Glipizide and Glimepiride matrix tablets were prepared by using *Aloe barbadensis miller* leaves mucilage, Guar gum, Povidone and were evaluated.

Similarly Glipizide and Glimepiride transdermal patches were prepared by using *Ficus bengalensis*, *Ficus carica*, *Ficus glomerata*, Povidone and were evaluated.

### 5.1 STANDARD CURVES OF DRUGS USED

#### 5.1.1 Standard Curve for Glipizide:

Table 4.1 shows the absorption reading of Glipizide standard solutions containing 2-20 µg/mL of drug in phosphate buffer pH 7.4. The experiment was performed in triplicate and mean value was considered in the study.

Fig. 4.1 shows the standard calibration curve for Glipizide with $y= 0.043x+ 0.014$ and regression value ($R^2$) of 0.999. The calculation of drug content, *in-vitro* dissolution and *in-vitro* diffusion rate studies were based on this standard curve.

#### 5.1.2 Standard Curve for Glimepiride:

Table 4.2 shows the absorption reading of Glimepiride standard solutions containing 2-20 µg/mL of drug in phosphate buffer pH 7.4. The experiment was performed in triplicate and mean value was considered in the study.

Fig. 4.2 shows the standard calibration curve for Glimepiride with $y= 0.044x+ 0.015$ and regression value ($R^2$) of 0.997. The
calculation of drug content, \textit{in-vitro} dissolution and \textit{in-vitro} diffusion rate studies were based on this standard curve.

\section*{5.2 CHARACTERIZATION OF MUCILAGES:}

\subsection{5.2.1. Physicochemical characterization of \textit{Aloe barbadensis miller} mucilage:}

\textit{Aloe barbadensis miller} leaf mucilage is first time used as release retardant in the present investigation. So, physicochemical characterization of the mucilage was performed. The extracted mucilage was in brownish yellow in colour which was slowly soluble in water and produced a hage viscous solution with a slightly acidic pH of 6.5. The mucilage gave a yield of $23 \pm 2.173\,\text{g/kg}$ of mucilage. The average particle size was $165.15\pm10.265\,\mu\text{m}$ and the LOD was $4.20\pm2.573\,\text{mg}$ indicating less amount of moisture content in the mucilage. The mucilage was found to have good swelling properties as the swelling ratio was $45\pm3.841$. The observed melting point of the mucilage was $220\pm5.0^\circ\text{C}$ with charring. The density of a $0.5\%\,\text{w/v}$ liquid was nearer to 1 ($0.997\pm0.055$). The mucilage has a minimal bio burden. The powdered mucilage was found to have excellent flow properties as the angle of repose was $27.96\pm1.684^\circ$ ($25\text{-}30^\circ$) and Hausner ratio $0.855\pm0.047$ (<1.25). The mucilage has excellent compressibility property as it has a compressibility index of $14.447\pm0.023$. All these experiments were performed in triplicates and tabulated in table 4.3.
5.2.2. Physicochemical characterization of *Ficus bengalensis*, *Ficus carica* and *Ficus glomerata* mucilage:

The percent yield of *Ficus glomerata* fruit mucilage was more (125±10.567%), when compared with *Ficus bengalensis* and *Ficus carica* fruit mucilage as they gave only 32±2.974% and 78±5.948% of yield respectively. All these mucilage were soluble and forms colloidal solution, in Luke warm water. They are practically insoluble in ethanol, acetone, ether and chloroform with characteristic odour and Lustrous appearance. All these mucilages gave positive test for carbohydrates. The average particle size of *Ficus bengalensis*, *Ficus carica* and *Ficus glomerata* fruit mucilage were 185.36±12.984, 205.25±11.957 and 212.58±20.515 µm respectively. The weight loss on drying of these mucilages was identical and minimal acid insoluble ash. The swelling index of *Ficus glomerata* fruit mucilage was more (85±11.246), when compared with *Ficus bengalensis* and *Ficus carica* fruit mucilage as they have only 30±5.198 and 50±2.361 respectively.

All these mucilages gave positive test for carbohydrate and negative tests for Tannins. All these mucilages were free from sulphates and chlorides. All these mucilages have negligible foreign matter, Arsenic and other Lead. The melting points of *F. bengalensis*, *F. carica* and *F. glomerata* fruit mucilage were 175±2.5°C, 185±3.0°C and 200±2.0°C respectively and they charred at these temperatures. The density of 0.5% w/v solutions of *F. bengalensis*, *F. carica* and *F.
*glomerata* fruit mucilages were 0.998±0.125, 1.257±0.132 and 1.368±0.099 respectively. The powdered mucilages were found to have excellent flow properties as the angle of repose was falls between 25-30° and Hausner ratio less than 1.25. The mucilage has good compressibility properties as they have compressibility index was in between 12-16. All these mucilages have minimal bio burden. All these parameters were shown in table 4.4.

