SOLUBILITY ENHANCEMENT OF ANTIDIABETIC DRUG (GLIBENCLAMIDE)

Dissertation submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI

In partial fulfillment of the requirements for the award of the degree of

MASTER OF PHARMACY

(PHARMACEUTICS)

By

(REG.NO:261310402)

Under the guidance of

Dr. Mrs.J. JeyaAnanthi., M.Pharm,Ph.D

DEPARTMENT OF PHARMACEUTICS,

ARULMIGU KALASALINGAM COLLEGE OF PHARMACY, ANAND NAGAR, KRISHNANKOIL – 626 126

APRIL – 2015

CERTIFICATE

This is to certify that the investigation described in the dissertationentitle**"SOLUBILITY ENHANCEMENT OF ANTIDIABETIC DRUG (GLIBENCLAMIDE)"** submitted by **Reg.No:261310402** was carried out in the **Department of Pharmaceutics,** *Arulmigu Kalasalingam College of Pharmacy, Anand Nagar, Krishnankoil-626 126,*which is affiliated to**The Tamil Nadu Dr. M.G.R. Medical University, Chennai,** under my supervision and guidance for the partial fulfillment of degree of **MASTER OF PHARMACY**in **PHARMACEUTICS.**

Place: Krishnankoil.

Date:

                                  Dr. Mrs. J.Jeya Ananthi, M.Pharm,Ph.D,.
                                  HOD Department of Pharmaceutics,
                                  Arulmigu Kalasalingam College of Pharmacy,
                                  Anand nagar, Krishnankoil.

CERTIFICATE

This is to certify that the investigation described in the dissertation entitled "SOLUBILITY ENHANCEMENT OF ANTIDIABETIC DRUG (GLIBENCLAMIDE)" submitted by Reg.No:261310402 was carried out in the Department of Pharmaceutics, *Arulmigu Kalasalingam College of Pharmacy, Anand Nagar, Krishnankoil-626 126,* which is affiliated to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, under the supervision and guidance of Dr. Mrs.J.JEYA ANANTHI., M.Pharm., Ph.D., HOD Dept of Pharmaceutics for the partial fulfillment of degree of MASTER OF PHARMACY in PHARMACEUTICS.

Place:Krishnankoil.

Date:

Dr.M.PALANIVELU., M.Pharm., PhD.,
Principal,
Arulmigu Kalasalingam College of Pharmacy
Krishnankoil.

EVALUATION CERTIFICATE

This is to certifie That the dissertation Works entitled "SOLUBILITY ENHANCEMENT OF ANTIDIABETIC DRUG (GLIBENCLAMIDE)" submitted by Reg.No:261310402 to The Tamil Nadu Dr.M.G.R. Medical University, Chennai, in partial fulfillment of the requirements for the award of degree of MASTER OF PHARMACY in PHARMACEUTICS.

Centre: **Arulmigu Kalasalingam College of Pharmacy,**

   Krishnankoil.

Date:

Examiners:

1.

2.

ACKNOWLEDGEMENT

"Success is how high you bounce when you hit bottom"

"If you can dream it, you can do it"

The completion of my M. Pharmacy is not only fulfillment of my dreams but also the dreams of my parents who have taken lots of pain for me in completion of my higher studies. I solicit my deep sense of appreciation and love to my wonderful parents and consider my self-privilege to have seen an entity of almighty in them.

I consider it as a great honour to express my deep sense of gratitude and indebtedness to my guide Dr. Mrs.J.JEYA ANANTHI., M.Pharm., Ph.D.,HOD.Department of Pharmaceutics, Arulmigu Kalasalingam College of Pharmacy for his excellent guidance, constant encouragement and every scientific and personal concern throughout the course of investigation and successful completion of my work.

I express my deep sense of gratitude and obedience to our Principal **Dr.M.Palanivelu, M.Pharm., Ph.D.**, Arulmigu Kalasalingam College of Pharmacy for constant help, helpful suggestions and constructive criticism extended to me during the Course Of Study.

I am extremely thankful to our department staff **Mr.J.Anbu raj, M.Pharm. MBA, Mr.V.Sivakumar.,M.pharm.,Dr.Mr.V.Vinothabhusan.,M.Pharm.,Ph.D** Department Of Pharmaceutics.And **Dr.Mr.T.Panneer Selvam. M.Pharm., Ph.D** Department Of pharmaceutical Analysis.

Affectionately dedicated
to
My beloved Parents

INDEX

INTRODUCTION

As a result of the modern 'high throughput' approach to drug discovery, it has been estimated that up to 70% of the new chemical entities(NCEs) entering drug development possess insufficient aqueous solubility to allow adequate and consistent gastrointestinal (GI) absorption to ensure efficacy.

Molecules with poor solubility, often referred to as BCS Class II (poor solubility) or BCS Class IV (poor solubility and permeability), are typically impeded by poor and variable bioavailability. Higher drug doses can be used to compensate; however, this strategy can lead to side effects, food effects and inter subject variability. Consequently, a more sophisticated solution is required to assure the compound can be successfully developed.

Drug Product Design to Overcome Solubility Issues

The options available to the development team to address solubility problems fall into two broad categories:

*API modifications

*Formulation technology.

API modifications:

Potential API modifications include salt selection and polymorphism studies and cover particle-engineering approaches such as nanotechnology. These approaches seek to improve solubility through reducing the crystallinity within drug particles and increasing surface area.

Formulation technology:

Formulation technologies include amorphous solid dispersions and liquid systems, such as lipid and surfactant systems. These aim to enhance solubility through an improvement in intrinsic dissolution rate or by modifying the local environment around the dosage form.

SOLID DISPERSION TECHNOLOGY

The successful formulation of poorly water-soluble drugs is one of the major problems for pharmaceutical scientist. Over the years, a variety of solubilization techniques have been studied to improve the dissolution rate. To obtain more rapid and complete absorption such as using surfactant, hydro tropes and co-solvents, preparing co-precipitate, liquisolid compacts fast releasing microparticles interactive mixtures and number of researches had been carried to increase the solubility of poorly soluble drugs.[1]

Solid dispersion is one of the significant and widely used methods for solubility enhancement. Solid Dispersion technology has been successfully used to increase the dissolution rate and bioavailability of poorly water soluble drugs. Recently attempts are being made to incorporate porous materials in solids dispersion to increase to solubility. It has been widely used to improve the dissolution rate, solubility and oral absorption of poorly water-soluble drugs.[2]

There are practical limitationsof these techniques. The salt formation is not feasible for neutral compounds and the synthesis of appropriate saltforms of drugs that are weakly acidic or weakly basic may often not be practical. Even when salts can be prepared, an increased dissolution rate in the gastrointestinal tract may not be achieved in many cases because of the reconversion of salts into aggregates of their respective acid or base forms. The solubilization of drugs in organic solvents or in aqueous media by the use of surfactants and co-solventsleads to liquid

formulas that are usually undesirable from the viewpoints of patient acceptability and commercialization. Although particle size reduction is commonly used to increase dissolution rate, there is a practical limit to how much size reduction can be achieved by such commonly used methods as controlled crystallization, grinding, etc.
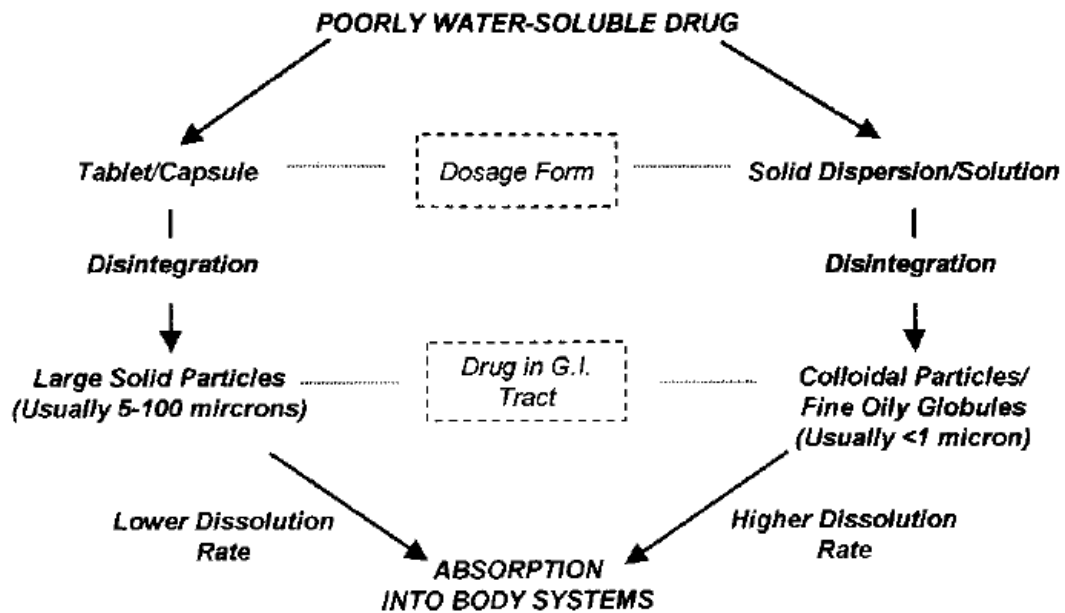
Figure 1—A schematic representation of the bioavailability enhancement of a poorly water-soluble drug by solid dispersion compared with conventional tablet or capsule.

the use of very fine powders in a dosage form may also be problematic because of handling difficulties and poor wettability.[3]

Polymers used in solid dispersions

Various Suitable water-soluble carriers include polymers such as polyethylene glycol, poloxamers, polyoxyethylenestearates, poly-epsilon-caprolactone, polyvinylpyrrolidone (PVP), polyvinylpyrrolidone-polyvinyl acetatecopolymer PVP-PVA (Kollidon VA64), poly-meth acrylic polymers (Eudragit RS, Eudragit RL, Eudragit NE, Eudragit E) and polyvinyl alcohol (PVA), hydroxypropylcellulose (HPC), hydroxypropylmethyl cellulose (HPMC), methyl

cellulose, and poly ethylene oxide (PEO). Further various molecular weight grades of these polymers have been used for the preparation of solid dispersion and solid solutions. Polymers and surface-active agent combinations are used. Superdisintegrants and Cyclo-dextrins are primarily used to enhance solubility, chemical protection, test masking and improved handling by the conversion of liquids into solids by entrapment.

Polymers containing acidic functional groups may be suitable for solid dispersions, which release the active substance in a preferred pH range providing acceptable absorption in the intestines. Such polymers may be one or more selected from the group comprising hydroxypropyl methylcellulose phthalate (HPMCAP), polyvinyl acetate phthalate (PVAP), and Hydroxypropyl methyl cellulose acetate succinate (HPMCAS), Alginates, Carbomers, carboxymethyl cellulose.

The weight ratio of active substance to polymer may be in a range from about 3: 1 to about 1: 20. However, narrow ranges of form about3: 1 to about 1: 5, such as, e.g., from about 1: 1 to about 1: 3 or above may also be used.[4]

SELECTION OF CARRIER(S)

The properties of the carrier have a profound influence on the dissolution characteristics of the dispersed   drug. A carrier ought to meet the following prerequisites for being suitable for increasing the dissolution rate of a drug [49]

It should be

- ❖ Freely water soluble with rapid dissolution properties

- ❖ Nontoxic and pharmacologically inert

- ❖ Heat stable with a low melting point for the melt method

- ❖ Soluble in a variety of solvents

❖ Preferably enhancing the aqueous solubility of the drug

❖ Chemically compatible with the drug

❖ Forming only weakly bounded complex with the drug[16]

Characteristics of Ideal polymer system

1.It should be chemically inert and free from leachable impurities.

2. It should be non toxic and compatible with the environment.

3. It should have good mechanical strength.

4. It should be easy and inexpensive to fabricate.

5. It should be easily sterilized.

6. It should demonstrate acceptable shelf life.[5.6]

Drug release mechanisms for polymeric drug delivery.

Two broad categories of polymer systems have been studied. The reservoir device involves the encapsulation of a drug within a polymer shell,while the matrix device describes a system in which a drug is physically entrapped with in a polymer network.[7]

Fig: 1.2possible drug release mechanisms for polymeric drug delivery

```
                        ┌─────────────────┐
                        │  DRUG RELEASE   │
                        └─────────────────┘
                                │
          ┌─────────────────────┼─────────────────────┐
   ┌─────────────┐     ┌─────────────────┐     ┌─────────────┐
   │  Diffusion  │     │     Polymer     │     │ Combination │
   └─────────────┘     │   Degradation   │     └─────────────┘
                       └─────────────────┘
                                │
          ┌─────────────────────┼─────────────────────┐
   ┌─────────────┐     ┌─────────────────┐     ┌─────────────┐
   │  Enzymatic  │     │   Hydrolysis    │     │ Combination │
   │ Degradation │     └─────────────────┘     └─────────────┘
   └─────────────┘              │
                  ┌─────────────┴─────────────┐
           ┌─────────────┐            ┌─────────────────┐
           │ Bulk Erosion│            │ Surface Erosion │
           └─────────────┘            └─────────────────┘
```
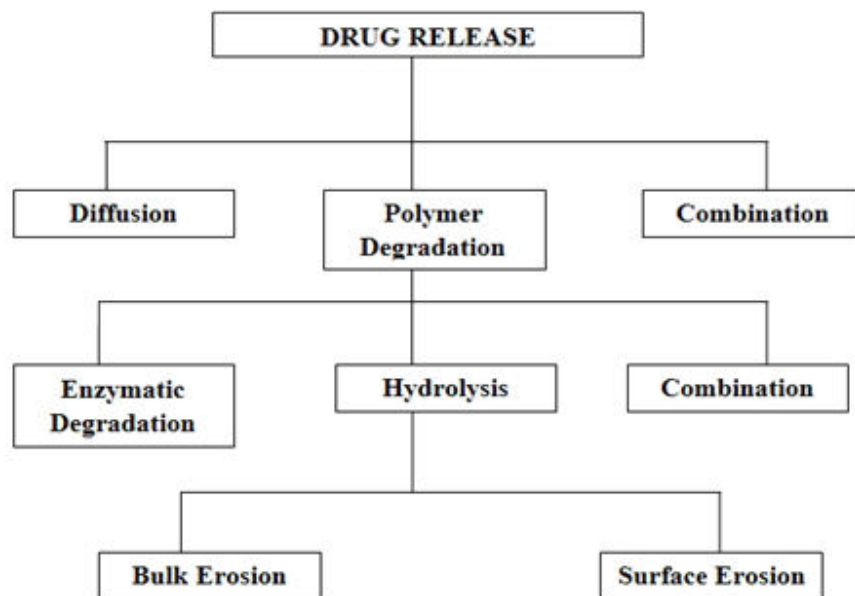
As shown in above figure the drug will be released over time either by diffusion out of the polymeric matrix or by erosion (due to degradation) of the polymer or by combination of two mechanisms.Reviews mathematicalaspectsof release of drug from polymer matericics.[8]

ADVANTAGES OF SOLID DISPERSIONS:

Generally, solid dispersion is mainly used

1. To reduced particle size.

2. To improve wet ability.

3. To improve porosity of drug.

4. To decrease the crystalline structure of drug in to amorphous form.

5. To improve dissolvability in water of a poorly water-soluble drug in a pharmaceutical.

6. To mask the taste of the drug substance.

7. To prepare rapid disintegration oral tablets.

8. To obtain a homogenous distribution of small amount of drugs at solid state.

9. To stabilize unstable drugs.

10. To dispense liquid or gaseous compounds.

11. To formulate a faster release priming dose in a sustained release dosage form.

12. To formulate sustained release dosage or prolonged release regimens of soluble drugs using poorly soluble or insoluble carriers.

1. Particles with reduced particle size

Molecular dispersions, as solid dispersions, represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers. A high surface area is formed, resulting in an increased dissolution rate and, consequently, improved bioavailability[9].

2. Particles with improved wet ability

A strong contribution to the enhancement of drug solubility is related to the drug wet ability improvement verified in solid dispersions[11]. It was observed that even carriers without any surface activity, such as urea improved drug wetability. Carrierswith surface activity, such as choliacid and bile salts.When used, can significantly increase the wet ability property of drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects[10].

3. Particles with higher porosity

Particles in solid dispersions have been found to have a higher degree of porosity[12]. The increase in porosity also depends on the carrier properties; for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate[13]. The increased porosity of solid dispersion particles also hastens the drug release profile.

4. Drugs in amorphous state

Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility[14]. The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process [15]. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that, if drugs precipitate, it i s as a Metastable polymorphic form with higher solubility than the most stable crystal form[9]. For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them[15].

