4.1. INTRODUCTION TO LIQUISOLID TECHNIQUE:

As described in Chapter 1, many techniques are being employed for the solubility enhancement of poorly soluble drugs to resolve the bioavailability issue due to inadequate dissolution rate. Various approaches make use of hydrophilic polymers as solubility enhancers acting through a variety of mechanisms such as amorphization, co-solvency, micelle formation or inclusion complexes. These techniques impart many advantageous effects in the formulation development. But usually these approaches show lack of stability and decreasing success rate over a period of storage. One of the remarkable demerits of solid dispersions, glass solutions, eutectic mixtures and inclusion complexes is formation of sticky and hygroscopic mass resulting in the poor flow characteristics\[^{51, 52}\]. Due to this set-back, industrial feasibility of the final dosage form becomes very difficult.

The liquisolid technology emerged as a new drug delivery system distinguished by its characteristics and ability to deliver variety of drugs. Liquisolid drug delivery system has gained attention of pharmaceutical researchers due to its contribution in the solubility enhancement as well as dissolution retarding approaches depending on the need and design of the formulation.

With the liquisolid technology as described and patented by Spireas\[^91\], a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected excipients.

Three major components in the formulation of liquisolid compacts are liquid medication, carrier and coat material. Other excipients such as use of disintegrant or release retarding polymers for modification of release profile are used as per the objective and need of the formulation.
The first component i.e. liquid medication can either be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles. Inert, preferably water-miscible organic solvent systems with high boiling point such as propylene glycol, liquid polyethylene glycols or glycerin are best suitable as ‘liquid vehicle’. The solubilization of the drug in a non-volatile solvent keeps the drug in uniformly and molecularly dispersed form. This creates opportunity to enhance the drug release.

The liquid medication is incorporated into the second component of the system i.e. the porous carrier material. Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the third component i.e. coat materials. Thus, an apparently dry, free flowing and compressible powder is obtained. Usually, microcrystalline cellulose is used as carrier material\textsuperscript{[213]}.

The third component i.e. coat material avoids the re-aggregation of the liquisolid particles and imparts higher flow characteristics. The coating also assists the dry-looking character of the system. Many times, amorphous silicon dioxide (colloidal silica) is used as coating material. The concept of liquisolid technology is depicted in Fig. 4.1.

Liquisolid formulation containing a drug solution or drug suspension of poorly soluble drugs in a solubilizing vehicle shows enhanced drug release due to increased surface area of drug available for release, increased aqueous solubility of the drug by co-solvency and improved wettability of the drug particles\textsuperscript{[214-219]}. Accordingly, this improved drug release may result in a higher drug absorption in the gastrointestinal tract and thus, an improved oral bioavailability\textsuperscript{[220,221]}. 
4.1.1. HISTORICAL DEVELOPMENT:

Liquisolid technology is the next generation of ‘powdered solutions’[213], an older technique which was based on the conversion of a solution of a drug in a nonvolatile solvent into a dry-looking, non-adherent powder by mainly adsorbing the liquid onto silica having large specific surfaces. However, such preparations have been studied for their dissolution profiles while being in a powder dispersion form and not as compressed entities, simply because they could not be compressed into tablets. In later developments on powdered solutions, compression enhancers and binders such as microcrystalline cellulose were incorporated in such systems to improve the compactability of the blend.

In these investigations, however, large quantities of silica were being used and the flow as well as compression properties of the product were never validated and optimized to the industrial specifications and requirements. Specifically, when such modified powdered solutions were compressed into tablets, they showed significant problems of ‘liquid squeezing out’ and unacceptably soft tablets. Thus the industrial application of such systems was hindered.

Liquisolid compacts, on the contrary, show acceptable flow and compressibility and deserve industrial application. In addition, the term ‘liquid medication’ does not only imply drug solutions, as in powdered solutions, but also drug suspensions, emulsions or liquid oily drugs. Therefore, in contrast to ‘powdered solutions’, the term ‘Liquisolid compacts’ is wider and more general and it may encompass four different formulation systems viz. powdered drug solutions, powdered drug suspensions, powdered drug emulsions and powdered liquid drugs.

Furthermore, the earlier term ‘powdered solution’ seems to be inadequate even in describing the original systems, since it has not been proven that the drug remains in
solution in the liquid vehicle after its deposition on the extremely large powder surface of silica used\textsuperscript{[223, 224]}.

4.1.2. CONCEPT OF LIQUISOLID SYSTEM:

When the drug dissolved in the liquid vehicle is incorporated into a carrier material which has a porous surface and closely matted fibers in its interior such as celluloses, both absorption and adsorption take place. The liquid initially absorbed in the interior of the particles is captured by its internal structure. After the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occurs. Then, the coating material having high adsorptive properties and large specific surface area provides the liquisolid system the desirable flow characteristics (Fig. 4.1) \textsuperscript{[91, 224]}. In liquisolid systems, the drug is already in solution form in liquid vehicle, while at the same time, it is carried by powder.

The wettability of the compacts in the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate from the liquisolid compacts. Non-volatile solvent present in the liquisolid system facilitates wetting of drug particles by decreasing interfacial tension between dissolution medium and tablet surface. Thus, due to substantial increase in wettability and effective surface area for dissolution, liquisolid compacts may be expected to reveal enhanced release profiles of water-insoluble drugs. Since dissolution of a non-polar drug is often the rate limiting step in gastrointestinal absorption, better bioavailability of an orally administered water-insoluble drug is achieved when the drug is already in solution, thereby displaying enhanced dissolution rates\textsuperscript{[214-224]}.

However, the drug release profile entirely depends on the characteristics of drug, carrier and vehicle used. Thus by altering these variables, liquisolid technique can be used for enhancing or retarding the drug release.
4.1.3. COMPONENTS OF LIQUISOLID SYSTEM:

The major formulation components of liquisolid compacts are:

1. **Carrier Material:**

   The carrier material should possess porous surface and closely matted fibers in the interior. Carriers are involved in the sorption process of liquid medication which improves the effective surface area for dissolution. These also assist the compression. Carriers due to relatively large, preferably porous particles, possess a sufficient adsorption property and matted fibers in interior contribute in absorption of liquid medication. e.g. various grades of cellulose\textsuperscript{[225]}, starch\textsuperscript{[226]}, lactose\textsuperscript{[227]}, sorbitol\textsuperscript{[228]} etc.

2. **Coating Material:**

   Coating material forms a uniform film around the particles of carrier. Thus they prevent the aggregation of particles as well as reduce the inter-particulate friction. This phenomenon improves the flowability as well as gives the liquisolid a dry-looking appearance by covering the wet carrier particles and by absorbing any excess liquid\textsuperscript{[91, 222, 223, 226]}. Coat materials are usually very fine (10 nm to 5,000 nm in
diameter) and highly adsorptive coating particles e.g. colloidal silica of various grades like Cab-O-Sil M5, Aerosil 200, Syloid 244FP etc.

3. **Non-Volatile Solvent:**

   The solvent selected should possess ability to dissolve adequate amount of the drug candidate. Inert, preferably water-miscible and not highly viscous organic solvent systems having high boiling point e.g. propylene glycol, liquid polyethylene glycols, polysorbates, glycerin, N, N-dimethylacetamide, fixed oils etc. are the suitable vehicles.

4. **Disintegrant:**

   The use of disintegrant, its type and concentration in the formulation will be mainly based on the objective of the investigation. For solubility enhancement studies, incorporation of super-disintegrant is encouraged. Most commonly used disintegrant is sodium starch glycolate (Explotab13, Pumogel etc.). While for matrix type of systems intended for sustained release, disintegration is not required.

4.1.4. **CLASSIFICATION OF LIQUISOLID SYSTEMS:**

A. **Based on the Type of liquid Medication:**

   Based on type of liquid medication used in the formulation, liquisolid systems may be classified into four subgroups:

   1. Powdered drug solutions
   2. Powdered drug suspensions
   3. Powdered drug emulsions
   4. Powdered liquid drugs

   The first three may be produced from the conversion of drug solutions or drug suspensions and emulsions, the later from the formulation of liquid drugs into liquisolid systems.
Since non-volatile solvents are used to prepare the drug solution or suspension, the liquid vehicle does not evaporate and thus, the drug carried within the liquid system, remains dispersed throughout the final product.

**B. Based on the Formulation Technique:**

Depending on the technique used, liquisolid systems may be classified into two categories:

1. Liquisolid compacts
2. Liquisolid microsystems

Liquisolid compacts are prepared using the previously outlined method to produce tablets or capsules, whereas the liquisolid microsystems are based on a new concept which employs similar methodology combined with the inclusion of an additive e.g. PVP, in the liquid medication which is incorporated into the carrier and coating materials to produce an acceptably flowing admixture for encapsulation. The advantage stemming from this new technique is that the resulting unit size of liquisolid microsystems may be as much as five times less than that of liquisolid compacts\(^{[91, 222, 226]}\).

**4.1.5. LIQUISOLID SYSTEM FOR CONTROLLED DRUG DELIVERY:**

Development of sustained release oral dosage forms is beneficial for optimal therapy in terms of efficacy, safety and patient compliance. Several methods have been developed to achieve this aim.

It is suggested that liquisolid technique has the potential to be optimized for the delay of drug dissolution rate and thereby production of sustained release systems. If hydrophobic carriers such as Eudragit RL and Eudragit RS are used instead of hydrophilic carries in liquisolid systems, sustained release systems can be obtained.
The mechanism of release prolongation is likely to be a more efficient encapsulation of drug particles by the hydrophobic polymers. The presence of non-volatile solvent reduces the glass transition temperature (Tg) of polymers and imparts flexibility. Therefore, reduction of Tg of the polymer might be the reason for the release prolongation of liquisolid tablets. In the temperature above the Tg, a better coalescence of the polymer particles occurs that forms a fine network and a matrix with lower porosity and higher tortuosity. In this way, the drug is surrounded and entangled by the polymer network, resulting in the restricted leaching of the drug thus, sustaining the release of drug from liquisolid matrices\cite{225}.

4.1.6. METHOD OF PREPARATION OF LIQUISOLID SYSTEM:

As shown in figure 4.2, a liquid drug can be converted into a dry-looking liquisolid system without being further chemically modified. If liquisolid system of a solid water-insoluble drug is to be formulated, it should be initially dissolved or suspended in a suitable non-volatile solvent system to produce a drug solution or drug suspension of desired concentration.

Next, a certain amount of the prepared drug solution or suspension or a liquid drug itself is incorporated into a specific quantity of carrier material which should be preferably of a porous nature and possessing sufficient absorption properties. The resulting wet mixture is then converted into a dry-looking, non adherent, free-flowing and readily compressible powder by the simple addition and mixing of a calculated amount of coating material. Excipients possessing fine and highly adsorptive particles are suitable for this step.

