6.1. SUMMARY AND CONCLUSIONS

Oral intake has been the most sought after route of drug administration owing to the wide acceptability of this “natural” route, improved patient compliance, low cost of therapy and ease of administration. For highly soluble and permeable BCS class I drugs, oral drug therapy for improving chronic disorders invariably calls for the development of controlled release (CR) products. Conventional CR formulations, however, suffer from the limitation of limited stay in the stomach and the upper GI tract, the preferred site of absorption for most of the drugs. Gastroretentive (GR) formulations, in this regard, offer a viable solution by providing a sustained release of drug at the desired location. Amongst the various GR systems, the floating DDS (FDDS) with bioadhesion constitute one of the most popular approaches for prolonging gastric retention. With a bulk density less than that of gastric fluids, a FDDS remains buoyant in the stomach for a prolonged period of time without affecting the gastric emptying rate. Nevertheless, an FDDS is effective only when the fluid level in the stomach is sufficiently high. As the stomach empties and the tablet is at the pylorus, the buoyancy of the dosage form may be impeded. This serious limitation can largely be overcome by enabling the FDDS to adhere to the mucous lining of stomach wall. Floating and bioadhesive DDS, therefore, greatly improve the possibility of increasing the residence time of DDS in the stomach, resulting in more effective absorption and increased bioavailability of drugs.

Glipizide is an anti-diabetic drug which maintains sugar level in type- II diabetes. Its short half-life (3.5 hrs.), low dose (5-20 mg), narrow absorption window, i.e., stomach and, high physicochemical stability, etc. make it an ideal drug for floating bioadhesive formulations.

Matrix type delivery systems are popular because of their ease of manufacture. It excludes complex production procedure such as coating and pelletization, and drug release from the dosage form is controlled mainly by the type and proportion of the polymers used in the preparation, both single and multi-particulate system may be developed for this, while multi-particulate system further decreases the irritation by distributing the drug concentration in subdivided unit.

FbD methodology with RSM efficiently surmounts the hiccup of balancing floatation and bioadhesion, employing variation in independent variables. It is well-documented to develop “the best possible” formulation under a given set of conditions circumventing unnecessary experimentation and thus, save, time, money and effort.
Thus objectives of the investigations were to develop and systematically optimize the effervescent floating-bioadhesive formulations of glipizide, single unit (tablet) and multiple units (beads), employing FbD approach.

The various conclusions drawn for Tablets and beads are listed below

6.1.1. FLOATING-BIOADHESIVE TABLET FORMULATIONS

- Preliminary studies, carried out with several polymers viz. CP 934P, CP 971P, HPMC K4M, HPMC K15M, indicated that the combination of CP 934P and HPMC K4M along with effervescent producing agent showed excellent promise for drug release prolongation, bioadhesion, and buoyant characteristics, respectively.

- All the controlled release floating-bioadhesive hydrophilic matrix formulations of glipizide, containing polymer blend of CP 934P and HPMC K4M, showed zero order drug release behaviour. Significant increase in $T_{60\%}$ was observed with increase in either CP 934P or HPMC K4M the influence of CP 934P being more pronounced.

- A descending, almost linear trend was observed in $Q_{16}$ with an increase either in CP 934P or HPMC K4M fraction. For all the formulations prepared using polymer blend of CP 934P and HPMC K4M, the values of $Q_{16}$ ranged between 89.65-95.17%, indicating the plausibility of the major amount of the drug release before the device is finally eliminated from the G.I. tract.

- BS increases linearly with increase in content of either polymer, the contribution of CP 934P being much greater than HPMC K4M. Buoyancy time tends to show nearly linear increasing and decreasing trends with increase in the levels of HPMC K4M and CP 934P levels, respectively.

- Exhaustive feasibility and grid searches as well as overlay plot were used to locate the optimized formulation ($T_{OPT} = $ HPMC K4M=78.96 mg and CP 934P=15.2 mg) which fulfilled maximum requisites because of better regulation of release rate, higher BS and more floatation time, it was also validated by six validation check points.