5. Rapid disintegration of oral tablets

Drug is formulated with hydrophilic carrier (e.g. PEG) as a solid dispersion to increase its aqueous solubility anddissolution. Then superdisintegrant (e.g. croscarmellose sodium) is used in tablet formulation to achieve rapid disintegration of tablets prepared by wet granulation method.

These rapidly disintegrating tablets can be used as an alternative to parenteral therapy enabling patient for self-medication even without the aid of water.

DISADVANTAGES OF SOLID DISPERSIONS:

Serajuddin (1999) identified some problems limiting the commercial application of solid dispersion which involved (a) its method of preparation, (b) reproducibility of its physicochemical properties, (c) its formulation into dosage forms, (d) the scale up of manufacturing processes, and (e) the physical and chemical stability of drug and vehicle. Solid dispersions are not broadly used in commercial products due to mainly the problem of crystallization of the components from amorphous state during processing (mechanical stress) or storage (temperature and humidity stress). Moisture may increase drug mobility and promote drug crystallization and thus may hamper storage stability of amorphous pharmaceuticals .Phase separation, crystal growth or conversion of a product to more stable structure from metastable crystalline form during storage are also considered to be major hurdles to commercialize solid Dispersions as they result in decreased solubility and thus dissolution rate[16].

LIMITATIONS OF SOLID DISPERSIONS

Although a great research interest in solid dispersion in the past four decades, the commercial utilization is very limited. Problems of solid dispersion involve (i) the physical and chemical stability of drugs and vehicles, (ii) method of preparation, (iii) reproducibility of its physicochemical properties, (iv)formulation of solid dispersion into dosage forms, and(v) scale-up of manufacturing processes [17].

CLASIFICACTION OF SOLID DISPERSION SYSTEMS

It is appropriate to classify various systems of solid dispersion on the basis of their major fast release mechanisms. Chiou and Riegelman classified solid dispersion into the following six

representative types: Simple eutectic mixtures, solid solutions, glass solution and glass suspensions, amorphous precipitations in a crystalline carrier, compound or complex formation, and combinations of the previous five types.

CATEGORIES OFSOLID DISPERSIONS

a. Simple eutectic mixtures

b. solid solutions

i)According to their miscibility

ii) According to the way in which the solvate molecules are distributed in the solvendum

i) According to their miscibility

❖ Continuous

❖ Discontinuous solid solutions.

ii) According to the way in which the solvate molecules are distributed in the solvendum

❖ Substitutional crystalline solid solutions.

❖ Interstitial crystalline solid solutions.

❖ Amorphous solid solutions.

c. Glass solution

d. amorphous precipitations in a crystalline carrier

Simple eutectic mixtures

Simultaneously, whereas when other compositions are cooled, one of the components starts to crystallize out before the other. Solid eutectic mixtures are usually prepared by rapid cooling of a co melt of the two compounds in order to obtain a physical mixture of very fine crystals of the two components. When a mixture with composition E, consisting of a slightly soluble drug and an inert, highly water soluble carrier, is dissolved in an aqueous medium, the carrier will dissolve rapidly, releasing very fine crystals of When a mixture of A and B with composition E is cooled, A and B crystallize out the drug [18,19]. The large surface area of the resulting suspension should result in an enhanced dissolution rate and thereby improved bioavailability.
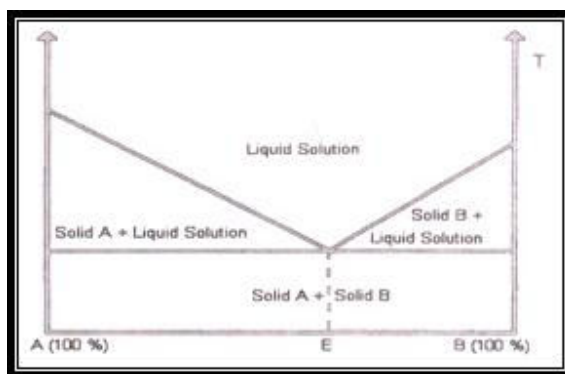

Fig:1.3 Phase diagram for a eutectic system

Solid solutions
Continuous solid solutions:

In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than

the bonding strength between the molecules of each of the individual components. Solid solutions of this type have not been reported in the pharmaceutical literature to date.

Discontinuous solid solutions:

In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. A typical phase diagram is shown in Fig. 1.4. Show the regions of true solid solutions. In these regions, one of the solid components is completely dissolved in the other solid component. Note that below a certain temperature, the mutual solubility's of the two components start to decrease. Due to practical considerations it has been suggested by Goldberg [20] that the term `solid solution' should only be applied when the mutual solubility of the two components exceeds 5%. Whether or not a given solid solution can be utilized as a dosage form strategy will depend not only on the mutual solubility of the two components but also on the dose of the drug component. The upper limit for the mass of a tablet or capsule is about 1 g. Assuming that the solubility of the drug in the carrier is 5%, doses of above 50 mg would not be feasible with this strategy. Obviously, if the drug solubility in the carrier is significantly higher than 5%, larger doses can be entertained.
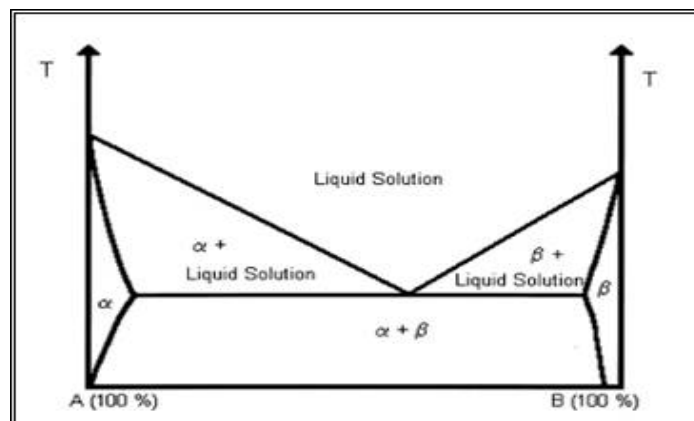

Fig:1.4 Phase diagram for a discontinuous solid solution

Substitutional crystalline, interstitial crystalline and amorphous solid solutions

Substitutional crystalline solid solutions:

Classical solid solutions have a crystalline structure, in which the solute molecules can either substitute for solvent molecules in the crystal lattice or into the interstices between the solvent molecules. A substitutional crystalline solid dispersion is depicted in Fig. 1.5. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules [21].
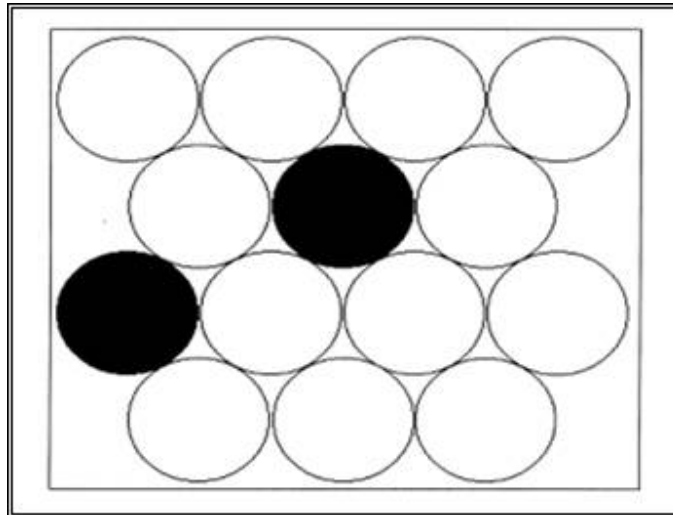

Fig:1.5Substitutional crystalline solid solution

Interstitial crystalline solid solutions

In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice (Figs. 1.6). As in the case of substitutional crystalline solid solutions, the relative molecular size is a crucial criterion for classifying the solid solution type. In the case of interstitial crystalline solid solutions, the solute molecules should have a

molecular diameter that is no greater than 0.59 of the solvent molecule's molecular diameter[22]. Furthermore, the volume of the solute molecules should be less than 20% of the solvent.
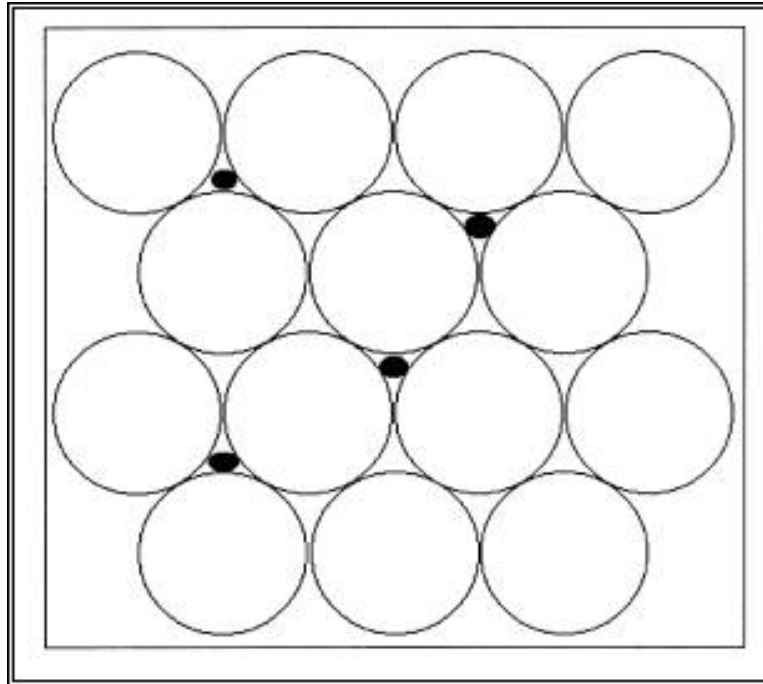

Fig:1.6 interstitial crystalline solid solution

Amorphous solid solutions:

In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent (Fig.1.7) Using griseofulvin in citric acid, Chiou and Riegelman[23]were the first to report the formation of an amorphous solid solution to improve a drug's dissolution properties. Other carriers that were used in early studies included urea and sugars such as sucrose, dextrose and galactose. More recently, organic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG) and various cellulose derivatives have been utilized for this purpose. Polymer carriers are particularly likely to form amorphous solid

solutions as the polymer itself is often present in the form of an amorphous polymer chain network. In addition, the solute molecules may serve to plasticize the polymer, leading to a reduction in its glass transition temperature.
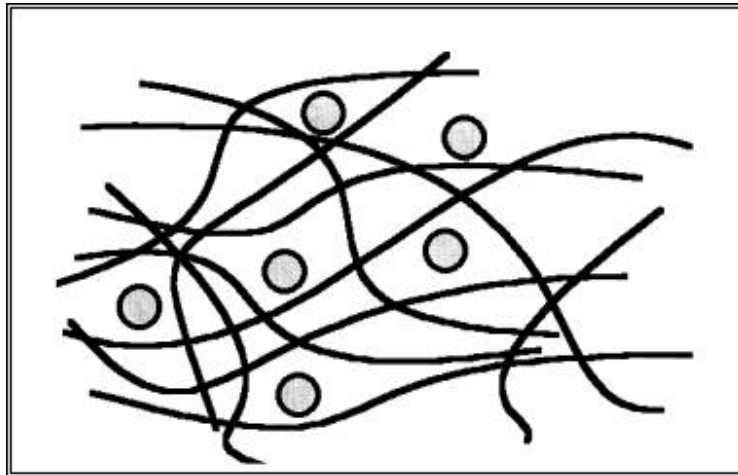

Fig:1.7: amorphous solid solution

Glass solutions and glass suspensions:

Chiou and Riegelman first introduced the concept of formation of a glass solution as another potential modification of dosage forms in increasing drug dissolution and absorption. A glass solution is a homogenous, glassy system in which a solute dissolves in a glassy solvent. The familiar term glass however, can be used to describe either a pure chemical or a mixture of chemicals in a glassy or vitreous state. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt. It is characterized by transparency and brittleness below the glass transition temperatureEg. On heating, it softens progressively and continuously without a sharp melting point. [22]

METHODS OF PREPERATION OF SOLID DISPERSIONS.

Melting method: [24]

The melting or fusion method, first proposed by Sekiguchi and Obi involves the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. Appropriately this has undergone many modifications in pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate. In addition, a super-saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process. The quenching technique gives a much finer dispersion of crystallites when used for simple eutectic mixtures. However many substances, either drugs or carriers, may decompose during the fusion process which employs high temperature. It may also cause evaporation of volatile drug or volatile carrier during the fusion process at high temperature. Some of the means to overcome these problems could be heating the physical mixture in a sealed container or melting it under vacuum or in presence of inert gas like nitrogen to prevent oxidative degradation of drug or carrier

Solvent method: [25]

In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The main advantage of the solvent method is thermal decomposition of drugs or

carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents.

However, some disadvantages are associated with this method such as

1) The higher cost of preparation.

2) The difficulty in completely removing liquid solvent.

3) The possible adverse effect of traces of the solvent on the chemical stability

4) The selection of a common volatile solvent.

5) The difficulty of reproducing crystal form.

6) In addition, a super saturation of the solute in the solid system cannot be attained   except in a system showing highly viscous properties

Melting solvent method (melt evaporation):[24]

It involves preparation of solid dispersions by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The 5 −10% (w/w) of liquid compounds can be incorporated into polyethylene glycol6000 without significant loss of its solid property. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. Also the liquid solvent used may affect the polymorphic form of the drug, which precipitates as the solid dispersion. This technique possesses unique advantages of both the fusion and solvent evaporation methods.

From a practical standpoint, it is only limited to drugs with a low therapeutic dose e.g. below 50 mg.

Melt extrusion method [26],[27], and [28]

The drug/carrier mix is typically processed with a twin-screw extruder. The drug/carrier mix is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about 1 min, which enables drugs that are somewhat thermo labile to be processed. Solid dispersion by this method is composed of active ingredient and carrier, and prepare by hot-stage extrusion using a co-rotating twin-screw extruder. The concentration of drug in the dispersions is always 40% (w/w). The screw-configuration consist of two mixing zones and three transport zones distribute over the entire barrel length, the feeding rate is fix at 1 kg/h and the screw rate is set at 300 rpm. The five temperature zones are set at 100, 130, 170, 180, and 185^0C from feeder to die. The extradites are collect after cooling at ambient temperature on a conveyer belt. Samples are milled for 1 min with a laboratory-cutting mill and sieve to exclude particles >355µm.
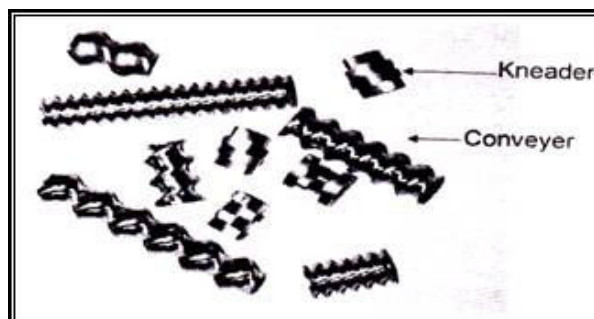

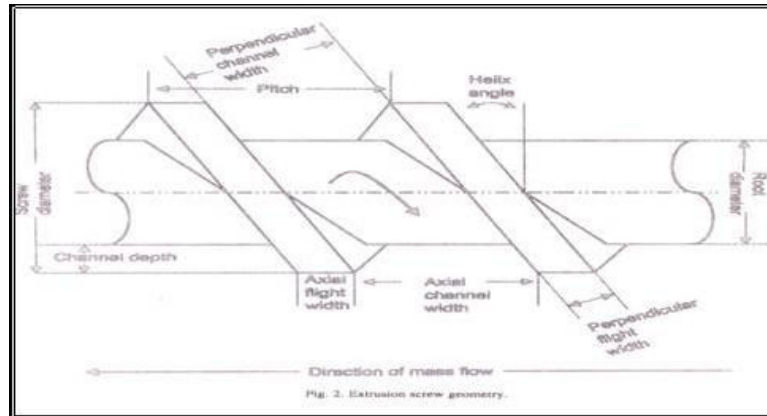**Fig:1.8Screw and kneading elements**

Fig:1.9 Extrusion screw geometry

Lyophilisation Technique

Freeze-drying involves transfer of heat and mass to and from the product under preparation [29]. This technique was proposed as an alternative technique to solvent evaporation. Lyophilisation has been thought of a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion.