Before compression or encapsulation, various adjuvant like lubricants and disintegrants (immediate release) or binders (sustained release) may be added to final liquisolid system to produce liquisolid compacts i.e. tablet or capsule\cite{91, 222, 223}.
4.1.7. MATHEMATICAL MODEL TO DESIGN LIQUISOLID SYSTEM:

The flowability and compressibility of liquisolid compacts are addressed simultaneously in the ‘new formulation mathematical model of liquisolid systems’. The model can be employed to compute the appropriate quantities of the carrier and coating materials required to produce acceptably flowing and compressible powders. The calculation of composition of carrier, coat and liquid medication is based on new fundamental powder properties called as ‘flowable liquid retention potential’ (Φ-value) and ‘compressible liquid retention potential’ (Ψ-number) of the constituent powder [91, 224].

The flowable liquid retention potential (Φ-value) of a powder is defined as the maximum amount of a given non-volatile liquid that can be retained inside its bulk (w/w) while maintaining acceptable flowability.

The compressible liquid retention potential (Ψ-number) of a powder is the maximum amount of a given non-volatile liquid, the powder can retain inside its bulk (w/w) while maintaining acceptable compactability, to produce compacts of suitable
hardness and friability, with no ‘liquid squeezing out’ phenomenon during the compression process.

The Φ-value of powders may be determined using the liquisolid flowability test. The Ψ-number of powders may be determined by liquisolid compressibility test which employs the ‘plasticity theories’ to evaluate the compaction properties of liquid/powder admixtures\[^{[91]}\].

The liquisolid flowability test is basically a titration-like procedure in which 25 to 30 g of mixture of the powders under investigation, with increasing amounts of a non-volatile solvent (i.e. liquid/solid weight composition) are prepared using a standard mixing process. The flow rates and consistencies are assessed using a Recording Powder Flow meter. The liquid/solid weight composition (w/w) in that admixture, which just complies with a desired and preselected limit of acceptable flowability, is taken as the Φ-value of the excipient. The non-volatile solvent used in the liquisolid flowability test should be the one selected to be included in the liquid medication (drug solution or drug suspension) of the targeted liquisolid product. While the study consisting the use of a liquid drug, the liquisolid flowability test should be conducted with the liquid drug itself. This value will change when different solvent or solvent system is employed\[^{[91, 222, 223, 226]}\].

According to the theories, the carrier and coating powder materials can retain only certain amount of liquid while maintaining acceptable flow and compression properties. Hence, the excipient ratio (R) or the carrier: coat ratio of the powder system used should be optimized.

\[
R = \frac{Q}{q} \quad (4.1)
\]

R represents the ratio between the weights of carrier (Q) and coating material (q) present in the formulation. An acceptably flowing and compressible liquisolid system
can be prepared only if a maximum liquid on the carrier material is not exceeded. Such a characteristic amount of liquid is termed as Liquid load factor (Lf), which is defined as the ratio of the weight of liquid medication (W) over the weight of the carrier powder (Q) in the system, which should be possessed by an acceptably flowing and compressible liquisolid system.

\[
LF = \frac{W}{Q}
\]  
(4.2)

The relationship between the powder excipients ratio (R) and liquid load factor (Lf) of the formulations can be given as follows:

\[
LF = \Phi + \varphi \left( \frac{1}{R} \right)
\]  
(4.3)

Where, \( \Phi \) and \( \varphi \) are the \( \Phi \)-values of carrier and coat material respectively.

In order to calculate the required ingredient quantities, the flowable liquid retention potentials (\( \Phi \)-values) of powder excipients were utilized based on reported values in the literature\[^{91,223}\]. As from equation 4.3, \( \Phi \) and \( \varphi \) and are constants, R and Lf were determined from the linear relationship of Lf versus 1/R to calculate the required weights of the excipients used. Next, according to the used liquid vehicle concentration, different weights of the liquid drug solution (W) are used. Thus by knowing both Lf and W, the appropriate quantities of carrier (Q) and coating (q) powder materials required to convert a given amount of liquid medication (W) into an acceptably flowing and compressible liquisolid system could be calculated from equations 4.1 and 4.2.
4.1.8. MECHANISMS OF ENHANCEMENT OF DRUG RELEASE:

Several mechanisms of enhanced drug release have been postulated for liquisolid systems. The three main proposed mechanisms include increased surface area of drug available for release, increased aqueous solubility of the drug due to presence of non-volatile vehicle and improved wettability of the drug particles due to cosolvent effect of the vehicle used\textsuperscript{[215, 227, 229]}.

\textbf{a. Increased Effective Surface Area:}

If the drug within the liquisolid system is completely dissolved in the liquid vehicle, it is located in the powder substrate still in a solubilized and molecularly dispersed state. Therefore, the surface area of drug available for release is much greater than that of drug particles within directly compressed tablets\textsuperscript{[214-216, 222, 223]}.

Accordingly, with increasing drug content exceeding the solubility limit and thus, increasing fraction of undissolved drug in the liquid vehicle the release rate decreases. With various drugs it could be shown that the release rates are directly proportional to the fraction of the molecularly dispersed drug ($F_M$) in the liquid formulation\textsuperscript{[214, 216, 222, 225]}. $F_M$ is defined by Spireas as the ratio between the drug's solubility ($S_d$) in the given liquid vehicle and the actual drug concentration ($C_d$) in this vehicle carried by each system\textsuperscript{[222]}.

Therefore,

$$F_M = \frac{S_d}{C_d} \quad (4.4)$$

In addition it is thought that the adsorption and absorption of molecularly dispersed drug onto the surface and interior of the carrier particles impart increased effective surface area available for the mass transfer during the drug dissolution process.
b. Increased Aqueous Solubility:

In addition to the first mechanism of drug release enhancement, it is expected that the solubility of the drug might be increased with liquisolid systems. In fact, the relatively small amount of liquid vehicle in a liquisolid compact is not sufficient to increase the overall solubility of the drug in the aqueous medium. However, in the micro-environment of the solid/liquid interface between an individual primary liquisolid particle and the release medium, it is possible that the amount of liquid vehicle diffusing out of a single liquisolid particle together with the drug molecules might be sufficient to increase the aqueous solubility of the drug if the liquid vehicle can act as a cosolvent\textsuperscript{214-216, 222, 225}. The overall increase in the solubility of drugs caused by liquisolid systems was confirmed in various studies\textsuperscript{217, 230, 231}.

c. Improved Wetting Properties:

Due to the fact that the liquid vehicle can either act as surface active agent or has a low surface tension, wetting of the primary liquisolid particles is improved. Wettability of these systems can be demonstrated by contact angles\textsuperscript{215} and water rising times\textsuperscript{217, 230, 232}. Also the adsorption of the drug on the carrier particles increases the effective surface area, improving the contact of drug and wettability.

4.1.9. OPTIMIZATION OF LIQUISOLID FORMULATION FOR ENHANCED DRUG RELEASE:

The optimization of liquisolid system is mainly oriented towards improvement of dissolution rate and flow properties of the blend. As the release rates are directly proportional to the fraction of molecularly dispersed drug (\(F_M\)) in the liquid formulation a higher drug dose requires higher liquid amounts for desired release profile. Moreover, to obtain liquisolid systems with acceptable flowability and compactability, high levels of carrier and coating materials are needed. However, this
results in an increase in tablet weight, ultimately difficulty in manufacturing processing and swallowing. Therefore, to overcome these and various other problems of the liquisolid technology, several formulation parameters must be optimized. These factors are presented in Table 4.1.

**Table 4.1: Formulation parameters for liquisolid system with rapid drug release**

<table>
<thead>
<tr>
<th>Formulation parameter</th>
<th>Optimization</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquid vehicle</td>
<td>High drug solubility in the vehicle</td>
<td>Increased fraction of the molecularly dispersed drug ($F_M$)</td>
</tr>
<tr>
<td>Carrier and coating Materials</td>
<td>High specific surface area</td>
<td>Increased liquid load factor ($L_f$)</td>
</tr>
<tr>
<td>Addition of excipients</td>
<td>Polyvinyl pyrrolidone (PVP)</td>
<td>Increased liquid load factor ($L_f$)</td>
</tr>
<tr>
<td></td>
<td>Super-disintegrant</td>
<td>Increased viscosity of liquid vehicle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhibition of precipitation</td>
</tr>
<tr>
<td>Excipient ratio (R)</td>
<td>High R-value</td>
<td>Fast disintegration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhibition of precipitation</td>
</tr>
</tbody>
</table>

4.1.10. **ADVANTAGES OF LIQUISOLID TECHNOLOGY:**

i. Large number of water-insoluble solid drugs can be formulated.

ii. It can be applied to formulate liquid medications such as oily or liquid drugs.

iii. The technology involves simple manufacturing processes

iv. Better availability of an orally administered water-insoluble drug

v. Lower production cost than that of soft gelatin capsules

vi. Production set-up is similar to that of conventional tablets

vii. Viability of industrial production

viii. Exhibits enhanced *in vitro* and *in vivo* drug release as compared to commercial counterparts, including soft gelatin capsule preparations

ix. It can be used in controlled drug delivery
4.2. REVIEW OF LITERATURE:

Spireas\textsuperscript{[91, 226]} developed and patented a method of producing a free-flowing and compressible liquid/powder admixture of a liquid medication. The method involves conversion of the liquid medication into a liquisolid system using a carrier material and a coating material to be included in the liquisolid system. The patent describes the process of admixture of the liquid medication with optimum quantity of carrier material to make a wet mixture and blending it with the coating material to produce a non-adherent, free-flowing and compressible liquid/powder admixture. The amounts of liquid medication, carrier material and coating material were calculated by a mathematical model to optimize flow and compressibility according to values predetermined by liquisolid flowability and liquisolid compressibility tests.

Spireas et al.\textsuperscript{[222, 223]} in various studies, prepared directly compressible liquisolid formulations of prednisolone and hydrocortisone by applying the principles of patented procedure. The liquisolid formulation showed increased dissolution rates of these drugs showing the usefulness of the system.

Hosmani et al.\textsuperscript{[92]} reviewed the concepts and formulation parameters affecting the liquisolid technique as a novel formulation technology. The review comprises of the principle behind the liquisolid technology, applications of liquisolid system in the solubility enhancement as well as sustained release formulations. The evaluation parameters of the liquisolid formulation are also covered in the discussion.

Hosmani et al.\textsuperscript{[218]}, in a study, formulated liquisolid compacts of fenofibrate to improve dissolution and investigated \textit{in vitro} performance of prepared liquisolid systems. In this study, propylene glycol was used as a liquid vehicle. The formulations were found to increase the dissolution rate due to increased wetting and available surface area.
Javadzadeh et al.\textsuperscript{[214]} studied the effect of addition of surfactant on the dissolution behavior of piroxicam from liquisolid compacts in simulated gastric fluid and simulated intestinal fluid. Liquisolid tablet formulations containing various ratios of drug to Tween 80 were prepared keeping the ratio of microcrystalline cellulose (carrier) to colloidal silica (coating material) constant. The liquisolid compacts demonstrated significantly higher drug release rates than those of conventionally made capsules and directly compressed tablets containing micronized piroxicam. The addition of surfactant facilitated the drug release from liquisolid formulations.

