# DESIGN, DEVELOPMENT AND *IN VITRO* CHARACTERIZATION OF GLIBENCLAMIDE LIQUISOLID TABLET

*Dissertation submitted to*

*The Tamilnadu Dr. M.G.R Medical University, Chennai*

*In partial fulfillment for the requirement of the degree of*

**MASTER OF PHARMACY**
**(Pharmaceutics)**

**MARCH-2012**


**DEPARTMENT OF PHARMACEUTICS**

**KMCH COLLEGE OF PHARMACY**

**KOVAI ESTATE, KALAPPATTI ROAD,**

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**Submitted by**


**LINCY VARGHESE**


**Under the Guidance of**

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# CERTIFICATE

This is to certify that this dissertation work entitled **"DESIGN, DEVELOPMENT AND *IN VITRO* CHARACTERIZATION OF GLIBENCLAMIDE LIQUISOLID TABLET"** was carried out by **LINCY VARGHESE (Reg.no:26107107).** The work mentioned in the dissertation was carried out at the Department of Pharmaceutics, Coimbatore - 641 048, under the guidance of **Dr. N. ARUNKUMAR M.Pharm., Ph.D.,** for the partial fulfillment for the Degree of **Master of Pharmacy (Pharmaceutics)** and is forward to The Tamil Nadu Dr.M.G.R. Medical University, Chennai.

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# CERTIFICATE

This is to certify that the dissertation work entitled **"DESIGN , DEVELOPMENT AND *IN VITRO* CHARACTERIZATION OF GLIBENCLAMIDE LIQUISOLID TABLET"** submitted by **LINCY VARGHESE (Reg.no:26107107)** to the TamilNadu Dr.M.G.R.Medical University, Chennai, in partial fulfillment for the Degree of **Master of Pharmacy** in **Pharmaceutics** is a bonafide work carried out by the candidate under my guidance at the Department of Pharmaceutics, KMCH College of Pharmacy, Coimbatore, during the year 2011 – 2012.

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# EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"DESIGN , DEVELOPMENT AND *IN VITRO* CHARACTERIZATION OF GLIBENCLAMIDE LIQUISOLID TABLET"** Submitted by **LINCY VARGHESE**, university **Reg.No:26107107** to the TamilNadu Dr.M.G.R.Medical University, Chennai, in partial fulfillment for the Degree of **Master of Pharmacy** in **Pharmaceutics** is a bonafide work carried out by the candidate at the Department of Pharmaceutics, KMCH College of Pharmacy, Coimbatore, and was evaluated by us during the academic year 2011 – 2012.

**Examination Centre:** KMCH College of Pharmacy, Coimbatore – 48.

**Date:**

**Internal Examiner** **External Examiner**

**Convener of Examination**

# DECLARATION

I do hereby declare that this dissertation entitled **"DESIGN , DEVELOPMENT AND *IN VITRO* CHARACTERIZATION OF GLIBENCLAMIDE LIQUISOLID TABLET"** submitted to the TamilNadu Dr.M.G.R.Medical University, Chennai, in partial fulfillment for the Degree of **Master of Pharmacy** in **Pharmaceutics** was done by me under the guidance of **Dr.N.ARUNKUMAR M.Pharm., PhD.,** Asst Professor, Department of Pharmaceutics, KMCH College of Pharmacy, Coimbatore, during the year 2011 – 2012.

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Above all I dedicate myself before the unfailing presence of GOD and constant love and encouragement given to me by my beloved father, mother and brothers, who deserve the credit of success in whatever I did.

***LINCY VARGHESE***

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# ABBREVIATIONS

| | |
|---|---|
| e.g | Example |
| i.e. | That is |
| % | Percentage |
| Kg | Kilogram |
| CR | Cumulative release |
| PG | Propylene Glycol |
| mg | Miliigram |
| ml | Milliliter |
| µg | Microgram |
| w/w | Weight by volume |
| v/v | Volume by volume |
| avg | Average |
| hrs | Hours |
| pH | Hydrogen ion concentration |
| °C | Degree centigrade |
| RPM | Revolution per minute |
| T | Time |
| MCC | Microcrystalline |
| Abs | Absorbance |
| Conc | Concentration |
| Fig | Figure |
| Tab | Table |
| UV- VIS | Ultra violet and visible spectroscopy |
| Mm | millimetre |
| C.I | Compressibility index |
| XRPD | X-Ray powder diffraction |
| LS | Liquisolid system |
| EDTA | Ethylenediamine tetra acetate |
| CD | Cyclodextin |
| pKa | ionization constant |
| nm | nanometers |
| DSC | differential scanning calorimetry |
| PEG | poly ethylene glycol |
| CCS | cros caramellose sodium |
| RH | relative humidity |
| FTIR | fourier transform infrared |
| Tm | melting temperature |
| DR | dissolution rate |
| D | diffusion coefficient |
| IP | Indian pharmacopoeia |

# 1. INTRODUCTION

Aqueous solubility of any therapeutically active substance is a key property as it governs dissolution, absorption and thus the *in vivo* efficacy. Poorly water soluble compounds have solubility and dissolution related bioavailability problems. The dissolution rate is directly proportional to the solubility of drugs. Drugs with low aqueous solubility have low dissolution rates and hence suffer from oral bioavailability problems. The poor solubility and poor dissolution rate of poorly water soluble drugs in the aqueous gastro intestinal fluids often cause insufficient bioavailability. Other *in-vivo* consequences due to poor aqueous solubility include increased chances of food effect, more frequent incomplete drug release from the dosage form and higher inter-patient variability.

Improvement in solubility of a poorly water soluble drug would increase gastrointestinal absorption of the drug thereby increasing the bioavailability which may result in reduction of dose. Further, this would also decrease food effect and inter-patient variability. In effect, this would result in improving the therapeutic efficacy and increase patient compliance.

Nearly 40% [1] of the new chemical entities currently being discovered are poorly water soluble drugs. Thus, there is a greater need to develop a composition, which provides enhanced solubility of the poorly soluble drugs and increases its dissolution rate and thus improves its bioavailability to provide a formulation with reduced dose and better therapeutic efficacy and as a result overcomes the drawbacks presented by the prior art.

Drugs which are having poor water solubility are etoposide, glyburide, itraconazole, ampelopsin, valdecoxib, celecoxib, halofantrine, tarazepide, atovaquone, amphotericin B, paclitaxel and bupravaquone etc.

**TECHNIQUES OF SOLUBILITY ENHANCEMENT [2]**

There are various techniques available to improve the solubility of poorly soluble drugs. They are:

1. Physical Modification
    A. Particle size reduction
        a. Micronization
        b.Nanosuspension
    B. Modification of crystal habit
        a. Polymorphs
        b. Pseudopolymorphs
    C. Drug dispersion in carriers
        a. Eutectic mixtures
        b. Solid dispersions
    D. Complexation
        a. Use of complexing agents
    E. Solubilization by surfactants:
        a. microemulsion
        b. Self microemulsifying drug delivery systems
2. Chemical Modification
3. Other techniques
        a. Hydrotrophy
        b. Solubilizing agent
        c. Nanotechnology approaches
        d. Liquisolid Technique

**I. Physical Modification**

**A. <u>Particle size reduction</u>**:

Particle size reduction can be achieved by micronisation and nanosuspension. Each technique utilizes different equipments for reduction of the particle size.

**i. Micronization**

The solubility of drug is often related to drug particle size. By reducing the particle size, the surface area gets increases which improve the dissolution properties of the drug. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. Micronization is not suitable for drugs having high dose number because it does not change the saturation solubility of the drug [3].

**ii. Nanosuspension:**

Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilised by surfactants [4]. The advantages offered by nanosuspension is increased dissolution rate due to larger surface area exposed, while absence of Ostwald ripening is due to the uniform and narrow particle size range obtained, which eliminates the concentration gradient factor.

Techniques for the production of nanosuspension

**a.Homogenization**

The suspension is forced under pressure through a valve that has nano aperture. This causes bubbles of water to form which collapses as they come out of valves. This mechanism cracks the particles [5].

Three types of homogenizers are commonly used for particle size reduction in the pharmaceutical and biotechnology industries: conventional homogenizers, sonicators, and high shear fluid processors.

**b. Wet milling:**

Active drug in the presence of surfactant is defragmented by milling.

Other technique involves the spraying of a drug solution in a volatile organic solvent into a heated aqueous solution. Rapid solvent evaporation produces drug precipitation in the presence of surfactants.

The nanosuspension approach has been employed for drugs including tarazepide, atovaquone, amphotericin B, paclitaxel and bupravaquone [6]. All the formulations are in

the research stage. One major concern related to particle size reduction is the eventual conversion of the high-energy polymorph to a low energy crystalline form, which may not be therapeutically active one. Drying of nanosuspensions can be done by lyophilisation or spray drying.

**B. Modification of crystal habits**

Polymorphism is the ability of an element or compound to crystallize in more than one crystalline form. Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture, stability etc. Broadly polymorphs can be classified as enantiotropes and monotrophs based on thermodynamic properties. In the case of an enantiotropic system, one polymorph form can change reversibly into another at a definite transition temperature below the melting point, while no reversible transition is possible for monotrophs. Once the drug has been characterized under one of this category, further study involves the detection of metastable form of crystal. Metastable forms are associated with higher energy and thus higher solubility. Similarly the amorphous form of drug is always more suited than crystalline form due to higher energy associated and increase surface area.

Generally, the anhydrous form of a drug has greater solubility than the hydrates. This is because the hydrates are already in interaction with water and therefore have less energy for crystal breakup in comparison to the anhydrates (i.e. thermodynamically higher energy state) for further interaction with water. On the other hand, the organic (nonaqueous) solvates have greater solubility than the nonsolvates.

Some drugs can exist in amorphous form (i.e. having no internal crystal structure). Such drugs represent the highest energy state and can be considered as super cooled liquids. They have greater aqueous solubility than the crystalline forms because they require less energy to transfer a molecule into solvent. Thus, the order for dissolution of different solid forms of drug is

Amorphous >Metastable polymorph >Stable polymorph

Melting followed by a rapid cooling or recrystallization from different solvents can produce metastable forms of a drug.

**C. Drug dispersion in carriers**

The term “solid dispersions” refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the melting (fusion) method, solvent method, or fusion solvent-method [7]. Novel additional preparation techniques have included rapid precipitation by freeze drying [8] and using supercritical fluids [9] and

spray drying [10], often in the presence of amorphous hydrophilic polymers and also using methods such as melt extrusion. The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone [11], polyethylene glycols [12], Plasdone-S630 [13]. Many times surfactants may be also used in the formation of solid dispersion. Surfactants like Tween-80, Docusate sodium, Myrj-52, Pluronic-F68 and Sodium Lauryl Sulphate were frequently used in this type of preparations..

The solubility of etoposide [14], glyburide [15], itraconazole [16], ampelopsin [17], valdecoxib[18], celecoxib [19], halofantrine [20] has been improved by solid dispersion using suitable hydrophilic carriers.

The eutectic combination of chloramphenicol/urea [21] and sulphathiazole/ urea [22] served as examples for the preparation of a poorly soluble drug in a highly water soluble carrier.

**1. Hot Melt method**

In this method drug and carrier were melted together and then cooled in an ice bath. The resultant solid mass was then milled to reduce the particle size. Cooling leads to supersaturation, but due to solidification the dispersed drug becomes trapped within the carrier matrix. A molecular dispersion can be achieved or not, depends on the degree of supersaturation and rate of cooling used in the process [23]. An important requisite for the formation of solid dispersion by the hot melt method is the miscibility of the drug and the carrier in the molten form. When there are miscibility gaps in the phase diagram, this usually leads to a product that is not molecularly dispersed. Another important requisite is the thermostability of the drug and carrier.

**2. Solvent Evaporation Method**

In this method both the drug and the carrier are dissolved in a common solvent and the solvent is evaporated under vacuum to produce a solid solution. This enabled to produce a solid solution of the highly lipophilic drug in the highly water soluble carrier. An important prerequisite for the manufacture of a solid dispersion using the solvent method is that both the drug and the carrier are sufficiently soluble in the solvent. The solvent can be removed by various methods like by spray-drying or by freeze-drying. Temperatures used for solvent evaporation generally lie in the range 23-65˚ C.

The solid dispersion of the 5- lipoxygenase/cyclooxygenase inhibitor ER-34122 showed improved *in vitro* dissolution rate compared to the crystalline drug substance which was prepared by solvent evaporation. These techniques have problems such as negative effects of the solvents on the environment and high cost of production due to extra facility for removal of solvents [24].

Due to the toxicity potential of organic solvents employed in the solvent evaporation method, hot melt extrusion method is preferred in preparing solid solutions.

**3. Hot-melt Extrusion**

Melt extrusion was used as a manufacturing tool in the pharmaceutical industry as early as 1971 [25]. It has been reported that melt extrusion of miscible components results in amorphous solid solution formation, whereas extrusion of an immiscible component leads to amorphous drug dispersed in crystalline excipient. The process has been useful in the preparation of solid dispersions in a single step.

**D. Complexation**

Complexation is the association between two or more molecules to form a nonbonded entity with a well defined stoichiometry. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions. There are many types of complexing agents and a partial list can be found in below table.

**Table: 1 List of Complexing Agents [26] :**

| S.No | Chemical class | Examples |
|---|---|---|
| 1. | Inorganic | $I_B^-$ |
| 2. | Chelates | EDTA |
| 3. | Inclusion | Cyclodextin(CD) |

Factors affecting complexation [27]:

1. Steric effects
2. Electronic effects

a. Effect of proximity of charge to CD cavity
b. Effect of charge density
c. Effect of charge state of CD and drug

3. Temperature, additives and cosolvent effects

**E. Solubilization by surfactants**

Surfactants are molecules with distinct polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitterionic or nonionic. When small apolar molecules are added they can accumulate in the hydrophobic core of the micelles. This process of solubilization is very important in industrial and biological processes. The presence of surfactants may lower the surface tension and increase the solubility of the drug within an organic solvent [28].

**a.Microemulsion**

A microemulsion is a four-component system composed of external phase, internal phase, surfactant and cosurfactant. The addition of surfactant, which is predominately soluble in the internal phase unlike the cosurfactant, results in the formation of an optically clear, isotropic, thermodynamically stable emulsion. It is termed as microemulsion because of the internal or dispersed phase is < 0.1 μ droplet diameter. The formation of microemulsion is spontaneous and does not involve the input of external energy as in case of coarse emulsions. The surfactant and the cosurfactant alternate each other and form a mixed film at the interface, which contributes to the stability of the microemulsions[29]. Non-ionic surfactants, such as Tweens (polysorbates) and Labrafil (polyoxyethylated oleic glycerides), with high hyrophile-lipophile balances are often used to ensure immediate formation of oil-in-water droplets during production.

Advantages of microemulsion over coarse emulsion include its ease of preparation due to spontaneous formation, thermodynamic stability, transparent and elegant appearance, increased drug loading, enhanced penetration through the biological membranes, increased bioavailability [30], and less inter- and intra-individual variability in drug pharmacokinetics.