Melt Agglomeration Process

This technique has been used to prepare SD wherein the binder acts as a carrier. In addition, SD(s) are prepared either by heating binder, drug and excipient to a temperature above the melting point of the binder (melt- in procedure) or by spraying a dispersion of drug in molten binder on the heated excipient (spray-on procedure) by using a high shear mixer[30]. A rotary processor has been shown to be alternative equipment for melt agglomeration. The rotary

processor might be preferable to the high melt agglomeration because it is easier to control the temperature and because a higher binder content can be incorporated in the agglomerates[31]. The effect of binder type, method of manufacturing and particle size are critical parameters in preparation of SD(s) by melt agglomeration. Sincethese parameters result in variations in dissolution rates, mechanism of agglomerate formationand growth, agglomerate size, agglomerate size distribution and densification of agglomerates. It has been investigated that the melt in procedure gives a higher dissolution rates than the spray-on procedure with PEG 3000, poloxamer 188 and gelucire 50/13 attributed to immersion mechanism of agglomerate formation and growth. In addition the melt in procedure also results in homogenous distribution of drug in agglomerate. Larger particles results in densification of agglomerates while fine particle cause complete adhesion to the mass to bowl shortly after melting attributed to distribution and coalescence of the fine particles [32].

The use of surfactant

The utility of the surfactant systems in solubilization is well known. Adsorption of surfactant on solid surface can modify their hydrophobicity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion, floatation, wetting, solubilization, detergency, and enhanced oil recovery and corrosion inhibition. Surfactants have also been reported to cause salvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glass transition temperature and the combined glass transition temperature of solid dispersions. Because of these unique properties, surfactants have attracted the attention of investigators for preparation of solid dispersions [33, 34].

Electro spinning

Electro spinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle[35]. This process involves the application of a strong electrostatic field over a conductive capillary attaching to a reservoir containing a polymer solution or melt and a conductive collection screen. Upon increasing the electrostatic field strength up to but not exceeding a critical value, charge species accumulated on the surface of a pendant drop destabilize the hemispherical shape into a conical shape (commonly known as Taylor s cone). Beyond the critical value, a charged polymer jet is ejected from the apex of the cone (as a way of relieving the charge built-up on the surface of the pendant drop). The ejected charged jet is then carried to the collection screen via the electrostatic force. The Columbic repulsion force is responsible for the thinning of the charged jet during its trajectory to the collection screen. The thinning down of the charged jet is limited by the viscosity increase, as the charged jet is dried [36]. This technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine, as it is simplest, the cheapest [37] this technique can be utilized for the preparation of solid dispersions in future.

Super Critical Fluid (Scf) Technology:

This technology has been introduced in the late 1980s and early 1990s, and experimental proofs of concept are abundant in the scientific literature for a plethora of model compounds from very different areas such as drugs and pharmaceutical compounds, polymers and biopolymers, explosives and energy materials, superconductors and catalyst precursor's dyes and biomolecules such as proteins and peptides. From the very beginning of supercritical fluid particle generation research, the formation of biocompatible polymer and drug-loaded

biopolymer micro-particles for pharmaceutical applications has been studied intensively by a number of researcher groups[38] CFs either as solvent: rapid expansion from supercritical solution (RESS) or anti solvent: gas antisolvent (GAS), supercritical antisolvent (SAS), solution enhanced dispersion by supercritical fluids (SEDS) and/or dispersing fluid: GAS, SEDS, particles from gas-saturated solution (PGSS). Conventional methods, i.e. Spray drying, solvent evaporation and hot melt method often result in low yield, high residual solvent content or thermal degradation of the active substance[39] the supercritical fluid antisolvent techniques, carbon dioxide is used as an anti solvent for the solute but as a solvent with respect to the organic solvent. Different acronyms were used by various authors to denote micronization processes: aerosol solvent extraction system (ASES), precipitation with a compressed fluid antisolvent (PCA), gas anti-solvent (GAS), solution enhanced dispersion by supercritical fluids (SEDS) and supercritical anti-solvent (SAS). The SAS process involves the spraying of the solution composed of the solute and of the organic solvent into a continuous supercritical phase flowing concurrently[40] use of supercritical carbon dioxide is advantageous as it is much easier to remove from the polymeric materials when the process is complete, even though a small amount of carbon dioxide remains trapped inside the polymer; it poses no danger to the patient. In addition the ability of carbon dioxide to plasticize and swell polymers can also be exploited and the process can be carried out near room temperature [41] Moreover, supercritical fluids are used to lower the temperature of melt dispersion process by reducing the melting temperature of dispersed active agent. The reason for this depression is the solubility of the lighter component (dense gas) in the forming phase (heavier component) [42]

Effervescent method:

Effervescent solid dispersions incorporate sodium bicarbonate and organic acids (citric, tartaric or succinic), which react with each other to yield an effervescent mixture. By combining poorly soluble drugs with organic acids, one should obtain an effervescent solid dispersion, which may increase the dissolution and absorption rates of poorly soluble drugs. Citric acid/sodium bicarbonate was found to be the most effective carrier for releasing prednisone and primidone and sodium bicarbonate/succinic acid was observed to be the best carrier for griseofulvin. Such dispersion can be made by fusion technique as explained above [43]

Adsorption on insoluble carriers:

These dispersions are also referred to as surface solid dispersions. In this method, the support material is suspended in a solution of the drug followed by evaporation of the solvent. The resulting material contains the drug in a "molecularly micronized" state on the surface of the carrier. Here, adsorbents maintain the concentration gradient (Cs-Ct), to its maximum, thus increasing the dissolution rate. A special technique under these methods is the fluidized bed system. It involves first preparation of spraying solution by dissolving both drug and carrier and then sugar spheres are charged to fluidized bed granulator and coated.

These spheres are fluidized by spraying solution and the coated pellets are dried. Solid dispersion of poorly water-soluble drug nifedipine was prepared in hydroxypropylmethylcellulose (HPMC) on sugar spheres using this technique [44].

Direct capsule filling:

Direct filling of hard gelatin capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystallinity of the drug. This molten dispersion forms a solid plug inside the capsule on cooling to room temperature, reducing cross contamination and

operator exposure in a dust-free environment, better fill weight and content uniformity was obtained than with the powder-fill technique. However, PEG was not a suitable carrier for the direct capsule-filling method as the water-soluble carrier dissolved more rapidly than the drug, resulting in drug rich

layers formed over the surface of dissolving plugs, which prevented further dissolution of the drug[45,46].

Dropping solution method:

The dropping method facilitate the crystallization of different chemicals and produces round particles from melted solid dispersions. In laboratory-scale preparation, a solid dispersion of a melted drug-carrier mixture is pipetted and then dropped onto a plate, where it solidifies into round particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. Because viscosity is highly temperature-dependent, it is very important to adjust the temperature so that when the melt is dropped onto the plate it solidifies to a spherical shape[47].

The use of carriers that solidify at room temperature may aid the dropping process. The dropping method not only simplifies the manufacturing process, but also gives a higher is solution rate. It does not use organic solvents and, therefore, has none of the problems associated with solvent evaporation. The method also avoids the pulverization, sifting and compressibility difficulties encountered with the other melt methods. Disadvantages of the dropping method are that only thermo stable drugs can be used and the physical instability of solid dispersions is a further challenge.

Co-precipitation method:

Co-precipitation is a recognized technique for increasing the dissolution of poorly water soluble drugs, so as to consequently improve bioavailability. In this method non solvent is added drop wise to the drug and carrier solution, under constant stirring. In the course of the non solvent addition, the drug and carrier are co-precipitated to form micro particles. At the end, the resulted micro particle suspension is filtered and dried40. The required quantity of polymer and the drug were mixed and then solvent was added to obtain clear solution. The Solution was first dried under vacuum at room temperature and kept inside incubator (370c) for 12 hrs. Finally it was passed through sieves41[48].

Nanoparticles

Nanoparticles are particles between 1 and 100 nanometers in size. In nanotechnology, a particle is defined as a small object that behaves as a whole unit with respect to its transport and properties. Particles are further classified according to diameter. Ultrafine particles are the same as nanoparticles and between 1 and 100 nanometers in size. Coarse particles cover a range between 2,500 and 10,000 nanometers. Fine particles are sized between 100 and 2,500 nanometers. Nanoparticles are of great scientific interest as they are, in effect, a bridge between bulk materials and atomic or molecular structures. A bulk material should have constant physical properties regardless of its size, but at the nano-scale size-dependent properties are often observed. Thus, the properties of materials change as their size approaches the nanoscale and as the percentage of atoms at the surface of a material becomes significant. For bulk materials larger than one micrometer (or micron), the percentage of atoms at the surface is insignificant in relation to the number of atoms in the bulk of the material. The interesting and sometimes

unexpected properties of nanoparticles are therefore largely due to the large surface area of the material, which dominates the contributions made by the small bulk of the material.

Nanoparticles often possess unexpected optical properties as they are small enough to confine their electrons and produce quantum effects. For example gold nanoparticles appear deep-red to black in solution. Nanoparticles of yellow gold and grey silicon are red in color. Gold nanoparticles melt at much lower temperatures (~300 °C for 2.5 nm size) than the gold slabs (1064 °C); Absorption of solar radiation is much higher in materials composed of nanoparticles than it is in thin films of continuous sheets of material. In both solar PV and solar thermal applications, controlling the size, shape, and material of the particles, it is possible to control solar absorption.

Other size-dependent property changes include quantum confinement in semiconductor particles, surface Plasmon resonance in some metal particles and superparamagnetism in magnetic materials. What would appear ironic is that the changes in physical properties are not always desirable. Ferromagnetic materials smaller than 10 nm can switch their magnetization direction using room temperature thermal energy, thus making them unsuitable for memory storage. Suspensions of nanoparticles are possible since the interaction of the particle surface with the solvent is strong enough to overcome density differences, which otherwise usually result in a material either sinking or floating in a liquid. The high surface area to volume ratio of nanoparticles provides a tremendous driving force for diffusion, especially at elevated temperatures. Sintering can take place at lower temperatures, over shorter time scales than for larger particles. In theory, this does not affect the density of the final product, though flow difficulties and the tendency of nanoparticles to agglomerate complicates matters. Moreover, nanoparticles have been found to impart some extra properties to various day to day

products. For example, the presence of titanium dioxide nanoparticles imparts what we call the self-cleaning effect, and, the size being nano-range, the particles cannot be observed. Zinc oxide particles have been found to have superior UV blocking properties compared to its bulk substitute. This is one of the reasons why it is often used in the preparation of sunscreen lotions, and is completely photostable. Clay nanoparticles when incorporated into polymer matrices increase reinforcement, leading to stronger plastics, verifiable by a higher glass transition temperature and other mechanical property tests. These nanoparticles are hard, and impart their properties to the polymer (plastic). Nanoparticles have also been attached to textile fibers in order to create smart and functional clothing.Metal, dielectric, and semiconductor nanoparticles have been formed, as well as hybrid structures (e.g., core–shell nanoparticles). Nanoparticles made of semiconducting material may also be labeled quantum dots if they are small enough (typically sub 10 nm) that quantization of electronic energy levels occurs. Such nanoscale particles are used in biomedical applications as drug carriers or imaging agents. Semi-solid and soft nanoparticles have been manufactured. A prototype nanoparticle of semi-solid nature is the liposome. Various types of liposome nanoparticles are currently used clinically as delivery systems for anticancer drugs and vaccines.

Nanoparticles with one half hydrophilic and the other half hydrophobic are termedJanus and are particularly effective for stabilizing emulsions. They can self-assemble at water/oil interfaces and act as solid surfactants.[50]

Nanoparticle Applications in Medicine

The surface change of protein filled nanoparticles has been shown to affect the ability of the nanoparticle to stimulate immune responses. Researchers are thinking that these

nanoparticles may be used in inhalable vaccines. Researchers at Rice University have demonstrated that cerium oxide nanoparticles act as an antioxidant to remove oxygen free radicals that are present in a patient's bloodstream following a traumatic injury. The nanoparticles absorb the oxygen free radicals and then release the oxygen in a less dangerous state, freeing up the nanoparticle to absorb more free radicals. Researchers are developing ways to use carbon nanoparticles called nanodiamonds in medical applications. For example nanodiamonds with protein molecules attached can be used to increase bone growth around dental or joint implants. Researchers are testing the use of chemotherapy drugs attached to nanodiamonds to treat brain tumors. Other researchers are testing the use of chemotherapy drugs attached to nanodiamonds to treat leukemia.[51]

LITERATURE REVIEW

D.m.patel, r.r.shah, et al.,have studied solid dispersions of piroxicam with peg-4000, pvp k-30, prepared by solvent evaporation technique and release profile was studied in USP xxiii dissolution apparatus in simulated gastric fluid. It was found that piroxicam release was much higher from solid dispersions than pure drug sample.[52]

M.Gopalrao, R.Suneetha, et al.,Observed that improved dissolution of naproxen solid dispersion with pvp, peg-4000, peg-6000.peg-20000, methyl cellulose and β-cyclodexrin than the pure drug powder. Among the carrier studied it was found that naproxen b-cyclodextrin solid dispersion showed highest improvement in dissolution.[53]

M.M.Soniwala, P.R..Patel, et al.,studied the dissolution proile of rofecoxiib by formulating solid dispersions of rofecoxin with various hydrophilic carriers i.e. peg-6000, pvp k-30, Eudragit e-100 and inclusion complex of β-cyclodextrin in 0.1n hc1. Rofecoxib forms eutectic mixture with peg-6000. Inclusion complex with β-cyclodextrin showed enhanced dissolution rate compared to other formulation and pure drug.[54]

K.P.R.Choudhary, Sheikh Srinivasa, et al., showed that complex of itraconazole with β-cyclodextrin and hydroxyl propy1 β-cyclodextrin in aqueous solution has improved solubility and dissolution of itraconazole. The complexes were prepared by kneading method and co-vaporization. Higher dissolution rate was observed in kneaded complexes than co-vaporization method.[55]

Nagarsenker M.S.et al.reported the influence of Hydroxy propy1 β-cyclodextrin on dissolution of piroxicam and on irritation to stomach or rat upon oral administration. The dissolution of

piroxicam from solid dispersions was found to have improved considerably over that of the pure drug alone. Co-evaporated and freeze dried dispersions caused significant reduction in irritation to stomach mucosa of rat upon oral administration.[56]

K.P.R.Choudhary, R. Hymnet al. Studied solid dispersions of Meloxicam with PVP, HPMC, HPC and PEG-6000 & solvent deposited system on lactose, soluble starch, microcrystalline cellulose, discalcuim phosphate. A marked enhancement in the dissolution rate and dissolution efficiency of Meloxicam was observed with all solid dispersions. Among all PVP solid dispersion showed highest dissolution rate enhancement.[57]

Manimaran.V, Damoadharanet al.,prepare solid dispersion of Glibenclamide using different carriers such as PEG 6000, polyvinylpyrolidine (PVP) andPoloxamers in different ratios (1:1, 1:2, 1:3, 1:4 and 1:5) by Solvent Evaporation method. Drug carrier interactions were analysed by X-rayDiffraction and Infra-Red Spectroscopy. Dissolution studies using the USP paddle method were performed for all solid dispersions. All solidDispersions showed increased dissolution rate as compared to pure Glibenclamide and PVP was found to be better than PEG and Poloxamer. TheTablets were formulated using solid dispersion of Glibenclamide containing PVP as carrier. The tablets containing solid dispersion exhibited betterDissolution profile than commercial tablets. Thus solid dispersion technique can be successfully used for improvement of dissolution ofGlibenclamide.[58]

.P.R. Choudhary, G. Kamalkara, et al.,prepared complex of nifedipine with β-cyclodextrin and Hydroxy propy1 β-cyclodextrin and the possibility of improving solubility and the dissolution rate of Nifedipine-Cyclodextrin inclusion complexes in the design of mucoadhesive tablets for sustained release were investigated; the phase solubility studies also were carried out. The solubility and dissolution rates were markedly enhanced by complex formation.