In another study, Javadzadeh et al.\textsuperscript{[215]} investigated the effect of amount of different co-solvents (non-volatile vehicles) in liquisolid compacts on the dissolution behavior of indomethacin. Liquisolid tablets showed enhanced rate of indomethacin dissolution. It was interpreted that the fraction of molecularly dispersed drug (F\textsubscript{M}) in the liquid medication of liquisolid systems was directly proportional to their indomethacin dissolution rate.

Javadzadeh et al.\textsuperscript{[225]} discussed liquisolid technique as a potential technology also for the retardation of drug dissolution rate. In the study, propranolol hydrochloride was dispersed in polysorbate 80 as the liquid vehicle. The hydrophobic polymers like Eudragit RL and Eudragit RS were used as the carrier and silica as the coating material. The effect of drug concentration, loading factor, thermal treating and aging on the release profile of propranolol hydrochloride from liquisolid compacts were investigated in simulated gastric fluid and simulated intestinal fluid.

Javadzadeh et al.\textsuperscript{[227]} in another study prepared different liquisolid formulations of carbamazepine by dissolving the drug in the hydrophilic liquids and adsorbing the solution onto the surface of silica. In order to reduce the amounts of carrier and coat material in liquisolid formulations, some additives like PVP, HPMC and PEG 35000
were added to liquid medication to increase loading factor. The effects of various ratios of carrier to coating material, PVP concentration, effect of aging and type of the carrier on dissolution rate of liquisolid compacts were studied.

*Javadzadeh et al.* [228] studied dissolution behavior of piroxicam from liquisolid compacts in simulated gastric fluid and simulated intestinal fluid. Several liquisolid tablets formulations were prepared containing various ratios of drug and Tween 80.

*Nokhodchi et al.* [216] studied the effect of type and concentration of vehicles on the dissolution rate of a poorly soluble drug (indomethacin) from liquisolid compacts. The authors attempted to correlate the dissolution rate and fraction of drug in the molecularly dispersed form ($F_M$).

*Nokhodchi et al.* [219], in their expert opinion, expressed the views about the opportunities of liquisolid technique in the solubility enhancement of poorly water-soluble drugs as well as delayed release formulations of highly water-soluble drugs.

*Khaled et al.* [221] carried out a study to evaluate the absorption characteristics of developed hydrochlorothiazide liquisolid tablets using male beagle dogs as experimental animal. Comparison of bioavailability from prepared and optimized liquisolid formulation was done with reference commercial tablets. The pharmacokinetic study in dogs in a randomized two-way crossover design showed the evidence of enhancement of bioavailability of the drug with liquisolid tablets.

*Fahmy et al.* [224] attempted to improve famotidine dissolution through its formulation into liquisolid systems and investigated *in vitro* and *in vivo* performance of drug from the prepared liquisolid tablets. The bioavailability study indicated that bioavailability from the prepared optimal liquisolid formula did not differ significantly from bioavailability from the marketed famotidine tablets.
4.3. OBJECTIVES:

As discussed previously, solubility and dissolution of poorly water-soluble drug is the rate limiting step for the oral absorption. Hence the solubility enhancement strategy is the solution for the enhancement of bioavailability of lipophilic drugs especially from BCS Class II.

Many approaches and technologies of solubility enhancement are discussed in Chapter 1. Each approach is having various merits along with some demerits. Major problems associated with most of the methods of solubility enhancement like solid dispersion or inclusion complex is poor flow rate and less compressibility due to formation highly hygroscopic, sticky and wet dosage form. Salt formation requires extensive salt selection study. This creates a remarkable deficit in the industrial feasibility of those techniques in spite of good ability to improvement in solubility. Other problems include lack of stability of these dosage forms which show recrystallization of amorphous drug leading to altered dissolution rate due to aging process.

On the contrary, liquisolid technology provides a platform for solubility enhancement due to the presence of drug in a molecularly dispersed form in a non-volatile solvent as well as high effective surface area, along with better flowability and compressibility due to use of directly compressible carrier and coat material. As the vehicle used is non-volatile, the drug in solution always remains in molecularly dispersed form. Also due to the adsorption and absorption of dissolved drug in the particles of carrier material prevents the re-aggregation of drug eliminating the possibility of recrystallization of drug and change in the dosage form performance during shelf-life.
Glipizide (GPZ) is a second generation sulfonylurea oral hypoglycemic agent that can acutely lower the blood glucose level by stimulating the insulin release and is typically prescribed to treat diabetes mellitus type II (NIDDM) \[^{233, 234}\]. GPZ is insoluble in water and hence, its dissolution is considered to be the rate determining step in its oral absorption \[^{235}\].

In the current investigation, attempts are made to prepare and optimize liquisolid compacts of glipizide with the intention of enhanced dissolution rate with acceptable flow properties as well as better oral bioavailability. The study was carried out with following objectives:

1. Application of statistical methods of experimental design like factorial design for formulation of liquisolid compacts of glipizide.
2. Precompression study for evaluation of flow characteristics of the prepared liquisolid blend.
3. Evaluation of tablet properties.
4. Comparison of dissolution profiles of different formulations by statistical methods.
5. Selection of optimized batch with good flow and compression characteristics and enhanced dissolution rate.
6. Comparison between \textit{in vivo} performances of drug alone and optimized liquisolid formulation.
4.4. PLAN OF WORK:

1. Review of literature
2. Procurement of materials
3. Experimental
   A. Authentication of drug
      a. Melting point
      b. FTIR-spectra
   B. Compatibility study
   C. Calibration curve of GPZ
   D. Determination of solubility of glipizide in non-volatile solvent
   E. Formulation of liquisolid compact.
   F. Precompression study
      a. Interaction study by FTIR spectroscopy
      b. Thermal study by Differential Scanning Calorimetry (DSC)
      c. Flow properties
   G. Tablet evaluation
      a. Tablet characteristics like appearance, dimension
      b. Tablet hardness and friability
      c. In vitro dissolution study
   H. In vivo pharmacodynamic study on rats
   I. Stability study of optimized formulation
4. Compilation of data
4.5. **DRUG PROFILE:**

**GLIPIZIDE\textsuperscript{[236]}**

Glipizide is an oral hypoglycemic drug from the sulfonylurea class.

**Chemical Name:**

1-cyclohexyl-3-[(p-[2-(5-methylpyrazinecarboxamido) ethyl] phenyl)sulfonyl]urea

**Chemical Structure:**

![Chemical Structure of Glipizide](Fig. 4.3: Chemical Structure of Glipizide)

**Molecular Formula:** \( \text{C}_{21}\text{H}_{27}\text{N}_{5}\text{O}_{4}\text{S} \)

**Molecular Weight:** 445.55

**Melting point:** 208-209°C

**Description:**

It is a white to off white crystalline, odorless powder with a pKa of 5.9.

**Solubility:**

It is insoluble in water and alcohols, but soluble in 0.1 N NaOH. It is freely soluble in dimethyl formamide.

**Pharmacodynamics\textsuperscript{[237]}:**

Glipizide, a second-generation sulfonylurea, is used with food to lower blood glucose in patients with diabetes mellitus type II. The primary mode of action of glipizide in experimental animals appears to be the stimulation of insulin secretion
from the β-cells of pancreatic islet tissue and is thus dependent on functioning of β-cells in the pancreatic islets. In humans, glipizide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning of β-cells in the pancreatic islets. Stimulation of insulin secretion by glipizide in response to a meal is undoubtedly of major importance. Fasting insulin levels are not elevated even on long-term glipizide administration, but the postprandial insulin response continues to be enhanced after at least 6 months of treatment. Some patients fail to respond initially or gradually lose their responsiveness to sulfonyleurea drugs including glipizide.

**Mechanism of Action**\(^{[237]}\):

Sulfonylureas are likely bind to ATP-sensitive potassium-channel receptors on the pancreatic cell surface, reducing K\(^+\) conductance and causing depolarization of the membrane. Depolarization stimulates calcium ion influx through voltage-sensitive calcium channels, raising intracellular concentrations of Ca\(^{++}\) ions, which induces the secretion by exocytosis of insulin.

**Pharmacokinetics**\(^{[238]}\):

Glipizide is completely but variably absorbed following oral administration in an immediate release dosage form. Peak plasma concentration is attained within 1.5-2.0 hr after a single dose administration. The mean apparent volume of distribution was approximately 10 L. Glipizide is about 98-99% bound to serum proteins, primarily to albumin. No accumulation of drug was observed in patients with NIDDM during chronic dosing with glipizide. Glipizide is eliminated primarily by hepatic biotransformation. The major metabolites of glipizide are products of aromatic hydroxylation and have no hypoglycemic activity. A minor metabolite accounting for less than 2% of a dose, an acetylaminoethyl benzene derivative, is reported to have
1/10 to 1/3 as much hypoglycemic effects as the parent compound. Less than 10% of a dose is excreted as unchanged drug in urine and feces. Approximately 90% of a dose is excreted as biotransformation products in urine (80%) and feces (10%). The mean total body clearance of glipizide was approximately 3 L/hr after single intravenous doses in patients with type-II diabetes. The elimination half-life ranges from 2-3 hr.

Indication:

Glipizide is indicated for use as an adjunct to diet for the control of hyperglycemia and its associated symptomatology in patients with non-insulin-dependent diabetes mellitus.

Contraindication:

Glipizide is contraindicated in patients with known hypersensitivity to glipizide, diabetes mellitus Type I, diabetic ketoacidosis, with or without coma.

Drug Interactions:

The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including non-steroidal anti-inflammatory agents and other drugs that are highly protein bound such as salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors and β-adrenergic blocking agents. When such drugs are administered to a patient receiving GPZ, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from the patient receiving GPZ, the patient should be observed closely for loss of control. In vitro binding studies with human serum proteins indicate that glipizide binds differently than tolbutamide and does not interact with salicylates or dicumarol. However, caution must be exercised in extrapolating these findings to the clinical situation and in the use of glipizide with these drugs.
Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs and isoniazid. When such drugs are administered to the patient receiving glipizide, the patient should be closely observed for loss of control. In case of withdrawal of these drugs from the patient receiving glipizide, observation must be done closely for hypoglycemia.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported.

**Adverse Reactions:**

Hypoglycemia, gastro-intestinal disturbances, allergic reactions including erythema, urticaria.
4.6. POLYMER PROFILE:

4.6.1 MICRCRYSTALLINE CELLULOSE\textsuperscript{[239-247]}

1. Nonproprietary Names

BP: Microcrystalline cellulose

JP: Microcrystalline cellulose

Ph Eur: Cellulosum microcristallinum

USPNF: Microcrystalline cellulose

2. Synonyms:

Avicel PH, Celex, Cellulose gel, Celphere, Ceolus KG, crystalline cellulose, E460, Emcocel, Ethispheres, Fibrocel, Pharmacel, Tabulose, Vivapur.

3. Chemical Name: Cellulose

4. Chemical Structure:

\begin{center}
\includegraphics[width=0.8\textwidth]{Fig_4.4.png}
\end{center}

\textbf{Fig. 4.4: Chemical Structure of Microcrystalline Cellulose}

5. Empirical Formula: \( (\text{C}_6\text{H}_{10}\text{O}_5)_n \)

6. Molecular Weight: \( \approx 36000 \) where \( n \approx 220 \).

7. Functional Category:

Adsorbent, suspending agent, diluent in tablet and capsule, tablet disintegrant.
8. **Description:**

   It is purified, partially depolymerized, cellulose that occurs as a white, odorless and tasteless powder.