5.2.3. Viscosity of *Aloe barbadensis*, *Ficus bengalensis*, *Ficus carica* and *Ficus glomerata* mucilage vs. Sod. CMC

The viscosity of 0.1, 0.2, 0.3, 0.4 and 0.5% w/v solutions of *Aloe barbadensis* leaf mucilage, *F. bengalensis*, *F. carica* and *F. glomerata* fruit mucilages were compared with known popularly using viscosity modifying agent Sod. CMC. The viscosities of these solutions were identical with Sod. CMC and these values were tabulated in table 4.5.

5.3 IDENTIFICATION AND DRUG-EXCIPIENT COMPATIBILITY STUDIES

5.3.1. Identification

Both Glipizide & Glimepiride were soluble in Dichloromethane, sparingly soluble in Acetone and freely soluble in dil. NaOH, KOH solutions. The melting point of Glipizide was 225±2.5°C, whereas Glimepiride has 205±3.0°C
Ultra-violet Spectrum:

The ultra violet absorption spectrums for Glipizide and Glimepiride were determined separately in 0.1 M Sodium Hydroxide solution using 1 cm silica cells with a UV Visible Spectrophotometer-117 (Systronics, Mumbai, India). Glipizide and Glimepiride showed characteristic curve with maxima at 223 nm and 230 nm respectively. The spectrums were represented in Fig. 4.3 and 4.4.

5.3.2. Compatibility Studies:

Preformulation compatibility studies of pure drug Glipizide and Glimepiride with all excipients used were carried out prior to the preparation of matrix tablets/ transdermal patches.

5.3.2.1 Ultra-violet Spectrum:

UV spectrums of pure Glipizide, Glimepiride and in combination with excipients were obtained. The λ max of Glipizide/Glimepiride were found in the spectrums, indicates that there was no negative interaction of Glipizide and Glimepiride with the excipients used, which were shown in Fig. 4.3 and 4.4.

5.3.2.2 Differential Scanning Calorimetry (DSC):

The interactions of polymers used in the formulations with Glipizide, Glimepiride were studied using DSC studies. The graphs were shown in Fig. 4.7 to 4.14.

The DSC scan of Glipizide showed a short endothermic peak at 239.50 °C. The thermo gram of Glipizide with Aloe barbadensis miller leaves mucilage, Ficus carica and Ficus glomerata fruit mucilages
showed an endothermic peak of drug at 193.20°C, 239.21°C and 228.56°C respectively indicating a slight change in terms of shifting towards the lower temperature. It has been reported that the quantity of material used effects the peak shape and enthalpy. Thus these minor changes in the melting endotherm in the drug could be due to the mixing of the drug and polymers which lower the purity of each component in the mixture and may not necessarily indicate potential incompatibility.

The DSC scan of Glimepiride showed a short endothermic peak at 205.94°C. The thermo gram of Glimepiride with Aloe barbadensis miller leaves mucilage/Ficus carica/Ficus glomerata fruit mucilages showed an endothermic peak of drug at 189.48°C, 242.95°C and 229.52°C respectively indicating a slight change in terms of shifting towards the lower temperature. Thus these minor changes in the melting endotherm in the drug could be due to the mixing of the drug and polymers which lower the purity of each component in the mixture and may not necessarily indicate potential incompatibility.

5.3.2.3 FT Infra-red Spectrum:

FTIR spectrums of pure Glipizide, Glimepiride, excipients and combination of Glipizide/Glimepiride with excipients were obtained, which were shown in Fig. 4.15 to 4.31.

The infrared spectrum of the Glipizide sample supplied by Dr. Reddy’s Labs was recorded using potassium bromide disc method with a FTIR spectrophotometer (Shimadzu Corporation, Japan). The
major peaks were at 1056, 1349, 1594 and 3387 cm\(^{-1}\). (Refer Fig. 4.15).

The infrared spectrum of the Glimepiride sample supplied by Dr. Reddy's Labs was recorded using potassium bromide disc method with a FTIR spectrometer (Shimadzu Corporation, Japan). The major peaks were at 1034, 1076, 1349, 1594 and 3382 cm\(^{-1}\). (Refer Fig. 4.16).

All the characteristic peaks of Glipizide were found in the IR spectrums of Glipizide-polymers spectrum, which were shown in Fig. 4.17 to 4.26. And all the characteristic peaks of Glimepiride were found in the IR spectrums of Glimepiride-polymers spectrum, which were shown in Fig. 4.27 to 4.31.

This indicates the compatibility of Glipizide/Glimepiride with the polymers used. It shows that there was no chemical incompatibility between the drug and polymers used.