Mucoadhesive tablets formulated with Nifedipine gave very low release, whereas the tablet prepared with cyclodextrin complex showed controlled and complete release.[59]

V. Kusum Devi, P. Vijayalaxmiet al.,prepared solid dispersions of celecoxib with different carriers in different ratio and subjected to solubility and dissolution rate studies. All formulation showed improve solubility as well as dissolution rate am one which PVP-Viny1 Acetate polymer showed highest dissolution rate that other carriers.[60]

NeelamSeedheret al.examined the solubility enhancement of Cox-2 inhibitors, celecoxib, rofecoxib, meloxicam, and nimesulide, using a series of pure solvents and solvent mixtures. Water, Alcohols, Glycols, Glycerol, and Polyethylene Glycol 400 (PEG 400) were used as solvents and water-Ethanol, Glycerol-Ethanol, and polyethylene Glycol-Ethanol were used as mixed-solvent systems. The aqueous solubility of clecoxib, Rofecoxib, and Nimesulide was enhanced significantly by using Ethanol as the second solvent.[61]

Taneja L. N. et al.,have reported the in-vitro characterization and bioavailability assessment of solid dispersions of ketoprofen. The polymers used are PEG-6000 and poloxamer 188. Both solid dispersions and physical mixtures showed improved dissolution[62]

R.Kaliselvam, G. S. Prasad et al.,prepared Mebendazole and β-cyclodextrin molecular inclusion complexes, Mebendazole solid dispersion with PEG 6000 by solvent method in different ration and physical mixtures. The enhancement of dissolution of Mebendazole depends on carrier used and nature of formula i.e. physical mixture, solid dispersion or molecular inclusion complex. Dissolution rate and dissolution efficiency were improved by both molecular inclusion complex and solid dispersion in all ratio that physical mixture and pure drug.[63]

Kuchekar B.S.et al.have reported on solid dispersions of paracetamol using β-cyclodextrin and dextrin. Uniform drug distribution was found in all solid dispersions. Swati Rawat, Laila F Et.el.,

studied five marketed formulation of Rofecoxib to estimate their dissolution rate and compared with two laboratory made test formulations prepared with β-cyclodextrin by kneading method. Study showed poor drug release characteristic from marketed formulation as compared to laboratory made formmulation.[64]

S. Jagatpal Reddy, U. R. Gadsoorkaret al.,prepared solid dispersion of Glicalzide with PEG 4000, PEG 6000 by solvent method and subjected to dissolution studies. Pure Gliclazide showed only 45% dissolution after 60 min up PH 7.4 buffer where as solid dispersions prepared showed increased dissolution that pure drug.[65]

Suresh D. Kumavat*1, YogeshChaudhariet al.,enhance the solubility of poorly water soluble drug Glibenclamide via the Solid Dispersion technique by Spray drying method. Solid dispersions (SD) of libenclamide-Plasdone S630in the ratio of 1:1, 1:2, 1:4, 1:6 and 1:8 were prepared in an attempt to increase the solubility and dissolution rate of the drug. Solubility, dissolution, Scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR) of solid dispersions, physical mixtures (PM) and Glibenclamidewere evaluated. Both solubility and dissolution of drug solid dispersions were significantly greater than those observed for physical mixtures and intact pure Glibenclamide. The differential scanning calorimetry indicated that the high energy amorphous Glibenclamide was obtained from all solid dispersions. It was found that the optimum weight ratio for Glibenclamide-Plasdone S630 is 1:8. The 1:8 solid dispersion shows highest Dissolution rate owing to itsamorphous nature and reduced particle size.[66]

MuktaKhadilkar, Jasmine Avari, et al.,studied solid dispersion of ketoprofen prepared by fusion method using Mannitol and PEG-6000 as carriers. All solid dispersions showed increased dissolution rate when compared with pure Ketoprofen release.[67]

Parikh R.K. Mansuri N.S. et al.,presented dissolution enhancement of Nimesulide using complexation and salt formulation technique. The complex of Nimesulide with β cyclodextrinand salt with L-Arginine and L-Lysine shows significant increase in the dissolution of the drug as compared to pure drug.[68]

Ganesan V., Sandhya K. G. et al.,studied physical solubility and dissolution rate of Flurbiprofen suspension employing its solid dispersions with HMS, PVP, PEG and Dextrin and were evaluated for particle size, physical stability and dissolution rate, Flurbiprofen solid dispersion exhibited good suspendability and gave higher dissolution rate than those formulated with Flubiprofen alone.[69]

SanjulaBaboota, Suraj P. Agrawalet al.,formulated Meloxicam Cyclodextrin inclusion complexes and incorporated to tablets containing inclusion complexes. β-cyclodextrin, Hydroxy propy1 β-Cyclodextrin inclusion complexes were prepared by freeze drying method and evaluated by FTIR, X-RD, DTA , SEM,. The solubility and in-vitro release indicated increased solubility and dissolution rate compared to free drug.[7]

SengodanGurusamy, Vijaykumaret al.,prepared solid dispersion of Meloxicam with skimmed milk and evaluated for solubility and dissolution profile. Result showed that the solubility of the solid dispersion of the drug was three times greater than pure drug, also significant improvement in rate of dissolution to drug than physical mixture.[71]

KashappaGoud H. Desai et al.,carried our solubility studies of valdecoxib in presence of carriers, co-solvent and surfactant. Carriers used were Mannitol, peg4000, peg6000, peg8000 and urea. Surfactant tween20, tween 80 and SLS and co-solvent like ethanol, methanol and glycerol. The solubility of valdecoxib was found increased more by PEG4000 as carrier. Ethanol as a solvent and SLS as a surfactant compared to others and pure drug.[72]

ChengshengLill. L. et al.,presented a study to enhance dissolution rate of rofecoxib using solid dispersion with urea. A systematic increase in the solubility behaviors of Rofecoxib was observed with increase in concentration of carriers in water.[73]

Pan R. N., Chon J. H. et al.,studied solid dispersion system of water insoluble piroxicam in PEG-4000 and urea, prepared by fusion and solvent method. The in-vitro dissolution studies showed that the dispersion system containing piroxicam with carriers gave faster dissolution than simple physical mixtures and pure drug sample.[7]

F.Cilurzo, P. Mingheti., et al.,studied sublingual administration of nifidipine solid dispersions by using sublingual i.e. low viscosity HPCM in different ratios were prepared by spray drying technique and the structure was studied. Dissolution properties from solid dispersions were verified; it showed improved dissolution than physical mixture of nifidipine with HPMC and pure sample of nifidipine.[75]

Duncam Q.M. Craig et al.,studied mechanism of drug release from solid dispersion in wear soluble in polymer, and observed the enhanced dissolution rate and efficiency due to formation of eutectic mixture and reduced particle sizes of various drugs due to formation of solid dispersions.[76]

S. Verneyen, N. Balton., et al.,presented the mechanism of increased dissolution of Diazepam &Temazepam from PEG-6000 solid dispersions. This study clearly showed that addition with PEG-6000 of Diazepam and Temazepam improves their dissolution rate. Solid dispersions prepared by solvent evaporation method and fusion method showed enhanced dissolution than physical mixtures and pure drug sample.[77]

SudhaR.Vippogunta, et al., studied solid state characterization of Nifedipine solid dispersions prepared with pluronic F-68 and Gelucire 50/13. They enhanced rate and extent of water uptake by formulation. The dissolution rate was determined and was found to be enhanced.[78]

Ahmad M. Abdul Fatteha, et al. Performed study on low aqueous solubility and bioavailability of Halofantrine and suggested formulation of solid dispersions with PVP K-30, PEG-8000, Gelucir 44-14, Sodium Taurocholate and also physical mixtures. The dissolution of Halofantrine from the physical mixtures was higher than pure form. The formulation of Halofantrine in solid dispersions significantly improved dissolution rate comparative to physical mixtures and pure form.[79]

F.Damian, N. Blaton, et al., studied physical stability of solid dispersion of an antiviral agent UC-781 with PEG-6000, Gelucir 44/14 and PVP K30 prepared by solvent evaporation method and fusion method. Solid dispersions were stored from 0 to 25 ^{0}C (25% RH) and their physicochemical properties were analyzed, also studied rate of dissolution from solid dispersion with storage time. All solid dispersion showed sufficient stability and enhanced dissolution rate.[80]

Omar Saeed et al., (2009) reported about Knowledge of modifiable risk factors of Coronary Atherosclerotic Heart Disease (CASHD) among a sample in India. Study suggests that there is a lack of awareness among a sampled Indian population regarding modifiable risk factors of CASHD.[81]

Laurent P et al., (2012) proposed a hot melt dispersion method to prepare new sustained release ibuprofen composite microparticles of a solid lipid at ambient temperature using cetyl alcohol. The dispersion of colloidal silicon dioxide nanoparticles (hydrophilic Aerosil® 200 or hydrophobic Aerosil® R974) either in the oily phase or in the aqueous phase led to the

preparation of large (about 400µm diameter) surfactant free; free-flowing particles. Crystalline state of ibuprofen and lipid has an influence on the drug release kinetics thus increase in the size of the composite solid lipid microparticles.[82]

Rosanna Tursilli et al., (2007) projected in their work that a Solid lipid microparticles (SLM) loaded with the sun screen agent, octyl-dimethylaminobenzoate (ODAB), enhances sunscreen photostability. The microparticles were produced by melt dispersion technique using glycerylbehenate as lipidic material and poloxamer 188 as an emulsifier. The prepared SLMs achieved a reduction of sunscreen photodegradation in the hydrogel vehicle (ODAB loss is decreased). Therefore, the efficacy of the ODAB-loaded SLMs was markedly affected by the vehicle.[83]

SeverineJaspart et al., (2007) proposed Solid lipid microparticles (SLM) as a drug carrier compared to liposomes and polymeric microspheres. The aim of this work is to use SLMs to impart a sustained release profile to a model drug, salbutamol acetonide (SA). SA-loaded SLMs were prepared by hot emulsion technique followed by high-shear homogenization. In vitro release study of SA from SLMs showed that the release rate of a drug has increased with SA loading but remained in every case lower than the dissolution rate of pure SA.[84]

Helmut Reithmeier et al., (2001) prepared SLMs using somatostatin, a peptide with a high therapeutic potential. It has a short biological half-life hence encapsulated with in microparticles by a modified solvent evaporation and melt dispersion method. The encapsulation efficiency of the peptide into glyceryltripalmitatemicroparticles was found to be influenced by method of its preparation and the physical state of peptide to be incorporated. Microparticles prepared by melt dispersion method showed better results than the solvent evaporation technique.[85]

Giovannelli L et al., (2005) recommended SLMs using Hot Air Coating (HAC) technique to prepare microparticulate systems containing nifedipine. Binary mixtures constituting of nifedipine and cetearylalcohol (CA) in different proportions (30:70,50:50, 70:30) were studied and homogenized by milling or mixing. Experimental results showed evidence that milling pre-treatment of mixtures, has significant effects on the properties of the lipid coated microparticles.[86]

Sudhir S C et al., (2010) showed Paclitaxel delivered intratumorally in PLGA microparticles, or the commercial Paclitaxel Injection. In this the larger PLGA microparticles adheres to mucus on the cell surface and release paclitaxel locally, and enhances cellular association of paclitaxel. At last it was concluded that, sustained release of PLGA microparticles increased cellular concentration, and enhanced anti tumor efficacy of paclitaxel compared to nanoparticles and Paclitaxel Injection.[87]

NicoletaButoescu et al., (2009) suggested that Superparamagnetic iron oxide nanoparticles (SPIONs) are attractive materials that have been widely used in medicine for diagnostic imaging and therapeutic applications. SPIONs and corticosteriod dexamethasone acetate (DXM) are co-encapsulated into PLGA microparticles for treating local inflammatory conditions such as arthritis. Results showed that the microparticles have an excellent biocompatibility with synoviocytes and they are internalized through a phagocytic process. Microparticles used as a carrier represent a suitable magnetically retainable intra-articular drug delivery system for treating joint diseases such as arthritis or osteoarthritis.[88]

PLANE OF WORK

The study was planned to carry out as follows,

Stage I

A) Preliminary investigations

    i. Screening ofCarriers.

    ii. Effect of carries on Solubility

Stage II

B) Formulation of solid dispersions for different carriers.

    i. Physical mixture.

    ii. Solvent evaporation method.

    iii. Droppings method.

    iv. Wet grinding method.

C) Formulation of nanoparticles by different methods.

    i. Sonication method.

    ii. Antisolvent method.

To perform *in vitro*dissolution studies and dissolution rate of prepared formulations and marketed available drug using dissolution apparatus (LABINDIA, DS 2000, Mumbai, India).

Stage III

D) Characterization of ideal formulations

    i. Drug Content in formulations

    ii. X-ray Diffraction studies

   iii. Infrared Spectroscopy

   iv. Chromatographic study

   v. Particle Size Analysis

StageIV

E) kinetic analysis of dissolution data

     The release rate and mechanism of drug release from the prepared formulations were analyzed by fitting the dissolution data into various release models such as:

   i. zero order

   ii. First order

STAGE V

F) Stability Studies of some ideal batches.

STAGE VI

G) Comparison of marketed available formulation.

DRUGPROFILE.

Glibenclamide and diabetes[89]

In recent years, developed nations have witnessed an explosive increase in the occurrence of diabetes mellitus (DM) predominantly related to lifestyle changes and the resulting surge in obesity. The metabolic consequences of prolonged hyperglycemia and dyslipidemia (including accelerated atherosclerosis, chronic kidney disease, and blindness) impose an enormous burden on patients with diabetes mellitus and on the public health system. Improvements in our understanding of the pathogenesis of diabetes and its complications and in the therapy and prevention of diabetes are critical to meeting this health care challenge. The Glibenclamide nanoparticles may be favor treatment of type 2 diabetes mellitus as a chronic disease and perhaps will provide the following

ADVANTAGES:

a) Decreased drug doses and side effects

b) Enhanced patient compliance.

Furthermore, some studies have shown that absorption may be decrease in hyperglycemic patients and nanoparticles may increase absorption of drug by optimizing its interaction with the site of action and also by directly transporting it through the intestinal mucosa to the systemic circulation.

Appearance and solubility:

Glibenclamide is a white or almost white, crystalline powder. It is practically insoluble in water and in ether, slightly soluble in alcohol and in methyl alcohol, ethanol, and acetone and sparingly soluble in dichloromethane. It dissolves in dilute solutions of alkali hydroxides.
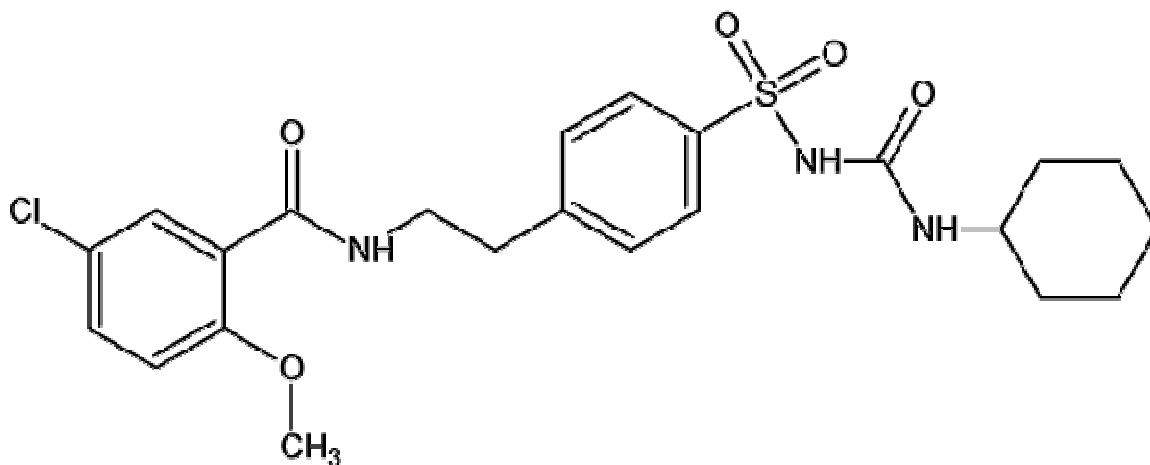
Structure formula

.

Fig:4.1 .Molecular structure of Glibenclamide.

Mechanism of action:

Glibenclamide, like other Sulfonylurea's, causes hypoglycemia by stimulating insulin release from pancreatic ß cells. Its effect in the treatment of diabetes, however, is more complex. The acute administration of sulfonylurea's to type 2 DM patients' increases insulin release from the pancreas. Sulfonylureas also may further increase insulin levels by reducing hepatic clearance of the hormone. In the initial months of sulfonylurea treatment, the fasting plasma insulin levels and insulin responses to oral glucose challenges are shown to be increased. With chronic administration, circulating insulin levels decline to those that existed before treatment, but despite this reduction in insulin levels, reduced plasma glucose levels are maintained.

Pharmacokinetics:

Glibenclamide is readily absorbed from the gastrointestinal tract and the pike plasma concentrations can usually occur within 2 to 4 hours. It is extensively bound to plasma proteins and absorption may be slower in hyperglycemic patients and may differ upon the particle size of

preparation used. It is almost completely metabolized and the principle metabolite is very weekly active in the liver. Approximately 50% of a dose is excreted in the urine and 50% via the bile in to the feaces.

