceutical ingredients in the fabrication of a dosage form. The definition of preformulation proposed by Akers is ‘the necessary testing which encompasses all studies enacted on a new drug compound in order to produce useful information for subsequent formulation of a stable and biopharmaceutically suitable drug dosage form’. Preformulation is usually defined as the science of the physicochemical characterization of candidate drugs. However, any studies carried out to define the conditions under which the candidate drug should be formulated can also be termed preformulation.
The goals of preformulation studies are to choose the correct form of the drug substance, evaluate its physical properties, and to generate a thorough understanding of the materials' stability under the conditions that will lead to development of an optimal drug delivery system.

Physicochemical parameters of drug includes solubility, molecular formula and molecular weight, density, flow property and compressibility, particle size distribution, partition coefficient, ionization constant, preferable polymorphic form, preferable dissolution method (medium), stability and compatibility with other compounds (excipients) are generally conducted in basic Preformulation studies.

Apart from these parameters lot of other parameters are also ascertained as and when required. Special studies are conducted depending on the type of dosage form and the type of drug molecule. GPZ is an established drug and physicochemical properties of it have been reported elsewhere. It is practically insoluble in water and ethanol and slightly soluble in methylene chloride and acetone. It dissolves in dilute solution of alkali hydroxide. The PKa Value of glipizide is 5.9. GPZ is BCS (biopharmaceutical classification system) class-II drug (Low solubility and High permeability). The maximum spectrophotometric absorption wave length ($\lambda_{max}$) of glipizide in acetone and aqueous buffer is 276 nm. The objectives of this chapter is to access the various physiochemical and pharmaceutical properties of GPZ; to generate the standard calibration curve of GPZ in 0.1 N HCl and aqueous buffers (for the estimation of concentration of drug in respective mediums i.e. solubility and dissolution samples); to access the compatibility between the drug and excipients, to be used in the formulation of controlled release formulation.
5.2 Materials

Glipizide (GPZ) was obtained as gift sample from Glenmark Pharmaceuticals Ltd, Nashik; Microcrystalline cellulose (MCC), Croscarmellose sodium (CCS), Polyvinyl pyrrolidone (PVP), Hydroxy propyl methyl cellulose (HPMC), Carbopol, Chitosan, Sodium bicarbonate, Magnesium stearate, Aerosol and Talc were procured from SD fines Ltd, Mumbai. All other chemicals used were of analytical grade and purchased from Merck India Ltd and Rankem Ltd, Mumbai.

FT-IR (8400S, Shimadzu, Japan), Differential scanning calorimeter (JADE DSC, Perkin Elmer, USA), UV-Visible Spectrophotometer (UV-1601, Shimadzu, Japan), Digital weighing balance (Contech instruments Ltd, Mumbai), Magnetic stirrer (Remi Motors Ltd, Mumbai), Digital ultra sonicating cleaner (Loba Chemie, Mumbai), Hot air oven, (Universal, Narang Scientific, India) and pH Meter (VHS Electronics, Mumbai) were used during the investigation.

5.3 Methods

5.3.1 Standard calibration curve of glipizide

- Calibration curve in 0.1 N HCl (pH 1.2)

Accurately weighed quantity of GPZ (25 mg) was taken in a 250 ml cleaned and dried volumetric flask. Methanol was added into the flask up to 250 ml and sonicated for 30 min to dissolve glipizide completely. The concentration of the primary stock solution so obtained was 100μg/ml. Then serial dilution were prepared in the concentration range of 2 to 14 μg/ml, with 0.1 N HCl\(^\text{10}\). Working standard solution (14μg/ml) was chosen arbitrarily and scanned in a UV-Visible spectrophotometer (Shimadzu UV-1601 UV/VIS double beam spectrophotometer) within the wavelength range of 190 nm to 400 nm to

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determine the absorption maximum ($\lambda_{\text{max}}$) of the drug. The absorbance of the working standard solutions (2µg/ml to 14µg/ml) at $\lambda_{\text{max}}$ was used to plot a standard curve of the drug between absorbance and concentrations.