5.4 STUDIES ON FORMULATED MATRIX TABLETS:

Flow Properties:

Dried Aloe barbadensis miller leaves mucilage was found to have excellent flow properties as the angle of repose was 27.96±1.684 \(^{\circ}\) (25-30\(^{\circ}\)) and Hausner ratio 1.165±0.039 (<1.25).
Whereas dried Guar gum was found to have poor flow properties as the angle of repose was 38.72±1.115° (25-30°) but it has Hausner ratio 1.179±0.040 (<1.25) indicates good flow properties. Povidone was found to have excellent flow properties as the angle of repose was 29.69±1.565° (25-30°) and Hausner ratio 1.160±0.031 (<1.25).

All these experiments were performed in for 5 times and tabulated in table 4.25 to 4.28.

**General Appearance:**

Tablets of all formulations were round in shape, small in size (8mm diameter) with flat surface and having a good physical appearance.

**Thickness:**

The Thickness of formulated Glipizide matrix tablets were ranged from 3.33±0.0147 to 3.84±0.235 mm and shown in Table 4.29.

The Thickness of formulated Glimepiride matrix tablets were ranged from 3.35±0.09 to 3.74±0.098mm and shown in table 4.30.

**Diameter**

**Mean Diameter of Glipizide Matrix Tablets**

The Diameter of formulated Glipizide matrix tablets were ranged from 5.00±0.236 to 5.08±0.235 mm and shown in Table 4.31

The Diameter of formulated Glimepiride matrix tablets were ranged from 5.02±0.147 to 5.09±0.465 mm and shown in Table 4.32
**Weight Variation:**

Twenty tablets of each formulation were evaluated. The average weights of each formulation were recorded in Table 4.33 and 4.34. Matrix tablets prepared with Glipizide with Aloe barbadensis leaf mucilage (GPA) and Glipizide with Povidone (GPP) were passed the uniformity of the weight test as the values obtained were within the I.P. specifications i.e. none of the tablet deviated outside ± 7.5% of total weight of the tablet (for 200 mg of tablet).

Whereas matrix tablets prepared with Glipizide with Guar gum (GPG-1, GPG-3 and GPG-5) failed the test. The average weights of each formulation of Glipizide were recorded in Table 4.33.

On the other hand matrix tablets prepared with Glimepiride with *Aloe barbadensis* leaf mucilage (GMA) and Glimepiride with Povidone (GMP) were passed the uniformity of the weight test as the values obtained were within the I.P. specifications i.e. none of the tablet deviated outside ± 7.5% of total weight of the tablet (for 200 mg of tablet).

Whereas matrix tablets prepared with Glimepiride with Guar gum (GMG) failed the test. The average weights of each formulation of Glimepiride were recorded in Table 4.34.

**Hardness:**

Three tablets of each formulation were evaluated and mean hardness values were recorded in Table 4.35 and 4.36. The entire formulated tablets were found to have hardness more than 4 kg/cm².
each (5.20 to 9.40 kg/cm²). The values revealed that all formulated tablets were having good mechanical strength.

**Friability:**

Friability values for each formulation were recorded in Table 4.37 and 4.38. Percent friability ranged from 0.11 to 0.88 (< 1%) for all formulations. The values obtained showed that the tablets of all the formulations were having good compactness and mechanical strength.

**Content Uniformity of Active Ingredient:**

Drug content in GPA tablets was 98.99±9.56 to 101.26±8.94%, whereas GPG tablets contain 95.94±2.56 to 99.87±12.01%, GPP tablets contain 99.49±9.23 to 101.78±11.19% and optimized formulation GPAP contains 98.58±9.15 to 99.99±0.26% of Glipizide.

Drug content in GMA tablets was 99.46±10.03 to 101.05±9.81%, whereas GMG tablets contain 95.94±13.51 to 99.94±6.89%, GMP tablets contain 99.65±1.57 to 101.54±13.04% and optimized formulation GMAP contains 95.98±12.51 to 101.45±8.52% of Glimepiride.

Table 4.39 and 4.40 shows the results of drug content uniformity in each formulation. Replicates (three) of each test were conducted. The data were analyzed for mean and standard deviation. All the tablets pass the uniformity of content test.
**Swelling Index**

Swelling properties of formulated Glipizide and Glimepiride matrix tablets were performed and shown in Fig. 4.33 to 4.40, which represents the swelling of formulated tablets were polymer concentration dependent. All the formulations showed uniformity in swelling as the increase in polymer concentration.

**Scanning Electron Microscopy (SEM) studies of matrix tablets**

The SEM of GPAP-5 at different intervals of dissolution(0, 1, 2 and 3 h) was shown in Fig. 4.41. It shows that the release of drug from the matrix tablets was by diffusion and erosion.

**In vitro drug release studies**

The *in-vitro* dissolution was studied in phosphate buffer pH 7.4. The *in-vitro* dissolution studies were carried out in triplicate and the results shown in the tables were mean of replicate values. *In-vitro* release data obtained for matrix tablets were tabulated in Table 4.41 to 4.47 and in represented in Fig. 4.42 to 4.49.