Uses and administration:

Glibenclamide is a sulphonylurea hypoglycemic. It is orally administrated in the treatment of type 2 diabetes mellitus and has duration of action of up to 24 hours. The usual initial dose of conventional formulations in type 2 diabetes mellitus is 2.5 to 5 mg daily with breakfast. In the case of micronized preparations of Glibenclamide, the drug is formulated with a smaller particle size, and display enhanced bioavailability. The usual initial dose of such preparation (GlynaseTM) is 1.5 to 3 mg daily.

Adverse effects

Gastrointestinal disturbances such as nausea, vomiting, heartburn, anorexia, diarrhea, and a metallic taste may occur with sulfonylurea and are usually mild and dose dependent; increased appetite and weight gain may also occur. Skin rashes and pruritus and photosensitivity have been reported. Rashes are usually hypersensitivity reactions and may progress to more serious disorders. Furthermore mild hypoglycemia may be seen. Severe hypoglycemia is usually an Indication of over dosage and is relatively uncommon. Hypoglycemia is more likely with long-acting sulphonylurea such as chlorpropamide and Glibenclamide, which have been associated with severe, prolonged, and sometimes fatal hypoglycemia.

Dosage forms

The following dosage forms are currently used for Glibenclamide:

BP 1998: Glibenclamide tablets;

USP 23: glyburide tablets.

Other names: micronase, diabeta

POLYMER PROFILE

Polymer profile [90]

UREA

Nonproprietary Name:

Urea

Synonyms

Berural70, Carbamide, Nimin.

Chemical Name

Urea

Molecular Formula:

$CH_4 NO_2$

Molecular Weight:

60.06

Melting Point

$133^0 C$

Functional Category

Binder, Sealant, Filler, Analytical reagent and Humectant.

Description:

White prismatic odorless crystals/ powder and saline in taste

Solubility:

Freely soluble in water, 1gm/100ml of ethanol, 10.7gm/100ml of methanol, 150gm/ml of glycerol.

Stability and Storage:

Stable in solid state and should be stored in tightly closed container, in cool and dry place.

POLYETHYLENE GLYCOL-6000

Nonproprietary Name:

      BP: Macrogol 300

      USPNF: Polyethylene glycol

Synonyms

      Breox PEG; Carbowax; Polyoxyethylene glycol;

Chemical Name

      α- Hydro-ω-Hydroxy-poly (oxy-1,2-ethanediyl)[25322-68-**3]**

Structure formula
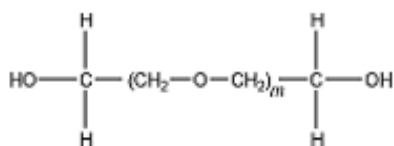
Fig:4.2 .Molecular structure of PEG.

Molecular Formula:

      $HOCH_2 (CH_2OCH_2)_{mCH2OH}$

Molecular Weight:

      5000-7000

Melting Point

      $55\text{-}63^{0}$ C

Functional Category

Polymer, suppository base, ointment base, emulsion stabilizer.

Description:

White prismatic odorless crystals/ powder and bitter in taste

Solubility:

Soluble in water, acetone, alcohol, dichloromethane,ethanol and methanol

Stability and Storage:

Stable in solid state and should be stored in tightly closed container, in cool and dry

place.

Chitosan[91]

Nonproprietary Names

BP: Chitosan HydrochloridePhEur: Chitosan Hydrochloride

Synonyms

2-Amino-2-deoxy-(1,4)-b-D-glucopyranan; chitosani hydrochloridum;deacetylated chitin; deacetylchitin; b-1,4-poly-D-glucosamine;poly-D-glucosamine; poly-(1,4-b-D-glucopyranosamine).

Chemical Name:

Poly-b-(1,4)-2-Amino-2-deoxy-D-glucose [9012-76-4]

Molecular Weight

Molecular weight by 10 000–1 000,

Functional Category

Coating agent; disintegrant; film-forming agent; mucoadhesive; tablet binder; viscosity increasing agent.

Description

Flakes Fiber formation is quite common during precipitation and

TheChitosan may look 'cotton like'.

Solubility

Sparingly soluble in water; practically insoluble in ethanol (95%), other organic solvents, and neutral or alkali solutions at pH above approximately 6.5. Chitosan dissolves readily in dilute and concentrated solutions of most organic Stability and Storage Conditions Chitosan powder is a stable material at room temperature, although it is hygroscopic after drying. Chitosan should be stored in a tightly closed container in a cool, dry place. The PhEur 6.5 specifies that Chitosan should be stored at a temperature of 2–88C.

Incompatibilities

Chitosan is incompatible with strong oxidizing agents.

LIST OF EQUIPMENTS/INSRTRUMENTS

Table No5.1

S.No	Equipments/Instruments	Manufacturer/Source
1.	Electronic Balance	SHIMADZU ELB 300
2.	Hot plate	SRI MAHALAKSHMI INSTRUMENTS MADURAI
3.	Hot Air Oven	ELCON
4.	Magnetic Stirrer	REMI
5.	TLC Plate	Astra Scientific Systems(p) Ltd. VM-02
6.	Dissolution Test Apparatus	LABINDIA DISSOO 2000
7.	FT IR	SHIMADZU
8.	UV spectrophotometer	SHIMADZU UV-1700
9.	XRD	BRUKER ECO D8
10.	pH Meter	AGRONIL 511
11.	Microscope	A.K.C.P
12	Size analyzer	Malvern
13	Tablet Compression machine	Rimek mini press-1
14	Disintegration test apparatus	Rolex

MATERIALS AND MANUFACTURER

Table No 6.1:

S.No	NAME OF THE MATERIAL	SOURCE/SUPPLIER/MANUFACTURER
1.	GLIBENCLAMIDE	GIFT SAMPLE FROM PHARMAFABRIKAN
2.	PEG 6000	GIFT SAMPLE FROM CAPLINPOINT
3.	UREA	NICE LABORATORIES KOCHI, KERALA.
4.	CHITOSAN	SISCO RESEARCH LABORATORIES
5.	METHANOL	HIMEDIA MUMBAI
6.	ETHANOL	CHANGSHU YANGYUAN CHEMICAL CHINA
7.	ACETONE	HI-PURE FINE CHEM INDUSTRIES, CHENNAI.
8.	CHLOROFORM	HIMEDIA MUMBAI
9.	SPANE 80	OXFORD LABORATORY MUMBAI
10.	Hcl	RANKEM LABORATORY AMBATTUR
11.	Kcl	FISCHER CHEMIC LTDCHENNAI

EXPERIMENTAL WORKS

DEVELOPMENT OF CALIBRATION CURVE:

Preparation of Buffer Solution (pH-1.2)[92]

250ml of 0.2Ml Potassium chloride solution (14.911 gm of KCL in 1000ml) and 425ml of0.2N Hydrochloric acid (7.292 gm in 1000ml) were mixed properly and the volume was made up to 1000ml with distilled water.

Preparation of Standard Solution of Glibenclamide[93]

A Solution of 5mg Glibenclamide was prepared by dissolving in 100ml methanol, from which 1ml was withdrawn in separate volumetric flask and diluted to 10ml with Hcl buffer to produce 5µg/ml concentration and absorbance at 302 nm 1

Preparation of Working Solution:

From standard solution, 0.5, 1, 1.5, 2, 2.5, and 3ml was withdrawn in six 10ml volumetric flasks and diluted to 10ml with HCL buffer pH 1.2 to produce concentration 2.5, 5, 7.5, 10, 12.5 and 15 respectively. The solutions were analyzed by U.V. spectrophotometer at 302nm and results were recorded. The calibration graph was plotted as concentration on X-axis Vs absorbance onY-axis

Table No 7.1:

Standard curve of Glibenclamide

S.No	Concentration (µg/ml)	Slope	Avg slope
1	2.5	0.0164	
2.	5.0	0.0160	
3.	7.5	0.0153	0.0160
4.	10.0	0.0163	
5.	12.5	0.0158	
6.	15.0	0.0164	

Figure 7.1

Standard curve of Glibenclamide

$y = 0.016x - 0.001$
$R^2 = 0.998$
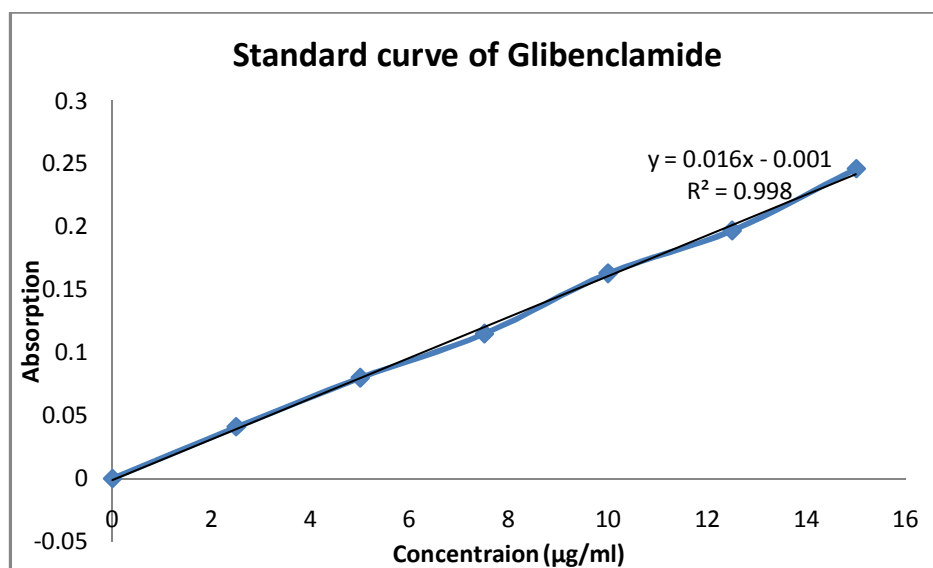
PRILIMINARY INVESTIGATIONS:

a) SCREENING OF CARRIER[94]

Carriers used for study were PEG-6000, UREA, βCyclodextrin, PVP K30 and CITOSAN. The Solid dispersion of PEG6000, Urea, PVP K90 and Chitosan were prepared by physical mixing   method, Solid dispersion of PEG 6000, Urea and PVP K30 were prepared by solvent evaporation and Dropping method. Chatoyant and PVPK30 were prepared by wet grinding method using ratio 1:1 of Drug: Carrier and were screened for yield, texture and color, physical characteristics and suitability in preparation.

b) Effect of Carriers solubility:

Known amount of samples of solid dispersion and nanoparticles was added in 50 ml of distilled water and kept for 24 hrs occasional stirring. After 24hrs contents were filtered by the wattman filter paper, and appropriate dilutions were made with 0.2M Hcl buffer and absorbance of the resultant solution was measured at 302 nm and extrapolated on standard graph to determine the concentration.

FORMULATION OF SOLID DISPERSIONS

Preparation of solid dispersion by Physical mixture method[95]

Physical Mixture of drug with PEG6000, Ureaand Chitosan were prepared by separately at three different ratios 1:1, 1:2 and 1:3. Accurately weighed 100mg drug was taken and mixed with 100,200 and 300mg of PEG6000, Ureaand Chitosan Physical mixture were prepared by triturating the powder mix in pestle mortar for 3 to 5 minutes. Subsequent to this the mixture was passed through sieve number 60 having meshsize of 250μm.Thenaccuratelyweighed 50 mg of physical mixture of Glibenclamide was used sprinkled directly to surface of the dissolution medium. And dissolution studies were carried out with TYPEII (LABINDIA, DISSO 2000) dissolution apparatus at a stirring speed of 100 rpm and 0.2 M hydrochloric acid at (pH 1.2) 37 ± 0.5°C as the dissolution medium.

Preparation of solid dispersion by Solvent evaporation method[96]

In Solvent evaporation method, drug with PEG6000 and Urea were prepared by separately at three different ratios 1:1,1:2 and 1:3. Accurately weighed 100mg drug was taken and mixed with 100,200 and 300mg of PEG6000 and Urea Were dissolved in methanol andconstant stirring. Solution was evaporated under low pressure to get the solid dispersion. Then accuratelyweighed 50 mg solventevaporated of Glibenclamide was used sprinkled directly to surface of the dissolution medium. And dissolution studies were carried out withTYPE II (LABINDIA, DISSO 2000) dissolution apparatus at a stirring speed of 100 rpm and 0.2 M hydrochloric acid at (pH 1.2) 37 ± 0.5°C as the dissolution medium.

Preparation of solid dispersion by dropping method[97]

In Dropping method, drug with PEG6000 and Urea Were prepared by separately at three different ratios 1:1,1:2 and 1:3. Accurately weighed 100mg drug was taken and mixed with

100,200 and 300mg of PEG6000 and Urea. A solid dispersion of a melted drug and carrier is pipette and then dropping onto a plate, where it solidified in to round or spherical particles. Then accuratelyweighed 50 mg of Dropping Glibenclamide was used sprinkled directly to surface of the dissolution medium. And dissolution studies were carried out withTYPE II (LABINDIA, DISSO 2000) dissolution apparatus at a stirring speed of 100 rpm and 0.2 M hydrochloric acid at (pH 1.2) $37 \pm 0.5°C$ as the dissolution medium.

Preparation of solid dispersion by Wet grinding method[98]

In wet grinding method drug with Chitosan were prepared by separately at three different ratios 1:1,1:2 and 1:3 Accurately weighed 100mg drug was taken and mixed with 100,200 and 300mg of Chitosan in mortar porcelain for 5 minutes .Methanol was then added to the mixture just enough to form dough texture. The mixture was grinded for 30 minutes. The obtained dough was dried at 50^0C for 8 hrs, and thenaccuratelyweighed 50 mg of Glibenclamide was used sprinkled directly to surface of the dissolution medium. And dissolution studies were carried out withTYPE II (LABINDIA, DISSO 2000) dissolution apparatus at a stirring speed of 100 rpm and 0.2 M hydrochloric acid at (pH 1.2) $37 \pm 0.5°C$ as the dissolution medium.

FORMULATION OF NANOPARTICLES

Sonication method[99]

The nanoparticles were prepared by an emulsion–solvent evaporation method. Typically, a solution of 100 mg of Glibenclamide in ethanol was mixed with 10mL of aqueous solution. This mixture was homogenized for 10 min by vortex and then sonicated using a micro tip probe sonicator set at 55Wof energy output (SONICATOR MM 1010) during 1 min to produce the oil-in-water emulsion. The organic phase was evaporated during 20 min using a rotative evaporator under partial vacuum. The nanoparticles were recovered by ultracentrifugation (21,000 rpm, 25 min, Hitachi). Then collect and accurately weighed 50 mg of Glibenclamide was used sprinkled directly to surface of the dissolution medium. And dissolution studies were carried out withTYPE II (LABINDIA, DISSO 2000) dissolution apparatus at a stirring speed of 100 rpm and 0.2 M hydrochloric acid at (pH 1.2) $37 \pm 0.5°C$ as the dissolution medium.

Anti solvent method[100]

Glibenclamidenanoparticles were prepared by the precipitation technique which is also called Anti solvent precipitation method. Glibenclamide was dissolved in 3ml of Methanol, Ethanol and Acetone .Were prepared by separately at room temperature this was poured into 10ml water containing surfactants (Span 80) maintained at a temperature of 50^0C and subsequently stirred at agitation speed of 250revolution per minute (rpm) on magnetic stirrer for1 hour to allow the volatile solvent to evaporate. Addition of organic solvents by means of syringe drop by drop positioned with the needle directly into surfactant containing water. Then collect and accurately weighed 50 mg of Glibenclamide was used sprinkled directly to surface of the dissolution medium. And dissolution studies were carried out with   TYPEII (LABINDIA,DISSO 2000) dissolution apparatus at a stirring speed of 100 rpm and 0.2 M hydrochloric acid at (pH 1.2) $37 \pm 0.5°C$ as the dissolution medium.

IN- VITRO RELEASE STUDIES[101]

     IN-VITRO dissolution studies of all formulations were carried out using 900 ml of 0.2 M hydrochloric acid at (pH 1.2) 37 ± 0.5°C as the dissolution medium in a Type IIapparatus (LABINDIA,DISSO 2000)   at a stirring speed of 100 rpm. Accurately weighed pureGlibenclamide solid dispersions and nanoparticles containing 50 mg of GB was used sprinkled directly to surface of the dissolution medium. Five milliliter sample solution of dissolution medium were withdrawn at the   time interval 10,20,30,40,50and 60min and immediately replaced with an equal volume of the dissolution medium (maintained at 37 ± 0.5°C) in order to maintain constant volume of dissolution medium. The withdrawn samples were filtered and analyzed for drug content at 302 nm and cumulative percentage of drug dissolved was calculated. The amount of drug removed in each sample was compensated in the calculations. All experiments were performed in triplicate. Drug release kinetics was also determined for Different kinetic models (zero-order and first-order).

