Chapter 8

Summary and Conclusion
Due to the difficulty in developing new drugs, more and more emphasis has been given in developing new drug delivery systems for existing drugs as well as new chemical entities. Drugs can be delivered to patients by more than one route and by more than one type of dosage form. Even though “dosage form” and “drug delivery system” are used interchangeably, “drug delivery system” implies that a technology has been used to deliver a drug to the desired body site for drug release with a predetermined rate. Among various drug delivery systems, oral extended release (ER) formulation is the most commonly used.

In the present project based on different drug release mechanisms, to formulate extended release tablets different technologies have been used, where gliclazide was investigated. Gliclazide belongs to sulphonylurea class of anti-diabetic drugs. Gliclazide (oral hypoglycemic drug) is widely used in the treatment of non insulin dependent diabetes mellitus. However, usage can be limited as in certain patients an immediate release form can result in higher short term concentration in blood. An extended release dosage form makes it possible for such peaks in blood to be avoided and enables consistent concentration in blood to be obtained. This makes it possible to reduce undesirable effects that may occur as a result of the peak effect which are accompanied by hydro electrolytic and metabolic type disorders associated with variations in the plasma levels of the active ingredients.

Extended release tablets and a brief history of their emergence as a drug delivery system and their advantages over immediate release dosage form have been discussed. Detailed literature search on the various technologies for manufacturing of extended release dosage form has been carried out and recorded. Technologies investigated are matrix technology, hot melt granulation technology and multiparticulate technology. Literature search pertaining to various technologies of production and application of extended release tablets has been elaborated in continuation. It covers characterisation of extended release tablets of various drugs. It also briefly mentions about diabetes and anti-diabetic drugs. Introduction covers a comprehensive review on technologies that has been used for the development of a non–infringing formulation of drug Gliclazide. For developing gliclazide extended release tablets by non infringing route indepth patent search was done.

EP patent no. EP1148871, by Servier laboratories which expires in October 2019, mainly claims the matrix tablet formulation for the prolonged release of gliclazide using a combination of glucose syrup and polymer which gives pH non sensitive drug release. Also claims preparation method of gliclazide MR tablets. Another patent by Servier lab. patent no.
EP1064935 which expires in June 2020 claims polymethacrylates as binders to form matrix pellets. Patent EP 0806202 expiring in May 2017, claims the cellulose derivatives as polymer in an amount not exceeding 15% along with lipophilic binder having HLB coefficient of less than 10. This patent do not claim tablet formulation. There are many other related patents listed but claims do not hamper development of gliclazide extended release tablets. Formulations with three different technologies are made bypassing all three patents. In matrix technology cellulose polymer concentration used is more than 15% concentration and manufacturing process of tablets is changed which gave pH sensitive drug release profile, in hot melt granulation technology, waxy substance used was polyethylene glycol and cellulose polymer in the concentration more than 15%. To formulate gliclazide ER tablets by pellet technology, the patent no. EP1064935 claims the solid controlled release pharmaceutical composition, characterized in that it comprises a thermoformed mixture of at least one active ingredient and of one or more polymers selected from the group consisting of the polymethacrylates, without plasticizer. The release of the active ingredients being controlled solely by nature of the polymethacrylates used, by amount thereof relative to active ingredient(s) and by the technique employed in the manufacture of the composition, the polymethacrylates used in the thermoformed mixture belonging to family of eudragit products. Thus to overcome these claims gliclazide immediate release pellets were made by extrusion and spheronization and further coated so as to achieve desired release profile.

Rationale and objective behind the project is that many diseases are still major causes for morbidity and mortality. There are not enough effective and sufficient drugs to control these diseases. However, to launch new molecules as drugs is too costly a proposition. Hence, to recover cost of development new molecule is allowed to be patented for some time. After patent expiry, other companies may launch same molecule as generic version. To make drug therapy cost effective, it is necessary to reduce cost of drug development while taking care of safety and efficacy of drug product. Thus, generic drugs have to pass limited clinical trials in the form of comparative bioavailability or bioequivalence study. This accelerates the process of development and takes care of safety issues. This view is also supported by regulatory authorities. To make drug therapy more cost effective, it is necessary to optimize cost of drug by developing generic product, while taking care of safety and efficacy of drug product. Brand product of Gliclazide MR tablets is reported as matrix tablets. Servier labs. (innovator) has three patents for gliclazide ER tablets which covers the formulations by different technologies. But the marketed product is made by matrix technology. Hence same product made by different technologies is an innovative step in development.
Research work involved evaluating extended release dosage form of anti-diabetic drug by three different technologies to formulate a non-infringing formulation as generic for Europe or ROW markets. Anti-diabetic drug Gliclazide was selected for development of extended release dosage form. Gliclazide drug is used extensively as an anti-diabetic drug, the dose of the drug ranges from 30 mg to 320 mg in divided doses.