**II. <u>Chemical Modifications:-</u>**

For organic solutes that are ionizable, changing the pH of the system may be simplest and most effective means of increasing aqueous solubility. Under the proper conditions, the solubility of an ionizable drug can increase exponentially by adjusting the pH of the solution. A drug that can be efficiently solubilized by pH control should be either weak acid with a low pKa or a weak base with a high pKa. Similar to the lack of effect of heat on the solubility of non-polar substances, there is little effect of pH on nonionizable substances. Nonionizable, hydrophobic substances can have improved solubility by changing the dielectric constant (a ratio of the capacitance of one material to a reference standard) of the solvent by the use of co-solvents rather than the pH of the solvent.

The use of salt forms is a well known technique to enhanced dissolution profiles. Salt formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs[31].An alkaloid base is, generally, slightly soluble in water, but if the pH of medium is reduced by addition of acid, and the solubility of the base is increased as the pH continues to be reduced. The reason for this increase in solubility is that the base is converted to a salt, which is relatively soluble in water (e.g. Tribasic calcium phosphate).The solubility of slightly soluble acid increased

as the pH is increased by addition of alkali, the reason being that a salt is formed (e.g. Aspirin, Theophylline, Barbiturates).

**III. <u>Other techniques</u>:**

**1. Hydrotrophy:**

Hydrotrophy designate the increase in solubility in water due to the presence of large amount of additives. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotrophic agents (sodium benzoate, sodium acetate, sodium alginate, and urea) and the solute [32].

Example: Solubilisation of Theophylline with sodium acetate and sodium alginate

**2. Solubilizing agents:**

The solubility of poorly soluble drug can also be improved by various solubilizing materials. PEG 400 is used for improving the solubility of hydrochlorthiazide[33]. Modified gum karaya , a recently developed excipient was evaluated as carrier for dissolution enhancement of poorly soluble drug, nimodipine[31]. The aqueous solubility of the antimalarial agent halofantrine is increased by the addition of caffeine and nicotinamide [34].

**3. Nanotechnology approaches:**

Nanotechnology will be used to improve drugs that have poor solubility. Nanotechnology refers broadly to the study and use of materials and structures at the nanoscale level of approximately 100 nanometers (nm) or less. For many new chemical entities of very low solubility, oral bioavailability enhancement by micronisation is not sufficient because micronized product has the tendency of agglomeration, which leads to decreased effective surface area for dissolution and the next step taken was Nanonisation [35].

**4. Liquisolid technique: [36]**

With the liquisolid technology, a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected excipients named the carrier and coating material. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles, is incorporated into the porous carrier material (Fig. 1). Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles. Thus, an apparently dry, free flowing, and compressible powder is obtained. Usually, microcrystalline cellulose is used as carrier material and amorphous silicon dioxide (colloidal silica) as coating material. Various excipients such as

lubricants and disintegrants may be added to the liquisolid system to produce liquisolid compacts (Fig 2).

Liquisolid compacts of poorly soluble drugs containing a drug solution or drug suspension in a solubilising vehicle show enhanced drug release due to an increased surface area of drug available for release, an increased aqueous solubility of the drug, and an improved wettability of the drug particles. Accordingly, this improved drug release may result in a higher drug absorption in the gastrointestinal tract and thus, an improved oral bioavailability.

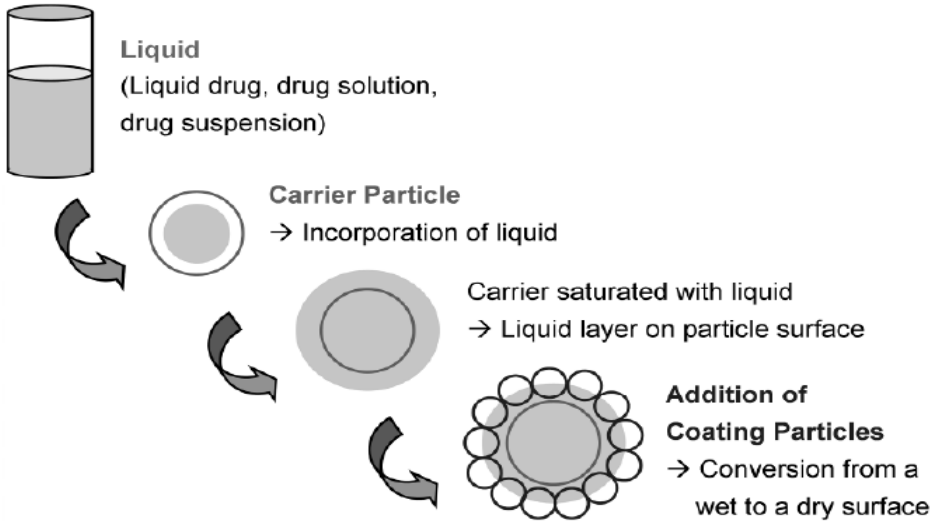



**Fig 1: Schematic representation of liquisolid system**

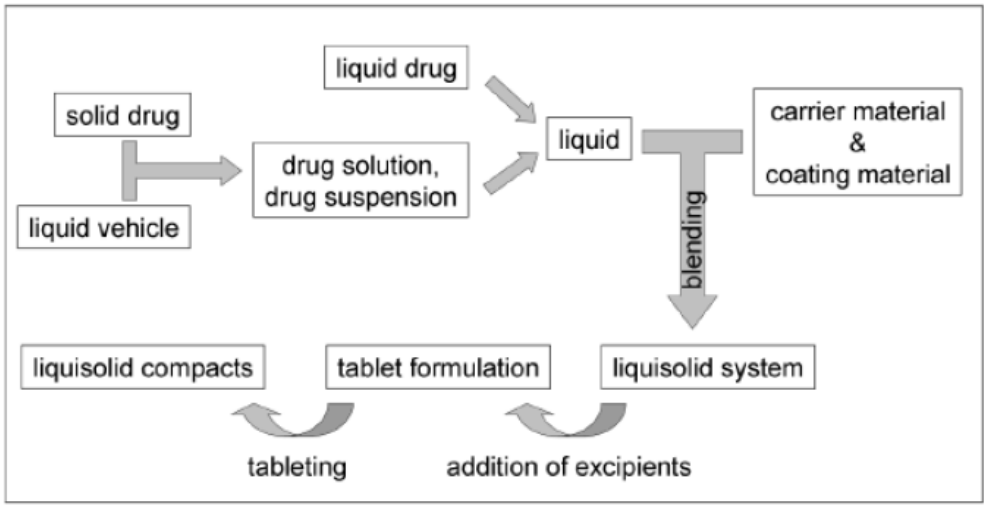



**Fig 2: Schemaic outline of steps involved in the preparation of liquisolid compacts**

## THEORY OF LIQUISOLID SYSTEMS

A powder can retain only limited amounts of liquid while maintaining acceptable flow and compression properties. To calculate the required amounts of powder excipients (carrier and coating materials) a mathematical approach for the formulation of liquisolid systems has been developed by Spireas [37]. This approach is based on the flowable (Φ-value) and compressible (Ψ-number) liquid retention potential introducing constants for each powder/liquid combination.

The Φ-value of a powder represents the maximum amount of a given non-volatile liquid that can be retained inside its bulk [w/w] while maintaining an acceptable flowability. The flowability may be determined from the powder flow or by measurement of the angle of repose. The Ψ-number of a powder is defined as the maximum amount of liquid the powder can retain inside its bulk [w/w] while maintaining acceptable compactability resulting in compacts of sufficient hardness with no liquid leaking out during compression. The compactability may be determined by the so-called "pactisity" which describes the maximum (plateau) crushing strength of a one-gram tablet compacted at sufficiently high compression forces. The terms "acceptable flow and compression properties" imply the desired and thus preselected flow and compaction properties which must be met by the final liquisolid formulation.

Depending on the excipient ratio (R) of the powder substrate an acceptably flowing and compressible liquisolid system can be obtained only if a maximum liquid load on the carrier material is not exceeded. This liquid/carrier ratio is termed "liquid load factor Lf [w/w] and is defined as the weight ratio of the liquid formulation (W) and the carrier material (Q) in the system:

$$Lf = W/Q \text{------} (1)$$

R represents the ratio between the weights of the carrier (Q) and the coating (q) material present in the formulation:

$$R = Q/q \text{------} (2)$$

The liquid load factor that ensures acceptable flowability (Lf ) can be determined by:

$$Lf = \Phi + \varphi . (1/R) \text{ ----- } (3)$$

Where Φ and φ are the Φ-values of the carrier and coating material, respectively. Similarly, the liquid load factor for production of liquisolid systems with acceptable compactability (ΨLf) can be determined by:

$$Lf = \Psi + \Psi . (1/R) \text{ ------- } (4)$$

Where Ψ and ψ are the Ψ-numbers of the carrier and coating material, respectively. In Table 1 examples of liquisolid formulation parameters of various powder excipients with commonly used liquid vehicles.

## MECHANISMS OF ENHANCED DRUG RELEASE FROM LIQUISOLID SYSTEMS

Several mechanisms of enhanced drug release have been postulated for liquisolid systems. The three main suggested mechanisms include an increased surface area of drug available for release, an increased aqueous solubility of the drug, and an improved wettability of the drug particles[43] . Formation of a complex between the drug and excipients or any changes in crystallinity of the drug could be ruled out using DSC and XRPD measurements.

### a. Increased drug surface

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, molecularly dispersed state. Therefore, the surface area of drug available for release is much greater than that of drug particles within directly compressed tablets.

### b. Increased aqueous solubility of the drug

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 dissolution medium. However, at the solid/liquid interface between an individual liquisolid primary particle and the release medium it is possible that in this microenvironment 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 acts as a cosolvent.

**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 liquisolid primary particles is improved. Wettability of these systems has been demonstrated by measurement of contact angles and water rising times.

## OPTIMIZATION OF LIQUISOLID FORMULATIONS WITH ENHANCED DRUG RELEASE

The liquisolid technology has been successfully applied to low dose, poorly water soluble drugs. The formulation of a high dose, poorly soluble drug is one of the limitations of the liquisolid technology. As the release rates are directly proportional to the fraction of molecularly dispersed drug (FM) in the liquid formulation a higher drug dose requires higher liquid amounts for a 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 leading to tablet sizes which are difficult to swallow. Therefore, to overcome this and various other problems of the liquisolid technology several formulation parameters may be optimized.

**Table 2: Optimization of formulation parameters for liquisolid systems with immediate Drug release**

| Formulation parameters | Optimization | Effects |
|---|---|---|
| Liquid vehicle | High drug solubility in the vehicle | Increased fraction of the molecularly dispersed drug |
| Carrier and coating material | High specific surface area | Increased liquid load factor |
| Addition of excipients | polyvinylpyrrolidine | Increased liquid load factor<br>Increased viscosity of liquid vehicle |
| Excipient ratio | High R value | Fast disintegration<br>Inhibition of precipitation |

## ADVANTAGES OF LIQUISOLID SYSTEMS [37]:

- Number of water-insoluble solid drugs can be formulated into liquisolid systems.
- Can be applied to formulate liquid medications such as oily liquid drugs.
- Better availability of an orally administered water insoluble drug.
- Lower production cost than that of soft gelatin capsules
- Production of liquisolid systems is similar to that of conventional tablets.
- Can be used for formulation of liquid oily drugs
- Exhibits enhanced *in-vitro* and *in-vivo* drug release as compared to commercial counterparts, including soft gelatin capsule preparations.
- Can be used in controlled drug delivery.
- Drug release can be modified using suitable formulation ingredients
- Drug can be molecularly dispersed in the formulation.
- Capability of industrial production is also possible.
- Enhanced bioavailability can be obtained as compared to conventional tablets.

## LIMITATIONS:

- Low drug loading capacities.
- Requirement of high solubility of drug in non-volatile liquid vehicles.

## APPLICATIONS:

- Rapid release rates are obtained in liquisolid formulations
- These can be efficiently used for water insoluble solid drugs or liquid lipophilic drugs.
- Sustained release of drugs which are water soluble drugs such as propranolol hydrochloride has been obtained by the use of this technique.
- Solubility and dissolution enhancement.
- Designing of controlled release tablets.
- Application in probiotics.

# 2. REVIEW OF LITERATURE

**Sanjeevgubbi et.al** [38] formulated and evaluated liquisolid compacts of Bromhexine Hydrochloride using Avicel PH 102, Aerosil 200 and Explotab. The *in vitro* dissolution property of slightly water soluble Bromhexine hydrochloride (BXH) was improved by exploring the potential of Liquisolid system (LS). The interaction between drug and excipients in prepared LS compacts were studied by differential scanning calorimetry (DSC) and X- ray powder diffraction (XRPD). The drug release rates of LS compacts were distinctly higher as compared to directly compressed tablets, which show significant benefit of LS in increasing wetting properties and surface area of drug available for dissolution. The DSC and XRD studies confirms no significant interaction between the drug and excipients used in LS compacts.

**Majid Saeedi et.al** [39] developed liquisolid system of indomethacin. They showed that the liquisolid formulations exhibited significantly higher drug dissolution rates in comparison with directly compressed tablet. The enhanced rate of indomethacin dissolution derived from liquisolid tablets was probably due to an increase in wetting properties and surface area of drug particles available for dissolution. Moreover, it was indicated that the fraction of molecularly dispersed drug (FM) in the liquid medication of liquisolid systems was directly proportional to their indomethacin dissolution rate (DR). An attempt was made to correlate the percentage drug dissolved in 10 min with the solubility of indomethacin in PEG 200 and glycerin.

**Khalid M. El-Say et.al** [40] prepared and characterised liquisolid compacts of Rofecoxib. The effect of powder substrate composition on the flowability and compressibility of liquisolid compacts were evaluated. Specifically, several liquisolid formulations, containing 25-mg Rofecoxib, which containing different carrier to coating ratios in their powder substrates and a fixed liquid medication, were prepared. The dissolution profiles of Rofecoxib liquisolid tablets were determined according to USP method. The obtained dissolution profiles were compared to that of a commercial product. The formulated liquisolid systems exhibited acceptable flowability and compressibility. In addition, liquisolid tablets displayed significant enhancement of the dissolution profiles compared to that of commercial one.

**Indrajeet D. Gonjari et.al** [41] formulated and evaluated sustained release liquisolid compact formulations of tramadol hydrochloride. Comparison of dissolution profiles of prepared compacts with marketed preparation was also done. Liquisolid sustained release formulations were prepared by using HPMC K4M as adjuvant for sustaining release. The prepared liquisolid compacts are new dosage forms showing more sustained release behavior as compared to marketed sustained formulations. Two Way ANOVA results showed significant difference in dissolution profiles. This systematic approach to the formulation was found to be useful in analyzing sustained release of tramadol hydrochloride. The application and evaluation of model dependent methods are more complicated. These methods give acceptable model approach which is indication of true relationship between percent drug release and time variables, including statistical assumptions.

**Y. Javadzadeh et. al** [42] studied the dissolution rate of piroxicam using liquisolid compacts . In this study several liquisolid tablets formulations containing various ratios of drug:Tween 80 (ranging from 10% to 50% w/w) were prepared. The ratio of microcrystalline cellulose (carrier) to silica (coating powder material) was kept constant in all formulations. The results showed that liquisolid compacts demonstrated significantly higher drug release rates than those of conventionally made (capsules and directly compressed tablets containing micronized piroxicam). This was due to an increase in wetting properties and surface of drug available for dissolution.