- **Calibration curve in phosphate buffer, pH 4.5**

  The primary stock solution of GPZ (100µg/ml) was prepared in PBS, pH 4.5 and serial dilution (2, 4, 6, 8, 10 and 14 µg/ml) of the drug was prepared by diluting the primary stock solution in phosphate buffer, pH 4.5. Standard solution (14µg/ml) was scanned in a UV-Visible spectrophotometer within the range of 190 nm to 400 nm wavelength to determine the $\lambda_{\text{max}}$ of the drug. The absorbance of the standard solutions at $\lambda_{\text{max}}$ was plotted against the concentrations used to obtain the standard calibration curve of GPZ in PBS, pH 4.5.

- **Calibration curve in phosphate buffer, pH 6.8**

  The primary stock of GPZ (100µg/ml) was prepared in PBS, pH 6.8 and standard solutions (5, 10, 15, 20, 25, 30 and 35µg/ml) of the drug was prepared by diluting the primary stock solution with phosphate buffer, pH 6.8. Standard solution (30µg/ml) was scanned in a UV-Visible spectrophotometer within the range of 190 nm to 400 nm wavelength to determine the $\lambda_{\text{max}}$ of the drug. The absorbance of the standard solutions at $\lambda_{\text{max}}$ was plotted against the concentrations used to obtain the standard calibration curve of GPZ in phosphate buffer, pH 6.8.

- **Calibration curve in phosphate buffer, pH 7.4**

  The main stock of GPZ (100µg/ml) was prepared in PBS, pH 7.4 and subsequently diluted with phosphate buffer, pH 7.4 to obtain the series of standard solution (5, 10, 15, 20, 25, 30 and 35 µg/ml). Standard solution (30µg/ml) was scanned in UV-Visible
spectrophotometer within range of 190 nm to 400 nm wavelength to determine the $\lambda_{\text{max}}$ of the drug. The absorbance of series of standard solutions at $\lambda_{\text{max}}$ was plotted against the concentrations to obtain the standard calibration curve of GPZ in phosphate buffer, pH 7.4

5.3.2 Determination of saturation solubility of glipizide

Different aqueous mediums like 0.1N HCl, pH 1.2; phosphate buffer, pH 4.5; phosphate buffer, pH 6.8 and phosphate buffer 7.4 were selected for solubility study of GPZ. Saturation solubility of GPZ was determined using following standard procedure i.e. excess (known) amount of drug was added with stirring in the respective medium in 100 ml volumetric flasks at room temperature (25°C) for 48 hr. The flasks containing drug solutions were covered by aluminum foil to protect from light. After 48 hr the samples were filtered through 0.45μm nylon filters. The UV absorbance of the solutions after appropriate dilution was determined at 276 nm and the amount of drug dissolved was calculated using calibration curve of the drug in the respective medium.

5.3.3 Moisture content of glipizide

The moisture content of the drug was determined by Karl Fischer titrator as per the procedure described below.

- Standardization of Karl Fischer reagent

Dehydrated methanol (20ml) and sodium tartarate (100 mg) was stirred for 1 minute and titrated against the Karl Fischer reagent to electrometric end point. The water equivalent factor in ‘mg’ of water per ‘ml’ of reagent was calculated by using the formula,

$$ F = \frac{2 \times 18.02 \times w}{V_DPS, Utkal University, Odisha} $$

(5.1)
Where, ‘F’ is the water equivalent factor, ‘w’, weight in mg of dehydrated sodium tartarate, ‘v’, volume of Karl Fischer reagent (ml). The molecular weight of sodium tartarate is 230.08, and the Karl Fischer constant is 18.02.

- **Sample analysis**

  An accurately weighed drug sample (50 mg) was stirred for 1 min in about 75ml of dehydrated methanol and titrated against the Karl Fischer reagent. The total volume of the reagent consumed (S) to obtain the electrometric end point was noted. The water content was calculated by multiplying ‘S’ with water equivalent factor (F) i.e.

  \[
  \text{Water content} = S \times F
  \]

- **5.3.4 Flow properties of glipizide powder**

  The flow properties of the powder was judged from the angle of repose, compressibility index and hausner ratio. Powdered sample of GPZ was passed through sieve No 100 and the powder was subjected to the following method of determination of flow properties.