- The pharmacokinetic performance of the optimized formulations was promising vis-à-vis the marketed formulation. The formulations are likely to perform even better in the light of higher gastro-retentivity imparted by bioadhesive and buoyant characteristics of the polymers.

- An appropriate balancing between the levels of the two polymers (HPMC K4M and CP 934P) is imperative to acquire maximum extension in drug release, adequate bioadhesion and floatation time. The increased CP levels were instrumental in attaining maximal prolongation of drug release and
bioadhesion, while the role of HPMC was stellar in governing the buoyant characteristics of the formulation.

 ✓ An appropriate use of optimization methodology helped to predict the best possible formulation, as percent error in prognosis was only between –1.12 and 0.86 %. The design chosen, i.e., CCD, mathematical model for generation of polynomial, i.e., MLRA, and method for locating the optimum, i.e., grid search, were successfully utilized for embarking upon the optimal formulation(s).

 ✓ Accelerated stability studies of the optimized formulation carried out for three months showed no significant loss in drug assay and controlled drug release characteristics. On comparison with a marketed brand, the overall drug release performance of the optimized formulation was found to be comparable.

 ✓ The in vivo studies, carried out in rabbits and healthy human volunteers, corroborated significant improvement in the gastric retention time of the optimized formulation to 6-7 hours without disintegration.

 ✓ Conclusively, the current study attained the successful design, development and optimization of once-a-day tablet formulation of glipizide.

6.1.2. FLOATING-BIOADHESIVE BEADS FORMULATION

 ✓ Preliminary studies, based on literature available on alginate beads carried out with several polymers viz. CT, CP 934P, HPMC K4M indicated that the combination of CT with calcium chloride in formulation of calcium alginate liquid paraffin beads showed excellent promise for drug release prolongation and, bio-adhesion, respectively in floating beads.

 ✓ Extensive literature search indicates that the optimization of the oral drug delivery devices has become a regular phenomenon round the globe.

 ✓ All the controlled release beads formulations of glipizide, containing blend of polymer SA and CT, and low density liquid paraffin, showed non-fickian drug release behaviour.

 ✓ A descending, almost linear trend was observed in $Q_{10}$ with an increase in LLP fraction as well as alginate. For all the formulations prepared using polymer blend of SA, CT with calcium chloride, and LLP the values of $Q_{10}$ ranged between 80-98%, indicating the plausibility of the major amount of the drug release before the device is finally eliminated from the GI tract.

 ✓ Evaluation of seven formulations, chosen as optimal from grid searches, indicated that the formulation $B_{\text{OPT}}$ (SA= 3.14g and LP= 12.9 ml) fulfilled maximum requisites because of better regulation of release rate, higher EE and better floating properties.
An appropriate balancing between the levels of the alginate and LLP is imperative to acquire maximum extension in drug release and adequate floating along with better EE. The increased alginate and LLP were instrumental in attaining prolongation of drug release and floating at the same time increase in alginate results in release prolongation and decrease floating.

An appropriate use of optimization methodology helped to predict the best possible formulation, as percent error in prognosis was only between –2.22 and 0.93 %. The design chosen, i.e., CCD, mathematical model for generation of polynomial, i.e., MLRA, and method for locating the optimum, i.e., grid search, were successfully utilized for embarking upon the optimal formulation(s).

In vivo performance of the optimized formulations may further improve in the light of higher gastroretentivity imparted by floating characteristics of the LLP.

In vivo studies confirm the retention of the dosage form in the stomach, and drug release characteristics are found to be similar with marketed brand. Stability at accelerated stability studies further strengthen the acceptance of formulation.

Conclusively, the current study attained the successful design, development and optimization of once-a-day multi-particulate formulation of glipizide.

6.2 FUTURE POTENTIAL

The techniques used in the present work for preparation of tablets and beads may be easily transferred in to high scale manufacturing facility.

Both technology considerations, i.e. risk involved and high scale manufacturing facilities availability as well as commercial consideration, i.e. potential commercial application and abundant availability of potential market for the products are satisfied by drug and dosage form.

Hence, the studies can be safely regarded as a platform technology in the manufacture of floating bioadhesive CR formulations.