**Spiro Spireas** [43] prepared liquisolid compacts of prednisolone to enhance its dissolution rate.The *in-vitro* release characteristics of prednisolone were studied at different dissolution conditions. Liquisolid compacts demonstrated significantly higher drug release rates, in different dissolution media and volumes, compared to tablets prepared by the direct compression method. It was also observed that the drug dissolution rate from liquisolid tablets was independent of the volume of dissolution medium, in contrast to the plain tablets which exhibited declining drug release patterns with decreasing dissolution volumes.

**Amrit B. Karmarkar** [44] formulated and evaluated liquisolid compacts of Fenofibrate using different ratio of carrier and drug concentration.The purpose of present study was to improve fenofibrate dissolution through its formulation into liquisolid tablets and then to investigate *in vitro* performance of prepared liquisolid systems. X-ray powder

diffraction and Differential Scanning Calorimetry were used for evaluation of physicochemical properties of Fenofibrate in liquisolid tablets. Stereomicroscopy was used to assess morphological characteristics of liquisolid formulation. Enhanced drug release profiles due to increased wetting properties and surface of drug available for dissolution was obtained in case of liquisolid tablets.

**Sanjeev Raghavendra Gubbi** [45] formulated and characterised Atorvastatin liquisolid compacts.The ATR liquisolid compacts were prepared using Avicel PH 102 and Aerosil 200 as the carrier and coating material, respectively. XRD studies showed complete inhibition of crystallinity in the ATR liquisolid compacts. It is transformed into an amorphous form which has the highest energy and solubility. The DSC study confirmed the absence of any interaction between the drug and excipients used in the preparation of ATR liquisolid compacts. The in vitro dissolution study confirmed enhanced drug release from liquisolid compacts compared with directly compressed counterparts and this was independent of the type and volume of the dissolution medium. The liquisolid compacts showed an improvement in bioavailability compared with their directly compressed counterparts. It was observed that aging had no significant effect on the hardness, disintegration time and dissolution profile of the liquisolid compacts.

**Hitendra S. Mahajan et.al** [46]formulated and evaluated liquisolid compacts of Glipizide using treated Gellan gum as the disintegrant.This study aims to prepare immediate release glipizide liquisolid tablets using Avicel PH-102 and Aerosil 200 as the carrier and coating material respectively to increase dissolution rate of poorly soluble glipizide. They also evaluated treated Gellan gum as disintegrant in the preparation of liquisolid tablets. The results obtained shows that all glipizide liquisolid tablets exhibits higher dissolution rates than those of marketed glipizide tablets. Dissolution rates increases with increasing concentration of liquid vehicles and maximum drug release achieved by formulations containing Polyethylene glycol 400 (PEG 400) as a liquid vehicle. The results of XRD and thermal analysis did not show any changes in crystallinity of drug and interaction between glipizide and excipients during the formulation process.

**Ali Nokhodchi et. al** [47]developed Liquisolid Theophylline to sustain the drug release from matrix compacts. Liquisolid tablets were prepared by mixing liquid medication with silica–Eudragit RL or RS followed by the compaction of the mixture. The interaction between excipients and theophylline was investigated by differential scanning

calorimetry. Comparison study of physicomechnanical properties of liquisolid tablets with conventional tablets showed that most of liquisolid formulations had superior flowability and compactibility in comparison with physical mixtures. The results suggested that the presence of non-volatile cosolvent is vital to produce slow release pattern for some of liquisolid compacts. The type of cosolvent had significant effect on drug release and it was revealed that by changing the type of cosolvent the desirable release profile is achievable. The sustained release action of HPMC was enhanced in liquisolid compacts in comparison to simple sustained release matrix tablets.

**Yousef Javadzadeh et . al** [48] studied the effect of liquisolid technique in reducing the dissolution rate and thereby producing a sustained release systems. In the present study, propranolol hydrochloride was dispersed in polysorbate 80 as the liquid vehicle. Then a binary mixture of carrier–coating materials (Eudragit RL or RS as the carrier and silica as the coating material)was added to the liquid medication under continuous mixing in a mortar. Propranolol HCl tablets prepared by liquisolid technique showed greater retardation properties in comparison with conventional matrix tablets. This investigation provided evidence that polysorbate 80 (Tween 80) has important role in sustaining the release of drug from liquisolid matrices. X-ray crystallography and DSC ruled out any changes in crystallinity or complex formation during the manufacturing process of liquisolid formulations.

**Veerareddy et.al** [49] formulated and evaluated liquisolid compacts of meloxicam. Dissolution efficiency, mean dissolution time and relative dissolution rate of liquisolid compacts were calculated and compared to marketed formulation. The degree of interaction between the Meloxicam and excipients was studied by differential scanning calorimetry and X-ray diffraction were used and results revealed that, there was a loss of meloxicam crystallanity upon liquisolid formulation and almost molecularly dispersed state, which contributed to the enhanced drug dissolution properties. The optimized liquisolid compact showed higher dissolution rates and dissolution efficiency compared to commercial product.

**Amal A. Elkordy et .al** [50] studied the improvement in dissolution rate of Furosemide using Liquisolid technique. Several liquisolid tablets were prepared using microcrystalline cellulose (Avicel® pH-101) and fumed silica (Cab-O-Sil® M-5) as the carrier and coating materials, respectively. Polyoxyethylene- polyoxypropylene-

polyoxyethylene block copolymer (Synperonic® PE/L 81); 1, 2, 3-propanetriol, homopolymer, (9Z)-9-octadecenoate (Caprol® PGE-860) and polyethylene glycol 400 (PEG 400) were used as non- volatile water-miscible liquid vehicles. The ratio of carrier to coating material was kept constant in all formulations at 20 to 1. The *in-vitro* release characteristics of the drug from tablets formulated by direct compression (as reference) and liquisolid technique, were studied in two different dissolution media. Differential scanning calorimetry (DSC) and Fourier Transform infrared spectroscopy (FT-IR) were performed.The results showed that all formulations exhibited higher percentage of drug dissolved in water (pH 6.4–6.6) compared to that at acidic medium (pH 1.2). Liquisolid compacts containing Synperonic® PE/L 81 demonstrated higher release rate at the different pH values. Formulations with PEG 400 displayed lower drug release rate, compared to conventional and liquisolid tablets Caprol® PGE-860, as a liquid vehicle, failed to produce furosemide liquisolid compacts.

**Amal A. Elkordy** [51] formulated Liquisolid tablets of naproxen and evaluated the effects of different formulation variables, i.e. type of non-volatile liquid vehicles and drug concentrations, on drug dissolution rates. The liquisolid tablets were formulated with three different liquid vehicles, namely Cremophor EL , Synperonic PE/L61, and poly ethylene glycol 400 at two drug concentrations, 20%w/w and 40%w/w. Avicel PH102 was used as a carrier material, Cab-o-sil M-5 as a coating material and maize starch as a disintegrant. It was found that liquisolid tablets formulated with Cremophor EL at drug concentration of 20%w/w produced high dissolution profile with acceptable tablet properties. The stability studies showed that the dissolution profiles of liquisolid tablets prepared with Cremophor EL were not affected by ageing significantly. Furthermore, DSC revealed that drug particles in liquisolid formulations were completely solubilised.

**A. V. Yadav et al** [52] formulated and evaluated orodispersible liquisolid compacts of aceclofenac by using different dissolution enhancers and studied the effect of way of addition of superdisintegrants on rate dissolution of aceclofenac. Liquisolid compacts of aceclofenac were prepared by dispersing the drug in various dissolution enhancing agents(Propylene glycol, Polyethylene glycol 400 and Tween 80 in 1:1 ratio with drug ), then addition of diluents, superdisintegratns (like Cross carmelose Sodium, Cross povidone and Sodium starch glycolate) in various ways and in combinations finally with the addition of glidants and lubricants. All liquisolid compacts being orodispersible

rapidly disintegrated within 3 minutes with enhanced dissolution properties over the conventional tablet of aceclofenac. Among all formulations, Tween 80 liquisolid compact containing cross carmelose sodium showed highest dissolution.

**Spireas et al** [53]studied the effect of powder substrate composition on the dissolution properties of methyclothiazide, a practically insoluble diuretic agent, as the model drug. Liquisolid tablets of methyclothiazide containing a 5% w/w drug solution in polyethylene glycol 400 were prepared using powder substrates of different carrier: coating ratios in their powder substrates from 5 to 70. Dissolution study showed enhanced cumulative release.

**El-Adawy** [54] formulated nifedipine, a practically insoluble antianginal agent, in liquisolid tablets. Several liquisolid, 10 mg, tablet formulations containing different carrier/coat ratios in their powder substrate and different liquid medication of nifedipine in PEG 600, or Tween 80 was prepared. Avicel PH 200 and Cab-O-Sil were used as carrier and coating material, respectively, in different ratios and a standard 5% w/w of the disintegrant sodium starch glycolate (Explotab®) was added in all systems. The study showed enhanced dissolution rate when compared to conventional tablet.

**Nokhodchi et al** [55] used the technique of liquisolid compacts to formulate and enhance the *in-vitro* release of piroxicam, which was formulated into 10mg liquisolid tablets consisting of similar powder excipients and Tween 80 with different drug concentrations in their liquid medications.They have also utilized the liquisolid technique to increase dissolution rate of indomethacin and studied the effect of type and concentration of vehicles on the dissolution rate of a poorly soluble drug, indomethacin, from liquisolid compacts.

From the above literature survey it was understood that liquisolid system is a promising method for improving the solubility of poorly soluble drugs. So in this present study liquisolid technique is used as a method for improving the solubility, and thereby the dissolution rate of Glibenclamide, which is a poorly soluble drug.

# 3. AIM AND OBJECTIVE

Glibenclamide is an antidiabetic drug which belongs to the class sulfonyl ureas. It is poorly water soluble and hence have less oral bioavailability of about 40%. Since Glibenclamide is a poorly soluble drug it is classified under class II drugs as per BCS classification. Solubility plays a vital role in determining the *invitro* absorption of the drug, and hence the problem of poor solubility needs to be addressed with great care in formulating poorly soluble drugs. Among the various method adopted to increase the solubility of drugs, liquisolid technique seems to be a promising technology.

The aim and objective of the study was to improve the solubility and dissolution characteristics of Glibenclamide using liquisolid technology.

# 4. PLAN OF WORK

1. Preformulation studies
2. Preparation of Liquisolid powder
3. Preparation of tablet by direct compression method
4. Evaluation test
    a. Hardness
    b. Friability
    c. Weight variation
    d. Assay
    e. Disintegration test
    f. Dissolution studies
    g. X-Ray Diffraction
    h. DSC Analysis
5. Stability study

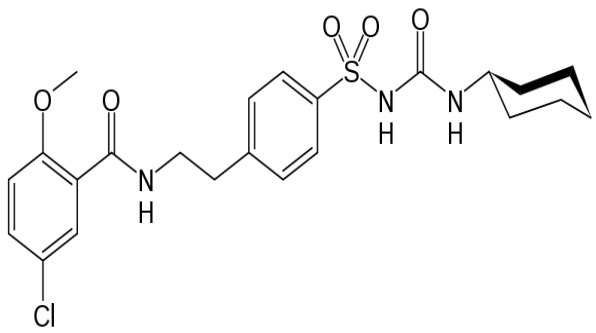
# 5. DRUG PROFILE

## GLIBENCLAMIDE[56]

**Chemical IUPAC name:** 1-[[4-[2-[(5-Chloro-2-methoxybenzoyl) amino] ethyl] phenyl] sulphonyl-3-cyclohexyl urea.

**Empirical Formula:** $C_{23}H_{28}ClN_3O_5S$

**Structural formula:**




**Description:** white or almost white, crystalline powder.

Bioavailability**:** 42%

Half Life **:** 24hrs

**Mechanism of Action:**

Glibenclamide exerts pancreatic and extrapancreatic actions. It stimulates an increase in insulin release by the pancreatic β-cells. It may also reduce hepatic gluconeogenesis and glycogenolysis. Increased glucose uptake in the liver and utilization in the skeletal muscles.

**Absorption:** Readily absorbed from the GI tract (oral); peak plasma concentrations after 2-4 hr.

**Distribution:**Protein-binding:Extensive.

**Metabolism:**Hepatic; converted to very weakly active metabolite .

**Excretion :** Urine (50%); faeces (50%).

**Dose and administration:**

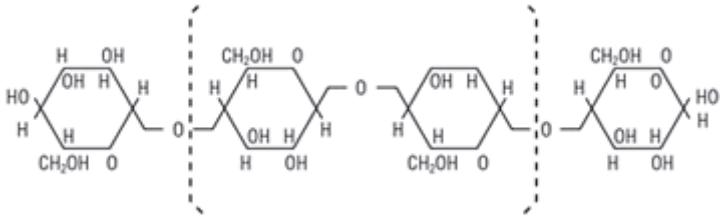
Administered by oral route

Dose : 5-10 mg

Maximum dose : 15mg in 24 hr

# 6. MICROCRYSTALLINE CELLULOSE[57]

**1. Structural formula :**



**2. Nonproprietary name :**

- BP **:** Microcrystalline cellulose
- JP **:** Microcrystalline cellulose
- PhEur **:** Cellulosum microcrystallinum
- USPNF **:** Microcrystalline cellulose

**3. Synonym** **:** Avicel ; Cellulose gel ; tabulose Crystalline cellulose; E460; Emcocel Fibrocel;vivacel

**4. Chemical name** **:** Cellulose

**5. Empirical formula** **:** $(c_6H_{10}O_5)n$

**6. Molecular weight** **:** ≈36000 where n≈220.

**7. Functional category** **:** Adsorbent;suspending agent; capsule and tablet diluents; tablet disintegrant**.**

**8. Physical state** **:** It is a purified, partially depolymerised Cellulose that occurs white odourless, Tasteless,crystalline powder composed of porous particles.It is commercially available in different particle size and moisture grades which have different properties and applications.

**9. Typical properties :**

**Density (bulk)** **:** 0.337 g/cm$^3$

**Density (tapped)** **:** 0.478 g/cm$^3$

**Density (true)** **:** 1.512-1.668 g/cm$^3$

**Melting point** **:** Chars at 260-270$^o$C

**Moisture content** **:** Less than 5% w/w

**10. Solubility** : Slightly soluble in 5%w/v sodium Hydroxide solution,Practically insoluble in water,dilute acids, and most Organic solvents.

**11. Stability and storage condition:**

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

**12. Incompatibilities** : Incompatible with strong Oxidizing agents.

**13. Applications:**

It is widely used in pharmaceuticals, primarily as a binder/ diluents in oral tablet and capsule formulations.Where it is used in both wet granulation and direct compression processes. Microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.It is also used in cosmetics and food products.

## COLLOIDAL SILICON DIOXIDE[58]

**1.Structural formula** : $Sio_2$

2.**Non-proprietary name** :

- BP : Colloidal anhydrous silica
- PhEur : silica colloidalis anhydrica
- USP : Colloidal silicon dioxide

**3.Synonyms** : Aerosil, fumed silica, cab-o-sil, colloidal silica, silica anhydride, silicon dioxide fumed, wacker HDK

**4.Chemical name** : Silica

**5.Empirical formula** : $Sio_2$

**6.Molecular weight** : 60.08

**7.Functional category** : Adsorbent, anticaking agent, glidant, suspen ding agent, tablet disintegrant, viscosity increasing agent.