The results of *in-vitro* dissolution studies obtained in these formulations were plotted in five models of data treatments as follows.


b. Log cumulative % of drug retained Vs. Time.

c. Cumulative % of drug released Vs. Square root of time (Higuchi’s plot).

d. Log cumulative percentage of drug released Vs. Log time (Korsmeyer Peppa’s plot)

e. (% Drug Retained) $1/3$ Vs. Time (Hixson Crowell’s plot).
**In vitro Drug Release Studies from Matrix tablets**

Fig. 4.45 shows the plot of cumulative percentage of drug released as a function of time for different Glipizide matrix tablets (Zero order release). Cumulative percentage drug released has been found 99.2, 98.9, 99.85, 99.1 and 88.64 for the matrix tablets GPAP-1, GPAP-2, GPAP-3, GPAP-4 and GPAP-5 respectively at the end of 12 h.

Fig. 4.53 shows the plot of cumulative percentage of drug released as a function of time for different Glimepiride matrix tablets. Cumulative percentage drug released has been found 99.8, 99.5, 99.7, 99 and 89.8 for the matrix tablets GMAP-1, GMAP-2, GMAP-3, GMAP-4 and GMAP-5 respectively at the end of 12 h.

*In-vitro* dissolution studies clearly showed that the Glipizide and Glimepiride formulations containing *Aloe barbadensis miller* leaves mucilage showed good controlled release patterns as compared to Guar gum and Povidone.

Attempts were made to fit the data to study order of release. A first order release would be predicted by eq. 28.

\[
\log W = \log W_0 - \frac{Kt}{2.303} \tag{28}
\]

Where,

\( W \) = Amount of drug remained in matrix.

\( W_0 \) = Initial amount of drug in matrix.

\( K \) = First order rate constant.

\( T \) = Time.

Similarly, zero order release would be predicted by eq. 29.
\[
d\frac{Cs}{dt} = K_o \quad \text{(29)}
\]

Where, 
\[ C_S \] = Concentration of the drug present in the matrix.
\[ K_o \] = Proportionality factor i.e. reaction rate constant.
\[ T \] = Time

Since \( C_S \) is a constant, \( x \) - the amount of drug released can be described as in eq. 30.

\[
d\frac{x}{dt} = k \quad \text{(30)}
\]

Integration of equation yields eq. 31.

\[
x = kt + t \text{ constant} \quad \text{(31)}
\]

If the plot of log cumulative percentage remaining v/s time yields a straight line, the release follows first order kinetics. Similarly, the plot of cumulative percentage released v/s time, if yields a straight line, the release follows zero order kinetics.

Fig. 4.46 shows the plot of log cumulative % drug retained vs. time (First Order) for different formulation of GPAP matrix tablets. Since these plots did not yield a straight line, the data was subjected to linear regression analysis (r), the results of which were shown in table 4.46. The 'r' values obtained for first order kinetics were found to be - 0.97846, -0.99684, -0.97261, -0.99259 and 0.9823 for formulations GPAP-1 to GPAP-5 respectively. And those for zero order kinetics 0.99039, 0.992511, 0.99661, 0.988149 and -0.995252 for formulations GPAP-1 to GPAP-5 respectively. Since greater degree of association best fitted with zero order kinetic models. It can be
concluded that, all the matrix tablets followed zero order kinetics as the release pattern of the drug.

Fig 4.54 shows Plot of log cumulative % drug retained vs. time (First Order) for different formulation of GMAP matrix tablets (first order plot). Since these plots did not yield a straight line, the data was subjected to linear regression analysis (r), the results of which were shown in Table. 4.53. The 'r' values obtained for first order kinetics were found to be 0.9796, 0.9821, 0.9821, 0.9852 and 0.9819 for formulations GPAP-1 to GPAP-5 respectively. And those for zero order kinetics 0.7080, 0.7811, 0.9126, 0.9307 and 0.9204 for formulations GMAP-1 to GMAP-5 respectively. Since greater degree of association best fitted with zero order kinetic models, it can be concluded that, all the matrix tablets followed zero order kinetics as the release pattern of the drug.

The rate constant of first order release was calculated from the slope value by multiplying with 2.303.

The rate constant for zero order plots can be obtained by using eq. 32.

\[ K_0 = -\text{slope} \]  (32)

The data when treated according to Higuchi’s diffusion equation \( Q = Kt^{1/2} \) indicated that the formulations released the drug by diffusion.

Fig. 4.47 shows Higuchi’s plot and regression values given in table. 4.47 were 0.971738, 0.996448, 0.98504, 0.993489 and 0.993936 for GPAP-1 to GPAP-5 respectively. Fig. 4.55 shows Higuchi’s plot and
regression values given in Table 4.54 were 0.9795, 0.9869, 0.9940, 0.9913 and 0.9938 for GMAP-1 to GMAP-5 respectively.