Kinetic analysis of dissolution data

Drug release kinetic mechanism:

     To analyze the mechanism of drug release form the formulation, the dissolution profile of all the batches were fitted to zero order and first order to ascertain the kinetic modeling of drug release.

Zero order:

     In many of the modified release dosage form particularly controlled or sustained release dosage form (those dosage forms that release the drug in planned, predictable and slower than normal manner) is zero order kinetics.

$$Q = K_0 t$$

Were, Q is the amount of drug release at time, t and K_0 is the release constant.

First Order:

The dissolution data was fitted to first order equation

$$In(100-Q) = In100 = k_1 t$$

Were k_1 is the release rate constant

Chromatographic Study[102]

Thin layer chromatographic method was used to study whether there was any interaction between Glibenclamide and carriers used for formulations, the test solution were prepared by dissolving all test formulation in Methanol and standard solution was prepared from pure Glibenclamide in same solvent. The TLC plates were prepared by spreading silica Gel G on dry glass plate in thin layer as stationary phase. The plats were activated at 110^0c for one hour.10µl of each of the test solution were applied separately to theplats usingmicropipette. The spots were allowed to dry and chromatogram was developed using solvent system consisting of65:6:12:30 Benzene: Acetic acid: Ethyl acetate: Acetone or 9:9:1:1 Chloroform:Cyclohexane:ethanol: Acetic acid as mobile phase.

The plate was removed from developing chamber and solvent front was marked. The solvent was evaporated by drying in hot air oven and spots were detected in iodine chamber. The spots obtained with all the test solution and their Rf values were compared with standard solution. TheRf value was calculated by the following formula.

$$\text{Rf value} = \frac{\text{Distance traveled by solute}}{\text{Distance traveled by solvent}}$$

Estimation of Drug Content[93]

The drug contents in solid dispersion and nanoparticles were determined by the UV-spectroscopic method. An accurately weighed quantity of solid dispersion and nanoparticles equivalent to 5 mg of GBM was transferred to a 100 ml volumetric flask containing 100 ml of methanol and dissolved. The solution was then filtered through the filter paper. 1 ml of this solution was diluted 10 times with 0.2 M HCL buffer solutions and the absorbance was measured at 302 nm.

I.R. Studies[103]

   To know about the interaction between the drug and carriers used in the formulation, the IR analysis was carried out. The IR spectra of pure Glibenclamide, solid dispersions ratio of 1:1 and nanoparticles was studied by FTIR It is scanned over the Frequency range of 4000-500 cm^{-1}

XRD Studies[104]

TheXRD studies for analyzing structural nature of Glibenclamide, solid dispersion and nanoparticle formulation of Glibenclamide. The samples were placed in sample cell and spread evenly. The sample cell was placed in X-ray Diffractometer (BRUKER ECO D8). The samples were scanned over the frequency range of 10-80.

PARTICLE SIZE ANALYSIS OF SOLID DISPERSION[105]

An ordinary compound microscope was used for this purpose. The ordinary microscope is used for the measurement of particle size in the range of 0.2 to 100 μm. Test material, diluted or undiluted is mounted on a slide and placed on a mechanical stage. The eyepiece of the microscope is fitted with a micrometer, using which the sizes of particles are determined. Eyepiece micrometer should be calibrated using a standard stage micrometer. In this, one millimeter is divided into 100 equal divisions and hence, each division is equal to 10 μm. The eyepiece micrometer, which is linear, consists of 100 divisions. Calibration is undertaken to find out the measure of each division.

Procedure:

A small amount of prepared solid dispersions of physical mixture, dropping, solvent evaporation and wet grinding formulations were diluted with petroleum ether. A few drops of this suspension were transferred onto a glass slide and focused in a microscope. The number of division of eyepiece micrometer determined the diameters of 300 particles randomly. This is then converted in to microns and then average particle size was determined.

PARTICLE SIZE ANALYSIS OF NANOPARTICLES:

The prepared Nanoparticles size can be analysed, by using **Malvern size analyzer**. In this analytical method the samples were dispersed in water and placed in a sample cell (Disposable sizing cuvette). Then the cuvette were placed in analyzer we set the measurement position(mm). The analyzer can be run and analyze the particle size distribution of sample and average particle size of samples (diameter in nanometric range). Size distribution can be determined by plotting a graph by intensity (Percent) vs. size (d.nm)

STABILITY STUDIES[105]:

To evaluate the stability of drug, Glibenclamide, and the effect of carriers after storing at different Temperature and Relative Humidity for 30 days stability studies were carried out

About 100mg of equivalent of Glibenclamide formulations were taken in well closed containers from ideal batches and stored separately at $40^0C\pm 2^0C$/75% RH $\pm$ 6% (Accelerated testing) and $30^0C\pm 2^0C$/60% RH $\pm$ 5% (Alternate testing). From these, sample equivalent to 20 mg of Glibenclamide was removed at the interval if 10, 20, 30 days and analyzed the drug content by spectrophotometrically at 302 nm.

RESULTS AND DISCUSSIONS

Table No:8.1

Formulation code

SI.NO	Method of preparation (DRUG:CARRIER:METHOD:RATIO)	FORMULATION CODE
1	Pure Glibenclamide	GB
2	GlibenclamidePeg600 physical mixture 1:1	GPP1
3	GlibenclamidePeg600 physical mixture 1:2	GPP1
4	GlibenclamidePeg600 physical mixture 1:3	GPP1
5	GlibenclamidePeg600 dropping method 1:1	GPD1
6	GlibenclamidePeg600 dropping method 1:2	GPD1
7	GlibenclamidePeg600 dropping method 1:3	GPD1
8	GlibenclamidePeg600 solvent evaporation 1:1	GPS1
9	GlibenclamidePeg600 solvent evaporation 1:2	GPS1
10	GlibenclamidePeg600 solvent evaporation 1:3	GPS1
11	Glibenclamide Urea physical mixture 1:1	GUP1
12	GlibenclamideUrea physical mixture 1:2	GUP1
13	GlibenclamideUrea physical mixture 1:3	GUP1
14	GlibenclamideUrea dropping method 1:1	GUD1
15	GlibenclamideUrea dropping method 1:2	GUD1
16	GlibenclamideUrea dropping method 1:3	GUD1

17	GlibenclamideUrea solvent evaporation 1:1	GUS1
18	GlibenclamideUrea solvent evaporation 1:2	GUS1
19	GlibenclamideUrea solvent evaporation 1:3	GUS1
20	Glibenclamide Chitosan physical mixture 1:1	GCP1
21	Glibenclamide Chitosan physical mixture 1:2	GCP1
22	Glibenclamide Chitosan physical mixture 1:3	GCP1
23	Glibenclamide Chitosan wet grinding 1:1	GCW1
24	Glibenclamide Chitosan wet grinding 1:2	GCW1
25	Glibenclamide Chitosan wet grinding 1:3	GCW1
26	Glibenclamide Methanol spane 80 nanoparticles	GMSN1
27	Glibenclamide Ethanol spane 80 nanoparticles	GESN2
28	Glibenclamide Acetone spane 80 nanoparticles	GASN3
29	Glibenclamide sonicated nanoparticles	GSN

Screening of Carriers:

For the screening study, the carriers PEG 6000,β-Cyclodextrin, Urea, Chitosan and PVP K30 were used to prepare solid dispersion of Glibenclamide; only PEG 6000, Urea and Chitosan were used to prepare solid dispersions. The observations of the screening study are shown in**TableNo:8.2**from the screening studies, it was possible to prepare the solid dispersion system of Glibenclamide by solvent evaporation and dropping method withPEG6000 and Urea.

Wet grinding method Chitosanand PEG6000, Ureaand Chitosan by physical mixing method

TableNo:8.2

Screening of Carriers (Drug:Polymer = 100mg: 100mg)

Carrier	Miscible/Immiscible	Discoloration	Final texture	Final color	yield
PEG600	Miscible	—	Crystalline Solid	White	182mg
Urea	Miscible	—	Crystalline Glassy solid	White	178mg
Chitosan	Miscible	—	Fine Solid	Pale Yellow	187mg

Effect of Carriers on Solubility of Glibenclamide

To find out the effect of carriers on solubility of pure drug (Glibenclamide), solubility study was carried out using 1:1solid dispersion and nanoparticle of drug formulations in distilled water. The results are shown in **TableNo:8.3**

TableNo:8.3

Effect of Carriers on Solubility of Glibenclamide

S.No	Formulation Code	Solubility µg/ml
1.	**GB**	.335
2.	**GPP1**	1.68
3.	**GUP1**	2.01
4.	**GCP1**	1.81
5.	**GMSN1**	.673
6.	**GESN2**	.773
7.	**GASN3**	.893
8.	**GSN1**	.542

Estimation of drug content:

All the Solid dispersions and nanoparticles were extracted with Methanol and the extract was suitably diluted with 0.2 M Hcl buffer pH 1.2. The Glibenclamide content was estimated spectrophotometrically 302 nm.

The formulation PEG600 physical mixing:(GPP1) 95.9%, (GPP2)97.8 and (GPP3)98.2, The formulation PEG600dropping method: (GPD1)97, (GPD1) 97.6 and (GPD3)98.6, The formulation PEG600 solvent evaporation method: (GPS1)97.4, (GPS2)95.6 and (GPS3)96.4, The formulation UREA physical mixing:(GUP1)97.4, (GUP2)96.6 and (GUP3)98.4. The formulation UREAdropping method:(GUD1)97, (GUD2)97.2 and (GUD3)98.2 The formulation UREA solvent evaporation method:(GUS1)97.6, (GUS2)97.6 and (GUS3)98.6, The formulation CHITOSAN physical mixing:(GCP1)95.2, (GCP2)95.8 and (GCP3)96.6, formulation CHITOSAN Wet grinding :(GCW1)97.2, (GCW2)98.4 and (GCW3)98, The nanoparticle formulations: (GMSN1) 98.6, (GESN2)98, (GASN3)98.4 and (GSN)98.6. The results are presented in**TableNo: 8.4**. The results showed that the percentage of Glibenclamide was ranging from 95-98% in all formulations itrevealsthat the drug, in all dispersed and conforms homogeneous mixing of drug and carriers. However slight variation of Glibenclamide may be due to physically loss of drug and instrumental or handling error.

TableNo8.4

Estimation of drug content

S.No	Drug :carrier ratio and Formulation code	% Glibenclamide
1	1:1PEG 6000 (GPP1)	95.9
2	1:2PEG 6000 (GPP2)	97.8
3	1:3PEG 6000 (GPP3)	98.2
4	1:1PEG 6000 (GPD1)	97
5	1:2PEG 6000 (GPD2)	97.6
6	1:3PEG 6000 (GPD3)	98.6
7	1:1PEG 6000 (GPS1)	97.4
8	1:2PEG 6000 (GPS2)	95.6
9	1:3PEG 6000 (GPS3)	96.4
10	1:1 UREA (GUP1)	97.4
11	1:2 UREA (GUP2)	96.6
12	1:3 UREA (GUP3)	98.4
13	1:1 UREA (GUD1)	97
14	1:2 UREA (GUD2)	97.2
15	1:3 UREA (GUD3)	98.2

S.No	Drug :carrier ratio and Formulation code	% Glibenclamide
16	1:1 UREA (GUS1)	97.6
17	1:2 UREA (GUS2)	97.6
18	1:3 UREA (GUS3)	98.6
19	1:1 CHITOSAN (GCP1)	95.2
20	1:2 CHITOSAN (GCP2)	95.8
21	1:3 CHITOSAN (GCP3)	96.6
22	1:1 CHITOSAN (GCW1)	97.2
23	1:2 CHITOSAN (GCW2)	98.4
24	1:3 CHITOSAN (GCW3)	98
25	GMSN1	98.6
26	GESN2	98
27	GASN3	98.4
28	GSN	98.6

IN-VITRO RELEAESTUDIES:

The ultimate aim of this work was to develop a suitable formulation for Glibenclamide .which can dissolve maximum amount of drug in 1 hour .Hence, different batches of solid dispersions and nanoparticles were studied for *in-vitro* dissolution. The results are shown in **TablesNo:8.5, 8.6, 8.8, 8.10,8.12, 8.14, 8.16, 8.18, 8.20, 8.22** The results are also plotted in the form of % drug release Vs time as shown in **Figures:8.1, 8.2, 8.5, 8.8, 8.11, 8.14, 8.17, 8.20, 8.23, and 8.26**

In the batches of solid dispersions prepared**(Physical mixture) with PEG6000**, the maximum dissolution of Glibenclamide, at the end of 1 hour, was observed with 1:3 combination of Physical mixture .At the end of 1 hour, this combination was able to release 26.88% of drug. The least dissolution of Glibenclamide was observed with 1:1 combination, which able to release only 25.01% of Glibenclamide .Whereas, the other combination s 1:2 has released 26.1% of drug after 1hr.

In the batches of solid dispersions prepared**(Dropping method) with PEG6000**, the maximum dissolution of Glibenclamide, at the end of 1 hour, was observed with 1:3 combination of dropping solid dispersions .At the end of 1 hour, this combination was able to release 29.59% of drug. The least dissolution of Glibenclamide was observed with 1:1 combination, which able to release only 28.01% of Glibenclamide .Whereas, the other combinations 1:2 has released 28.83% of drug after 1hr.

In the batches of solid dispersions prepared**(Solvent evaporation) with PEG6000**, the maximum dissolution of Glibenclamide, at the end of 1 hour, was observed with 1:3 combination of Solvent evaporated solid dispersions .At the end of 1 hour, this combination

was able to release 38.81% of drug. The least dissolution of Glibenclamide was observed with 1:1 combinations, which able to release only 31.60% of Glibenclamide .Whereas, the other combination s 1:2 havereleased 35.43% of drug after 1hr.

Solid dispersion prepared by solvent evaporation method showed more release then physical mixture and dropping Solid dispersions of Glibenclamide with PEG6000.

In the batches of solid dispersions prepared**(Physical mixture) with Urea**, the maximum dissolution of Glibenclamide, at the end of 1 hour, was observed with 1:3 combination of Physical mixture .At the end of 1 hour, this combination was able to release 42.52% of drug. The least dissolution of Glibenclamide was observed with 1:1 combinations, which able to release only 38.13% of Glibenclamide .Whereas, the other combination s 1:2 have released 40.50% of drug after 1hr.

In the batches of solid dispersions prepared**(Dropping method) with Urea**, the maximum dissolution of Glibenclamide, at the end of 1 hour, was observed with 1:3 combination of dropping solid dispersions .At the end of 1 hour, this combination was able to release 44.44% of drug. The least dissolution of Glibenclamide was observed with 1:1 combinations, which able to release only 40.56% of Glibenclamide .Whereas, the other combination s 1:2 have released 43.87% of drug after 1hr.

In the batches of solid dispersions prepared**(Solvent evaporation) with Urea,** the maximum dissolution of Glibenclamide, at the end of 1 hour, was observed with 1:3 combination of Solvent evaporated solid dispersions .At the end of 1 hour, this combination was able to release 60.05% of drug. The least dissolution of Glibenclamide was observed with 1:1 combinations, which able to release only 47.82% of Glibenclamide .Whereas, the other combination s 1:2 have released 54.78% of drug after 1hr.

Solid dispersion prepared by solvent evaporation method showed more release then physical mixture and dropping Solid dispersions of Glibenclamide with Urea.

In the batches of solid dispersions prepared**(Physical mixture) with Chitosan**, the maximum dissolution of Glibenclamide, at the end of 1 hour, was observed with 1:3 combination of Physical mixture .At the end of 1 hour, this combination was able to release 31.50% of drug. The least dissolution of Glibenclamide was observed with 1:1 combination, which able to release only 23.63% of Glibenclamide .Whereas, the other combination s 1:2 has released 28.01%of drug after 1hr.