Gliclazide and all the excipients used in the formulation made by different technologies were standardized as per specifications in Ph. Eur. and as per the COA provided by the approved vendors. The drug profile which includes structure, IUPAC name, molecular weight, physiochemical properties, mechanism of action, dosing information and pharmacokinetics have been described. It also includes detailed information about the clinical applications, administration, contraindications, over dosage information, storage and stability, along with the standardization of the drug as per the manufacturer’s certificate of analysis (COA). The chapter mentions the profile of the excipients used in the formulation development. Standardization of the excipient as per the vendors COA is enclosed in appendix. This chapter also gives drug and excipient characterization by differential scanning calorimetry (DSC).

The main body of project deals with complete experimental work. It starts with analytical validation followed by preformulation studies, formulation development and evaluation of formulations made by three different technologies, scale up and stability studies and bioequivalence studies.

The analytical method verification and part validation for gliclazide and formulations thereof is also covered. Gliclazide is official in European pharmacopeia and Gliclazide tablets in Indian Pharmacopeia, the analytical methods given were verified and validated, in the lab. conditions.

UV Spectrophotometric method was used for the determination of dissolution profile and assay of gliclazide. UV spectrophotometric method of analysis showed a UV absorbance at 226 nm and 290 nm. Calibration curve obtained in water and methanol (as the drug has poor solubility in water), was found to be linear in the concentration range of 2.5 – 17.5µg/ml with $r^2 = 0.9967$.

HPLC method of analysis was used for related substances determination in gliclazide and its formulations.
Gliclazide formulation is official in Indian pharmacopeia, the same method was used for estimation of gliclazide extended release tablets made by three technologies: matrix technology, hot melt granulation technology and multiparticulate unit dose technology. For assay and dissolution profile the drug was estimated using UV spectrophotometric method at 226 nm and 290 nm. Method was verified and partially validated using precision and system suitability studies. For related substances the method given was by HPLC, which was also verified.

In the Preformulation studies, the binary mixtures of drug and the excipients were prepared in the ratio as present in dosage form, and exposed to 40°C/75% RH in open condition and 25°C/60%RH in open and closed conditions. The binary mixtures were also subjected to 60°C for one week and were analyzed using X ray diffraction. XRD patterns of control sample and exposed samples were studied. XRD patterns obtained were overlaid to check any incompatibility. Forced degradation studies of gliclazide was done to understand the robustness of analytical method.

Gliclazide extended release tablets were to match the dissolution profile and other physical parameters with Diamicron MR tablets 30 mg, from Servier labs. France. Extended release tablets were developed to deliver gliclazide over a period of 10 hrs. made by different technologies.

Gliclazide extended release tablets by matrix technology
Gliclazide extended release tablets of gliclazide were developed by matrix technology. Various polymers such as Polyethylene oxide, Xanthan gum, Sodium alginate, Copolymer of Polyvinyl alcohol and Povidone and combination of hydroxypropylmethyl cellulose were evaluated. Method used for preparation of tablets was slugging/deslugging as the wet granulation method was covered in the innovators patent.

Formulation development was initiated using Polyethylene oxide as the rate controlling polymer in the concentration of 47.5%. Formulation when evaluated chemically, showed drug release profile slower in comparison with Diamicron MR tablets. Physical properties of the tablets were satisfactory. To match dissolution profile, polymer concentration was decreased gradually and formulation with polymer concentration of 22.5% showed satisfactory physical properties having desired dissolution profile. Formulation was packed in Alu/Alu blisters and kept for stability. Formulation at one month 40°C/75% RH, when analyzed showed faster dissolution profile in comparison with the initial drug release profile. Hence formulation was
not continued further as Polyox WSR coagulant has been reported to alter its polymer structure due to oxidation.

Gliclazide ER tablet formulations were also prepared using Xanthan gum as rate controlling polymer. Formulation was made with similar process described earlier. Polymer was used in concentration of 29% and analysed for dissolution profile. To match dissolution profile Xanthan gum concentration was reduced from 29% to 7.5%. Physical attributes of extended release tablets were satisfactory. But main criterion to attain a satisfactory product was dissolution profile which could not be achieved even after reducing concentration of polymer to 7.5%. Hence this approach was discontinued, because as a general rule to achieve uniform distribution of polymer in matrix blend, the concentration of polymer should be around 5%.