Further to know the release pattern of Glipizide and Glimepiride from matrix tablets, the results were analyzed according to Korsmeyer Peppa’s exponential eq. 33.

\[ q = K t^n \]  \hspace{1cm} (33)

Where, \( q \) is fraction of drug released up to time \( t \), \( k \) denotes a constant, \( n \) is the released exponent indicative of the mechanism of release.

The slope \( n \) was computed to know whether the release was Fickian or non-Fickian. For non-Fickian release (\( n \) values=0.5 to 1.0), while for Fickian diffusion (\( n \) value= \( \leq \)0.5).

The slope values for Glipizide matrix tablets were tabulated in Table 4.47 and shown in Fig. 4.48. The values were 0.162456, 0.171559, 0.287578, 0.313169 and 0.304558 for formulation GPAP-1 to GPAP-5. The values of \( n \) were less than 0.5 for all the formulations. So, all formulations follow the Fickian release.

The slope values for Glimepiride matrix tablets were tabulated in Table 4.54 and shown in 4.56. The values were observed to be 0.3438, 0.3786, 0.4896, 0.5206 and 0.47982 for formulation GMAP-1 to GMAP-5. The values of \( n \) were less than 0.5 for all the formulations except GMAP-4. So, GMAP-1, GMAP-2, GMAP-3 and GMAP-5 formulations follows the Fickian release.
The *in-vitro* release data was further plotted as \((1-m_t/m_\infty)^{1/3}\) vs. Time proposed by Hixson Crowell’s to verify whether the drug release is by erosion mechanism and it can be represented as eq. 34

\[
3\sqrt{1 - m_t/m_\infty} = K_t \quad \text{--------- (34)}
\]

Where \(m_t\) = Drug release at time \(t\)

\(m_\infty\) = Drug originally present in the tablet

Fig. 4.49 shows the plots of \((1-m_t/m_\infty)^{1/3}\) vs. Time and shown in Table 4.47. The regression coefficient values of the plots for different matrix tablets. The 'r' values were found to be -0.98355, -0.99574, -0.98517, -0.99441 and -0.99214 for formulations GPAP-1 to GPAP-5 respectively. The above observations showed that the drug release from different matrix tablets fitted well to the *erosion mechanism*. The slope of line indicated that the rate of disappearance of the tablets by erosion. The slope was calculated and it was found to be -0.00043, -0.0003, -0.00084, -0.00083 and -0.00092 for matrix tablets GPAP-1 to GPAP-5 respectively.

The *In-vitro* release and release kinetics was fitted best for GPAP-5 and GMAP-5 formulations.

The *in-vitro* drug release from optimized matrix tablets (GPAP-5) were compared with the marketed tablets. The marketed tablets produced a slope \(y = 7.5154x + 17.662\) and regression \((R^2)\) value 0.9122; on the other hand the optimized formulation (GPAP-5) produced a slope \(y = 6.7625x + 14.811\) and regression \((R^2)\) value 0.9204. The comparison was shown in Fig. 4.58.
The *in-vitro* drug release from optimized matrix tablets (GMAP-5) were not compared with the marketed tablets because no controlled release marketed formulations are available in market.

**In Vivo Evaluation**

**aj) In vivo Evaluation of Matrix Tablets**

The optimized formulations (GPAP-5 and GMAP-5) were selected for *in vivo* studies.

Mean fasting blood glucose levels (mg/dL) (MFBGL) of Glipizide matrix tablets (GPAP-5) was shown in Table 4.55.

Mean % Reduced blood glucose levels with Glipizide matrix tablets (GPAP-5) was represented in Table 4.56 and shown in Fig. 4.59. And the GPAP-5 shown very highly significant values (P***<0.001) compared with orally given Glipizide pure drug.

Similarly mean fasting blood glucose levels (mg/dL) (MFBGL) of Glimepiride matrix tablets (GMAP-5) was shown in table 4.57 and GMAP-5 shown very highly significant values (P***<0.001) compared to Glimepiride Pure Drug.

Mean % Reduced blood glucose levels with Glimepiride matrix tablets (GMAP-5) was represented in Table 4.58 and shown in Fig. 4.60. And the GMAP-5 shown very highly significant values (P***<0.001) compared to oral Glipizide pure drug.

**Pharmacokinetic Evaluation:**

GPAP-5 matrix tablets were selected and evaluated for pharmacokinetic evaluation by Reverse Phase HPLC.
Calibration curve for the Estimation of Glipizide in Plasma Samples by HPLC Method was represented in Table 4.59 and shown in Fig. 4.61 and shows $y=380.64x-0.3558$ and regression value ($R^2$) of 0.9993.

Serum Concentrations of Glipizide Following the oral Administration Glipizide (A) and GPAP-5(B) in Rabbits ($n = 6$) was represented in Table 4.60, which were shown in Fig. 4.62 which proves the release of Glipizide from GPAP-5 was controlled.

The summary of pharmacokinetic (bio-availability study) parameters by giving Glipizide oral and optimized matrix tablets (GPAP-5) was shown in Table 4.61. And the values were as follows.