9. **Solubility:**

   It is slightly soluble in 5% w/v solution of sodium hydroxide solution and practically insoluble in water, dilute acids and most organic solvents.

9. **Pharmaceutical Uses:**

   It is used as binder and diluent in both direct compression and wet granulation methods of tablet manufacturing$^{[239-245]}$. In addition, microcrystalline cellulose has some lubricant and disintegrant properties that makes it useful in tableting$^{[246]}$. Various grades of microcrystalline cellulose can be also used as sustained release as well as mucoadhesive polymer due to its swelling and bioadhesive characteristics$^{[247]}$.

10. **Stability and Storage Conditions:**

    Microcrystalline cellulose is a hygroscopic though stable material. The bulk material should be stored in a well-closed container in a cool and dry place.

11. **Incompatibilities:**

    Microcrystalline cellulose is incompatible with strong oxidizing agents.

12. **Safety:**

    Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a relatively non-toxic and non-irritant material. Microcrystalline cellulose is not absorbed systemically following oral administration and thus has little toxic potential. Consumption of large quantities of cellulose may have a laxative effect, although this is unlikely to be a problem when cellulose is used as an excipient in pharmaceutical formulations and food industry.
4.6.2 COLLOIDAL SILICON DIOXIDE\textsuperscript{[248]}

1. Nonproprietary Names

BP: Colloidal Anhydrous Silica
JP: Light Anhydrous Silicic Acid
Ph Eur: Silica, Colloidal Anhydrous
USPNF: Colloidal Silicon Dioxide

2. Synonyms:

Aerosil, Cab-O-Sil, colloidal silica, fumed silica, fumed silicon dioxide, hochdisperses silicum dioxid, silica colloidalis anhydrica, silica sol, silicic anhydride, silicon dioxide colloidal, silicon dioxide fumed, synthetic amorphous silica.

3. Chemical Name: Silica

4. Empirical Formula: SiO\textsubscript{2}

5. Molecular Weight: 60.08

6. Description:

Colloidal silicon dioxide is submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white, odorless, tasteless and amorphous powder.

7. Typical Properties:

\textbf{pH}: 3.8-4.2 (4\% w/v aqueous dispersion) and 3.5-4.0 (10\% w/v aqueous dispersion) for Cab-O-Sil M-5P

\textbf{Bulk Density}: 0.029-0.042 g/cm\textsuperscript{3}

\textbf{Melting Point}: 1600°C

\textbf{Particle Size Distribution}: Primary particle size is 7-16 nm. Aerosil forms loose agglomerates of 10-200 µm.

\textbf{Refractive Index}: 1.46
**Solubility:**

It is practically insoluble in organic solvents, water and acids, except hydrofluoric acid. It is soluble in hot solutions of alkali hydroxide. It Forms a colloidal dispersion with water. For Aerosil, solubility in water is 150 mg/L at 25°C (pH 7).

**8. Functional Category:**

Adsorbent, anti-caking agent, emulsion stabilizer, glidant, suspending agent, tablet disintegrant, thermal stabilizer, viscosity increasing agent

**9. Applications in Pharmaceutical Formulation:**

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics and food products. Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders\(^{249}\) in a number of processes such as tableting\(^{250-252}\) and capsule filling.

It is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations\(^{253}\). With other ingredients of similar refractive index, transparent gels may be formed. The degree of increase in viscosity depends on the polarity of the liquid. Polar liquids generally require a greater concentration of colloidal silicon dioxide than non-polar liquids. Viscosity is largely independent of temperature.

However, changes to the pH of a system may affect the viscosity. When used in aqueous systems at a pH 0-7.5, it is effective in increasing the viscosity of a system. While, at a pH greater than 7.5, the viscosity increasing properties of colloidal silicon dioxide are reduced and at a pH greater than 10.7, this ability is lost entirely since the silicon dioxide dissolves to form silicates.

In aerosols, other than those for inhalation, colloidal silicon dioxide is used to promote particulate suspension, eliminate hard settling and minimize the clogging of
spray nozzles. Colloidal silicon dioxide is also used as a tablet disintegrant and as an adsorbent dispersing agent for liquids in powders\textsuperscript{254}. It is frequently added to suppository formulations containing lipophilic excipients to increase viscosity, prevent sedimentation during molding and decrease the release rate\textsuperscript{255, 256}.

It is also used as adsorbent during the preparation of wax microspheres\textsuperscript{257} as a thickening agent for topical preparations\textsuperscript{258} and has been used to aid the freeze-drying of nanocapsule and nanosphere suspensions\textsuperscript{259}.

10. Stability and Storage Conditions:

Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. Colloidal silicon dioxide powder should be stored in a well-closed container.

11. Incompatibilities:

It is incompatible with diethyl stilbestrol preparations.

12. Safety:

Aerosil is widely used in oral and topical pharmaceutical products and is generally regarded as an essentially non-toxic and non-irritant excipient. However, intra-peritoneal and subcutaneous injection may produce local tissue reactions and/or granulomas. Colloidal silicon dioxide therefore, should not be administered parenterally.
4.7 EXPERIMENTAL:

4.7.1 Materials

Glipizide was kindly gifted by Ajanta Pharma, Mumbai. Avicel PH 102, Avicel PH 200 and Aerosil 200 were kindly gifted by Okasa Pharmaceuticals (India) and Sodium starch glycolate was gifted by Shital Chemicals (India). Polyethylene glycol 200 was purchased from Loba Chemie (India). All other reagents and chemicals were of analytical grade.

4.7.2 Drug Authentication:

4.7.2.1 Melting Point Determination:

Melting points of GPZ was checked for drug authentication by conventional capillary method and reported uncorrected.

4.7.2.2 FTIR Spectra:

FTIR absorption spectrum of drug was recorded using a spectrometer (Nexus 670, Nicolet Instrument Co.) equipped with a DTGS detector. KBr disks were prepared (2 mg sample in 200 mg KCl) and scanned over a range of 400-4000 cm\(^{-1}\) with a resolution of 4 cm\(^{-1}\).

4.7.3 Determination of Solubility:

Solubility of GPZ in distilled water and PEG 200 was determined by Higuchi-Connor’s method\(^{[154]}\). Excess quantity of GPZ was added to 10 ml of solvents under study in screw capped vials and shaken on rotary shaker for 48 hr at 25°C. After equilibration for 24 hr, the solutions were filtered through a 0.45 µm filter and analyzed by UV-spectrophotometry (Systronics Double Beam Spectrophotometer-2201) at 276 nm. For solubility determination in PEG 200, the solution containing same concentration of PEG without drug was taken as blank sample. The readings were taken in triplicates.
4.7.4 Mathematical Model for Design of Liquisolid Formulation:

The formulation design of liquisolid systems was done according to mathematical model described by Spireas et al.\textsuperscript{[91].}

In the present work, Polyethylene Glycol 200 was used as non-volatile liquid vehicle. Avicel PH102 and Avicel PH200 (Microcrystalline cellulose) were incorporated individually as carrier materials. Aerosil 200 (Colloidal silica) was selected as the coating material.

To attain optimal GPZ solubility in liquisolid formulations, concentration of drug in liquid vehicle PEG 200 (%D) was taken as 10, 15 and 20 g%. Depending on the literature review, the carrier: coat ratio (R) was varied from 10, 15 and 20. According to theories, the carrier and coating powder materials can retain only certain amount of liquid while maintaining acceptable flowability and compressibility. Hence carrier material as well as liquid content must be optimum to elicit good drug solubility without affecting flowability and compressibility as well as to avoid ‘liquid squeeze out’ phenomenon.

The compositions of various batches for the understanding of individual and combined effect of each variable on the performance of final dosage form were decided by applying $3^2$-full factorial design (Table 4.2 and 4.3). Drug percentage in the liquid medication and carrier to coat ratio were taken as independent variables. Detailed compositions of batches prepared with two grades of microcrystalline cellulose \textit{viz.} Avicel PH102 and Avicel PH200 as carrier are depicted in Table 4.4.

After R is taken as variable in the factorial design, to calculate the quantities of each excipient, the mathematical model developed by Spireas was used. Mathematical model equation for Avicel PH102 and Aerosil 200 in PEG 200 can be given according to $\Phi$ -values given by Spireas et al.\textsuperscript{[91,226]}
\[ Lf = 0.005 + 3.26 \left( \frac{1}{R} \right) \]  

Likewise, the equation for Avicel PH 200 and Aerosil 200 in PEG 200 is:

\[ Lf = 0.02 + 2.44 \left( \frac{1}{R} \right) \]

Based on this equation, \( Lf \) is calculated by using different \( R \) values.

**Table 4.2- Factorial Design for Preparation of Liquisolid Batches**

<table>
<thead>
<tr>
<th>Batch Code</th>
<th>Variable levels in Coded form</th>
<th>( X_1 )</th>
<th>( X_2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-1</td>
<td>-1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>-1</td>
<td>+1</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>-1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>+1</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>+1</td>
<td>-1</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>+1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>+1</td>
<td>+1</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4.3- Translation of Coded Values in Factorial Design**

<table>
<thead>
<tr>
<th>Variable levels</th>
<th>Low (-1)</th>
<th>Medium (0)</th>
<th>High (+1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( X_1 )= Carrier: Coat ratio (R)</td>
<td>10</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>( X_2 )= % Drug in liquid medication</td>
<td>10</td>
<td>15</td>
<td>20</td>
</tr>
</tbody>
</table>
### Table 4.4: Composition of Liquisolid System