  - **Angle of repose of the powder**

    Angle of repose was determined using the funnel method. The powder was poured through a funnel that was raised vertically on the plane surface until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (θ) was calculated using the formula.

    \[
    \theta = \tan^{-1}(h/r)
    \]

  - **Bulk density of the powder**
Apparent bulk density \((D_b)\) was determined by pouring the drug powder into a graduated cylinder. The bulk volume \((V_b)\) and weight of the powder \((M)\) was determined. The bulk density was calculated using the formula:

\[
D_b = \frac{M}{V_b}
\]  \hspace{1cm} (5.4)

- **Tapped density of the powder**

The measuring cylinder containing a known mass of powder was tapped for 100 times. The minimum volume \((V_t)\) occupied in the cylinder and the weight \((M)\) of the blend was measured. The tapped density \((D_t)\) was calculated using the following formula,

\[
D_t = \frac{M}{V_t}
\]  \hspace{1cm} (5.5)

- **Compressibility Index of the powder**

The simplest way for measurement of flowability of powder is compressibility, an indication by which a material can be induced to flow is given by compressibility index \((CI)\) which is calculated as follows,

\[
CI = \left[ \frac{D_t - D_b}{D_t} \right] \times 100
\]  \hspace{1cm} (5.6)

The value below 15% indicates a powder with good flow characteristics, whereas above 25% indicate poor flowability.

- **Hausner ratio of the powder**

Hausner ratio\(^{12}\) is calculated by the following formula,

\[
\text{Hausner ratio} = \frac{D_t}{D_b}
\]  \hspace{1cm} (5.7)

Where \(D_t\) is tapped density and \(D_b\) is bulk density, Lower Hausner ratio (<1.25) indicates better flow properties and vice versa\(^{13}\).

5.3.5 Particle size distribution study of glipizide by laser diffraction

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The technique of laser diffraction is based on the principle that particles passing through a laser beam will scatter light at an angle that is directly related to their size: large particles scatter at low angles, whereas small particles scatter at high angles. The laser diffraction is accurately described by the Fraunhofer Approximation\textsuperscript{14} and the Mie theory\textsuperscript{15}, with the assumption of spherical particle morphology. In the laser diffraction technique the measurable particle size ranges is from 50 nm to 1000 \( \mu \text{m} \).

A sample of GPZ suspension (1.5\% w/v) was prepared with distilled water. A small ultrasonic treatment was applied for breaking up loosely-held agglomerates. Sample was subjected for laser diffraction study in Master sizer (Malvern).

5.3.6 Melting point determination of glipizide

Melting point of GPZ was determined by using capillary tube method.

5.3.7 FT-IR spectroscopic study of Glipizide

FT-IR spectra of glipizide were recorded on a FT-IR spectrophotometer (JASCO 5300) in the range of 4000-500 cm\(^{-1}\) using potassium bromide discs.

5.3.8 Differential scanning calorimetric study

A differential scanning calorimeter (JADE DSC, PerkinElmer, USA) was used for thermal analysis of drug. Drug sample (passed through 60-mesh sieve) were weighed directly in the DSC aluminum pan and scanned in the temperature range of 50–300\( ^\circ\text{C} \) under an atmosphere of dry nitrogen. The rate of heating was 20\( ^\circ\text{C} \)/min and thermograms obtained were observed for identification of drug.

5.3.9 Isothermal stress testing for drug-excipients compatibility studies

In isothermal stress testing (IST) studies\textsuperscript{16,17}, drug and different excipients (Table 5.6) were weighed directly in 4ml glass vials \((n = 2)\) and mixed on a vortex mixer for 2 min.
In each of the vials, water (10% v/w) was added and the drug-excipients 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 in a Hot air oven. These samples were periodically examined for any unusual color change. After 3 weeks of storage at the above conditions, samples were quantitatively analyzed using UV-Visible spectrophotometer. Drug-excipients blends without added water stored in refrigerator served as controls.