The $C_{\text{max}}$ was found to be 0.91 (µg/mL), the $T_{\text{max}}$ was found to be 6.0 h, the AUC was found to be 15.86 µg .h/mL, AUMC was found to be 69.25 µg .h/mL, the $K_a$ was found to 0.156 h⁻¹, the Mean Resident Time was found to be12.33 h and the bioavailability was found to be114.8%.

**Accelerated Stability Studies of Optimized Matrix Tablets (GPAP-5):**

The optimized matrix tablets (GPAP-5) were kept at 40°C and 75% RH for 90 days.

The summary of physicochemical properties of GPAP-5 matrix tablets before and after accelerated stability studies shown in Table 4.62 indicates no significant change in physicochemical properties of matrix tablets before and after accelerated stability testing.
Plots of Residual Drug vs. Days for selected Glipizide Matrix Tablets (GPAP-5) After 30 Days Storage [Stability Studies] (40°C and 75% RH) and shown in Fig.4.63.

Plots of Residual Drug vs. Days for selected Glipizide Matrix Tablets (GPAP-5) After 60 Days Storage [Stability Studies] (40°C and 75% RH) and shown in Fig.4.64.

Plots of Residual Drug vs. Days for selected Glipizide Matrix Tablets (GPAP-5) After 90 Days Storage [Stability Studies] (40°C and 75% RH) and shown in Fig.4.65.

The selected GPAP-5 matrix tablets were found to stable meeting all of its predetermined specification. Here it was checked only for relevant compendia specifications for tablets and *In vitro* degradation studies. There was no change in appearance, average weight, hardness, friability and drug content.

## 5.5 STUDIES ON FORMULATED TRANSDERMAL PATCHES

**Thickness**

Thickness of formulated Glipizide transdermal patches were shown in table 4.64 and it ranges from 630±35.6 to 775±48.3 µm, whereas Glimepiride transdermal patches were 620±58 to 766±56.9µm and shown in table 4.65, indicating the uniformity in thickness.

**Uniformity of weight**

Weights of formulated Glipizide and Glimepiride transdermal patches were ranged from 1.524±0.15 to 1.745±0.06 g, 1.521±0.12 to
1.752±0.15g respectively and shown in Table 4.66 and 4.67, indicating the uniformity in weight.

**Moisture content**

The moisture content in formulated Glipizide and Glimepiride transdermal patches were ranged from 2.111±0.14 to 3.125±0.23% and 2.023±0.12 to 2.969±0.35% respectively which were shown in Table 4.68 and 4.69 indicating the low amounts of moisture content in prepared patches.

**Flatness and Elongation Brake**

The percentage Elongation of formulated Glipizide and Glimepiride transdermal patches were ranged from 15.33±0.89 to 42.49±0.61% and 14.19±0.15 to 43.33±0.28% respectively and shown in Table 4.70 and 4.71 indicating the flexibility of prepared patches.

**Tensile Strength**

The tensile strength of Glipizide and Glimepiride transdermal patches were ranged from 0.294 ± 0.14 to 0.458± 0.26 and 0.245 ± 0.15 to 0. 466 ± 0.12 N/mm² showed in table 4.76 and 4.77 indicating the satisfactory strength of prepared patches.

**Folding Endurance:**

The folding endurance of Glipizide and Glimepiride transdermal patches was ranged from 95±1.2 to 124±0.9 and 95±1.2 to 124±0.9 shown in Table 4.78 and 4.79 indicated the flexibility of prepared patches.

**Moisture Uptake**

The moisture uptake of Glipizide and Glimepiride transdermal patches at RH 75% was ranged from 2.210± 0.96 to 5.124±0.57% and
1.206± 0.37 to 6.145± 0.01% respectively and shown in Table 4.72 and 4.74 respectively.

The moisture uptake of Glipizide and Glimepiride transdermal patches at RH 93% was ranged from 3.120± 0.14 to 8.180±0.61% and 3.458±0.48 to 9.354±0.87 % shown in Table 4.73 and 4.75 respectively.

**Drug Content:**

The drug content of Glipizide and Glimepiride transdermal patches was ranged from 88.6 ± 0.34 to 101.7±0.12% and 81.5 ± 0.36 to 101.9± 0.21% shown in Table 4.80 and 4.81 respectively, indicating the uniformity of drug content in the patches.

**Skin Irritation Test (Visual Evaluation of Skin)**

The selected Glipizide and Glimepiride transdermal patches (GPFGP-5 and GMFGP-5) did not produce any significant irritation comparatively with standard Formalin solution. The details were tabulated in Table 4.100.

**Scanning Electron Microscopy (SEM) of transdermal patches:**

The SEM of Glipizide with dried fruit mucilage of *Ficus carica* was shown in Fig 4.67, which indicates that there was proper impregnation of Glipizide with *Ficus carica* fruit mucilage.