**8.Physical state** : It is a light, loose, bluish-white coloured,odourless, tasteless, nongritty amorphous powder.

**9.Typical properties** :

Density(bulk) : 0.029-0.042 g/cm$^3$

pH : 3.5-4.4 (4% w/v aqueous dispersion)

**10.Stability & storage condition** : It is hygroscopic, but absorbs large quantities of water without liquefying. It should be stored in a well-closed container.

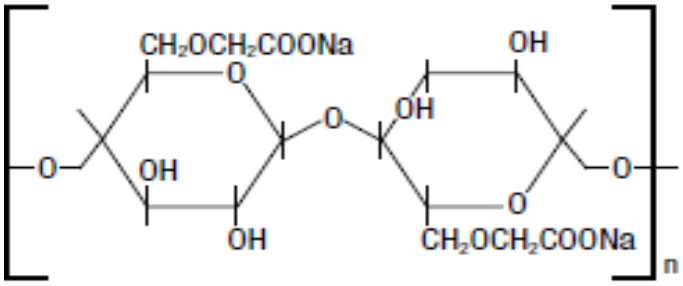
**11.Incompatibilities** : Incompatible with diethyl stilbesterol preparations.

**12.Applications :**

Colloidal silicon dioxide is widely used in pharmaceutical formulations to improve the flow properties of dry powders. The concentration of silicon dioxide used as glidant is 0.1-0.5%. It is also used in cosmetics and food products.

## CROS CARMELLOSE SODIUM

**1.Structural formula :**




**2. Non-proprietary name :**

- BP : Croscarmellose sodium
- JPE : Croscarmellose sodium
- USP : Croscarmellose sodium

**3. Synonym** : Ac-Di-Sol, Solutab, Primellose, Pharmacel Xl

**4. Chemical name** : Cellulose, carboxy methyl ether,

| | | |
|---|---|---|
| **5. Molecular weight** | **:** | 90,000-7,00,000**.** |
| **6. Physical state** | **:** | Croscarmellose sodium occurs as an odourless, white coloured powder. |
| **7.Functional category** | **:** | Tablet and capsule disintegrant |
| **8. Typical properties** | **:** | |
| Density(bulk**)** | **:** | 0.529 g/$cm^3$ |
| Density(tapped) | **:** | 0.819 g/$cm^3$ |
| Density(true) | **:** | 1.543 g/$cm^3$ |
| **9.Solubility** | **:** | Insoluble in water, rapidly swells to 4-8 times of its original volume on contact with water. |

**10. Stability & storage condition:**

Croscarmellose sodium is a stable though hygroscopic material. It should be stored in a well-closed container in a cool, dry place.

**11. Incompatibilities**:

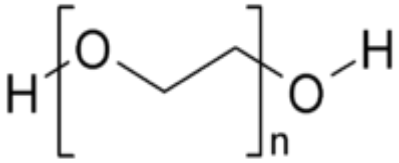
The efficacy of croscarmellose sodium , may be slightly reduced in tablet formulations prepared by either wet granulation or direct compression process which contains hygroscopic excipients such as sorbitol.

**12. Applications:**

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for tablet, capsules and granules. In tablet formulations, croscarmellose sodium may be used in both direct compression and wet granulation processes.

# PROPYLENE GLYCOL[59]

**Structural formula:**




| | | |
|---|---|---|
| **Nonproprietary names** | **:** | BP:Propylene glycol,PhEur:Propylenglycolum. |
| **Synonyms** | **:** | 1,2-Dihydroxypropane;2-hydroxypropanol; propane-1,2-diol. |
| **Chemical name** | **:** | 1,2-Propanediol. |
| **Empirical formula and molecular weight** | **:** | $C_3H_8O_2$ ,76.1 |
| **Functional category** | **:** | Antimicrobial preservative, disinfectant, humectant, stabilizer for vitamins. |
| **Incompatibilities** | **:** | Propylene glycol is incompatible with oxidizing reagents such as potassium permanganate. |
| **Solubility** | **:** | Miscible with acetone, chloroform, ethanol(95%),glycerin and water;soluble 1in 6 parts of ether;not miscible with light mineral oil or fixed oils,but will dissolve some essential oils. |
| **Typical properties** | **:** | Density: 1.038 g/cm$^3$ at 20◦C. |

**Applications:**

Propylene glycol has become widely used as a solvent,extractant,and preservative in a variety of parenteral and non-parenteral pharmaceutical formulations.It is commonly used as a plastizer in aqueous film-coating formulations

# 7. MATERIALS AND METHODS

**Table 3: Instruments used**

| INSTRUMENTS | SUPPLIER/ MANUFACTURER |
|---|---|
| Single pan analytical balance | Amandi , Mumbai |
| Tablet punching machine | Rimek 12, Ahmedabad |
| Hardness tester | Campbell electronics –Mumbai |
| Roche friabilator | Campbell electronics –Mumbai |
| Dissolution apparatus | Campbell electronics –Mumbai |
| Disintegration apparatus | Campbell electronics –Mumbai |
| UV spectrophotometer | Schimadzu |

**Table 4: Materials used**

| MATERIAL | SUPPLIER/ MANUFACTURER |
|---|---|
| Glibenclamide | Capplin point , pondicherry |
| Propylene Glycol | Nice chemicals pvt .ltd,kerala |
| MCC | Mitutiyo,india |
| Aerosil | FMC Biopolymer,Ireland |
| Sodium starch glycolate | Ascot pharmachem Pvt Ltd,Gujarat |
| Cros carmellose sodium | DME Fonterra Excipients,USA |
| Magnesium stearate | Parag Fine Organics,Mumbai |
| Talc | CP Kelco US Inc. USA |

# METHODOLOGY

## 1. DETERMINATION OF $\lambda_{max}$:

Absorption spectra of Glibenclamide

**a)** Stock solution of 1mg/ml of Glibenclamide was prepared by dissolving 100mg of a drug in small quantity of methanol and sonicated for few minutes and diluted with phosphate buffer (pH 7.4).

**b)** The stock solution was serially diluted to get solutions in the range of 2-10µg/ml and $\lambda_{max}$ of the solution was found out by scanning the solution from 200-400 nm using UV-VS spectrometer.

**c)** The $\lambda_{max}$ of the solution was found to be 227 nm.

## 2. DETERMINATION OF STANDARD CURVE:

**a)** Stock solution of 1000µg/ml of Glibenclamide was prepared by dissolving 10mg of drug in small quantity of methanol and sonicated for few minutes and diluted with methanol to 10ml.

**b)** From this take 1 ml and make up to 10 ml using methanol to get a stock solution of 100 µg/ml.

**c)** From the above solution take 5ml and dilute to 50 ml using phosphate buffer to get a stock solution of 10 µg/ml.

**d)** The stock solution was serially diluted to get solutions in the range of 2-10µg/ml $\lambda_{max}$ of the solution was found out.

**e)** The absorbance of the different diluted solutions was measured in a UV spectrophotometer at 227nm.

**f)** A calibration curve was plotted by taking concentration of the solution in µg on X-axis and absorbance on Y-axis and correlation co-efficient “r” was calculated.

## 3. DETERMINATION OF SOLUBILITY

Solubility studies of glibenclamide were carried out in water, Propylene Glycol, Polyethylene Glycol 400, and Tween 80. Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the shaker for 48 h at 25 ± 0.5°C under constant vibration. After this period the solutions were filtered, diluted and analyzed by UV-spectrophotometer at 227 nm.

## 4. FORMULATION OF LIQUISOLID SYSTEM

1. Calculated quantities of Glibenclamide and propylene glycol was accurately weighed and mixed thoroughly in a motar to produce the drug solution.
2. Quantities of carrier and coating materials required were calculated based on 'R' value and were added into the drug solution and mixed thoroughly.
3. Mixing process is carried out in three steps :
    a. During first stage powder was blended for approximately one minute so that the liquid medication will equally distribute in the powder.
    b. In second stage, mixture was evenly spread as a uniform layer on the surfaces of mortar and left standing for approximately 5 min to allow drug solution to be absorbed in the interior of powder particles.
    c. In third stage, powder was scraped off the mortar surfaces by means of aluminum spatula and then blended with 5% super disintegrant (CCS), 2%magnesium stearate & 1 % talc for another 30 seconds in a similar to first stage. This gives final formulation of liquisolid tablets.

    Conventional tablet of pure drug was also prepared by direct compression technique to compare its release rate with that of liquisolid compacts.

**Table 5: Formulation chart of liquisolid tablets**

| Formulation | Drug concentration in PG (%w/w) | Excipient Ratio (R) | Liquid Load Factor (Lf) |
|---|---|---|---|
| LS-1 | 5 | 10 | 0.491 |
| LS-2 | 5 | 20 | 0.325 |
| LS-3 | 5 | 30 | 0.270 |
| LS-4 | 10 | 10 | 0.491 |
| LS-5 | 10 | 20 | 0.325 |
| LS-6 | 10 | 30 | 0.270 |
| LS-7 | 15 | 10 | 0.491 |
| LS-8 | 15 | 20 | 0.325 |
| LS-9 | 15 | 30 | 0.270 |
| LS-10 | 20 | 10 | 0.491 |
| LS-11 | 20 | 20 | 0.325 |
| LS-12 | 20 | 30 | 0.270 |

## 5. EVALUATION OF POWDER BLEND

Preformulation study is the characterization of the physiochemical parameters of the drug substance by the application of biopharmaceutical principles with the goal of designing an optimum drug delivery system. The characterization of drug and the drug - excipient compatibility information decides most of the subsequent events and approaches in development of the formulation**.** Preformulation study involves the physiochemical characterization of the drug, solubility determination of the drug, determination of the drug-excipient compatibility, development of the analytical methods and the stability studies.

The prepared powder blend were subjected to evaluation as per the methods suggested in the Indian Pharmacopoeia like Angle of repose, Bulk density, Tap density, Compressibility index, Hausner's ratio.

### a) Angle of repose [60]:

The angle of repose is the maximum angle which is formed between the surface of a pile of powder and horizontal surface. It is determined by the funnel method. A funnel was kept vertically at a specified height and the funnel bottom was closed. 10 gm of sample powder was filled inside the funnel. Then funnel was opened to release the powder to form a smooth conical heap which just touches the tip of the funnel. From the powder cone, the radius of the heap (r) and the height of the heap (h) were measured. The angle of repose is represented as 'θ' and is calculated using the following equation:

$$\mathbf{Tan\ \theta = h/r} \quad \text{…….. (5)}$$

Where, h = Height of the pile

$\mathbf{\theta = Tan^{-1} h/r}$ r = Radius of the pile

**Table 6: Flow properties and corresponding Angles of repose**

| FLOW PROPERTY | ANGLE OF REPOSE (DEGREES) |
|---|---|
| Excellent | 25-30 |
| Good | 31-35 |
| Fair | 36-40 |
| Passable | 41-45 |
| Poor | 46-55 |
| Very poor | 56-65 |
| Very, very poor | >66 |

**b) Bulk density [61]:**

The bulk densities of the samples were determined by transferring the accurately weighed sample of powder to the graduated 50 ml measuring cylinder. The initial volume (bulk volume) and weight was noted. The bulk density is calculated by the formula:

**Bulk Density = Weight of Sample / Bulk Volume .....(6)**

**c) Tapped density [61]:**

An accurately weighed powder sample was transferred to the graduated 50ml measuring cylinder and was placed on the tap density test apparatus. The apparatus was operated for a fixed number of taps. The final volume (tap volume) of the tapped massed was noted. The tapped density was calculated by using the formula:

**Tapped Density = Weight of Sample/ Tapped Volume …… (7)**

**d) Compressibility index:**

The bulk density, cohesiveness of the material, surface area, size and shape and the moisture content influences the Compressibility index. The compressibility index is determined from the bulk volume and tap volume. The basic method used for the determination of compressibility index is to measure the bulk volume and the final tapped volume after a fixed number of tapping until no change in volume occurs. It is represented in percentage.

**% Compressibility = (Tapped density - Bulk density) / Tapped density X 100 …….**

**(8)**

**Table 7: Scale of Flowability based on Compressibility Index**

| COMPRESSIBILITY INDEX (%) | FLOW CHARACTER |
|---|---|
| ≤10 | Excellent |
| 11-15 | Good |
| 16-20 | Fair |
| 21-25 | Passable |
| 26-31 | Poor |
| 32-37 | Very poor |
| >38 | Very, very poor |

**e) Hausner's ratio:**

Hausner's ratio is the ratio of the initial volume of the powder mass to the final volume of the powder mass obtained after the specified number of tapping

**Table 8: Scale of Flowability based on Hausner's Ratio**

| HAUSNER'S RATIO | FLOW CHARACTER |
|---|---|
| 1-1.11 | Excellent |
| 1.12-1.18 | Good |
| 1.19-1.25 | Fair |
| 1.26-1.34 | Passable |
| 1.35-1.45 | Poor |
| 1.46-1.59 | Very poor |
| >1.60 | Very, very poor |

**f) Assay of Blend**

Powder was weighed equivalent to 10 mg Glibenclamide and transfer to 100ml volumetric flask. Add few ml of methanol and sonicated for 10min.Then filter the solution through whatmann filter paper and made up to 100ml with phosphate buffer (pH 7.4). 1ml of resultant solution was taken and diluted to 100ml with phosphate buffer (pH 7.4) and the absorbance was measured at 227nm by UV spectrophotometer.

**g) Compatibility Studies:**

IR spectra matching approach was used for detection of any possible chemical interaction between drug and polymer. A physical mixture (1:1) of drug and polymer was prepared and mixed with the suitable quantity of potassium bromide. About 100mg of mixture was compressed to form a transparent pellet using a hydraulic press at 6tons pressure .It was scanned from 4000 to 400 cm-1 in FTIR spectrometer. The IR spectrum of the physical mixture was compared with those of pure drug and polymers and matching was done to detect any appearance or disappearance of peaks. The IR spectrums of the sample and of the Glibenclamide working/reference standard in the range of 4000 cm-1 to 400 cm-1 were taken by preparing dispersion in dry potassium bromide under the same operational conditions mentioned above

**6. Compression of Liquisolid Tablet**

Weigh accurately about 250 mg (according to Table : 12) of the mixture blend and fed into the die of single punch tablet press and compressed at 1.5N compression force using 8mm concave punches.

**7. Evaluation of Tablet**

**a) Weight variation test:**

20 tablets were selected at random and weighed individually. The average weight of each batch of tablet was calculated. Individual weights of the tablets were compared with the average weight. Since the tablet weighed around 250mg, IP specifies that the tablets pass the test if not more than two of the individual weights deviate from the average weight by more than 7.5%.

**Table 9: Weight variation limit as per IP**

| **Percentage deviation allowed under weight variation test** | |
|---|---|
| **Average weight of tablet** | **Percentage deviation** |
| ≤ 80mg | 10% |
| 80-250mg | 7.5% |
| ≥ 250mg | 5% |

**b) Thickness and Hardness**

Thickness was measured during tablet compression using Vernier caliper. Hardness of the tablet was measured by Pfizer tablet hardness tester. The tablets were held vertically in between the jaws which were pressed with hand until the tablet broken. The reading was noted from the needle of pressure dial which may be expressed in kilograms.