For sample preparation, 2ml of methanol was added into each vial. The mixture was vortexed for 3 min and transferred to 100ml volumetric flask. Vials were rinsed twice with methanol and the volume made up. The samples were centrifuged and the supernatant filtered through 0.45μm nylon membrane filters. After appropriate dilutions, samples were analyzed in UV-Visible spectrophotometer at 276 nm wavelength against blank and drug content was determined from the calibration curve prepared within the expected range.

5.3.10 Stability study of glipizide in simulated gastric and intestinal fluid

Three known concentrations (12, 8 and 4 μg/ml) of the drug in 25 ml of simulated gastric fluid (0.1N HCl) and 3 known concentrations (10, 20 and 30 μg/ml) in USP prescribed dissolution medium or simulated intestinal fluid (phosphate buffer, pH 6.8) were prepared in six volumetric flasks and were kept at room temperature for 96 hrs. The samples (5 ml) were withdrawn from each flask at 24, 48, 72 and 96 hrs of interval and filtered through 0.45-μm filters. The UV absorbance of the samples was determined at 276 nm against blank and the amount of drug remained unchanged was calculated using...
the calibration curves of the drug prepared in the above mentioned fluids. The percentage of deviation from the initial concentration was determined.

5.4 Result and Discussion

5.4.1 Standard calibration curve of Glipizide (GPZ)

The standard calibration curve of GPZ was plotted in various mediums (0.1N HCl, pH 1.2; phosphate buffer, pH 4.5; phosphate buffer (PBS), pH 6.8 and phosphate buffer, pH 7.4). The scanning of standard solution in each medium within the UV range results maximum absorption peak at the wavelength 276nm. It was observed that Beer-Lambert's law was obeyed within the concentration range of 2 to 14 µg/ml, 2 to 14 µg/ml, 5 to 35 and 5 to 35 µg/ml of the drug in 0.1N HCl, pH 1.2; PBS, pH 4.5, 6.8 and 7.4 respectively. The regression coefficient ($r^2$) values and linear regression equation of concentration verses absorbance of the entire calibration curves were presented in Figure 5.1 to 5.4. The $r^2$ values of the entire standard calibration curves were equivalent to 1 which indicated that the slope and intercept values of the linear calibration curve can be used to determine the concentration of drug sample in different medium.

5.4.2 Saturation solubility of glipizide

The pH of the gastrointestinal fluids is different (1.2 to 8.4) at various region of the gastrointestinal tract (GIT). The solubility study of GPZ was carried out in various buffer medium to access the solubility of the drug in different part of GIT. The result of saturation solubility study is shown in Figure 5.5 which revealed that the solubility of the drug increases as the pH of the medium increases (pH 1.2 < 4.5 < 6.8 < 7.4). As solubility of the drug is pH dependent, it may be suggested that the absorption of the drug will be
maximum at the lower part of the GIT. Glipizide is a weak acid with pKₐ of 5.9 and the solubility is expected to increase by rise in pH. As expected immediately above the pKₐ, the solubility increases significantly. The solubility of the drug in dissolution medium (PBS, pH 7.4) was found to be greater than the solubility of drug in 0.1N HCl, pH 1.2; PBS, pH 4.5 and 6.8. The result of the study suggested that the use of PBS, pH 7.4 will be appropriate dissolution medium for in vitro dissolution study for controlled release colon targeted formulations of GPZ than that of PBS pH 6.8.

5.4.3 Moisture content of glipizide:

The determination of moisture present in the drug sample by Karl Fischer titration resulted a value of 0.3 %w/w.

5.4.4 Flow properties of glipizide:

Values for angle of repose, compressibility index and hausner ratio of drug were found to be 44°, 32.48 % and 1.46 respectively. From the results it is evident that the drug has poor flow properties.