The SEM of Glipizide with dried mucilage of *Ficus glomerata* fruits was shown in Fig 4.68, which indicates that there was proper impregnation of Glipizide with *Ficus glimerata* fruit mucilage.
The SEM of Glipizide with dried mucilage of *Ficus glomerata* fruits mucilage and Povidone was shown in Fig 4.69, which indicates that there was proper impregnation of Glipizide with *Ficus glomerata* fruit mucilage and Povidone mixture.

The SEM of Glimepiride with dried fruit mucilage of *Ficus carica* was shown in Fig 4.70, which shows there was proper impregnation of Glimepiride with *Ficus carica* fruit mucilage.

The SEM of Glimepiride with dried fruit mucilage of *Ficus glomerata* was shown in Fig 4.71, which indicates that there was proper impregnation of Glimepiride with *Ficus glomerata* fruit mucilage.

The SEM of Glimepiride with dried fruit mucilage of *Ficus glomerata* and Povidone mixture was shown in Fig 4.72, which indicates that there was proper impregnation of Glimepiride with *Ficus glomerata* fruit mucilage and Povidone mixture.

**In Vitro Drug Permeation Profile of Transdermal Patches**

From the above studies GPFGP-5 and GMFGP-5 transdermal patches were optimized and selected for further kinetic modeling.

Drug permeation profile from Glipizide-*Ficus glomerata* fruit mucilage and Povidone patches (GPFGP-1, GPFGP-2, GPFGP-3, GPFGP-4 and GPFGP-5). The values were 94.05, 91.0, 90.4, 84.8 and 87.97 respectively at the end of 48 h, which were shown in Fig. 4.77 to 4.81.
Similarly In-vitro drug permeation data obtained for Glimepiride *Ficus glomerata* fruit mucilage and Povidone patches (GMFGP-1, GMFGP-2, GMFGP-3, GMFGP-4 and GMFGP-5) were tabulated in Table 4.48 to 4.54 and is represented in Fig. 4.82 to 4.90.

The results of in-vitro permeation studies obtained in these formulations were plotted in five models of data treatments as follows.

- Cumulative percentage of drug released Vs. Time. (Zero order Plot)
- Log cumulative % of drug retained Vs. Time. (First order Plot)
- Cumulative % of drug released Vs. Square root of time (Higuchi’s plot).
- Log cumulative percentage of drug released Vs. Log time (Korsmeyer Peppa’s plot)
- (% Drug Retained)\(^{1/3}\) Vs. Time (Hixson Crowell’s plot).

The Plot of cumulative % drug permeated vs. time for different transdermal patches of Glimepiride with *Ficus glomerata* fruit mucilage and Povidone (GMFGP-1, GMFGP-2, GMFGP-3, GMFGP-4 and GMFGP-5) (Zero order plot) with the values of 86.16, 86.87, 84.62, 92.57 and 93.24 respectively and the plot was shown in Fig 4.87.

Fig. 4.78 shows the plot of log cumulative % drug retained vs. time (First Order) for different formulation of Glipizide- *Ficus glomerata* fruit mucilage and Povidone matrix type patches. Since these plots did not yield a straight line, the data was subjected to linear regression analysis (r), the results of which were shown in Table
The 'r' values obtained for first order kinetics were found to be 0.9842, 0.9702, 0.9484, 0.8884 and -0.8496 for formulations GPFGP-1 to GPFGP-5 respectively. And the 'r' values for zero order kinetics 0.7545, 0.7491, 0.7398, 0.8395 and 0.8478 for formulations GPFGP-1 to GPFGP-5 respectively. Since greater degree of association best fitted with zero order kinetic models. It can be concluded that, all the matrix type transdermal patches followed zero order kinetics as the release pattern of the drug.

Fig 4.87 shows Plot of log cumulative % drug retained vs. time (First Order) for different formulation of Glimepiride- *Ficus glomerata* fruit mucilage matrix type transdermal patches (first order plot). Since these plots did not yield a straight line, the data was subjected to linear regression analysis (r), the results of which were shown in Table. 4.94. The 'r' values obtained for first order kinetics were found to be 0.9625, 0.9894, 0.9138, 0.9686 and 0.9908 for formulations GMFGP-1 to GMFGP-5 respectively. And those for zero order kinetics 0.8177, 0.8823, 0.4848, 0.8011 and 0.8365 for formulations GMFGP-1 to GMFGP-5 respectively. Since greater degree of association best fitted with zero order kinetic models, it can be concluded that, all the matrix type transdermal patches followed zero order kinetics as the release pattern of the drug.

The rate constant of first order release was calculated from the slope value by multiplying with 2.303.