In the batches of solid dispersions prepared**(Wet grinding method) with Chitosan**, the maximum dissolution of Glibenclamide, at the end of 1 hour, was observed with 1:3 combination of Solvent evaporated solid dispersions .At the end of 1 hour, this combination was able to release 43.87% of drug. The least dissolution of Glibenclamide was observed with 1:1 combination, which able to release only 30.94% of Glibenclamide .Whereas ,the other combination s 1:2 have released 37.12% of drug after 1hr. Solid dispersion prepared by Wet grinding method showed more release then physical mixture of Glibenclamide with Chitosan. Theof nanoparticles were prepared by **Anti solvent method with Methanol** was used as solvent (GMSN1) the maximum dissolution of Glibenclamide, at the end of 1 hour, was observed 30.15% of Glibenclamide.

The batches of nanoparticles were prepared by **Anti solvent method with Ethanol** was used as solvent (GMSN1) the maximum dissolution of Glibenclamide, at the end of 1 hour, was observed 31.50% of Glibenclamide.

The nanoparticles were prepared by **Anti solvent method with Acetone** was used as solvent (GASN1) the maximum dissolution of Glibenclamide, at the end of 1 hour, was observed 32.06% of Glibenclamide.

The nanoparticles were prepared by **Sonication method** (GSN) the maximum dissolution of Glibenclamide, at end of 1 hour, was observed 29.70% of Glibenclamide.

In comparison of prepared   nanoparticles are improve release of pure Glibenclamide. And nanoparticles prepared by anti solvent   method showed more release then Sonicated nanoparticles. And GASN3 showed more release then GMSN1&GESN2 of Glibenclamide.

The in vitro release was fitted to the various kinetic models.The drug release kinetics showed that the release was followed first order. Zero order and First order R2values was shown at TableNo:**8.8, 8.9, 8.11, 8.13, 8.15, 8.17, 8.19, 8.21 and 8.23.**Zero order and First order R2values are plotted in graph the Figure was shown **8.3, 8.4, 8.6, 8.7, 8.9, 8.10, 8.12, 8.13, 8.15, 8.16, 8.18, 8.19, 8.20, 8.21, 8.22, 8.24, 8.25, 8.27 and 8.28.**

Comparison of Dissolution of Pure Drug with Solid dispersions and nanoparticles

At the end of 60 minutes, the pure drug showed only6.64% dissolution,(**TableNo: 8.5-8.23 ,Figure 8.1-8.28**) whereas , the solid dispersions of physical mixture, dropping and solvent evaporation method have achieved release up to 26.88% , 29.59% and 38.81% (with PEG6000,)42.52%,44.44% and 60.05%(with Urea), and solid dispersions of physical mixture and wet grinding method have achieved release up to 31.50% and 43.87% (with Chitosan).Then nanoparticles are achieved released up to 30.15%(GMSN1),31.50%(GESN2),32.06%(GASN3) and 29.70%(GSN).It was observed that solid dispersion of drug with Urea showed highest dissolution followed by PEG6000 and Chitosan solid dispersion by solvent evaporation method. Physical mixture, dropping method and nanoparticles also improved the dissolution of Glibenclamide .but it was less compared to solid dispersion by solvent evaporation method.

TableNo:8.5

In-Vitro Release of pure Glibenclamide

S.No	Time	%Release
1	0	0
2.	10	1.13
3.	20	2.81
4.	30	3.60
5.	40	5.2
6.	50	6.07
7.	60	6.64

Figure: 8.1
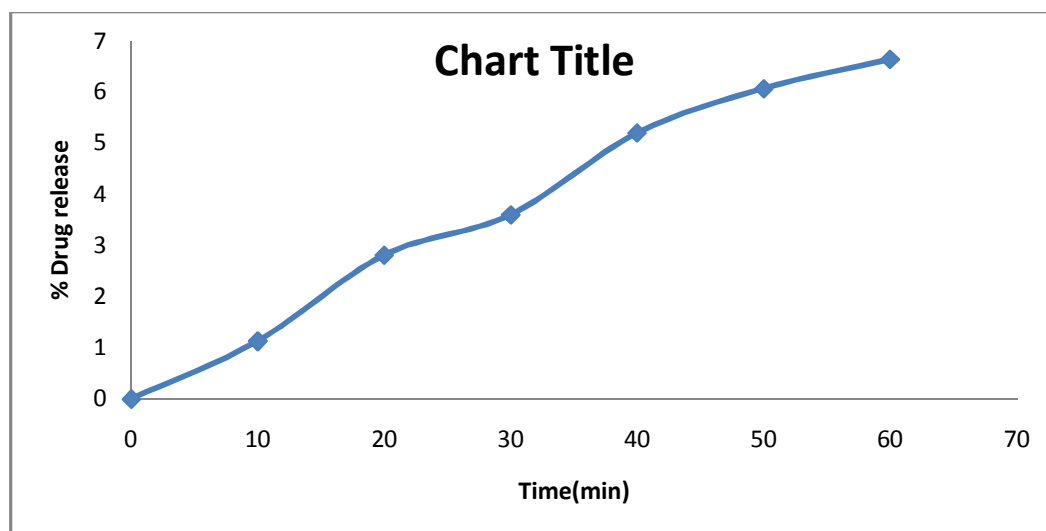
Figure 8.1: Cumulative % drug Release vs. time plot pureGlibenclamide

TableNo:8.6

In-Vitro **Release of Glibenclamide Solid dispersion by physical mixture with**

PEG6000

Time (min)	%Release of Glibenclamide		
	1:1	**1:2**	**1:3**
0	0	0	0
10	6.45	6.98	6.64
20	11.93	13.28	14.06
30	18.23	19.03	19.80
40	21.03	21.71	22.62
50	24.21	24.75	25.53
60	25.01	26.10	26.88

TableNo:8.7

Release kinetic of Glibenclamide Solid dispersion by physical mixture with

PEG6000

Formulation code	Zero order	First order
	R^2	R^2
GPP1	$R^2 = 0.948$	$R^2 = 0.961$
GPP2	$R^2 = 0.944$	$R^2 = 0.960$
GPP3	$R^2 = 0.939$	$R^2 = 0.955$
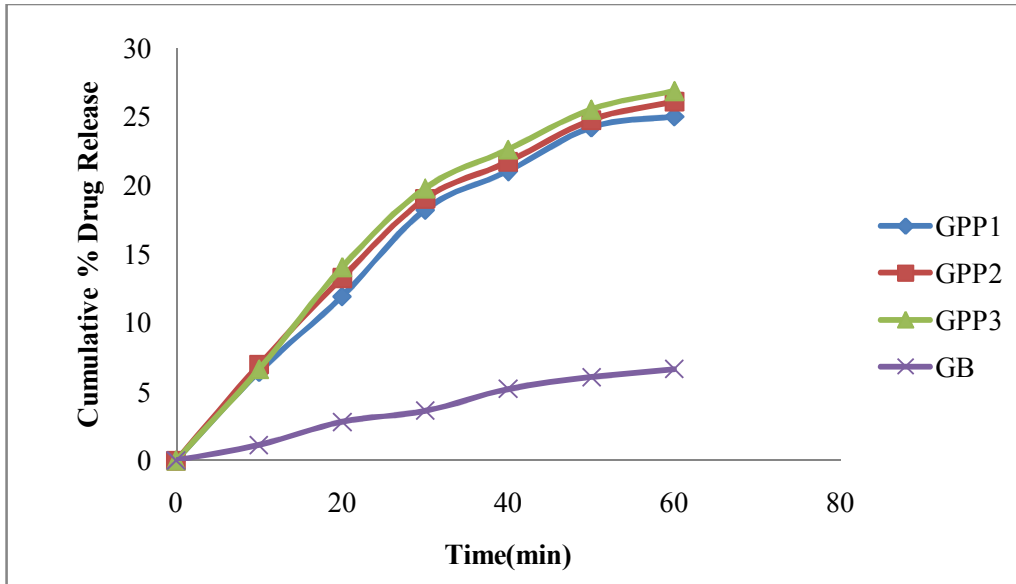
Figure 8.2: Cumulative % drug Release vs. time plot Glibenclamide solid dispersion by physical mixture with PEG6000
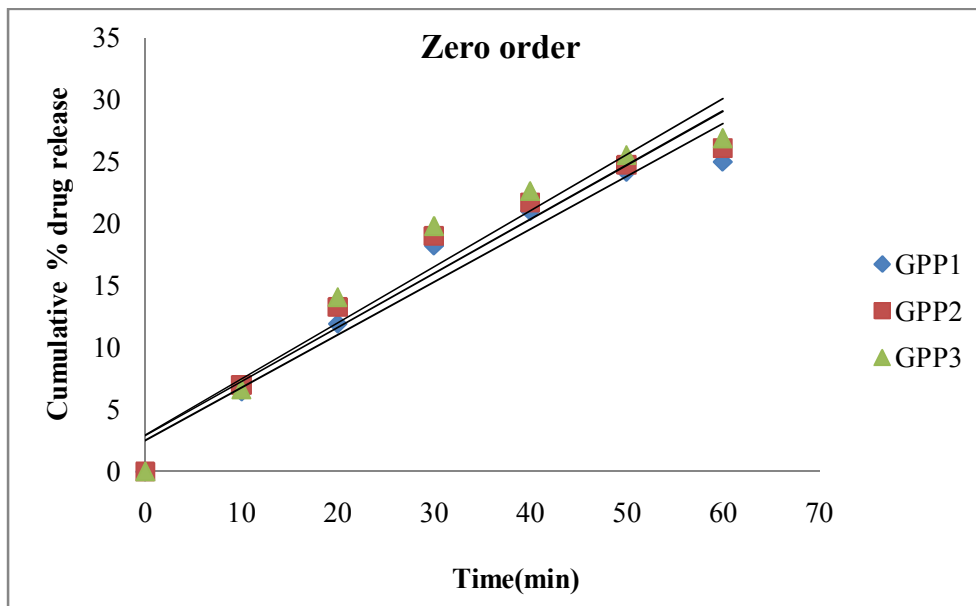
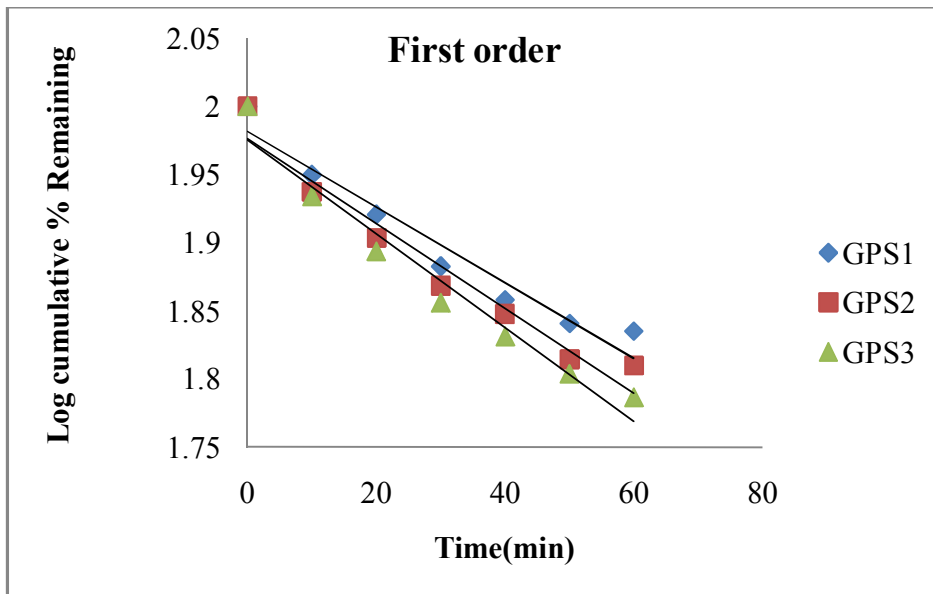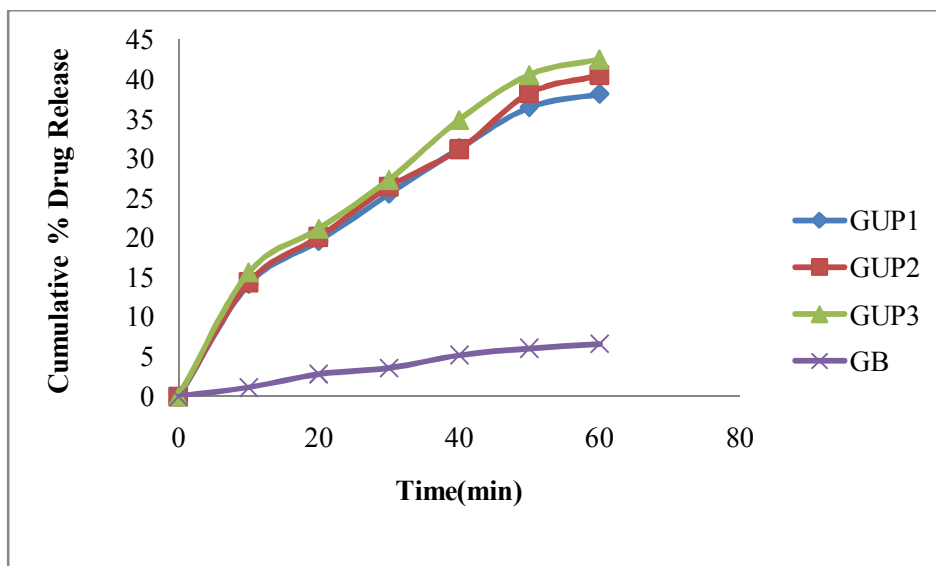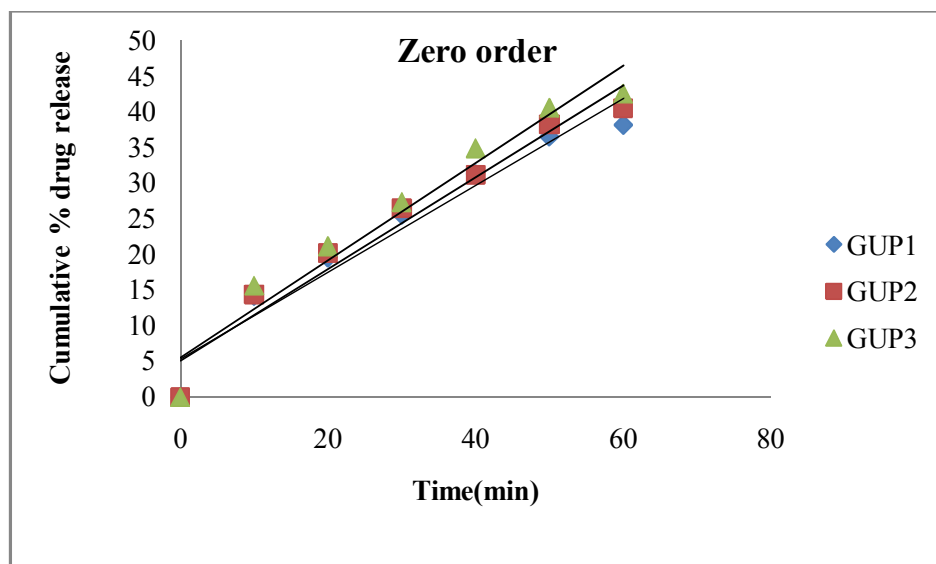Figure 8.3: Cumulative % drug Release vs. time plot Glibenclamide solid dispersion by physical mixture with PEG6000
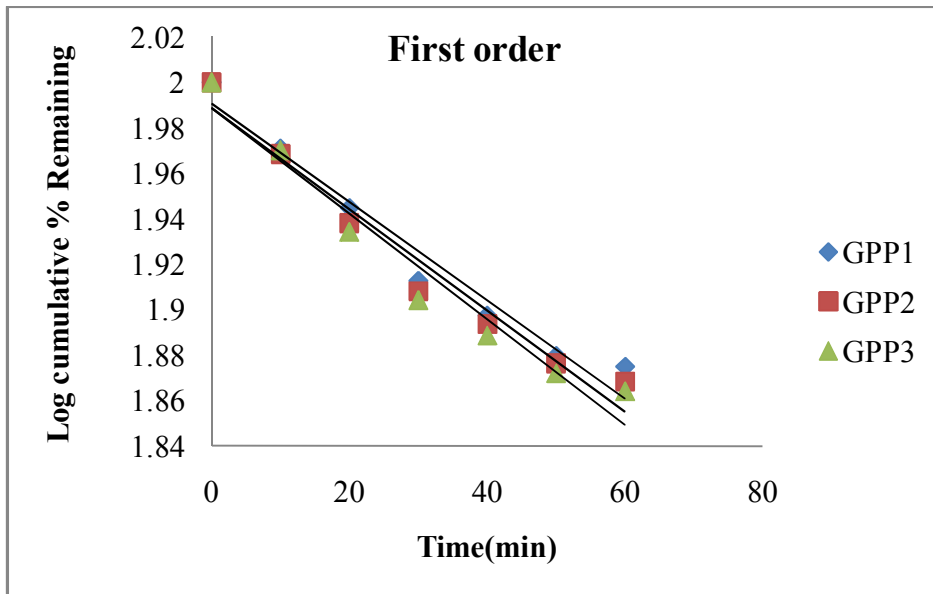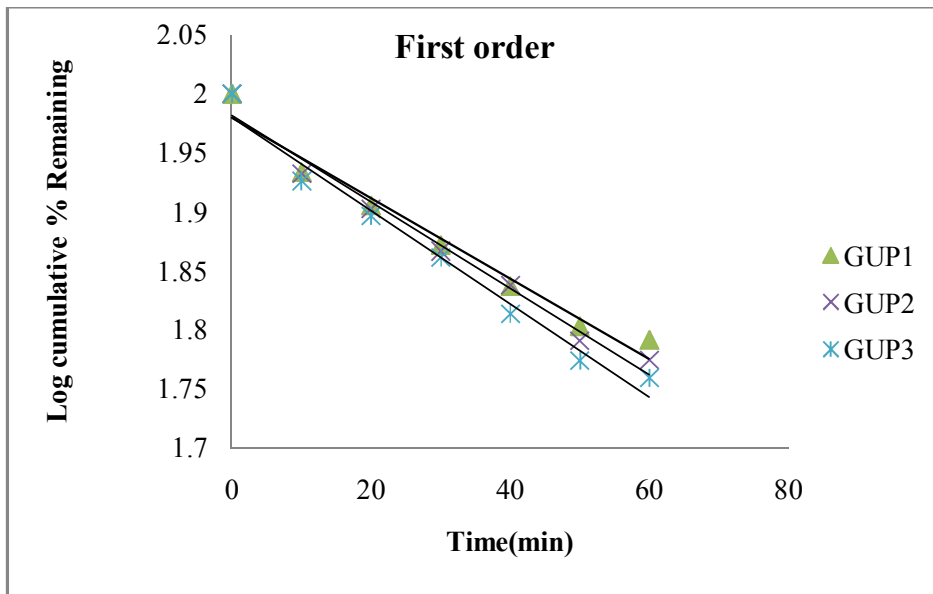
Figure 8.4: Log % remaining vs. Time plot Glibenclamide solid dispersion by physical mixture with PEG6000