5.4.5 Particle size distribution

The particle size of GPZ was analyzed in Malvern master sizer. The results shown in Table 5.1 and Figure 5.6 revealed that maximum percentage of drug particles (88.49 %w/w) was less than 104.71 μm. The particles of whole the drug sample was found to be with in the limit of 0.417 μm to 954.99 μm.

5.4.6 Melting point determination:

The melting point of the GPZ was found to be 207-209 °C which comply the reported (Chapter-2) value of the drug.

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5.4.7 FT-IR spectroscopic study:

The FT-IR spectrum of glipizide with the principal peaks is shown in the Figure 5.7 and the interpretation is given in Table 5.2. This result complies with the structure of the glipizide.

5.4.8 Differential Scanning Calorimetric study

The DSC thermogram of drug showed a sharp endothermic peak or peak of transition temperature ($T_{peak}$) at 214.14 °C (Figure 5.8) and the heat of fusion or enthalpy ($\Delta H_f$) was 135.63 J/g. This result again confirms the drug is glipizide.

5.4.9 Isothermal stress testing for drug-excipients compatibility studies

The excipients were tested using the technique of IST and the quantitative results are shown in Table 5.3. It can be seen from the results that there is slight reduction in the drug content after storage of drug-excipient blends under stressed conditions. Therefore, it is inferred that the selected excipients such as microcrystalline cellulose (MCC), Croscarmellose sodium (CCS), Polyvinyl pyrolidone (PVP), Hydroxy propyl methyl cellulose (HPMC), Carbopol, Chitosan, sodium bicarbonate, magnesium stearate, aerosol and talc can be used for the development of formulations.

5.4.10 Stability study of glipizide in simulated gastric and intestinal fluid

The stability study of the drug was carried out in simulated gastric (0.1N HCl, pH 1.2) and intestinal (phosphate buffer, pH 6.8) fluids. The result of stability study is depicted in Table 5.4. The results revealed that there was no change in initial concentrations of the drug in both the mediums after 96 hrs of storing it. It is apparent that the drug is stable in both the mediums used and can be used as dissolution medium.
5.5 Conclusion

The solubility of the drug increases when the pH of the medium is increased. The flow property of the drug powder was found to be poor, which needed to be improved during formulation development. The melting point value, FTIR spectrum and DSC thermogram confirm the drug is glipizide. The drug was found compatible with proposed excipients selected for formulations as per the results of IST study. The drug was stable in simulated gastric as well as in intestinal fluid up to 96 hrs.

5.6 References


Table 5.1 Particle size distribution of glipizide

<table>
<thead>
<tr>
<th>Range of particle size (µm)</th>
<th>Mean data (%w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.417 - 10.00</td>
<td>18.95</td>
</tr>
<tr>
<td>10.00 - 30.20</td>
<td>23.26</td>
</tr>
<tr>
<td>30.20 - 60.25</td>
<td>22.57</td>
</tr>
<tr>
<td>60.25 - 104.71</td>
<td>23.71</td>
</tr>
<tr>
<td>104.71 - 181.90</td>
<td>7.1</td>
</tr>
<tr>
<td>181.90 - 954.99</td>
<td>4.41</td>
</tr>
</tbody>
</table>

Table 5.2 Interpretation of functional groups of glipizide in the FTIR spectrum.

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>ν (cm⁻¹)</th>
<th>Functional group assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>3524.26</td>
<td>N-H stretching.</td>
</tr>
<tr>
<td>2.</td>
<td>3030.44</td>
<td>Aromatic –CH stretching.</td>
</tr>
<tr>
<td>3.</td>
<td>2943.64</td>
<td>Aliphatic C-H Stretching</td>
</tr>
<tr>
<td>4.</td>
<td>1689.80</td>
<td>C=O stretching.</td>
</tr>
<tr>
<td>5.</td>
<td>1605.8-1451.8</td>
<td>Aromatic C=C stretching.</td>
</tr>
<tr>
<td>6.</td>
<td>1070-1030</td>
<td>S=O Stretching</td>
</tr>
<tr>
<td>7.</td>
<td>1410</td>
<td>Aliphatic C-N stretching</td>
</tr>
</tbody>
</table>
Table 5.3 Results of IST study of Glipizide after 3 weeks of storage at stressed conditions