The rate constant for zero order plots can be obtained by using eq. 35.
\[ K_0 = -\text{slope} \ldots (35) \]

The data when treated according to Higuchi's diffusion equation \( (Q=Kt^{1/2}) \) indicated that the formulations released the drug by diffusion. Fig. 4.79 shows Higuchi’s plot and regression values given in Table 4.88 were 0.9956, 0.9983, 0.9799, 0.9981 and 0.9814 for GPFGP-1 to GPFGP-5 respectively. Fig. 4.88 shows Higuchi’s plot and regression values given in Table 4.94 were 0.9909, 0.9982, 0.9431, 0.9892 and 0.9961 for GMFGP-1 to GMFGP-5 respectively.

Further to know the release pattern of Glipizide and Glimepiride from matrix type transdermal patches, the results were analyzed according to Korsmeyer Peppa’s exponential eq. 36.

\[ q = Kt^n \ldots \ldots (36) \]

Where, \( q \) is fraction of drug released up to time (t), k denotes a constant, 'n' is the released exponent indicative of the mechanism of release.

The slope 'n' was computed to know whether the release was Fickian or non-Fickian. For non-Fickian release ('n' values=0.5 to 1.0), while for Fickian diffusion ('n' value= \(
\leq\) 0.5).

The slope values for Glipizide matrix type transdermal patches were tabulated in Table 4.88. The values were 0.5009, 0.5352, 0.7643, 0.5439 and 0.7471 for formulation GPFGP-1 to GPFGP-5. The values of 'n' were more than 0.5 for all the formulations. So, all formulations follow the Non-Fickian release.
The slope values for Glimepiride matrix type transdermal patches were tabulated in Table 4.95. The ‘r’ values were observed to be 0.9868, 0.9951, 0.9818, 0.9915 and 0.9949 for formulation GMFGP-1 to GMFGP-5.

The *in-vitro* release data was further plotted as $(1-\frac{m_t}{m_\infty})^{1/3}$ vs Time proposed by Hixson Crowell’s to verify whether the drug release is by erosion mechanism and it can be represented as eq. 37.

$$3\sqrt{1-\frac{m_t}{m_\infty}} = K_t \quad \text{-------- (37)}$$

Where $m_t = $ Drug release at time $t$

$m_\infty = $ Drug originally present in the formulation

Fig. 4.81 shows the plots of $(1-\frac{m_t}{m_\infty})^{1/3}$ vs. Time and shown in Table 4.88. The regression coefficient values of the plots for different matrix type transdermal patches. The ‘r’ values were found to be 0.9732, 0.9386, 0.9919, 0.9867 and 0.9615 for formulations GPFGP-1 to GPFGP-5 respectively.

Fig. 4.90 shows the plots of $(1-\frac{m_t}{m_\infty})^{1/3}$ vs. Time and shown in Table 4.95. The regression coefficient values of the plots for different matrix type transdermal patches. The ‘r’ values were found to be 0.9747, 0.9869, 0.8382, 0.9552 and 0.9836 for the formulations GMFGP-1 to GMFGP-5 respectively.

**b) In Vivo Evaluation of Transdermal Patches:**

GPFGP-5 and GMFGP-5 were selected for *in vivo* studies.
Mean Blood Glucose levels with blank patch and GPFGP-5 transdermal patch in Rabbits (n = 6) was represented in Table 4.96.

Mean % Reduced blood glucose levels with GPFGP-5 transdermal patches vs. blank in Rabbits (n = 6) was represented in Table 4.97 and shown in Fig. 4.91 and GPFGP-5 shown highly significant values (P***<0.001) compared with normal control.

Similarly mean Blood Glucose levels by giving blank and GMFGP-5 transdermal patches in Rabbits (n = 6) represented in Table 4.98.

Mean % Reduced blood glucose levels GMFGP-5 transdermal patches vs. blank in Rabbits (n = 6) was represented in Table 4.99 and shown in Fig. 4.92 and GMFGP-5 shown highly significant values (P***<0.001) compared with normal control.

**Accelerated Stability Studies of Optimized transdermal patches (GPFGP-5):**

Summary of physicochemical properties of GPFGP-5 patches before and after accelerated stability studies.

Selected matrix tablets (GPFGP-5) were kept at 40°C and 75% RH for 90 days.

The physicochemical properties of optimized patches (GPFGP-5) before and after accelerated stability studies were shown in table 4.101.
Plots of Residual Drug vs. Days for selected Glipizide patches (GPFGP -5) After 30 Days Storage [Stability Studies] (40°C and 75% RH) and shown in Fig.4.93.

Plots of Residual Drug vs. Days for selected Glipizide patches (GPFGP -5) After 60 Days Storage [Stability Studies] (40°C and 75% RH) and shown in Fig.4.94.

Plots of Residual Drug vs. Days for selected Glipizide patches (GPFGP -5) After 90 Days Storage [Stability Studies] (40°C and 75% RH) and shown in Fig.4.95.

The selected GPFGP-5 matrix type patches were found to stable meeting all of its predetermined specification. Here it was checked only for relevant compendia specifications for tablets and *In vitro* degradation studies. There was no change in appearance, average weight, hardness, friability and drug content.