<table>
<thead>
<tr>
<th>Carrier</th>
<th>Batch Code</th>
<th>R (X₁)</th>
<th>%D (w/v) (X₂)</th>
<th>Lf</th>
<th>Avicel (mg) (Q = W/Lf)</th>
<th>Aerosil 200 (mg) (Q = Q/R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avicel PH 102</td>
<td>A 1</td>
<td>10</td>
<td>10</td>
<td>0.331</td>
<td>325.4</td>
<td>32.5</td>
</tr>
<tr>
<td></td>
<td>A 2</td>
<td>15</td>
<td>15</td>
<td>0.331</td>
<td>216.9</td>
<td>21.7</td>
</tr>
<tr>
<td></td>
<td>A 3</td>
<td>20</td>
<td>20</td>
<td>0.331</td>
<td>162.7</td>
<td>16.3</td>
</tr>
<tr>
<td></td>
<td>A 4</td>
<td>15</td>
<td>10</td>
<td>0.222</td>
<td>449.8</td>
<td>30.0</td>
</tr>
<tr>
<td></td>
<td>A 5</td>
<td>15</td>
<td>15</td>
<td>0.222</td>
<td>299.9</td>
<td>20.0</td>
</tr>
<tr>
<td></td>
<td>A 6</td>
<td>20</td>
<td>20</td>
<td>0.222</td>
<td>224.9</td>
<td>15.0</td>
</tr>
<tr>
<td></td>
<td>A 7</td>
<td>20</td>
<td>10</td>
<td>0.168</td>
<td>595.2</td>
<td>29.8</td>
</tr>
<tr>
<td></td>
<td>A 8</td>
<td>15</td>
<td>10</td>
<td>0.168</td>
<td>396.8</td>
<td>19.8</td>
</tr>
<tr>
<td></td>
<td>A 9</td>
<td>15</td>
<td>20</td>
<td>0.168</td>
<td>297.6</td>
<td>14.9</td>
</tr>
<tr>
<td>Avicel PH 200</td>
<td>B 1</td>
<td>10</td>
<td>10</td>
<td>0.331</td>
<td>387.8</td>
<td>37.9</td>
</tr>
<tr>
<td></td>
<td>B 2</td>
<td>15</td>
<td>15</td>
<td>0.331</td>
<td>272.5</td>
<td>25.3</td>
</tr>
<tr>
<td></td>
<td>B 3</td>
<td>20</td>
<td>20</td>
<td>0.331</td>
<td>189.4</td>
<td>18.9</td>
</tr>
<tr>
<td></td>
<td>B 4</td>
<td>15</td>
<td>10</td>
<td>0.222</td>
<td>547.4</td>
<td>36.5</td>
</tr>
<tr>
<td></td>
<td>B 5</td>
<td>15</td>
<td>15</td>
<td>0.222</td>
<td>365.0</td>
<td>24.3</td>
</tr>
<tr>
<td></td>
<td>B 6</td>
<td>20</td>
<td>20</td>
<td>0.222</td>
<td>273.7</td>
<td>18.2</td>
</tr>
<tr>
<td></td>
<td>B 7</td>
<td>20</td>
<td>10</td>
<td>0.168</td>
<td>704.2</td>
<td>35.2</td>
</tr>
<tr>
<td></td>
<td>B 8</td>
<td>15</td>
<td>15</td>
<td>0.168</td>
<td>469.5</td>
<td>23.5</td>
</tr>
<tr>
<td></td>
<td>B 9</td>
<td>15</td>
<td>20</td>
<td>0.168</td>
<td>352.1</td>
<td>17.6</td>
</tr>
</tbody>
</table>

### 4.7.5 Preparation of Liquisolid Tablets:

Preparation of liquisolid formulation was done in a step wise manner as per the method described and patented by Spireas et al.[^91]. The steps involved preparation of liquid medication, incorporation of liquid on solid phase for subsequent adsorption of drug on carrier and addition of excipients for better pharmaceutical performance.

Calculated quantities of GPZ and non-volatile solvent Polyethylene Glycol 200 (PEG 200) were accurately weighed in 20 ml glass beaker and then heated to at a
controlled temperature at 80°C to produce a homogenous solution of desired %D. The hot medication was incorporated into a calculated quantity of carrier and coating material. Mixing process was carried out in three steps as described by Spireas et al. [91].

In the first stage, system was blended at an approximate mixing rate of one rotation per second for approximately one minute in order to evenly distribute liquid medication in powder.

In second stage, the liquid and powder admixture was evenly spread as uniform layer on the surfaces of mortar and left standing for about 5 min to allow sorption of drug solution in the interior of powder particles.

Lastly, powder was scraped off the surfaces with aluminum spatula and blended uniformly with 5% sodium starch glycolate used as super-disintegrant, for another 30 seconds. After precompression study, formulations were compressed by multi-station punch press (Mini press-II-DLM- Mfg. Karnavati Engineering, India).

4.7.6 Precompression Study:

The prerequisites for tableting of a powdered blend include good flow characteristics and compression behavior. Hence it is important for optimization to compare flowability and compressibility of the prepared blends.

The precompression study of liquisolid mixture was done by several micromeritic techniques as per Indian Pharmacopoeia 2007. Angle of repose, pour (bulk) density, tapped density, Carr’s index and Hausner’s ratio were employed to study the flow properties as well as compressibility of liquisolid formulations [260].
4.7.7 Thermal Analysis:

DSC can be used to study the thermal behavior and chemical compatibility between drug and excipients. It is also helpful to predict the crystallinity of solids.

DSC was performed using ‘Mettler Toledo DSC Star-E System’ to assess thermal behaviors of GPZ, Aerosil 200, Avicel PH102, Avicel PH200, GPZ: Aerosil 200 (1:1) mixture, GPZ: Avicel PH102 (1:1) mixture, GPZ: Avicel PH102: Aerosil 200 (1:1:1) mixture and liquisolid systems. Samples (2-3 mg) were placed in aluminum pans and lids at constant heating range of 10°C/min in an atmosphere of nitrogen gas flow at a rate of 40 ml/min using the range of 40-200°C.

4.7.8 Fourier Transform Infra-Red Spectroscopy:

FTIR absorption spectra of GPZ, Avicel, Aerosil, physical mixtures and the formulations were recorded for determination of compatibility between the drug and excipients using a spectrometer (Nexus 670, Nicolet Instrument Co.) equipped with a DTGS detector. KBr disks were prepared (2 mg sample in 200 mg KCl) and scanned over a range of 400- 4000 cm\(^{-1}\) with a resolution of 4 cm\(^{-1}\).

4.7.9 EVALUATION OF LIQUISOLID TABLETS\[260, 261]\:

4.7.9.1 Assay:

20 tablets were weighed and powdered in a glass mortar and pestle. An accurately weighed quantity of powder containing 15 mg of GPZ was dissolved in 30 ml of methanol with gentle heating on a water bath. The solution was cooled and methanol was added to it to make up to 50 ml. Absorbance of resulting solution was measured at 274 nm. The content was calculated taking 237 as the specific absorbance\[262]\.

4.7.9.2 Hardness:

The hardness of liquisolid tablets was determined by using Erweka tester in terms of Newton. Mean hardness was determined with a set of three readings.
4.7.9.3 Friability:

The friability of prepared liquisolid tablets was determined using Roche’s tablet friability tester.

4.7.9.4 Disintegration Time:

The disintegration time was measured using USP disintegration tester (Electrolab). Each evaluation was done in triplicate.

4.7.9.5 In vitro Dissolution Study:

The in vitro dissolution study of liquisolid formulations was performed using USP-XXIV Type-II paddle Apparatus-II (Electrolab TDT-06P, India). 900 ml saline phosphate buffer pH 7.4 maintained at 37±0.5°C was used as dissolution medium stirred at 50 rpm. 5 ml aliquots were periodically collected maintaining sink condition\(^{[263]}\). After filtration through 0.45 µm membrane filter, GPZ was estimated spectrophotometrically at 276 nm.

Dissolution profiles of liquisolid tablets and marketed formulation were statistically compared. The comparison between dissolution of formulations was made by model independent approach, model dependent approach and use of ANOVA\(^{[156]}\).

Model Independent Approach:

According to USFDA guidance for dissolution data equivalence, model independent approach is recommended. This involves use of similarity factor \(f_2\) which provides simple means to compare the data. ‘\(f_2\)’ is a logarithmic reciprocal square root transformation of the sum of squared error and is a measure of the similarity in the dissolution between two curves.

\[
f_2 = \log\left\{1 + (1/n) \sum_{t=1}^{n} |R_t - T_t|^2\right\}^{-0.5} \times 100
\]

(4.7)

where, \(n\) is the number of time points, \(R\) is the dissolution value of the reference at time \(t\) and \(T\) is the dissolution value of the test at time \(t\).
**Model Dependent Methods:**

The drug release from liquisolid compacts was analyzed by various mathematical models such as zero order, first order, Hixson-Crowell, Peppas and Matrix models\(^{[156]}\).

**Statistical Methods:**

Repeated measures two way ANOVA was used to determine effect of factors on dissolution. The drug dissolved was dependent variable and time was a repeated factor. The results showing \(p<0.05\) were considered as significant.

**4.7.9.6 In vivo Pharmacodynamic Study\(^{[43, 157]}\):**

Male Wistar rats weighing 150-200 g were obtained from National Toxicological Center Pune, India. They were housed in polypropylene cages with husk bedding, renewed every 48 hr under 12:12 hr light- dark cycle at around 25°C±2°C. They were fed with commercial pellet rat chow and given water *ad libitum*. The experiment was carried out according to the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), New Delhi, India and the Institutional Animal Ethical Committee (IAEC) approved protocol of this study (IAEC/2010-11/2A) at MVP College of Pharmacy, Nasik, Maharashtra.

**Induction of Diabetes in Rats by Alloxan:**

Chemically induced (alloxan) diabetes in animals was given by Frerichs and Creutzfeldt\(^{[158]}\). The compound turned out to be specifically cytotoxic to pancreatic β-cells. Triphasic time course is observed: an initial rise of glucose which is followed by a decrease, probably due to depletion of islets from insulin, again followed by a sustained increase of blood glucose. The alloxan-induced rat model represents an
acquired form of hyper-insulinemia, insulin resistance, hyper-triglyceridemia and consequently dementia.

**Dosing & Measurement of Blood Glucose Levels:**

Six groups of Wistar rats were allowed free access to standard laboratory diet and drinking fluid. Each group consisted of five wistar rats of either sex. Group I was assigned as ‘Control group’ while, animals from group II, III and IV were fasted overnight and were injected with freshly prepared alloxan solution intravenously at a dose of 75 mg/kg body weight to induce diabetes. Group II was kept as diabetic animals without treatment. Administration of drug and formulation was done in form of suspension. Group V and VI were assigned as normal rats treated with GPZ and formulation respectively. Groups III and V were given pure glipizide at a dose of 0.8 mg/kg and group IV and VI were given gliclazide formulation (Batch A 7) at a dose of 60.9 mg/kg (Table 4.5).

Blood samples were collected through retro-orbital plexus under ether anesthesia for determination of plasma glucose level on 0, 7, 14, 21 and 28th days for diabetic rats, while at 0, 1, 2, 4, 6 and 24 hr for normal rats. The blood glucose levels were determined using the glucose measuring biochemical kit (Span Diagnostics Ltd., Surat, Gujarat). The instrument was self-calibrated, and the samples were allowed to dry before the results were read to avoid contaminating the lens.

Statistical significance was tested by applying two-way ANOVA. The results showing $p<0.05$ were considered as significant.
Table 4.5: *In vivo* pharmacodynamic study of Glipizide Liquisolid Formulation

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Control Group-Normal</td>
<td>0.5ml/100 g, p.o.</td>
</tr>
<tr>
<td>II</td>
<td>Control Group-Untreated Diabetic</td>
<td>Alloxan: 75 mg/kg, i.v.</td>
</tr>
<tr>
<td>III</td>
<td>Diabetic rats treated with GLZ</td>
<td>8.3 mg/kg p.o. administered for 21days</td>
</tr>
<tr>
<td>IV</td>
<td>Diabetic rats treated with GLZ Formulation</td>
<td>24.9 mg/kg p.o. administered for 21days</td>
</tr>
<tr>
<td>V</td>
<td>Diabetic rats treated with GLZ</td>
<td>8.3 mg/kg p.o. administered</td>
</tr>
<tr>
<td>VI</td>
<td>Diabetic rats treated with GLZ Formulation</td>
<td>24.9 mg/kg p.o.</td>
</tr>
</tbody>
</table>

4.7.9.7 **Stability Study:**

Stability study was conducted as per ICH guidelines[159]. The stability of optimized formulation (A7) was monitored up to 3 month at accelerated stability conditions of temperature and relative humidity (30°C±2°C, RH 65%±5% and 40°C±2°C, RH 75%±5%). Samples were withdrawn after each month and characterized for assay, tablet characteristics and dissolution profile.
4.8 RESULTS & DISCUSSION:

4.8.1 Drug Authentication:

4.8.1.1 Melting Point:

Melting point of glipizide was found to be 209-211°C. The result was in good agreement with the literature[206].

