6.1 SUMMARY

6.1.1. Summary of Matrix Tablets

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body and also to achieve and maintain the desired plasma concentration of the drug for a particular period of time. Such limitations of the conventional dosage forms have paved way to an era of controlled and novel drug delivery systems.

Glipizide and Glimepiride, anti diabetic drugs, have been chosen as a model drugs in the formulation of matrix tablets drug delivery systems for the present work.

The formulated matrix tablets are economical to alter beneficially the properties of the existing drugs than developing new drug entities. Thus these anti diabetic drugs have been chosen.

For the above formulations, *Aloe barbadensis miller*, Guar Gum, Povidone were blended in varying proportions of Glipizide/Glimepiride.

UV spectrums of pure Glipizide, Glimepiride and in formulations showed $\lambda_{max}$ at 223 nm and 230 nm respectively, indicates that there was no negative interaction of Glipizide and Glimepiride with the excipients used.

The endothermic peaks in DSC scan of Glipizide/ Glimepiride formulations with *Aloe barbadensis miller* leaves mucilage, *Ficus carica* and *Ficus glomerata* fruit mucilages and Povidone showed slight change in 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.

The characteristic functional group peaks of Glipizide/Glimepiride in the FTIR spectrums were not getting disturbed even after mixing with the polymers used indicates the suitability of the polymers used with Glipizide/Glimepiride.

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

The SEM of Glipizide/Glimepiride with dried fruit mucilage of Ficus bengalensis, Ficus carica, Ficus glomerata and Povidone shows there was proper impregnation of drug with polymer used.

Matrix Tablets of Glipizide/Glimepiride with Aloe barbadensis miller leaf mucilage and Povidone in combination (GPAP) shown good physical appearance, uniformity in thickness, diameter and weights as per Pharmacopoeial specifications

Hardness of formulated matrix tablets were more than 5 kg/cm² and the Friability less than 1% revealed that Glipizide/Glimepiride with Aloe barbadensis miller leaf mucilage and Povidone matrix tablets (GPAP and GMAP) have good compactness and mechanical strength.

The content uniformity of Glipizide/Glimepiride with Aloe barbadensis miller leaf mucilage and Povidone matrix tablets (GPAP and GMAP) revealed that the drug was uniformly mixed in the polymers.
Matrix Tablets of Glipizide/Glimepiride with *Aloe barbadensis miller* leaf mucilage and Povidone in combination (GPAP) shown good swelling properties at first 2 h and steady swelling in next 10h which indicates the uniformity of swelling matrix tablets followed by drug release.

*In-vitro* dissolution studies revealed that the release rate of Glipizide/Glimepiride from matrix tablets were retarded with the increase in the proportion of *Aloe barbadensis miller* leaves mucilage and Povidone.

The kinetic data showed that the drug release from formulations was mainly due to diffusion and erosion mechanism as depicted by strong positive values of regression coefficient (r) obtained from the graph. Regression coefficient values indicated that the drug release pattern from Glipizide/Glimepiride with *Aloe barbadensis miller* leaf mucilage and Povidone matrix tablets matches nearly zero order release pattern. Korsmeyer Peppa’s plot indicates that almost all the formulations of Glipizide and Glimepiride with *Aloe barbadensis miller* leaf mucilage and Povidone matrix tablets followed Fickian release behavior.

The prepared Glipizide/Glimepiride with *Aloe barbadensis miller* leaf mucilage and Povidone matrix tablets were characterized for their flow properties, physicochemical properties, *in-vitro* drug release studies, *in-vivo* bioavailability studies. Almost all the formulations showed fairly acceptable values for all the parameters evaluated. The results were discussed in the chapter 5.
The Glipizide/Glimepiride with *Aloe barbadensis miller* leaf mucilage and Povidone matrix tablets showed good release patterns and steady plasma concentrations for longer periods. The cumulative release of GPAP-5 with marketed tablets shown the release form GPAP-5 is identical with marketed tablets. Thus the prepared GPAP-5 matrix tablets proved to be a potential candidate as a controlled release drug delivery device in this era of patenting novel and controlled release formulations.

Mean % reduced blood glucose levels with GPAP-5 shown very highly significant values (P***<0.001) compared to Glipizide by oral route.

Mean % reduced blood glucose levels with GMAP-5 shown very highly significant values (P***<0.001) compared to Glimepiride by oral route.