**c) Friability**

This is performed to evaluate the ability of tablet to withstand abrasions. Ten tablets were weighed and placed in the tumbling chamber of Roche friabilator which rotated for 100 revolutions at a speed of 25 rpm . The tablets were again weighed and the loss in weight indicated the friability. Friability value should not exceed 1 % according to IP specification.

$$\% \text{ Friability} = \frac{A-B}{B} \quad \text{..... (9)}$$

Where A=Initial weight of tablet

B=Weight of tablet after 100 revolution.

**d) Assay of tablet.**

Ten tablets were randomly weighed and crushed. Calculated the average weight and taken the powder equivalent to 10 mg of Glibenclamide base in a 100 ml volumetric flask. Add few ml methanol and sonicated for 10 minute. Then volume made up to 100 ml with phosphate buffer (pH 7.4).The 1mL of resultant solution diluted to 100mL with phosphate buffer (pH 7.4) and the absorbance was measured using UV spectrophotometer at 227nm [62].

**e) *Invitro*-Dissolution studies**

The Glibenclamide release from different formulations was determined using a USP XXIII paddle apparatus 2 under sink condition. The dissolution medium was 900 ml phosphate buffer (pH 7.4) at 37 ± 0.2 °C; paddle speed 50 rpm, to simulate *in vivo* conditions. All experiments were done in triplicate and average values were taken. The formulation prepared was subjected to dissolution tests for 1 hr. Sample (10 ml) was withdrawn at predetermined time intervals, filtered through Whatmann filter paper and

replaced by an equal volume of dissolution medium. Drug content in the dissolution sample was determined by UV spectrophotometer at 227nm.

**Dissolution Condition:**

| | |
|---|---|
| Apparatus | : USP XX111 paddle apparatus 2. |
| RPM | : 50 |
| Medium | : Phosphate buffer (pH 7.4) |
| Sampling Interval | : Every 10 minute. |
| Sampling Volume | : 10ml. |
| Study Period | : 1 hr |

**f) Differential scanning calorimetry (DSC)**

DSC (Q20 V24.2) was performed using assess thermotropic properties and thermal behaviors of Glibenclamide and of liquisolid system prepared. Samples (3-5mg) were placed in aluminum pans and lids at constant heating range of 10 °C/min, covering temperature range 30 to 300 °C. Nitrogen was used as purge gas through DSC cell.

**g) Xray powder diffraction analysis**

Crystallinity of the drug and the samples was determined using the XRD-6000 diffractometer with copper target. The conditions were: 40 kV voltages; 30 mA current. The samples were loaded on to the diffractometer and scanned over a range of $2\theta$ values from 10 to $80^{0}$ at a scan rate of $10.00^{0}$ /min.

**8. STABILITY STUDIES:**

The prepared formulations which showed best *in vitro* results was selected and kept for stability testing for 90 days. The tablets were kept at 40± 2°C/ 75%±5%RH in a stability chamber and samples were withdrawn at initial, $30^{th}$ , $60^{th}$ and $90^{th}$ day and evaluated for drug content, disintegration , dissolution study.

# 8. RESULTS AND DISCUSSION

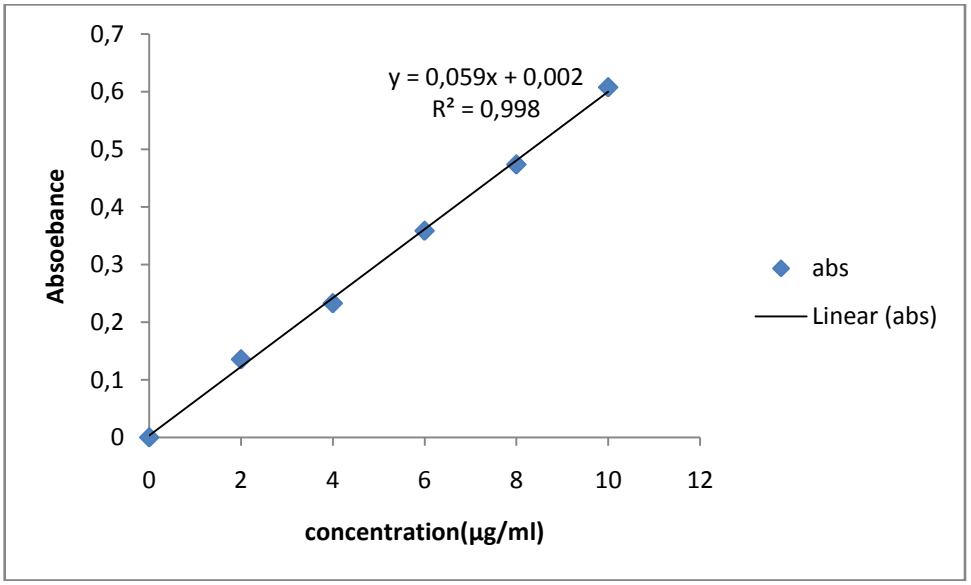
## 1. CALIBRATION CURVE OF GLIBENCLAMIDE

A calibration curve for Glibenclamide was constructed in phosphate buffer pH 7.4 by scanning the diluted drug solution at 227 nm using UV spectrophotometer. The linearity of the calibration curve was found to be in the range of 1-10µg/ml. A regression coefficient value of 0.998 was noticed for Glibenclamide.

**Table 10: Calibration Data of Glibenclamide**

| Concentration (µg/ml) | Absorbance |
|---|---|
| 0 | 0 |
| 2 | 0.1354 |
| 4 | 0.2328 |
| 6 | 0.3585 |
| 8 | 0.4736 |
| 10 | 0.6076 |

**Fig 3 : Calibration curve of Glibenclamide in Phoshate buffer pH 7.4 at 227nm**




## 2. SOLUBILITY STUDIES

The solubility of Glibenclamide in different solvents were studied to select the suitable solvent to be used in the formulation. The results obtained were given in Table.11. Glibenclamide showed a maximum solubility of 2.7407%w/w in propylene glycol (PG) followed by 1.837%w/w in Tween 80 and 0.5919%w/w in PEG 400. Maximum solubility of the drug is needed for preparing liquisolid compacts, as higher the solubility, the more the drug will be dissolved in the vehicle prior to the adsorption onto the carrier particles. As Propylene glycol showed greater solubility of the drug than the other two solvents, it was selected as the suitable solvent for preparing Glibenclamide liquisolid compacts in this study.

**Table 11: Solubility of Glibenclamide in different solvents**

| Solvents | Solubility (%w/w) |
|---|---|
| Propylene Glycol | 2.7407 |
| PEG 400 | 0.5919 |
| Tween 80 | 1.837 |
| Distilled Water | 0.004 |

## 3. APPLICATION OF NEW MATHEMATICAL MODEL FOR DESIGN OF LIQUISOLID SYSTEM

The liquisolid technique as suggested by Spireas et al[36], states that the drug dissolved in a liquid vehicle is incorporated into carrier and coating materials having porous structure and closely matted fibres in its interior, is a phenomenon of both adsorption and absorption. Coating materials like Aerosil PH 102 have high adsorptive capacity and greater surface area and thus gives the liquisolid systems the desirable flow and compaction properties.

To calculate the required quantities of carrier and coating materials, the flowable liquid-retention potentials (Φ values) of the powder materials were used. Spireas et al[36] has given a mathematical model equation for Avicel PH 102 and Aerosil 200 in propylene glycol according to values of Phi (Φ) which is given below.

$$Lf = 0.16 + 3.31\ (1 / R) \quad \text{..... (10)}$$

Where 0.16 is the Φ value for Avicel PH 102 and 3.31 for Aerosil 200. Based on this

equation, Liquid Load factor (Lf) was calculated by using different R values for all the formulations.

The quantity of carrier material (Q) required and the quantity of coating material (q) was calculated by using the following equation;

Amount of carrier material required (Q) = W/Lf..... (11)
Amount of coating material required (q) = Q/R..... (12)

where, W is the weight of the liquid medication, Lf is the liquid load factor, R is the coating and carrier material ratio. The formulation table according the above calculations is shown in Table 12.

**Table 12 Formulation chart**

| Formulation | Drug conc (%w/w) | R | Lf | Q (mg) | q (mg) | Fm |
|---|---|---|---|---|---|---|
| LS-1 | 5 | 10 | 0.491 | 213.85 | 21.38 | 0.54814 |
| LS-2 | | 20 | 0.325 | 323.07 | 16.15 | 0.54814 |
| LS-3 | | 30 | 0.270 | 388.88 | 12.96 | 0.54814 |
| LS-4 | 10 | 10 | 0.491 | 224.03 | 22.40 | 0.27407 |
| LS-5 | | 20 | 0.325 | 338.46 | 16.92 | 0.27407 |
| LS-6 | | 30 | 0.270 | 407.407 | 13.58 | 0.27407 |
| LS-7 | 15 | 10 | 0.491 | 234.21 | 23.42 | 0.1827 |
| LS-8 | | 20 | 0.325 | 353.84 | 17.69 | 0.1827 |
| LS-9 | | 30 | 0.270 | 425.93 | 14.19 | 0.1827 |
| LS-10 | 20 | 10 | 0.491 | 244.39 | 24.43 | 0.13703 |
| LS-11 | | 20 | 0.325 | 369.23 | 18.46 | 0.13703 |
| LS-12 | | 30 | 0.270 | 444.44 | 14.81 | 0.13703 |

R – carrier: coating ratio , Q –weight of carrier , q - weight of coating material, Fm – fraction of molecularly dispersed drug.

## 4. EVALUATION OF FLOWABILITY AND COMPRESSIBILITY OF LIQUISOLID POWDERS

Powder flow properties are crucial in handling and processing operations such as flow from hoppers, mixing and compression. The flow properties of the liquisolid system were influenced by physical, mechanical as well as environmental factors. The powder flowability can be determined by evaluating parameters such as the compressibility or Carr's index, Hausner's ratio and the Angle of repose.

As a general guide, powders with angles of repose greater than 50° have unsatisfactory flow properties, whereas minimum angles close to 25° correspond to very good flow properties [63]. Table (13) revealed that all the tested liquisolid systems had a satisfactory flow according to the obtained results of measuring the angle of repose for each liquisolid system. The range was from 30.13 to 37.78˚. The prepared Glibenclamide liquisolid systems can be arranged in ascending order, regarding the angle of repose measurements as follows: LS-12< LS-4< LS-11< LS-10< LS-6< LS-2< LS-5< LS-8< LS-1 < LS-9< LS- 3< LS-7.

The bulk and tapped densities for Glibenclamide liquisolid powders were illustrated in Table (13) , the mean densities of liquisolid powders were found to be from 0.285 to 0.419 g/cm$^3$ for bulk density and from 0.385 to 0.511 g/cm$^3$ for tapped density.

The powder has a good flowability, when the Hausner ratio is lower than 1.2, while it indicates poor flow when the value exceeds 1.2. It was showed that powders with interparticle friction, such as coarse spheres, had ratios of approximately 1.2, whereas more cohesive, less free-flowing powders such as flakes have Hausner ratios greater than 1.6.

Compressibility is indirectly related to the relative flow rate, cohesiveness, and particle size of a powder. A compressible material will be less flowable, and powders with compressibility values greater than 20-21 % have been found to exhibit poor flow properties [64]. The results obtained for evaluation of compressibility index and Hausner's ratio is given in Table 13.

Hausner ratio and Carr's index were calculated from the density values. These results revealed that LS-9, LS-10, LS-11 and LS-12 had Hausner ratio of 1.16, 1.19, 1.16 and

1.18, respectively, which were less than 1.2 and is an indication for good flowability and the rest formulae had low flowability because it had Hausner ratio more than 1.2. Formulae LS 3 and LS 5 in addition to LS- 9 to LS-12 had Carr's index values of less than 21% which supports the fact that these formulations have good flow and compaction properties.

**Table 13: Precompression studies**

| FORMULATIONS | ANGLE OF REPOSE | DENSITIES ($g/cm^3$) | | HAUSNERS RATIO | CARR'S INDEX |
|---|---|---|---|---|---|
| | | BULK | TAP | | |
| LS-1 | 36.53 | 0.298 | 0.385 | 1.29 | 22.5 |
| LS-2 | 34.21 | 0.312 | 0.403 | 1.31 | 22.6 |
| LS-3 | 34.13 | 0.364 | 0.453 | 1.24 | 19.6 |
| LS-4 | 32.59 | 0.285 | 0.425 | 1.49 | 32.9 |
| LS-5 | 34.95 | 0.416 | 0.511 | 1.22 | 18.6 |
| LS-6 | 33.68 | 0.321 | 0.496 | 1.54 | 35.2 |
| LS-7 | 37.78 | 0.357 | 0.473 | 1.32 | 24.52 |
| LS-8 | 35.17 | 0.364 | 0.463 | 1.27 | 21.38 |
| LS-9 | 36.62 | 0.419 | 0.490 | 1.16 | 14.48 |
| LS-10 | 33.47 | 0.395 | 0.473 | 1.19 | 16.4 |
| LS-11 | 33.18 | 0.412 | 0.482 | 1.16 | 14.52 |
| LS-12 | 30.13 | 0.407 | 0.483 | 1.18 | 15.73 |
| CT | 32.65 | 0.423 | 0.471 | 1.11 | 10.19 |

LS-Liquisolid tablet, CT – conventional tablet

## 5. COMPRESSION OF TABLET:

The liquisolid tablets were prepared by direct compression technique. The target weight of the prepared tablet was 250mg. The desired hardness is between 3-5kg/$cm^2$. All the tablets were found to be uniform in size and shape and no processing problems were encountered during compression process. Similarly conventional tablet of pure drug was also prepared by direct compression technique.

## 6. EVALUATION OF POST COMPRESSION PARAMETERS:

The mean hardness of the tablets ranged from 3.5 -5 kg/cm$^2$ , the mean of the hardness values were shown in Table (14). It was found that there is a relationship between liquid load factor and the hardness of the tablets. The Lf was inversely proportional to the hardness of the tablets ie when the Lf increased the hardness of the tablets will decrease. Formula LS-1, LS-5 were having Lf 0.491 and 0.325 and the mean hardness of them was 4 and 5. Also formula LS-4 and LS- were having Lf 0.491 and 0.270, and the mean hardness of them was 3.5and 5. And this finding was confirmed by third example where formula LS-10 and LS-12 were having Lf 0.491 and 0.270, and the mean hardness of them was 3 and 5 respectively. This can be explained by the fact that increasing Lf of the formula increases the amount of solvent used and decreases the amount of powder excipient and this subsequently, decrease the hardness of the tablets.

LS-6 showed the best result of friability test regarding to the loss of weight (0.006 %), while LS-5 had the largest weight loss (0.015%).

The disintegration time for the prepared Glibenclamide liquisolid tablets was shown in table (14). It was found that the mean of the disintegration times for all the investigated tablets were less than 16 minutes, which meets the Pharmacopoeial requirements. LS – 3 was found to be the fastest formula to be disintegrated (1.46 minutes) followed by LS-2, LS-6 and LS-5with disintegration times of 1.50, 2.10 and 2.45 minutes respectively. The slowest disintegration time was observed with the formula LS -10, which took 12.30 minutes to disintegrate.