4.8.1.2 FTIR Spectra:

FTIR spectra for GPZ, polymers, physical mixtures and liquisolid formulation are shown in Fig. 4.5. As can be seen, GPZ showed an intense peak at 3250.16 cm⁻¹, corresponding to N-H stretch, 1687.77 cm⁻¹ attributed to carbonyl functionality. Sulphonyl group in pure GPZ can be characterized by strong symmetric stretching peak at 1159.26 cm⁻¹ and anti-symmetric vibration peak at 1332.86 cm⁻¹. The presence of normal characteristic peaks of GPZ in the FTIR spectra authenticates the drug used as a pure substance.

4.8.2 Solubility Study:

Solubility of glipizide in distilled water was found to be 37.2±0.46 µg/ml, which shows that the drug is poorly water-soluble. Determination of drug solubility in non-volatile vehicle is done to ensure formation of molecular dispersion of the drug. The solubility of GPZ in PEG 200 was found to be 34.254±0.34 mg/ml. Thus good solubility of GPZ in PEG 200 indicates that PEG 200 can be used as vehicle for preparation of liquid medication.

4.8.3 Precompression Study:

Flow properties are the important parameters in the formulation and industrial application of tablet dosage form. Results of angle of repose, Carr’s index and Hausner’s ratio are depicted in the Table 4.6. In general, values of angle of repose more than 40° indicate powders with poor flowability; while angle of repose less than
20° is considered to be excellent\textsuperscript{[213]}. Thus the liquisolid formulations exhibit a good to excellent flow. Also Carr’s index and Hausner’s ratio indicate good flowability and compressibility.

Table 4.6: Precompression Study of Liquisolid Formulations

<table>
<thead>
<tr>
<th>Batch Code</th>
<th>Angle of repose</th>
<th>Carr’s Index</th>
<th>Hausner’s Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 1</td>
<td>27.69 ± 1.78</td>
<td>27.69 ± 1.78</td>
<td>18.40 ± 1.67</td>
</tr>
<tr>
<td>A 2</td>
<td>28.96 ± 2.41</td>
<td>28.96 ± 2.41</td>
<td>16.42 ± 5.14</td>
</tr>
<tr>
<td>A 3</td>
<td>31.84 ± 0.81</td>
<td>31.84 ± 0.81</td>
<td>15.64 ± 4.50</td>
</tr>
<tr>
<td>A 4</td>
<td>32.28 ± 2.33</td>
<td>32.28 ± 2.33</td>
<td>14.89 ± 2.52</td>
</tr>
<tr>
<td>A 5</td>
<td>34.63 ± 2.12</td>
<td>34.63 ± 2.12</td>
<td>18.80 ± 3.93</td>
</tr>
<tr>
<td>A 6</td>
<td>29.93 ± 1.27</td>
<td>29.93 ± 1.27</td>
<td>18.84 ± 2.26</td>
</tr>
<tr>
<td>A 7</td>
<td>25.81 ± 1.67</td>
<td>25.81 ± 1.67</td>
<td>16.44 ±0.38</td>
</tr>
<tr>
<td>A 8</td>
<td>26.71 ± 2.44</td>
<td>26.71 ± 2.44</td>
<td>19.05 ± 5.46</td>
</tr>
<tr>
<td>A 9</td>
<td>36.68 ± 2.45</td>
<td>36.68 ± 2.45</td>
<td>19.99 ± 1.97</td>
</tr>
<tr>
<td>B 1</td>
<td>34.39 ± 1.53</td>
<td>34.39 ± 1.53</td>
<td>20.04 ± 4.54</td>
</tr>
<tr>
<td>B 2</td>
<td>36.17 ± 1.71</td>
<td>36.17 ± 1.71</td>
<td>18.84 ± 2.26</td>
</tr>
<tr>
<td>B 3</td>
<td>35.89 ± 4.28</td>
<td>35.89 ± 4.28</td>
<td>19.18 ± 0.92</td>
</tr>
<tr>
<td>B 4</td>
<td>29.88 ± 0.23</td>
<td>29.88 ± 0.23</td>
<td>16.39 ± 3.76</td>
</tr>
<tr>
<td>B 5</td>
<td>32.94 ± 2.51</td>
<td>32.94 ± 2.51</td>
<td>17.56 ± 2.14</td>
</tr>
<tr>
<td>B 6</td>
<td>22.81 ± 2.2</td>
<td>22.81 ± 2.2</td>
<td>16.46 ± 1.91</td>
</tr>
<tr>
<td>B 7</td>
<td>32.89 ± 1.41</td>
<td>32.89 ± 1.41</td>
<td>19.23 ± 3.85</td>
</tr>
<tr>
<td>B 8</td>
<td>40.80 ± 0.67</td>
<td>40.80 ± 0.67</td>
<td>18.89 ± 1.92</td>
</tr>
<tr>
<td>B 9</td>
<td>25.16 ± 1.38</td>
<td>25.16 ± 1.38</td>
<td>15.00 ± 4.33</td>
</tr>
</tbody>
</table>
4.8.4 FTIR Spectroscopy:

From the spectra of physical mixtures and liquisolid preparation, it can be clearly seen that all the characteristic bands of GPZ remain unaffected in physical mixtures as well as formulations. Thus findings of FTIR spectra suggested absence of chemical interaction between GPZ and polymers and the prepared formulations were chemically stable. The reduced intensities of peaks of GPZ in all the samples can be attributed to lower concentration of drug in the polymeric phase.

Fig 4.5: FTIR study of liquisolid formulation
4.8.5. Thermal Analysis:

Differential Scanning Calorimetry (DSC) study was carried out to determine interaction between drug and excipients and stability of dosage form\[^{49}\]. Thermograms of drug, excipients, physical mixtures and liquisolid systems are represented in Figure 4.6 and 4.7.

A sharp melting endotherm of GPZ is noticed at 208°C indicating GPZ is pure as well as highly crystalline. Thermogram of Avicel PH 102 indicates presence of a broad endothermic peak at 90°C. Similarly, Avicel PH 200 demonstrates a broadened endotherm at 62°C. In the thermogram of Aerosil 200, no peak can be observed.

All the physical mixtures showed characteristic endotherm of GPZ indicative of drug-excipients compatibility. The major finding of the thermal study is that the endotherm corresponding to melting of GPZ was not observed in thermograms of liquisolid systems. The absence of endotherm ensures drug solubilization in vehicle and molecular dispersion of drug in liquisolid system. This phenomenon is one of the proposed mechanisms responsible for increased dissolution rates of liquisolid systems.
Fig. 4.6: DSC study of Avicel PH 102 Formulation

Fig. 4.7: DSC study of Avicel PH 200 Formulation
4.8.6 EVALUATION OF LIQUISOLID TABLETS:

4.8.6.1 Assay:

As represented in Table 4.7, the drug content in the liquisolid formulations was found to be in a range of 98.56±1.92 to 103.46±1.92%, thus prepared tablets comply with the pharmacopoeial limits for the drug content[263].

4.8.6.2 Hardness:

Tablet hardness is one of the important dosage form related factors that affects quality and performance of the dosage form. In general less hardness leads to fragile and brittle tablets resulting in poor friability and hence considered non-acceptable. On the other hand, harder tablets show slow down of the disintegration process and ultimately dissolution. Hence, hardness must be critically monitored in the tablet manufacturing.

Considering this, the hardness of liquisolid tablets was critically controlled during the compression step of each batch and was found in the range from 25.33±2.08 to 38.67±0.58 N (Table 4.7). Good compactness of tablet may be due to hydrogen bonding between Avicel molecules. As PEG 200 is an alcoholic compound, it may show hydrogen bonding due to presence of hydroxyl groups and contributes to compressibility.

4.8.6.3 Friability:

Friabilities are in the range of 0.049% to 0.428% which ensures acceptable resistance by tablets to withstand mechanical shocks.

4.8.6.4 Disintegration Time:

Disintegration time was ranging between 2 min to 7 min. Addition of sodium starch glycolate in the formulation gives faster disintegration which helps rapid release.
Table 4.7: Tablet characteristics of liquisolid system

<table>
<thead>
<tr>
<th>Batch Code</th>
<th>Tablet Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hardness</td>
</tr>
<tr>
<td>A 1</td>
<td>29.67±1.53</td>
</tr>
<tr>
<td>A 2</td>
<td>31.67±2.08</td>
</tr>
<tr>
<td>A 3</td>
<td>29.33±3.21</td>
</tr>
<tr>
<td>A 4</td>
<td>33.33±3.06</td>
</tr>
<tr>
<td>A 5</td>
<td>30.67±2.08</td>
</tr>
<tr>
<td>A 6</td>
<td>33.33±4.51</td>
</tr>
<tr>
<td>A 7</td>
<td>25.67±2.52</td>
</tr>
<tr>
<td>A 8</td>
<td>26.67±2.52</td>
</tr>
<tr>
<td>A 9</td>
<td>31.67±2.08</td>
</tr>
<tr>
<td>B 1</td>
<td>25.67±3.06</td>
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<tr>
<td>B 2</td>
<td>30.33±3.79</td>
</tr>
<tr>
<td>B 3</td>
<td>29.67±1.15</td>
</tr>
<tr>
<td>B 4</td>
<td>38.67±0.58</td>
</tr>
<tr>
<td>B 5</td>
<td>33.33±1.15</td>
</tr>
<tr>
<td>B 6</td>
<td>25.33±2.08</td>
</tr>
<tr>
<td>B 7</td>
<td>26.33±2.52</td>
</tr>
<tr>
<td>B 8</td>
<td>32.33±2.08</td>
</tr>
<tr>
<td>B 9</td>
<td>30.33±1.53</td>
</tr>
</tbody>
</table>

4.8.6.5  *In vitro* Dissolution Study:

Dissolution rates of liquisolid formulations were compared with GPZ alone and marketed formulations (Fig 4.8 to Fig. 4.22). The effect of two independent factors viz. carrier: coat concentration and percentage of drug in liquid medication is studied by contour plot of drug release at 10 min against two factors under consideration (Fig. 4.8).
From the dissolution profile of glipizide, it can be seen that only 39.85±2.2 % drug is dissolved after 60 min. The percent dissolution efficiency at 60 min of GPZ was found to be 19.91. Thus the dissolution was poor as well as incomplete suggesting the need of solubility enhancement.