<table>
<thead>
<tr>
<th>Sample</th>
<th>Ratio (drug : excipient)</th>
<th>Quantity unchanged (% w/w)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Control samples&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>GPZ</td>
<td></td>
<td>100.81 ± 0.72</td>
</tr>
<tr>
<td>GPZ + MCC</td>
<td>1:2</td>
<td>101.42 ± 1.34</td>
</tr>
<tr>
<td>GPZ + NaHCO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>3:1</td>
<td>100.53 ± 1.81</td>
</tr>
<tr>
<td>GPZ + manitol</td>
<td>1:2</td>
<td>101.42 ± 1.34</td>
</tr>
<tr>
<td>GPZ + Citric acid</td>
<td>3:1</td>
<td>99.48 ± 2.62</td>
</tr>
<tr>
<td>GPZ + CCS</td>
<td>1:1</td>
<td>100.73 ± 1.82</td>
</tr>
<tr>
<td>GPZ + Chitosan</td>
<td>1:1</td>
<td>101.21 ± 2.74</td>
</tr>
<tr>
<td>GPZ + HPMC</td>
<td>1:1</td>
<td>100.46 ± 0.86</td>
</tr>
<tr>
<td>GPZ + PVP</td>
<td>2:1</td>
<td>101.8 ± 1.48</td>
</tr>
<tr>
<td>GPZ + Talc</td>
<td>3:1</td>
<td>100.62 ± 2.68</td>
</tr>
<tr>
<td>GPZ + Mg Stearate</td>
<td>3:1</td>
<td>100.84 ± 1.92</td>
</tr>
<tr>
<td>GPZ + Carbopol</td>
<td>1:1</td>
<td>99.84 ± 1.72</td>
</tr>
<tr>
<td>GPZ + Aerosil</td>
<td>3:1</td>
<td>100.72 ± 2.17</td>
</tr>
</tbody>
</table>

<sup>a</sup> Values expressed as average ± standard deviation.
<sup>b</sup> Drug excipient blends without added water and stored in refrigerator.
<sup>c</sup> Drug excipient blends with 10% (w/w) added water and stored at 50 °C for 3 weeks.
Table 5.4 Stability study of glipizide in simulated gastric and intestinal fluid

<table>
<thead>
<tr>
<th>Time interval (hr)</th>
<th>Concentration (μg/ml)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.1N HCl, pH 1.2</td>
</tr>
<tr>
<td></td>
<td>Sample-1</td>
</tr>
<tr>
<td>0</td>
<td>12.00</td>
</tr>
<tr>
<td>24</td>
<td>11.92 ± 1.29</td>
</tr>
<tr>
<td>48</td>
<td>11.87 ± 1.08</td>
</tr>
<tr>
<td>72</td>
<td>11.85 ± 1.37</td>
</tr>
<tr>
<td>96</td>
<td>11.84 ± 0.86</td>
</tr>
</tbody>
</table>

\(^a\) Values expressed as average ± standard deviation.
Figure 5.1 Standard curve of glipizide in 0.1 M HCl, pH 1.2

\[ y = 0.0294x - 0.0045 \]
\[ R^2 = 0.9971 \]

Figure 5.2 Standard curve of glipizide in phosphate buffer pH 4.5

\[ y = 0.0292x + 0.0016 \]
\[ R^2 = 0.9972 \]
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Figure 5.3 Standard curve of glipizide in phosphate buffer pH 6.8

Figure 5.4 Standard curve of glipizide in phosphate buffer pH 7.4
Figure 5.5 Saturation solubility of glipizide at different pH

Figure 5.6 Particle size distribution of glipizide by Malvern master sizer
Chapter 5

Figure 5.7 FTIR spectrum of glipizide

Figure 5.8 DSC thermogram of glipizide