The data obtained from the disintegration test suggested that the powder excipient ratio (R) has an influence on the disintegration time of the liquisolid compacts. The powder excipient ratio (R) was found to be inversely proportional to the disintegration time of the tablets. Formula LS-1 LS-2 and LS-3were having the R values 10, 20 and 30, and their mean disintegration time were 3.20, 1.50 and 1.46 minutes respectively. This phenomenon can be explained by the fact that, increasing the R value leads to high carrier material content in the tablet, in this case microcrystalline cellulose (Avicel PH 102) which functions as a swellable disintegrant. Also, the highly hydrophilic characteristic of microcrystalline cellulose could increase the wetting of Glibenclamide and this subsequently, lead the tablet to be disintegrated quickly [65].

It was clear from Table 14 that all the investigated liquisolid tablets complied with the pharmacopoeial requirements with regard to their content uniformity, which was found to lie within the range of 96.12 to 101.2 %.

**Table 14: Post compression parameters**

| Formulations | Average Weight (mg) | Hardness (kg/cm$^2$) | Friability (%) | Disintegration time (min) | Content uniformity (%) |
|---|---|---|---|---|---|
| LS-1 | 253±3 | 4 | 0.007 | 3.20 | 96.5 |
| LS-2 | 251±9 | 4.5 | 0.009 | 1.50 | 96.7 |
| LS-3 | 250±5 | 5 | 0.013 | 1.46 | 99.3 |
| LS-4 | 248±1 | 3.5 | 0.015 | 3.45 | 98.6 |
| LS-5 | 246±2 | 5 | 0.008 | 2.45 | 99.7 |
| LS-6 | 253±4 | 5 | 0.006 | 2.10 | 97.3 |
| LS-7 | 250±1 | 3.5 | 0.019 | 4.21 | 101.2 |
| LS-8 | 249±5 | 4 | 0.007 | 4.57 | 98.5 |
| LS-9 | 250±2 | 5 | 0.014 | 5.32 | 99.1 |
| LS-10 | 250±6 | 3 | 0.017 | 12.30 | 96.12 |
| LS-11 | 254±4 | 4 | 0.006 | 9.40 | 96.6 |
| LS-12 | 255±2 | 5 | 0.008 | 7.25 | 98.7 |
| CT | 250±1 | 3.5 | 0.015 | 20.10 | 97.2 |
| MT | 10±5 | 4 | 0.009 | 18.15 | 96.9 |

LS-Liquisolid tablet, CT- Conventional tablet, MT- Marketed tablet

**7. COMPATIBILITY STUDIES:**

The spectrum obtained after the analysis is shown in Figs.4-7. The spectrum of the standard and the samples were then superimposed to find out any possible interactions between the drug and the polymers. All the characteristic peaks of Glibenclamide

mentioned in table (15) were also found in the spectrum formulations. The results suggests that the drug is intact in the formulations and there is no interaction found between the drug and the excipients.

**Table 15: Characteristic peaks of Glibenclamide**

| Serial number | Wavelength | Specification |
|---|---|---|
| 1. | 3315 $cm^{-1}$ | Amide NH stretching vibration |
| 2. | 1745$cm^{-1}$ | Amide C=O stretching |
| 3. | 1617$cm^{-1}$ | Amide NH bending |
| 4. | 1342$cm^{-1}$ | $SO_2$ stretching |
| 5. | 1430$cm^{-1}$ | $CH_2$ bending vibration |

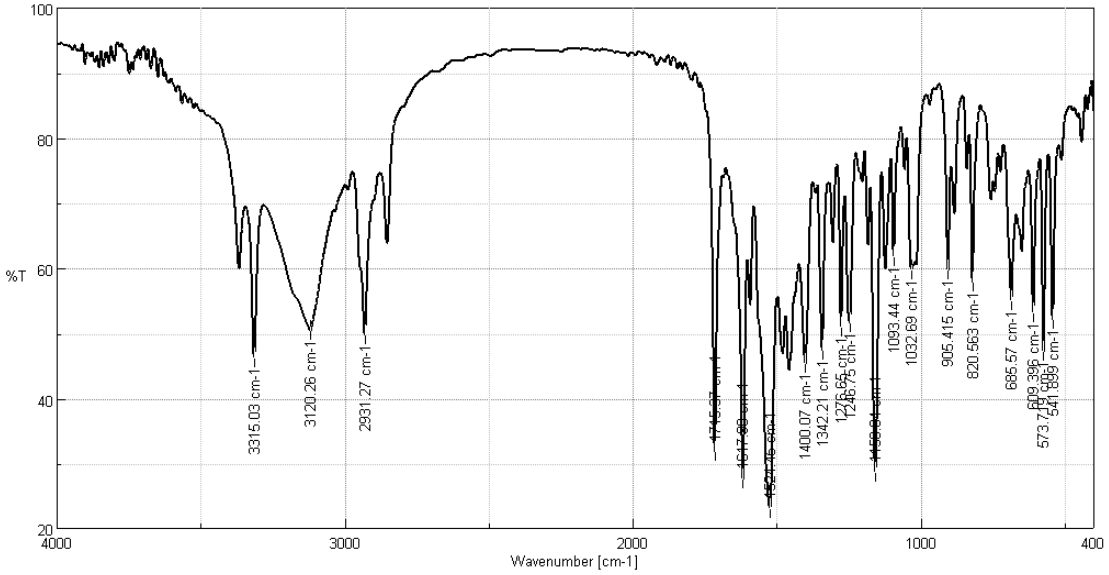



**FIGURE 4:IR OF GLIBENCLAMIDE**

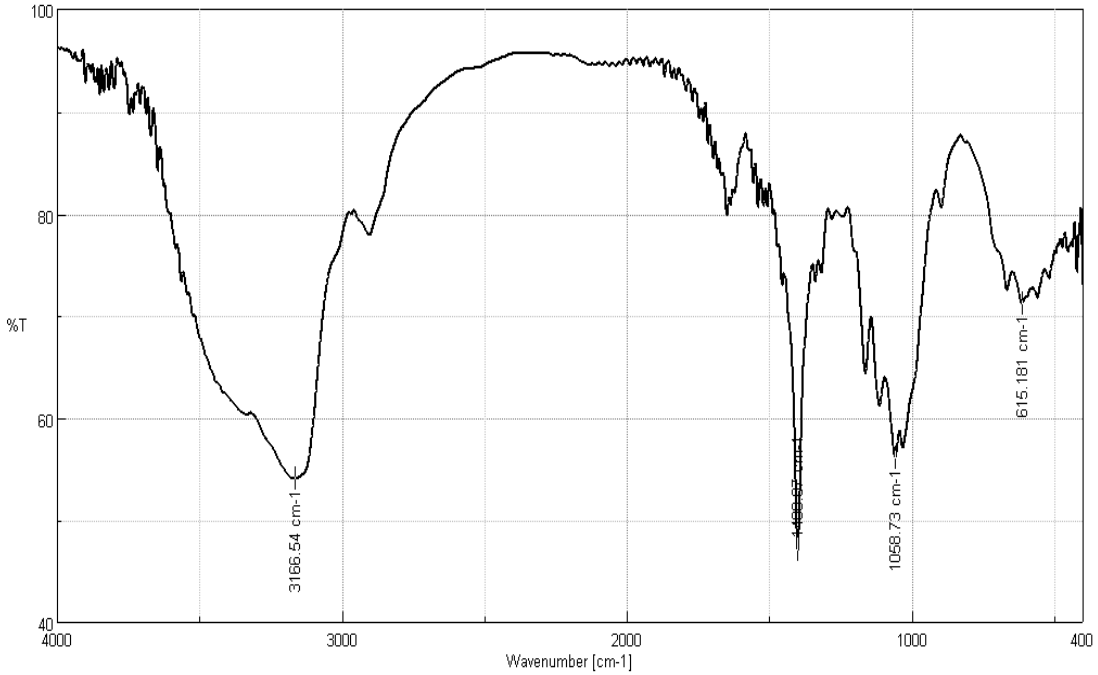



**FIGURE 5: IR OF MCC**

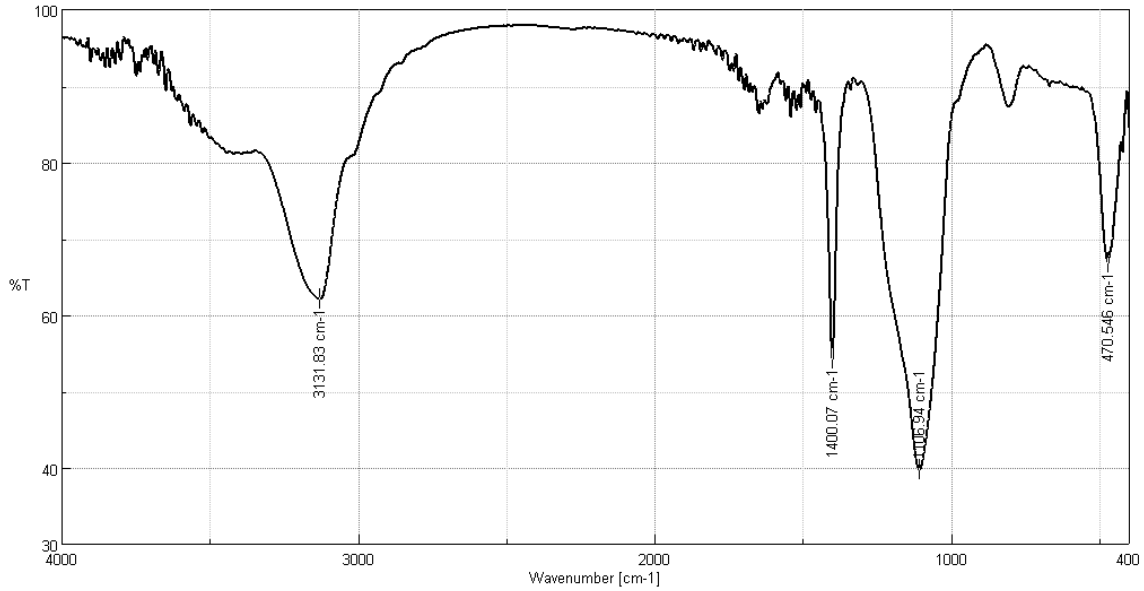



**FIGURE 6 :IR OF AEROSIL**

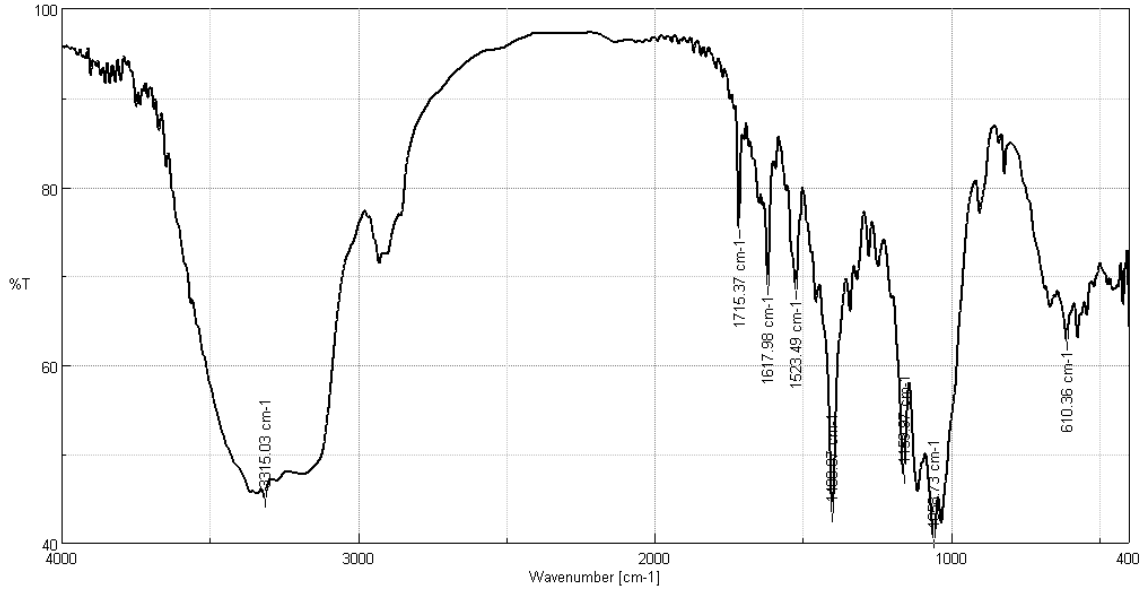



**FIGURE 7 IR OF LIQUISOLID FORMULATION**

## 8. DIFFERENTIAL SCANNING CALORIMETRY (DSC)

DSC studies were carried out to determine the interaction between drug and excipients in prepared liquisolid formulation and also to detect changes in the drug crystallinity. DSC thermograms of Glibenclamide and final liquisolid formulation system were represented in Figure 8 and 9. The DSC thermogram of pure glibenclamide (Fig. 8) gave a sharp characteristic peak at temperature range 177.12°C corresponding to its melting temperature (Tm). This shows that Glibenclamide used was in pure form. The DSC thermogram of liquisolid system (Fig. 9) does not feature a sharp characteristic peak of Glibenclamide at 177.12°C which ensures the formation of drug solution in liquisolid formulation and thus confirms that the drug was molecularly dispersed in liquisolid system. Also there is a broad peak at 86.85˚C which corresponds to the evaporation of water associated with Avicel PH 102 particles.