Formulation with the combination of hydroxypropylmethyl cellulose (HPMC K4M and HPMC K100 LV) in concentration of 44% showed comparative dissolution profile as compared to innovator Diamicron MR Tablet, France. The other parameters such as the blend uniformity, sieve analysis, Assay, related substances were also found to be within the specification limits. The optimized formulation was scaled up to 15 times as compared to the regular batch sizes. The method was optimized for process variables like blend uniformity, compression machine rpm and high and low hardness. Reproducibility batches were taken for the final batch for the formulation made by each technology and scaled up to check for problems in processing due to increase in the scale of the batch. For matrix tablets as the process was slugging/ deslugging equipment capacity was not a constraint, hence it was scaled up to 10,000 tablets and the samples were evaluated for the compression machine speed to check segregation of blend due to vibrations. Tablets were also checked for hardness parameters that are high, low and optimum hardness and parameters were evaluated using dissolution profile as indicator to study the influence of hardness on drug release.

**Gliclazide extended release tablets by hot melt granulation technology**

To develop gliclazide extended release tablets by hot melt granulation method, hydrophobic waxes hydrogenated castor oil and stearic acid were used. Hydrophilic waxy material polyethylene glycol 8000 along with hydroxypropylmethyl cellulose was used in the final formulations to get the desired dissolution profile. Here, the process variables were the temperature of the melted mass, granulation time, multi milling speed, time and finally, the hardness of the tablet to get the desired release profile. The final optimized formulation was scaled up to 15 times keeping in mid the commercialization of the product.
Gliclazide extended release tablets by multiparticulate unit dose technology

Gliclazide extended release tablets by multiparticulate unit dose technology were developed by first making gliclazide immediate release pellets, coating the pellets to get desired extended release of the drug, further blending with diluents and lubricants, compressing the tablets using the blend and finally coating the tablets for esthetic appeal. A systematic study to obtain formulation which gives the drug release profile similar to innovator product was carried out. Optimization studies were carried out in order to narrow down on the final formulation. The input variables studies were

i) Composition of the coating material used for coating the pellets to achieve desired drug release profile.

ii) Compression hardness which has effect on drug release due to rupture of the coating of pellets.

Optimized formulation was scaled four times the regular batch size. The batch was found to be reproducible with respect to its physical and chemical parameters.

Physiochemical parameters for the evaluation of gliclazide ER tablets using three different technologies

Gliclazide extended release tablets were evaluated for following parameters

- **Blend analysis**: The blend was analyzed for loss on drying, bulk density, tapped density, compressibility index, hausners’s ratio and sieve analysis.
- **In-process parameters**: Following parameters were evaluated for the in-process: Loss on drying of the tablets was measured using, hardness, thickness and friability
- **Description**: The tablets were checked for their physical appearance and colour.
- **Drug content**: The drug content was determined by UV spectrophotometer.
- **In-vitro dissolution profile**: In-vitro drug release was carried out by using dissolution apparatus at 50 rpm. pH 6.8 phosphate buffer was used as the dissolution medium and for multiple media dissolution pH 7.4 phosphate buffer and pH 4.5 acetate buffer was used and samples were withdrawn at various time points and analyzed by UV spectrophotometry.
- **Related substances**: Related substances were determined by HPLC.
- **Content uniformity**: The drug content was determined in 10 individual tablets by UV spectrophotometry.

Optimized formulations were packed in PVC/PVDC /Alu blisters, Alu/Alu blisters and HDPE bottles. All the packaging materials selected were analyzed as per the specifications. For
blisters vacuum leakage test was performed for checking the integrity of the blisters. Stability studies were carried out as per ICH guidelines at the following storage conditions: 40°C/75% RH as accelerated condition for 6 months, 30°C/65% RH as intermediate condition for one year (samples to be analyzed only if the formulation falls out of the limits as per the specifications at 40°C/75% RH) and 25°C/60% RH as long time condition to generate real time stability data. The samples at different storage conditions were withdrawn periodically and analyzed for physical and chemical stability. Parameters evaluated were: visual appearance, assay, dissolution profile, hardness, average weight and related substances.

Optimized formulation was chosen for the bioequivalence studies and COA generated was submitted for the studies. Cleaning was done by swipe method for all equipments used in the preparation of formulation. Bioequivalence studies were carried out with the selected formulation (prepared using combination of hydroxypropylmethyl cellulose polymer) and innovator - Diamicron MR tablets procured from France and provided by USV Ltd. The study design was balanced, open Label, analyst blind, single centre, two treatment, two period, two sequence, comparative bioavailability study of “Gliclazide ER tablets 30 mg” of SPP School of Pharmacy & Technology Management, SVKM’s NMIMS, Mumbai with “Diamicron MR tablets 30 mg” (containing Gliclazide 30 mg) of Servier Lab Ltd., France in healthy, adult, male, human subjects under fasting conditions in a randomized, crossover design. The bioequivalence studies was carried out at Drug Monitoring Research Institute, Rabale, Navi-Mumbai, and the study was monitored throughout.