Table 4.8 depicts the dissolution parameters of the liquisolid systems compared to the drug alone. All the liquisolid batches were found to increase the drug dissolution rate compared to glipizide alone as well as marketed formulation. It can be seen that the initial drug release within first 15 min. from all liquisolid formulation was remarkably increased compared to the drug alone. The fastest drug release was obtained from the batch A7, where complete drug was dissolved within 50 min. The mean dissolution time and percent dissolution efficiency of batch A7 at 50 min were 16.75 and 66.87 respectively. In comparison to the dissolution parameters of drug alone, this result shows a significant dissolution enhancement.

The initial rapid drug release from liquisolid formulation may be due to the use of super-disintegrant which causes a faster de-aggregation process leaving the liquisolid particles in the aqueous environment. This step may be followed by the rapid mass transfer from the carrier particles to the bulk of the solvent. During this step, the liquisolid technique brings about a faster dissolution by different proposed mechanisms of solubility enhancement which include phenomenon of drug being in the dissolved or molecularly dispersed state as well as absorption and adsorption of liquid medication in the internal structures of hydrophilic carrier material providing a greater effective surface area required for the mass transfer of drug molecules from adsorbed and absorbed liquid medication phase to the bulk of dissolution medium. The second mechanism is the co-solvency between the non-volatile hydrophilic solvent and water.
To determine the effect of independent variables on the dissolution, $3^2$-factorial design was applied. From the factorial equation (Equation 4.8), it can be concluded that the enhancement of drug release is dependent on both the factors under consideration. The carrier:coat concentration is positively influencing the solubilization as it provides a surface area for dissolution. It can be observed that more is the carrier:coat ration, better is the solubilization. The reasons behind the effect may be the availability of greater effective surface area due to more concentration of carrier. Less coat concentration imparts less hydrophobic characters to dosage form.

Drug concentration in the liquid medication shows negative effect on the dissolution property. This may be because of availability of more amount of solvent for better solubilization of drug.

$$Y = 38.4361 + 8.1105X_1 - 8.0228X_2 - 5.3322X_1X_2 - 0.8302X_1^2 - 3.4301X_2^2 \quad (4.8)$$

Fig. 4.8: Contour Plot of Release at 10 min from A1-A9 LS Batches
Fig. 4.9: Dissolution Profiles of Liquisolid Tablets: Avicel PH 102 Batches

Fig. 4.10: Dissolution Study of Liquisolid Tablets: Avicel PH 200 Batches
Table 4.8: Mean Dissolution Time & Dissolution Efficiency at 15 min and 30 min

<table>
<thead>
<tr>
<th>Batch</th>
<th>% DE</th>
<th>MDT</th>
<th>15 min</th>
<th>30 min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 min</td>
<td>30 min</td>
<td>15 min</td>
<td>30 min</td>
</tr>
<tr>
<td>GPZ</td>
<td>2.34</td>
<td>8.67</td>
<td>10.74</td>
<td>17.43</td>
</tr>
<tr>
<td>A 1</td>
<td>25.00</td>
<td>47.91</td>
<td>6.73</td>
<td>12.22</td>
</tr>
<tr>
<td>A 2</td>
<td>16.57</td>
<td>31.74</td>
<td>6.51</td>
<td>14.39</td>
</tr>
<tr>
<td>A 3</td>
<td>15.47</td>
<td>29.88</td>
<td>7.64</td>
<td>13.35</td>
</tr>
<tr>
<td>A 4</td>
<td>40.60</td>
<td>63.02</td>
<td>5.91</td>
<td>9.98</td>
</tr>
<tr>
<td>A 5</td>
<td>37.21</td>
<td>58.31</td>
<td>5.78</td>
<td>11.03</td>
</tr>
<tr>
<td>A 6</td>
<td>24.99</td>
<td>42.83</td>
<td>7.20</td>
<td>11.51</td>
</tr>
<tr>
<td>A 7</td>
<td>30.25</td>
<td>50.42</td>
<td>5.86</td>
<td>11.68</td>
</tr>
<tr>
<td>A 8</td>
<td>34.48</td>
<td>50.42</td>
<td>4.41</td>
<td>10.66</td>
</tr>
<tr>
<td>A 9</td>
<td>33.02</td>
<td>52.47</td>
<td>5.30</td>
<td>11.56</td>
</tr>
<tr>
<td>B 1</td>
<td>19.96</td>
<td>35.05</td>
<td>6.65</td>
<td>12.12</td>
</tr>
<tr>
<td>B 2</td>
<td>14.28</td>
<td>21.27</td>
<td>5.98</td>
<td>10.76</td>
</tr>
<tr>
<td>B 3</td>
<td>9.63</td>
<td>16.89</td>
<td>5.20</td>
<td>15.58</td>
</tr>
<tr>
<td>B 4</td>
<td>17.79</td>
<td>25.61</td>
<td>1.26</td>
<td>15.20</td>
</tr>
<tr>
<td>B 5</td>
<td>18.95</td>
<td>29.28</td>
<td>4.83</td>
<td>10.56</td>
</tr>
<tr>
<td>B 6</td>
<td>12.25</td>
<td>26.18</td>
<td>6.25</td>
<td>16.48</td>
</tr>
<tr>
<td>B 7</td>
<td>16.46</td>
<td>26.42</td>
<td>3.20</td>
<td>15.17</td>
</tr>
<tr>
<td>B 8</td>
<td>11.84</td>
<td>18.47</td>
<td>3.99</td>
<td>14.33</td>
</tr>
<tr>
<td>B 9</td>
<td>19.63</td>
<td>31.66</td>
<td>4.74</td>
<td>13.53</td>
</tr>
<tr>
<td>MKT</td>
<td>7.50</td>
<td>15.43</td>
<td>9.01</td>
<td>13.47</td>
</tr>
</tbody>
</table>
Effect of Carrier: Coat Ratio (R) on Dissolution:

Figures 4.11 to 4.16 emphasize on the effect of carrier to coat concentration ratio (R) on the drug dissolution rate. As it can be seen, increase in the R-value shows improved dissolution in case of both the carriers used.

According to “diffusion layer model” of dissolution, dissolution rate is in proportion to concentration gradient in stagnant diffusion layer\textsuperscript{[263]}. Drug dissolution is directly proportional to surface area available for dissolution i.e. effective surface area. The liquid medication is adsorbed and absorbed over the surface of hydrophilic carrier; effective surface available for mass transfer of drug molecules is tremendously increased. During the mass transfer process, as the drug is molecularly dispersed in the non-volatile solvent, the transfer of drug in the aqueous phase occurs as a separate molecular entity. Thus, the rate of drug dissolution is highly increased. If the carrier to coat ratio is increased, the surface area responsible for dissolution is also increased. Thus R-value imparts a positive effect on the dissolution rate of GPZ.

Another mechanism thought for the positive effect of R-value on dissolution might be decreased amount of coat material. The coat material, Aerosil (Colloidal silica), is used to enhance the flow characteristics of the blend. But due to the hydrophobic characteristics, it gives a negative effect on the wettability of the formulation. Hence the contact area of liquid medication is decreased resulting in poor solubilization. Increased R-value results in decrease in the percentage of Aerosil used in the formulation, thus the wettability is minimally affected.
Figure 4.11: Effect of R on Dissolution: Avicel PH 102 Batches with %D=10

Figure 4.12: Effect of R on Dissolution: Avicel PH 102 Batches with %D=15
Figure 4.13: Effect of R on Dissolution: Avicel PH 102 Batches with %D=20

Figure 4.14: Effect of R on Dissolution: Avicel PH 200 Batches with %D=10
Figure 4.15: Effect of R on Dissolution: Avicel PH 200 Batches with %D=15

Figure 4.16: Effect of R on Dissolution: Avicel PH 200 Batches with %D=20
Effect of % D on Dissolution:

From the factorial equation 4.8 and Fig. 4.17 to 4.22, it is observed that the decreased drug concentration in liquid medication is more useful in the dissolution rate enhancement. The inverse proportionality in drug strength in liquid medication and drug release rate might be due to availability of more amount of solvent for solubilization of drug. Less drug concentration in adequate amount of solvent results in drug in molecularly dispersed and solubilized form in final formulation. Presence of sufficient solvent also avoids recrystallization of drug improving the physical stability of formulation.

But this may lead to increased liquid load to the solid portion of the formulation. This may result in increased tablet weight as well as possibility of liquid squeeze out. Hence the addition of dilute medication to carrier is permissible only upto certain limit due to limited capacity of carrier to hold the liquid without squeezing out.

![Graph](image-url)

**Figure 4.17: Effect of %D on Dissolution: Avicel PH 102 Batches with R=10**
Fig. 4.18: Effect of %D on Dissolution: Avicel PH 102 Batches with R=15

Fig. 4.19: Effect of %D on Dissolution: Avicel PH 102 Batches with R=20
Fig. 4.20: Effect of %D on Dissolution: Avicel PH 200 Batches with R=10

Fig. 4.21: Effect of %D on Dissolution: Avicel PH 200 Batches with R=15
Effect of Grade of Avicel:

All liquisolid batches with Avicel PH 102 (A1-A9) demonstrated drug dissolution greater than 70.193±1.2 % at 40 min, while at the same time period LS batches with Avicel PH 200 as carrier material (B1-B9) demonstrated 49.193±3.61 % drug dissolution. Thus, Avicel PH 102 was found more efficient than Avicel PH 200 as a carrier material for solubility enhancement.

Statistical Comparison of Dissolution:

Model Independent Approach:

The model independent method such as similarity factor ($f_2$) provides simple way to compare dissolution data. USFDA guidance proposes that $f_2$-values of 50-100 indicate equivalence in dissolution profiles. Table 4.9 shows $f_2$-values of all the batches. The $f_2$-values of liquisolid batches were found to be dissimilar from dissolution profiles of marketed preparation. Only batch B3 showed $f_2$-values greater than 50, indicating similarity in dissolution profile and comparatively poor dissolution rate.
Table 4.9: \( f_2 \)-values of liquisolid formulation and marketed tablets

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Similarity factor</th>
<th>Dissolution profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>MKT &amp; A1</td>
<td>21.38</td>
<td>Dissimilar</td>
</tr>
<tr>
<td>MKT &amp; A2</td>
<td>26.99</td>
<td>Dissimilar</td>
</tr>
<tr>
<td>MKT &amp; A3</td>
<td>17.69</td>
<td>Dissimilar</td>
</tr>
<tr>
<td>MKT &amp; A4</td>
<td>13.07</td>
<td>Dissimilar</td>
</tr>
<tr>
<td>MKT &amp; A5</td>
<td>17.30</td>
<td>Dissimilar</td>
</tr>
<tr>
<td>MKT &amp; A6</td>
<td>26.24</td>
<td>Dissimilar</td>
</tr>
<tr>
<td>MKT &amp; A7</td>
<td>14.28</td>
<td>Dissimilar</td>
</tr>
<tr>
<td>MKT &amp; A8</td>
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<td>Dissimilar</td>
</tr>
<tr>
<td>MKT &amp; A9</td>
<td>20.20</td>
<td>Dissimilar</td>
</tr>
</tbody>
</table>

Model Dependent Method:

Although model independent methods are simple and easy to apply, they lack scientific justification. Different models of dissolution profile were used for comparison (Table 4.10). The results of these models indicate most of the liquisolid formulations followed Peppas model as “best fit model” depending on \( R^2 \)-value obtained from model fitting\[^{156}\].