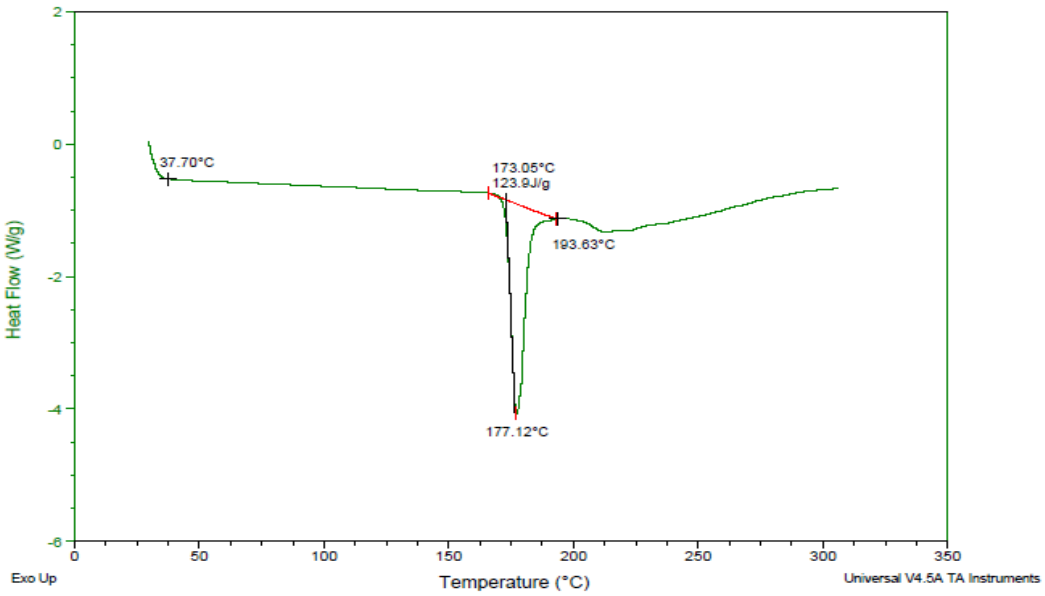



**FIGURE 8: DSC OF GLIBENCLAMIDE**

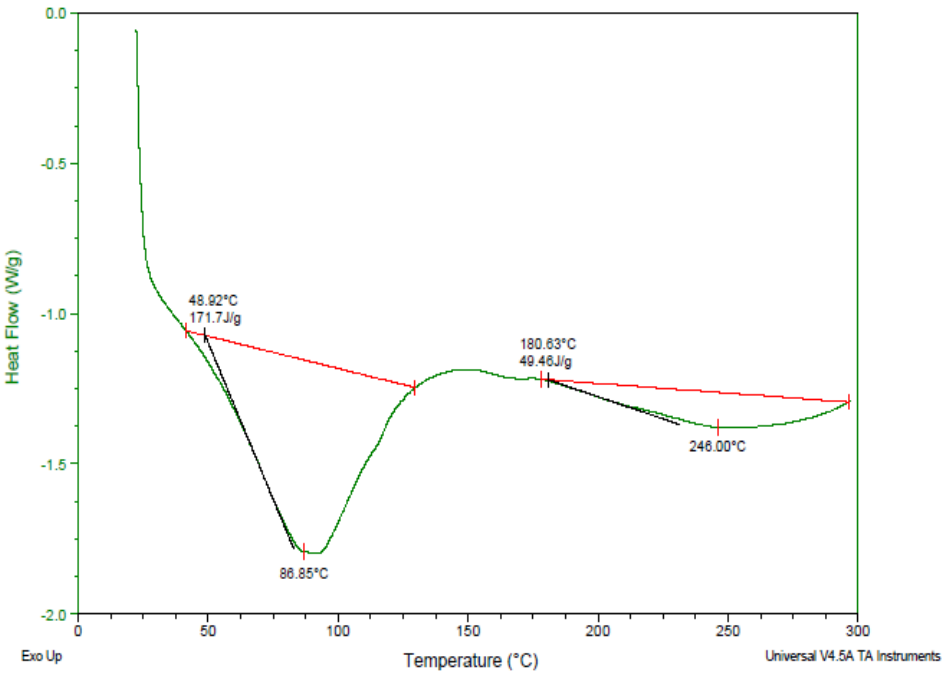



**FIGURE 9: DSC OF LIQUISOLID SYSTEM**

## 9. X-RAY POWDER DIFFRACTION (XRPD)

Polymorphic changes in the drug are important since they might affect the dissolution rate and in turn bioavailability. So, it was necessary to study the polymorphic changes of Glibenclamide in liquisolid compacts. Figs.10 and 11 shows the XRPD of pure drug and the liquisolid system Glibenclamide has sharp peaks at 18.84, 20.85, 19.40 and 22.94 at 2θ. Avicel PH 102 has a sharp diffraction peak at 23.29 at 2θ while the liquisolid powder had a sharp diffraction peak at 22.37 at 2θ which is evidence that Avicel PH 102 remains in its crystalline state. The absence of characteristic peaks of Glibenclamide in the liquisolid system shows the conversion of drug to an amorphous or solubilized form. The absence of crystallinity in the liquisolid system is due to the solubilization of drug in the liquid vehicle.

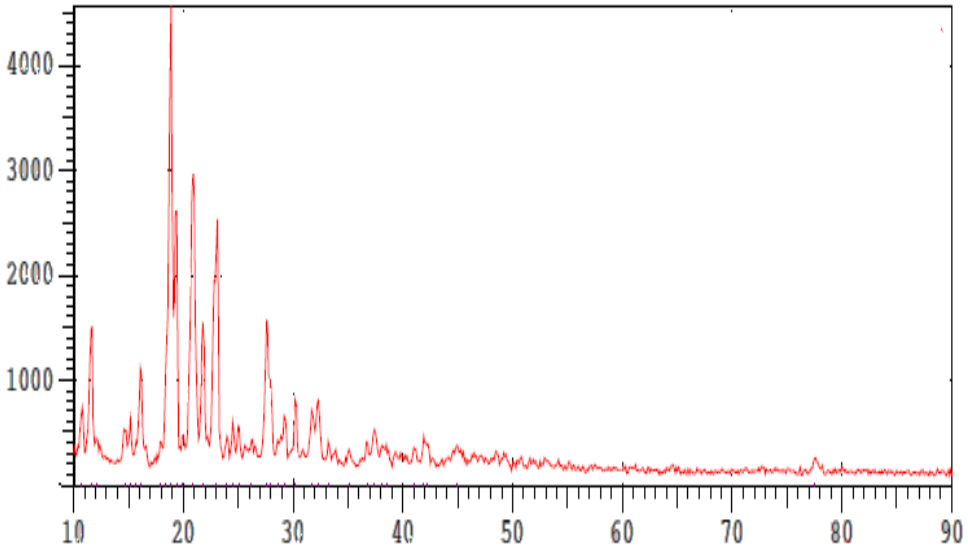



**FIGURE 10:X-RAY DIFFRACTOGRAM OF GLIBENCLAMIDE**

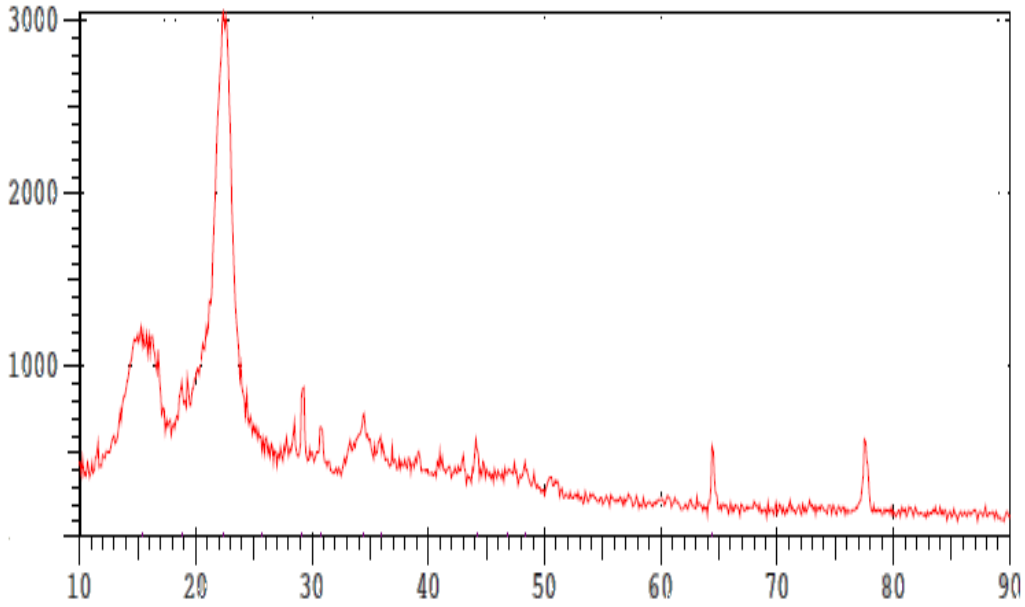



**FIGURE 11: X-RAY DIFFRACTOGRAM OF LIQUISOLID SYSTEM**

## 10. *IN VITRO* DISSOLUTION STUDY

Figs 12-16 show the dissolution profile of 12 formulations, conventional tablet of pure drug and marketed tablet. Liquisolid compacts displayed more distinct *in-vitro* release characteristics than the conventional and marketed drug. Among all, LS-3 showed higher release rate (91.35%) at the end of the $60^{th}$ min. Conventional tablet and marketed tablet showed only 35.73% and 33.22% cumulative release. It was confirmed that at 10 min LS-3 had the highest drug release 57.73% compared with 15.75% for the conventional tablet. Since the liquisolid compacts contain a solution of the drug in non volatile vehicle used for preparation of the liquisolid compacts, the drug surface available for dissolution is tremendously increased. In essence, after disintegration, the liquisolid primary particles suspended in the dissolving medium contain the drug in a molecularly dispersed state, whereas the directly compressed compacts are merely exposed micronized drug particles. Therefore, in the case of liquisolid compacts, the surface area of drug available for dissolution is much greater than that of the directly compressed compacts.

According to Noyes and Whitney, the drug dissolution rate (DR) is directly proportional not only to the concentration gradient (Cs-C) of the drug in the stagnant diffusion layer, but also to its surface area (S) available for dissolution. Moreover, since all dissolution tests for both Glibenclamide preparations were carried out at a constant rotational paddle speed (50 r/min) and identical dissolving media, it is assumed that the thickness (h) of the stagnant diffusion layer and the diffusion coefficient (D) of the drug molecules transported through it remain almost identical under each set of dissolution conditions. Therefore, the significantly increased surface area of the molecularly dispersed Glibenclamide in the liquisolid compacts may be principally responsible for their higher dissolution rates. The consistent and higher dissolution rate displayed by liquisolid compacts will improve the absorption of drug from the GI tract.

**Table 16 Percentage of drug release from liquisolid tablets, conventional and marketed tablets**

| Formulation | Time(hrs) | | | | | |
|---|---|---|---|---|---|---|
| | 10 | 20 | 30 | 40 | 50 | 60 |
| LS-1 | 48.56 | 59.73 | 65.19 | 72.32 | 81.92 | 85.97 |
| LS-2 | 52.92 | 61.43 | 67.66 | 76.96 | 83.64 | 88.62 |
| LS-3 | 57.73 | 65.94 | 69.17 | 78.53 | 86.72 | 91.35 |
| LS-4 | 25.96 | 37.52 | 48.39 | 59.38 | 70.37 | 77.47 |
| LS-5 | 27.12 | 40.35 | 51.55 | 69.75 | 78.41 | 80.34 |
| LS-6 | 29.19 | 42.72 | 55.69 | 71.33 | 80.53 | 83.68 |
| LS-7 | 20.79 | 32.13 | 40.59 | 54.24 | 63.95 | 71.84 |
| LS-8 | 21.98 | 35.63 | 43.74 | 56.19 | 67.33 | 74.57 |
| LS-9 | 25.96 | 39.52 | 48.42 | 59.37 | 70.69 | 76.38 |
| LS-10 | 12.13 | 27.95 | 32.31 | 41.82 | 53.73 | 65.31 |
| LS-11 | 10.31 | 29.33 | 37.53 | 42.29 | 57.54 | 67.95 |
| LS-12 | 14.73 | 32.64 | 41.30 | 48.73 | 60.14 | 69.77 |
| PURE DRUG | 15.75 | 27.50 | 31.91 | 33.32 | 35.20 | 35.73 |
| MARKETED | 17.52 | 26.06 | 27.21 | 30.28 | 31.14 | 33.22 |