The pharmacokinetic (bio-availability) study of optimized formulation (GPAP-5) shown the $C_{\text{max}}$ 0.91 (µg/mL), the $T_{\text{max}}$ 6.0 h, the AUC 15.86 µg .h/mL, AUMC 69.25 µg .h/mL, the $K_{a}$ 0.156 h⁻¹, the Mean Resident Time 12.33 h and the bioavailability 114.8%.

The optimized matrix tablets (GPAP-5) showed the same physicochemical properties and drug content (marginal decrease) before and after accelerated stability studies, indicates the prepared Glipizide *Aloe barbadensis miller* leaf mucilage and Povidone matrix tablets were stable even at accelerated storage conditions.
6.1.2. Summary of Transdermal Patches

Matrix type transdermal patches have been successfully developed to deliver various drugs via skin into the systemic circulation with considerable biomedical benefits.

Glipizide/Glimepiride, anti-diabetic drugs have been chosen as a model drugs in the formulation of transdermal drug delivery systems in the present work.

The formulated matrix type transdermal patches are economical to other polymers which are generally used for making transdermal patches. Repetitive administration of drugs will be minimized by formulating these anti-diabetic drugs in the form of transdermal patches.

Transdermal patches of Glipizide/Glimepiride were prepared by using various proportions of *Ficus bengalensis*, *Ficus carica*, *Ficus glomerata* fruits mucilage and Poly vinyl Pyrrolidone as matrix forming materials.

The prepared patches showed uniformity in thickness, weights, drug content and good tensile strengths indicates the suitability of the formulations for manufacturing and packing.

The prepared transdermal patches showed less content of moisture and moisture uptakes in them and satisfactory elongation break and folding endurance indicates the flexibility of prepared patches. These Physicochemical parameters revealed the suitability of *Ficus glomerata* fruit mucilage and Povidone together forms good quality transdermal patches.
When the patches were applied to the Rabbit’s back there was no visible erythema or edema was observed, indicates non irritating behavior of patches and polymers used.

The *in vitro* skin permeation of Glipizide/Glimepiride from transdermal patches in controlled manner revealed the feasibility of *Ficus glomerata* fruits mucilage and Povidone as matrix formers for making transdermal patches.

Mean % reduced Blood glucose levels with GPFGP-5 patches shown highly significant values (P**<0.01) compared to control (normal).

Mean % reduced Blood glucose levels with GMFGP-5 patches shown highly significant values (P**<0.01) when compared to normal control. The pharmacokinetic values of GPAP-5 were as follows.

The optimized matrix type transdermal patches (GPFGP-5) showed the same physicochemical properties and drug content (marginal decrease) before and after accelerated stability studies, indicates the prepared Glipizide *Ficus glomerata* fruits mucilage and Povidone transdermal patches were stable even at accelerated storage conditions.
6.2. CONCLUSION

6.2.1. Conclusion of Matrix Tablets

Matrix technique is gaining an importance in current days as a simplest technique for a controlled release of drugs. If a drug has right mix of physical chemistry and pharmacology, matrix tablets have a wide range of advantages. Many researches are aimed to discover an economical and effective polymer to release drug by this system. After preparation of matrix tablets, physicochemical studies, in vitro release studies, in vivo release studies, human studies and stability studies were performed. But all the prepared and evaluated matrix tablets must receive approval from FDA before sale.

The aim of this study was to explore the feasibility of matrix tablets of Glipizide/Glimepiride to Diabetes Mellitus. A satisfactory attempt was made to develop matrix tablets by using economical, easily available and natural polymer *Aloe barbadensis miller* leaves mucilage.

From the reproducible results obtained from the executed experiments it can be concluded that:

- Biocompatible and natural polymers like *Aloe barbadensis miller* leaf mucilage can be used to formulate matrix tablets of Glipizide/Glimepiride

- The release of Glipizide/Glimepiride from the formulations is retarded as the proportions of *Aloe barbadensis miller* leaves mucilage increased
In vitro drug release studies showed a steady release of Glipizide/Glimepiride from the formulated matrix tablets.

Formulations GPAP-5 and GMAP-5 showed a better controlled release.

The formulation GPAP-5 matrix tablets showed a kinetic release profile similar to the theoretical controlled release profile of the drug and could be regarded as the optimum formulation.

The in vivo studies revealed that the oral bioavailability of the drug increased than that of conventional dosage form.

Non Fickian diffusion was the drug release mechanism from the formulated matrix tablets. Aloe barbadensis miller leaves mucilage and Povidone in combination appears to be suitable for use as a pharmaceutical excipient in the formulation and manufacture of controlled release matrix tablets because of its good swelling, good flow properties and suitability for direct compression formulations.