Statistical Method:

Statistical methods based on ANOVA are most simple ways to determine discrimination in dissolution profiles. Statistically significant difference was observed in two-way ANOVA study in which the results showing two tailed \( p \)-value less than 0.05 were considered as significant. \( P \)-value was found to be 0.0472.
Table 4.10 (a)- Model dependent analysis of dissolution of Liquisolid formulations (A1-A9)

<table>
<thead>
<tr>
<th>Model</th>
<th>Zero Order</th>
<th>1st Order</th>
<th>Matrix</th>
<th>Peppas</th>
<th>Hix-Crowell</th>
<th>Best Fit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Batch</td>
<td>R²</td>
<td>K</td>
<td>R²</td>
<td>K</td>
<td>R²</td>
</tr>
<tr>
<td>A1</td>
<td>0.801</td>
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<td>0.950</td>
<td>-0.029</td>
<td>0.958</td>
<td>10.201</td>
</tr>
<tr>
<td>A2</td>
<td>0.801</td>
<td>1.192</td>
<td>0.950</td>
<td>-0.029</td>
<td>0.958</td>
<td>10.201</td>
</tr>
<tr>
<td>A3</td>
<td>0.793</td>
<td>1.069</td>
<td>0.921</td>
<td>-0.021</td>
<td>0.963</td>
<td>9.164</td>
</tr>
<tr>
<td>A4</td>
<td>0.277</td>
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<td>-</td>
<td>-</td>
<td>0.918</td>
<td>14.243</td>
</tr>
<tr>
<td>A5</td>
<td>-</td>
<td>1.322</td>
<td>-</td>
<td>-0.039</td>
<td>0.785</td>
<td>11.897</td>
</tr>
<tr>
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<td>10.072</td>
</tr>
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<td>A7</td>
<td>0.891</td>
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<td>-</td>
<td>-</td>
<td>0.984</td>
<td>14.255</td>
</tr>
<tr>
<td>A8</td>
<td>0.800</td>
<td>2.050</td>
<td>-</td>
<td>-</td>
<td>0.987</td>
<td>13.526</td>
</tr>
<tr>
<td>A9</td>
<td>-</td>
<td>1.275</td>
<td>0.817</td>
<td>-0.033</td>
<td>0.885</td>
<td>11.338</td>
</tr>
</tbody>
</table>
Table 4.10 (b) - Model dependent analysis of dissolution of Liquisolid formulations (B1-B9)

<table>
<thead>
<tr>
<th>Model</th>
<th>Zero Order</th>
<th>1st Order</th>
<th>Matrix</th>
<th>Peppas</th>
<th>Hix-Crowell</th>
<th>Best Fit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R^2$</td>
<td>$K$</td>
<td>$R^2$</td>
<td>$K$</td>
<td>$R^2$</td>
<td>$K$</td>
</tr>
<tr>
<td>Batch</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td>0.790</td>
<td>1.182</td>
<td>0.982</td>
<td>-0.029</td>
<td>0.977</td>
<td>10.139</td>
</tr>
<tr>
<td>B2</td>
<td>0.959</td>
<td>1.047</td>
<td>0.979</td>
<td>-0.024</td>
<td>0.965</td>
<td>8.662</td>
</tr>
<tr>
<td>B3</td>
<td>0.915</td>
<td>0.805</td>
<td>0.968</td>
<td>-0.012</td>
<td>0.963</td>
<td>6.737</td>
</tr>
<tr>
<td>B4</td>
<td>0.906</td>
<td>1.168</td>
<td>-</td>
<td>-</td>
<td>0.960</td>
<td>9.781</td>
</tr>
<tr>
<td>B5</td>
<td>0.901</td>
<td>1.206</td>
<td>-</td>
<td>-</td>
<td>0.974</td>
<td>10.140</td>
</tr>
<tr>
<td>B6</td>
<td>0.842</td>
<td>1.058</td>
<td>0.954</td>
<td>-0.021</td>
<td>0.955</td>
<td>8.989</td>
</tr>
<tr>
<td>B7</td>
<td>0.850</td>
<td>1.151</td>
<td>0.929</td>
<td>-0.027</td>
<td>0.951</td>
<td>9.754</td>
</tr>
<tr>
<td>B8</td>
<td>0.967</td>
<td>1.078</td>
<td>0.919</td>
<td>-0.029</td>
<td>0.947</td>
<td>8.846</td>
</tr>
<tr>
<td>B9</td>
<td>0.803</td>
<td>1.177</td>
<td>0.959</td>
<td>-0.028</td>
<td>0.967</td>
<td>10.073</td>
</tr>
</tbody>
</table>
4.8.6.6 **In vivo Pharmacodynamic Study:**

Best batch was selected depending on the data obtained from precompression study, tablet characteristics and *in vitro* dissolution profile. *In vivo* Pharmacodynamic study was performed in normal healthy as well as diabetes induced rats. Powdered GPZ was administered to the wistar rats in a suspension form. In normal rats, the decrease in glucose levels could be observed. This effect was gradually enhanced (Figure 4.23-4.25). The decrease in glucose levels reflects an increase of GZ in the blood levels as a result of the drug’s dissolution and absorption.

Kahn and Shechter\[^{161}\] have suggested that a 25% reduction in blood glucose levels is considered as a significant hypoglycemic effect.

In diabetic rats, it was found that GPZ alone had reduced the blood glucose level to 157.4±2.24 mg/ml on 7\(^{th}\) day, while the liquisolid system reduced blood glucose level to 141.4±4.36 mg/ml (Fig. 4.23). After 4 h, GPZ showed 29.52% decrease in blood glucose in normal rats, while in case of formulation, reduction in blood glucose level was found to be 41.43%.

After applying the t-test analysis for the data obtained from the percentage decrease in blood glucose concentration, a significant difference was observed between the untreated GPZ powder and the formulation (\(p = 0.022\)). This significant decrease was attributed to the improvement of the bioavailability of GPZ using liquisolid technique.
Fig. 4.23: Pharmacodynamic Study of Liquisolid Formulation in Diabetic Rats

Fig. 4.24: Pharmacodynamic Study of Liquisolid Formulation in Normal Rats
4.8.6.7 Stability Study:

The optimized liquisolid formulation (A7) was monitored for stability study for 3 months. The drug contents in formulations after 3 month were not significantly reduced; indicating chemical stability of drug. It was also observed that the hardness and disintegration time were not significantly affected by the exposure to accelerated temperature and humidity (Table 4.12). As shown in figure 4.26, the dissolution profiles during the period of stability study were found to be unaffected.

Hence the stability study indicates that the liquisolid dosage form possesses a good stability.
Table 4.11: Stability Study of Liquisolid Formulation

<table>
<thead>
<tr>
<th>Time (month)</th>
<th>Assay (% w/w)</th>
<th>Disintegration time (sec)</th>
<th>Hardness</th>
<th>% Friability</th>
<th>$Q_{15}$</th>
<th>$Q_{30}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100.08±3.38</td>
<td>176.7±2.9</td>
<td>25.67±2.52</td>
<td>0.393</td>
<td>69.38±1.4</td>
<td>91.37±1.87</td>
</tr>
<tr>
<td>1</td>
<td>99.40±2.11</td>
<td>171.66±10.4</td>
<td>24.00±2.65</td>
<td>0.398</td>
<td>66.76±6.22</td>
<td>90.86±2.33</td>
</tr>
<tr>
<td>2</td>
<td>99.23±1.34</td>
<td>178.33±2.9</td>
<td>25.33±3.06</td>
<td>0.322</td>
<td>60.80±1.72</td>
<td>91.08±2.52</td>
</tr>
<tr>
<td>3</td>
<td>99.40±0.59</td>
<td>186.66±5.77</td>
<td>24.33±4.16</td>
<td>0.354</td>
<td>65.75±1.16</td>
<td>91.18±2.12</td>
</tr>
</tbody>
</table>

Fig. 4.26: Dissolution Profile of Liquisolid Formulation during Accelerated Stability Study
4.9. CONCLUSION:

The purpose of the present study was to formulate the liquisolid system of glipizide for better dissolution rate accompanied by acceptable flow and compression characteristics. In this investigation, preformulation study was performed for authentication of drug and determination of drug solubility. Hence, from preformulation study following points were concluded.

Based on the information of melting point and FTIR spectra, the drug was confirmed to be authentic. The solubility of GPZ in distilled water is found to be $37.2 \pm 0.46 \mu g/ml$; also Dissolution of GPZ alone was very slow and also, incomplete up to 120 min. According to the findings, only $39.85 \pm 2.2 \%$ of drug is dissolved after 1 hr. Hence, as the intrinsic solubility as well as rate of drug dissolution is poor, there is strong need to enhance its solubility and dissolution rate.

The solubility of glipizide in PEG 200 was $34.254 \pm 0.34 mg/ml$. PEG 200 shows higher drug solubility hence can be considered as the acceptable solvent for the preparation of liquid medication portion of the system.

Liquisolid systems were formulated by the technique described and patented by Spireas et al. The systems were formulated with Avicel PH102 and Avicel PH200 as carrier materials. Aerosil 200 was used as coating material. Sodium starch glycolate was incorporated as super-disintegrant.

Chemical compatibility between drug and excipients was checked and confirmed by DSC and FTIR. A $3^2$-full factorial study design was utilized for the statistical comparison of the individual and combined effect of independent variables on dependent parameter like dissolution. The two variables were carrier to coat ratio and drug content in the liquid medication.
Liquisolid preparations were initially characterized by precompression study for flowability and compressibility. The formulations were found to possess good flow characteristics as well as satisfactory compressibility. The presence of PEG 200 can be considered to enhance the compactability of the formulation. The DSC thermogram of liquisolid system indicates the presence of the dissolved drug in the PEG 200.

Drug release rate was studied in saline phosphate buffer pH 7.4 and found to be enhanced in case of all liquisolid formulations. The factorial equation shows that the drug release is dependent on both the factors under consideration. Increased carrier to coat ratio and decreased drug concentration in the liquid medication demonstrated increased drug release rates.

*In vivo* pharmacodynamic study performed on normal and diabetic wistar rats shows that the liquisolid system was significantly effective to reduce the blood glucose level. This might be attributed to enhanced bioavailability due to improved dissolution characteristics of the hydrophobic drug.

The stability study showed that the drug contents as well as tablet properties like hardness, disintegration and dissolution profiles are not affected by stability conditions suggesting the chemical stability on exposure of accelerated conditions.

Finally, it can be concluded that, liquisolid formulation containing glipizide with Avicel as carrier and Aerosil as coating material is efficient to enhance the drug dissolution rate with acceptable flow and compression characteristics. Thus, liquisolid approach has potential application for formulation research in improvement of dissolution rate of glipizide.