LS – Liquisolid tablet

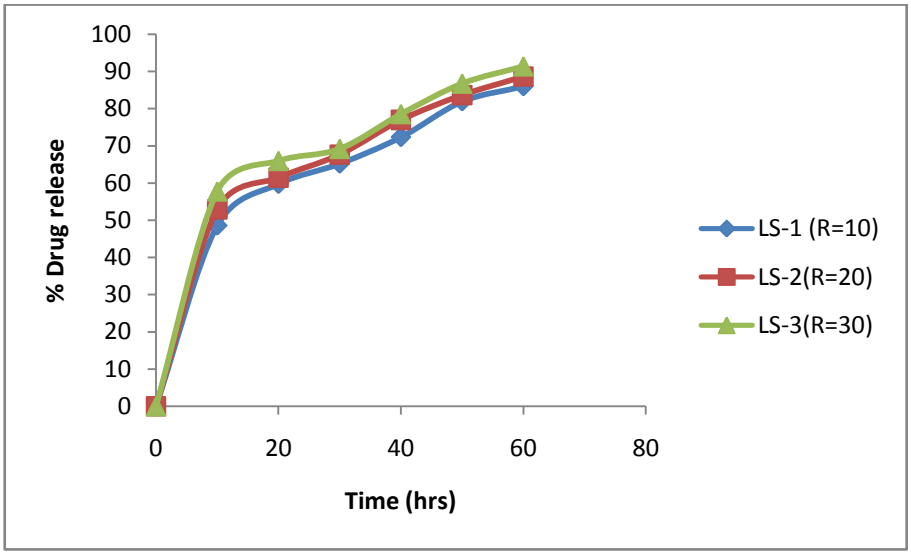



**Figure 12: Dissolution profile of formulations with 5 % drug concentration**

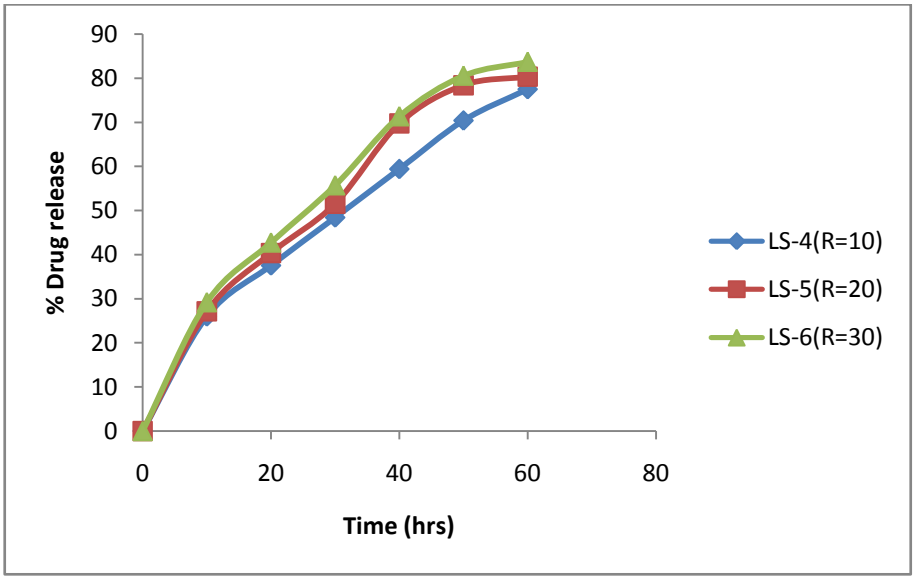



**Figure 13: Dissolution profile of formulations with 10% drug concentration**

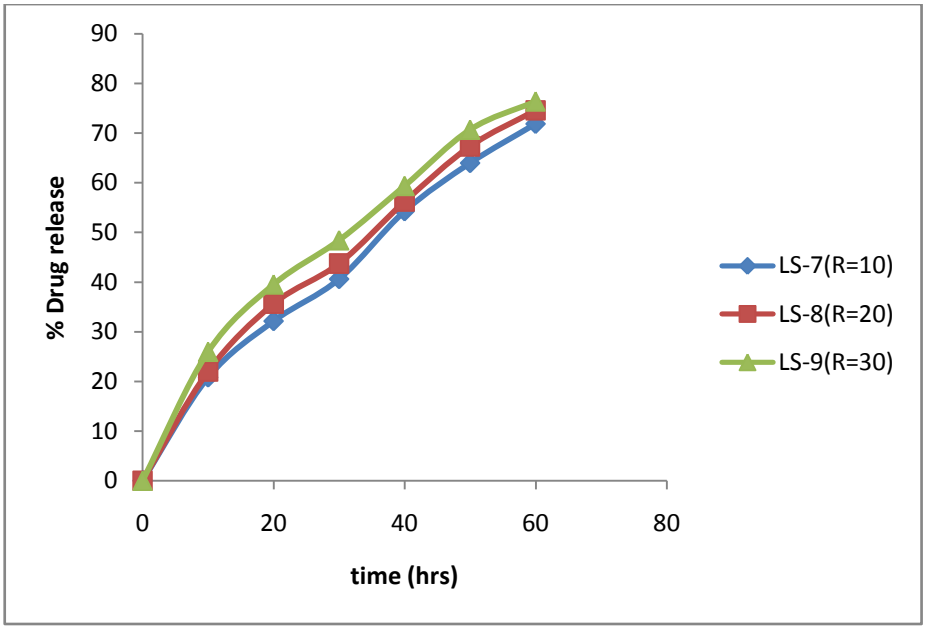



**Figure 14: Dissolution profile of formulations with 15% drug concentartion**

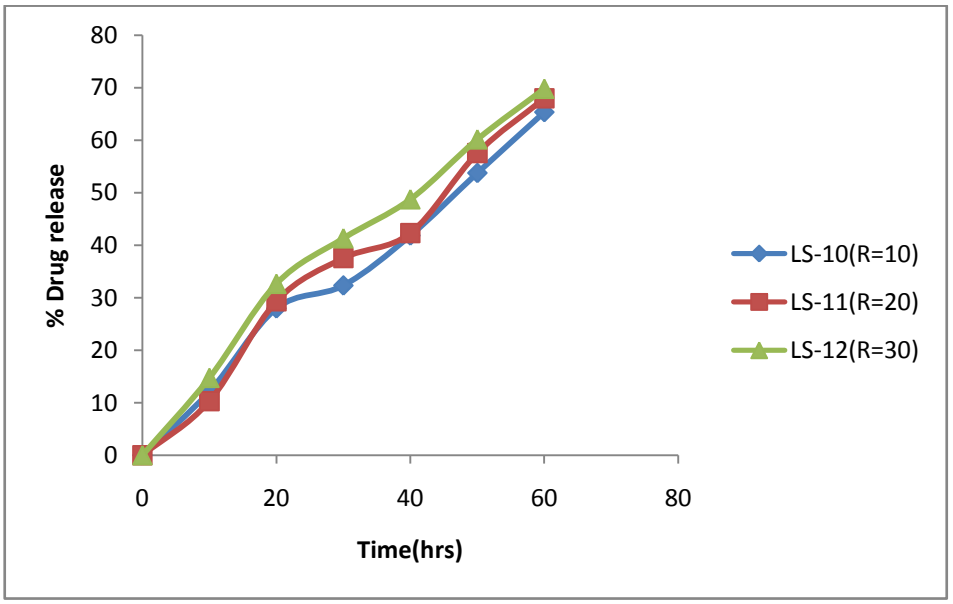



**Figure 15: Dissolution profile of formulations with 20% drug concentartion**

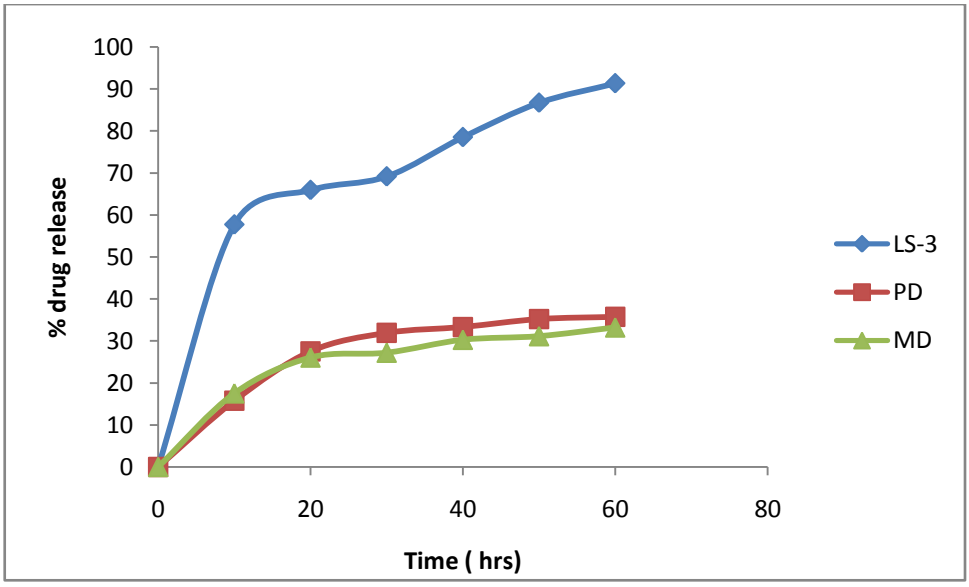



**Figure 16: Dissolution profile of best formulation (LS-3) pure drug and marketed tablet**

**a. Effect of drug concentration on release rate**:

Figs: 17 show that formulations with smaller drug concentration (5%w/w) have a higher dissolution than higher drug concentration (20%w/w).

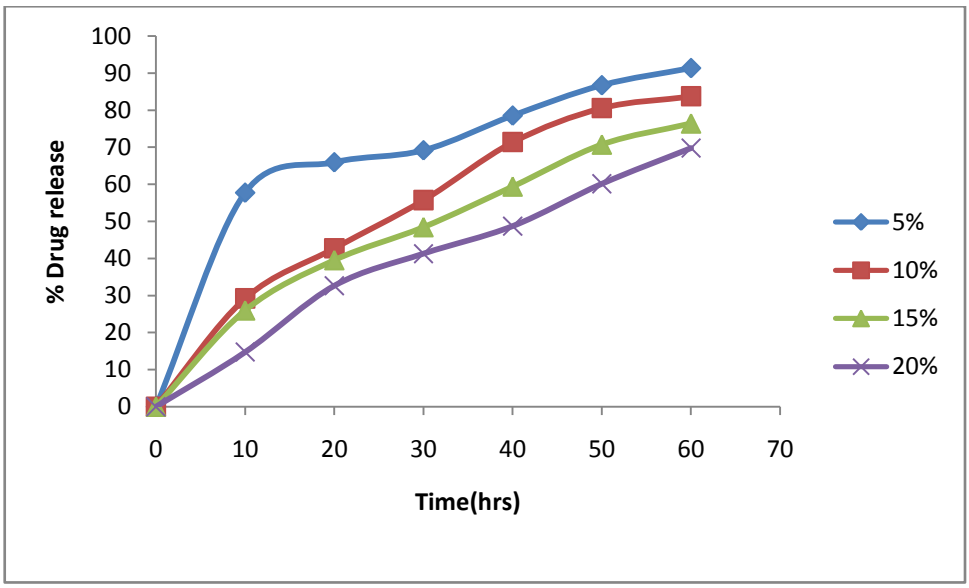



**Figure 17: Dissolution profile of formulations with excipient ratio 30 and different drug concentration.**

This can be explained by the dissolved drug in the liquid medication as follows:

$$FM=C_L/C_D \quad \text{..... (13)}$$

where FM is the fraction of molecularly dispersed or dissolved drug in liquid medication of the prepared liquisolid formulation, $C_L$ is the saturation solubility of Glibenclamide in the liquid vehicle and $C_D$ is the drug concentration in the liquid medication. According to Spireas et al, FM value cannot exceed unity. The saturation solubility of Glibencamide in PG is 2.7407%w/w (Table 11 ), by applying Eq. (13), it can be calculated that 52.4% of the drug was solubilised in LS-3 , 27.40% of Glibenclamide was solubilised in LS-6, 18.27% of Glibenclamide was solubilised in LS-9 and 13.703%w/w of Glibenclamide in LS-12. The higher the drug concentration in a liquisolid formulation, the lower will be the amount of drug solubilised in the liquid vehicle. Apparently, LS-3 which has 52.41% of drug available in solubilised form promote higher dissolution rate than LS-6, LS-9 and LS-12. It was proven that FM is directly proportional to the drug dissolution rate. The FM values of such liquisolid formulations were listed in Table (12). Another explanation for this phenomenon is that high concentration of the drug could precipitate within the silica (Aerosil) pores; thus, drug dissolution rate would be reduced. The potential of Glibenclamide to precipitate within the silica pores is depending on the solubility of the drug in the solvent, the degree of saturation of the drug solution or the interactions between drug and excipients .

**a. Effect of powder excipient ratio (R) on drug release:**

From the obtained results, it was clear that there exists a relationship between the powder excipient ratio and the *invitro* release of Glibenclamide from liquisolid tablets. The powder excipient ratio was directly proportional to the *in vitro* release i.e., when the powder excipient ratio increased, the release will increase. This finding was confirmed from the following results. Formulae LS-1, LS-2, and LS-3 were having R value 10, 20, 30, and the cumulative percent released were 85.97, 88.62, and 91.35%, respectively. Also, formulae LS-4, LS-5, and LS-6 were having R value equal to 10, 20, 30, and the cumulative percent released of them were 77.47, 80.34, and 83.68%, respectively. This may be attributed to the high microcrystalline cellulose content where Avicel PH 102 functions as a swellable disintegrant. In addition, the highly hydrophilic characteristic of microcrystalline cellulose could increase the wetting of Glibenclamide and enhance its dissolution.

## 11. STABILITY STUDIES:

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions. Here the tablets were loaded at accelerated condition at $40^0C \pm 2^0C$/75% RH±5%RH in a stability chamber. Samples were withdrawn at initial, 30, 60, and 90 days and evaluated for drug content, dissolution and disintegration time. The result showed that storage at 40 ºC had no effect on the drug content, disintegration time and dissolution time. This indicates that the technology is a promising technique to enhance the release rate without having any physical stability issues.

**Table .17 Stability study of Glibenclamide**

| **Condition 40ºC** | | | | | |
|---|---|---|---|---|---|
| **Sl.No** | **Parameters** | **L3** | | | |
| | | **Initial** | **30th day** | **60th day** | **90th day** |
| 1. | Drug content (%) | 99.3 | 98.9 | 98.7 | 99.4 |
| 2. | Disintegration time (min) | 1.46 | 1.55 | 1.4 | 1.5 |
| 3. | Dissolution (%CR in 1 hr) | 91.35 | 90.45 | 90.85 | 91.22 |

CR – cumulative release

# 9. SUMMARY

The present study was aimed at preparing Liquisolid compacts of Glibenclamide to enhance its dissolution rate. Glibenclamide is a poorly water soluble antidiabetic drug which belongs to BCS class II drugs. Hence it will be beneficial to increase its dissolution rate in order to improve its bioavailability by Liquisolid technique.

**Formulation**

In the preparation of liquisolid compacts, a suitable non volatile solvent having sufficient solubility for the drug should be chosen followed by a suitable carrier and coating materials. In this study, propylene glycol was selected as the liquid vehicle as it showed enhanced solubility than tween 80 and PEG 400. Avicel and aerosil were chosen as carrier &coating material. CCS was chosen as the super disintegrant. A total of 12 formulations were made using four different concentrations of drug (5,10,15 & 20% w/w) at three different R values i.e 10, 20 & 30.

**Preformulation Studies**

Preformulation studies of the prepared liquisolid powder blend of all the 12 formulations were performed. Parameters like angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio and swelling studies for the polymers were studied. The results obtained from the above studies showed that the prepared blend was having satisfactory fluidity and compressibility and hence can be processed into tablets by direct compression method.

**Compression of Tablets**

Tablets were compressed by direct compression method using Rimek Tablet punching machine to a target weight of about 250 mg. All the tablets prepared were having uniform size and thickness with a hardness of about 3.5-5kg/cm. There were no processing problems encountered during the compression process.

**Evaluation of Tablets**

The compressed tablets were then evaluated for various tests like hardness, weight variation, content uniformity, friability etc as per the method given by Indian Pharmacopeia All the 12 formulations passed in these tests with values within the limit prescribed by the IP. IR studies was also done to check the interaction between drug

and excipients and the result showed that the drug is intact and compatable with the excipients.

**Differential Scanning Calorimetry (DSC)**

DSC thermogram of Glibenclamide showed a sharp peak at 177.12 °C which corresponds to its melting point. This shows that the drug is in pure form. DSC thermogram of formulation does not showed any peak and hence ensures formation of drug solution in liquisolid formulation. This confirms that drug was molecularly dispersed in liquisolid system.

**X- Ray powder diffraction (XRPD)**

Sharp distinct characteristic peaks at 2θ diffraction angles for Glibenclamide at 18.84, 20.85, and 19.40 indicated its crystalline state. X-ray diffractogram of liquisolid powder showed absence of these distinct peaks. Hence absence of specific peaks in liquisolid system revealed that Glibenclamide has been completely converted to molecular form or solubilised form. This lack of crystallinity in the formulation might be due to solubilization of drug in liquid vehicle which was absorbed into carrier material and adsorbed onto carrier and coating materials.

***In Vitro* Drug Release Studies**

The *in vitro* drug release studies of all the formulations were studied using USP Type II Paddle apparatus with phosphate buffer pH 7.4 as the dissolution medium. The study was performed for 1h and an average of three determinations was reported. From the observed result it was noted that formulation with less drug concentration and high R value shown higher release rate. . The lower the drug concentration in a liquisolid formulation more will be the amount of drug solubilised in the liquid vehicle. Also, the highly hydrophilic characteristic of microcrystalline cellulose could increase the wetting of Glibenclamide and enhance its dissolution. Although all formulation shown good release rate than conventional and marketed tablet. LS-3 was chosen as the best formulation due to its higher percentage release.

# 10. CONCLUSION

Solubility is one of the major factors which affects the *in vivo* performance of the drug. Poorly soluble drugs throw a stiff challenge to the formulation scientists in producing a dosage form for such drugs with satisfactory dissolution profile. Among the various mechanisms used for improving the solubility and thereby the dissolution of these drugs, liquisolid technique is gaining much attention and importance in recent years. The availability of drug in the solubilised form and increase in the wettability of the powders by the dissolution media were some of the proposed mechanisms to explain the enhanced dissolution rate of poorly soluble drugs from such formulations.

Hence, in this study, liquisolid technique was chosen to enhance the dissolution properties of Glibenclamide. The Glibenclamide liquisolid compacts were prepared by using propylene glycol as the non volatile liquid vehicle. Avicel PH 102 and Aerosil 200 were used as the carrier and coating material, respectively. The flow properties of Glibenclamide liquisolid compacts showed an acceptable flowability. The hardness, friability, weight variation and disintegration tests were within acceptable limits. The *in vitro* dissolution study confirmed enhanced drug release from liquisolid compacts compared with conventional and marketed tablet. XRPD studies showed complete inhibition of crystallinity in the Glibenclamide liquisolid compacts suggesting that the drug has been transformed into amorphous form having more solubility than the parent drug. The DSC study also supported the findings of XRPD analysis and confirmed the absence of any interaction between the drug and excipients used in the preparation of Glibenclamide liquisolid compacts. The liquisolid tablets having drug concentration of 5%w/w (LS-3) with Lf value of 0.270 and R value of 30, was chosen as best formulation among the twelve batches, in terms of faster disintegration time, superior dissolution profile and acceptable tablet properties.

This research work has produced encouraging results in terms of increasing the *in vitro* dissolution of poorly soluble drugs such as glibenclamide using liquisolid technology and we expect a good correlation between the *in vitro* and *in vivo* performance of the formulations. The technique being simple and effective can also be extended to other poorly soluble drugs. The *in vivo* performance of the liquisolid compacts has to be studied using animal models to claim a complete success in the development of these formulations.

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