To investigate the efficacy of developed formulations in-vivo studies were performed at DMRI (Drug monitoring and research Institute) Navi-Mumbai, based on the protocol No. DMRI-PR10-205-GLIC, Version: 00, dated 06/09/10) and the ICF: English DMRI-PR10-205-GLIC, Version: 00, dated 06/09/10), & Marathi (ICF No.: DMRI-PR10-205-GLIC, Version: 00, dated 06/09/10) were reviewed by the IEC in the meeting held on 15/09/10.

The Ethics Committee approved the above mentioned Protocol and ICFs. The Chairman of IEC named CEC is Mr. C.M. Shrikhande.

**Ethical conduct of bioequivalence study**

This study was conducted ethically in accordance with the principles of the ICMR guidelines, Schedule Y 2005 of Drug & Cosmetic Act, India, the World Medical Association Declaration of Helsinki, Seoul, 2008 & the ICH (Step V), “Guidance on Good Clinical Practice” (GCP). The study did not commence until IEC approved the protocol with the corresponding ICFs.
Chapter 8

Summary and Conclusion

No subject was enrolled in the study without obtaining written informed consent and subjects were under medical supervision throughout their stay in the clinical facility to ensure safety and well being of the subjects.

Formulation of Gliclazide extended release tablets 30 mg made by three different technologies were found to give satisfactory results for all the evaluated parameters. Pharmacoeconomics for all the three formulations were done. Technological advances in the field of pharmaceutical manufacturing and achieving better therapeutic value from the modified release dosage forms has in turn put a pressure on the consumer and the manufacturer that how to strike a balance. Patented technologies and the high investment involved in infrastructure are other determinants for the cost of formulations. The cost of development of the product is already recovered by the brand product owner during the period for which the patents are granted and once the generic version of the formulation is developed the prices crash to as low as 1% of the original brand and still the manufacturer has to earn profits and continue development.

Three concepts which were considered to be vital for the study had been put under a scanner to ensure the objectives of affordability, manufacturing feasibility and the product profile (therapeutic efficacy) are not overlooked.

With the above in focus complete study of the product from the point of view of manufacturing convenience, infra-structure needs, therapeutic equivalence and cost has been done and the best fit has been recommended. The values will be considered in the context of present, a slight disagreement may prevail in terms of absolute figures but in terms of proportions the fact will speak of the state of the approach for development coupled with a serious concern for the suffering human and their welfare.

Data presented in thesis has reflected extensive work towards development of gliclazide extended release tablets using three technologies that is matrix technology, Hot melt granulation technology and Multiparticulate unit dose technology. Scale up studies was performed with larger batches and automated machines to confirm the commercial viability of developed formulations. Bioequivalence study was performed on human subjects.

The objective of the research work to develop a stable, non infringing gliclazide extended release tablet formulation as a generic for regulated market was successfully achieved. The formulation was developed using matrix, melt granulation and multiparticulate technologies.
Bioequivalence was carried out on the selected formulation in human subjects in fasting condition. Pharmacoeconomics of the developed formulation for the cost comparison was done. Thus all the objectives laid were met.

**Future scope**

Further if the formulation is to be taken for generic market, since pilot B. E studies is showing passing results as per the limits set by ICH guidelines. The Pilot scale batches and validation will have to be taken at the manufacturing plant to optimize the processing parameters. Pivotal B.E studies in fed, fasted condition and steady state studies will have to be performed so as to register the product as generics.
Table 8.1: Comparative performance of gliclazide extended release tablets by three technologies

<table>
<thead>
<tr>
<th></th>
<th>Matrix technology</th>
<th>Melt granulation technology</th>
<th>Multiparticulate unit dose technology</th>
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<td><strong>Tablet</strong></td>
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<td><img src="image2" alt="Image" /></td>
<td><img src="image3" alt="Image" /></td>
</tr>
<tr>
<td><strong>Description</strong></td>
<td>White to off white circular, biconvex uncoated tablets plain on both sides.</td>
<td>White to off white circular, flat beveled edged slightly dappled uncoated tablets plain on both sides.</td>
<td>White to off white circular, biconvex film coated tablets plain on both sides.</td>
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<tr>
<td><strong>Punch dimensions</strong></td>
<td>8.00 mm</td>
<td>7.00 mm</td>
<td>10.00 mm</td>
</tr>
<tr>
<td><strong>Packing</strong></td>
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<td>Alu-Alu blister</td>
<td>Alu-Alu blister</td>
</tr>
<tr>
<td><strong>Assay</strong></td>
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<td>99.8%</td>
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<tr>
<td><strong>Related substance (%)</strong></td>
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<td>(%)</td>
<td>(%)</td>
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<tr>
<td><strong>Impurity F</strong></td>
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<td>0.001</td>
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<tr>
<td><strong>Highest unknown impurity</strong></td>
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<td>0.048</td>
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<tr>
<td><strong>Total impurity (%)</strong></td>
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<td>0.161</td>
<td>0.158</td>
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<td><strong>Dissolution profile</strong></td>
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<tr>
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