It was concluded from the dissolution study, that the dried Aloe barbadensis miller leaves mucilage and Povidone combination can be used as an excipient for making controlled release matrix tablets.

The in-vivo tests in rabbit proved that the formulated matrix tablets could be a promising, satisfactory for controlled release.

Accelerated stability studies, proved that the formulation GPAP-5 is quite stable.
6.2.2. Conclusion of Transdermal Patches

TDDS are effective route of administration. Due to large merits of the TDDS, many researches are going on newer drugs via TDDS. A transdermal patch has components viz., drug, liners, adherents, permeation enhancers, backing layer, plasticizers and solvents, which play a vital role in the release of drug via skin. The transdermal patches were evaluated for physicochemical studies, in vitro permeation studies, skin irritation studies, animal studies and accelerated stability studies. But these transdermal patches must receive approval from FDA before sent in to market. TDDS provide an opportunity to offer more therapeutic options to patients for optimizing their care.

From the experimental results it can be concluded that,

i) Biocompatible and natural polymers like Ficus bengalensis, Ficus carica and Ficus glomerata fruits mucilage can be used to formulate matrix type transdermal patches.

ii) The permeation of Glipizide/Glimepiride from the formulations is retarded as the proportions of mucilage increased.

iii) In vitro permeation studies showed a steady release of Glipizide/Glimepiride from the formulated matrix transdermal patches.

iv) Formulations GPFGP-5 and GMFGP-5 showed a better controlled release
v) *Ficus bengalensis*, *Ficus carica* and *Ficus glomerata* fruits mucilage appears to be suitable for use as a matrix former in the formulation matrix type transdermal patches.

vi) *Ficus glomerata* fruits mucilage and Povidone combination found to be suitable for use as a matrix former in the formulation and manufacture of controlled release matrix transdermal patches.

It can be concluded that the prepared transdermal patches were having satisfactory physical parameters and permeation profiles. Hence it is concluded that Glipizide/ Glimepiride transdermal patches can be prepared with *Ficus glomerata* fruit mucilage and Povidone which are economical and effective.

**6.3. Recommendations:**

**6.3.1. Recommendations for matrix tablets**

Present work was a satisfactory study in designing and characterizing the matrix tablets capable of causing controlled release of Glipizide/Glimepiride in predetermined manner using a combination of synthetic (Povidone K-30) and Natural (Aloe barbadensis miller leaf mucilage). Further the work can be extended as:

- Establish *in vitro* and *in vivo* correlation to guarantee the efficacy and bioavailability of the matrix tablets
- Further detailed *in vivo* bioavailability studies to be performed to establish the efficacy of these formulations
- The natural polymer used guarantees its safety. So, clinical trials to be conducted to correlate the *in vivo* data with in vitro values.
Further preclinical and clinical trials are required to warrant the use of the dosage form in human beings.

The study was performed to check the release retarding properties of the natural polymer used. It is further recommended for future research for dose calculation for controlled release matrix tablets.

The pharmacodynamics studies to be established in diabetic animals
- Pre-clinical trials are to be performed for glimepiride containing tablets
- The study can be extrapolated to clinical trials. Since the polymers used are of natural origin with maximum safety

6.3.2. Recommendations for matrix transdermal patches

Present work was a satisfactory study in designing and characterizing the matrix transdermal patches capable of producing controlled release of Glipizide/Glimepiride in predetermined manner using a combination of synthetic (Povidone K-30) and Natural (Ficus bengalensis/ F. carica/F. reticulate fruit mucilage). Further the work can be extended as:

- Establish *in vitro* and *in vivo* correlation to guarantee the efficacy and bioavailability of the matrix transdermal patches
- Further detailed *in vivo* bioavailability studies to be performed to establish the efficacy of these formulations
- The natural polymer used guarantees its safety. So, clinical trials to be conducted to correlate the *in vivo* data with *in vitro* values.
Further preclinical and clinical trials are required to warrant the use of the dosage form in human beings.

The study was performed to check the release retarding properties of the natural polymer used. It is further recommended for future research for dose calculation for matrix transdermal patches.

The pharmacodynamics studies to be established in diabetic animals.

A detailed pre-clinical data is yet to be established to find out flux, lag time etc.

The study can be extrapolated to clinical trials. Since the polymers used are of natural origin with maximum safety

7. REFERENCES