Table No:8.8

In-Vitro Release of Glibenclamide Solid dispersion by Dropping method withPEG6000

Time (min)	%Release of Glibenclamide		
	1:1	1:2	1:3
0	0	0	0
10	7.31	7.76	9.2
20	14.85	15.41	16.76
30	22.16	20.04	21.49
40	23.63	23.85	24.41
50	26.67	26.88	27.56
60	28.83	28..83	29.59

TableNo:8.9

Release kinetics of Glibenclamide Solid dispersion by Dropping method withPEG6000

| Formulation code	Zero order	First order
	R^2	R^2
GPD1	$R^2 = 0.920$	$R^2 = 0.938$
GPD2	$R^2 = 0.947$	$R^2 = 0.965$
GPD3	$R^2 = 0.930$	$R^2 = 0.952$
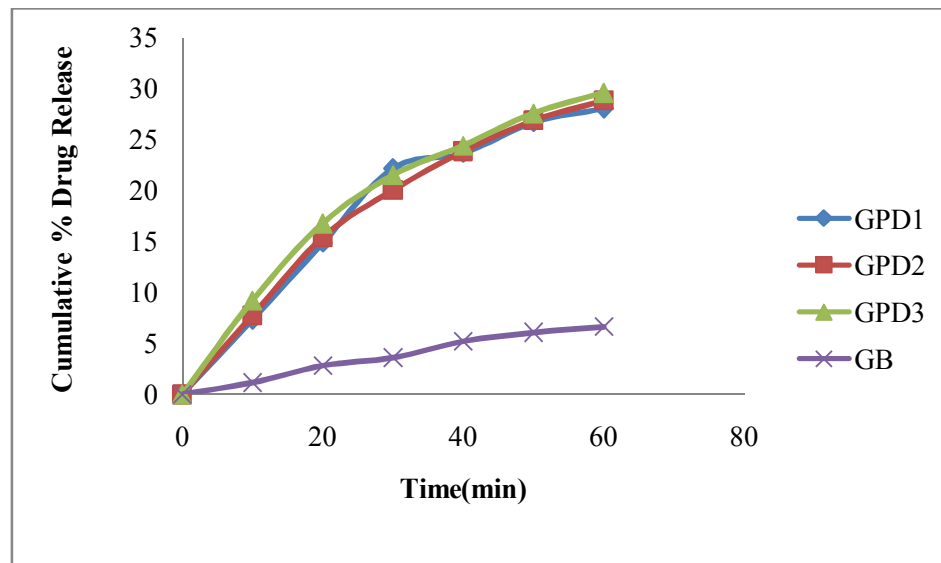
Figure 8.5: Cumulative % drug Release vs. time plot Glibenclamide solid
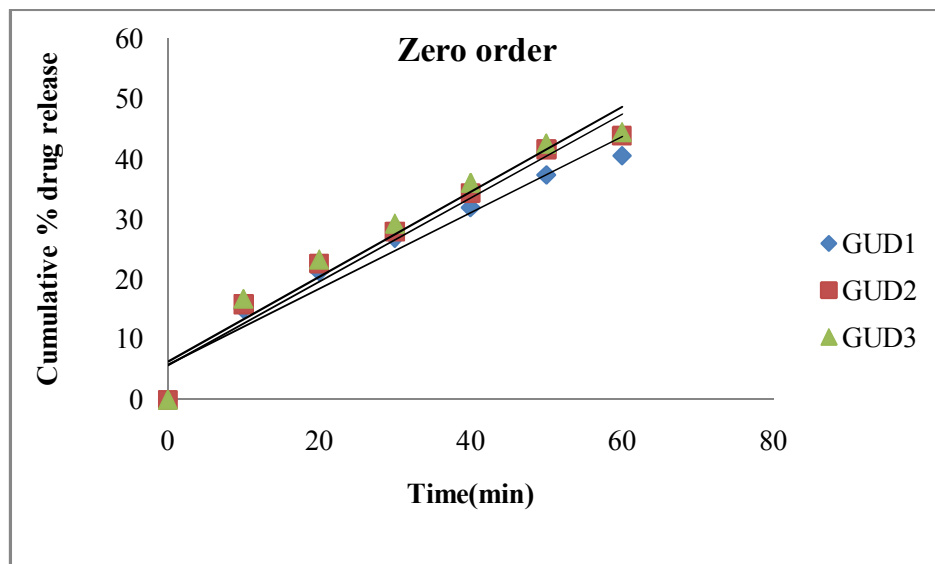
dispersion by Dropping method with PEG6000
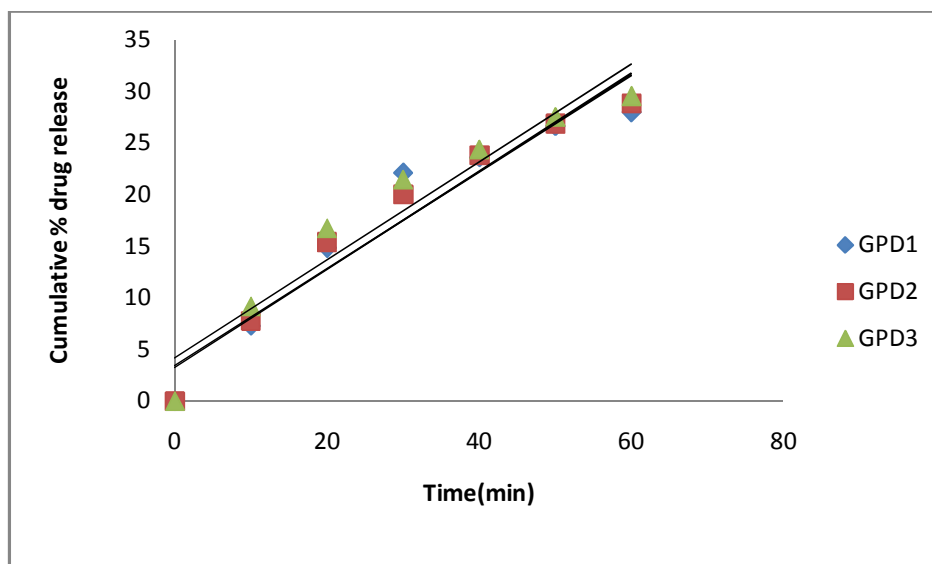
Figure 8.6: Cumulative % drug Release vs. time plot Glibenclamide solid
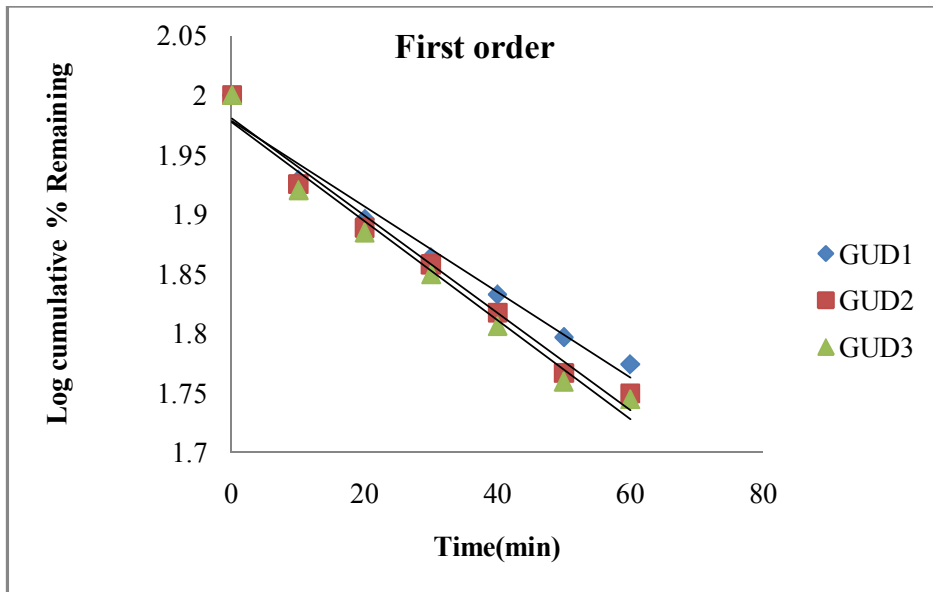
dispersion by Dropping method with PEG6000
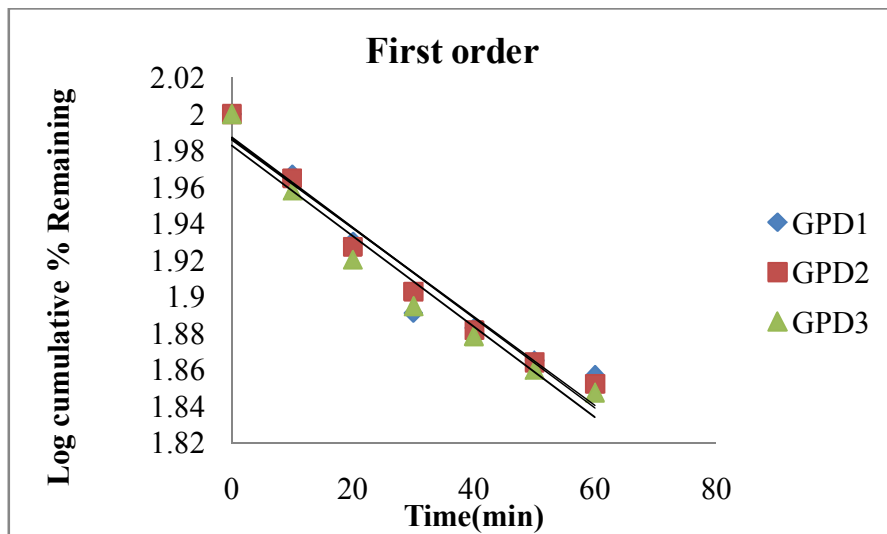
Figure 8.7: Log % remaining vs. Time plot Glibenclamide solid dispersion by

dropping method with PEG6000

TableNo:8.10
In-Vitro Release of Glibenclamide Solid dispersion by Solvent evaporation with PEG6000

Time (min)	%Release of Glibenclamide		
	1:1	1:2	1:3
0	0	0	0
10	10.91	13.38	14.06
20	16.68	19.91	21.71
30	23.67	26.1	28.23
40	27.9	29.58	32.18
50	30.71	34.76	36.33
60	31.6	35.43	38.81

TableNo:8.11

Release kinetics of Glibenclamide Solid dispersion by Solvent evaporation with PEG6000

| Formulation code	Zero order	First order
	R^2	R^2
GPS1	$R^2 = 0.925$	$R^2 = 0.947$
GPS2	$R^2 = 0.921$	$R^2 = 0.950$
GPS3	$R^2 = 0.925$	$R^2 = 0.958$
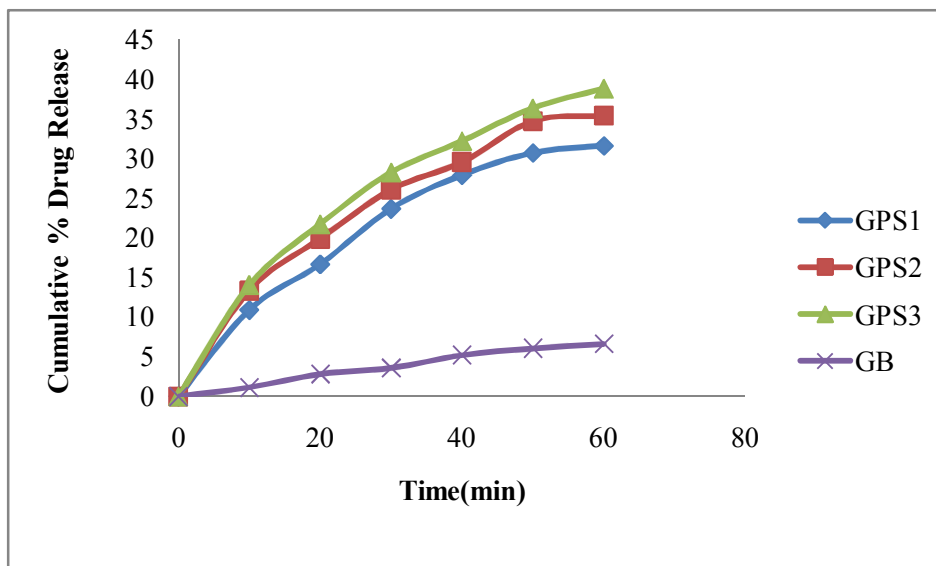
Figure 8.8: Cumulative % drug Release vs. time plot Glibenclamide solid

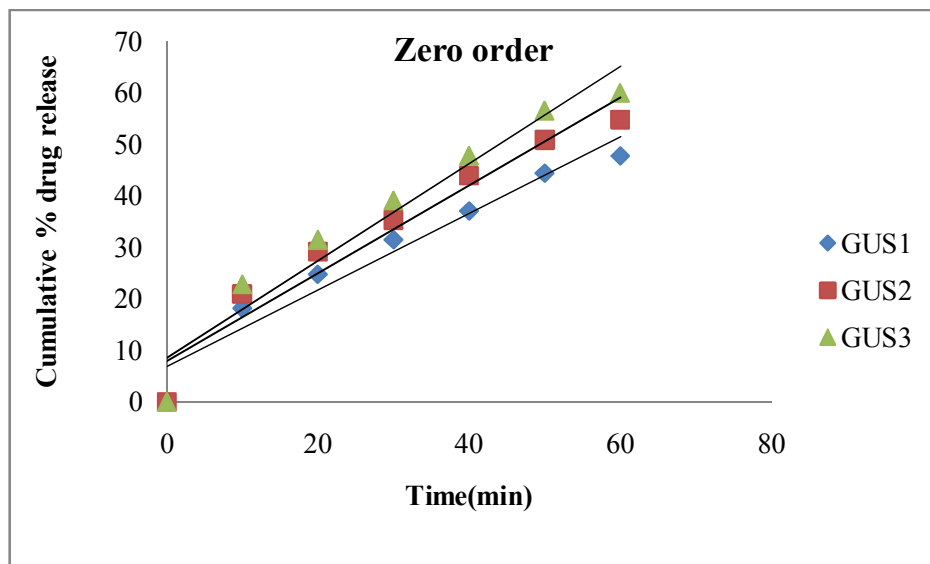dispersion by Solvent evaporationwith PEG6000
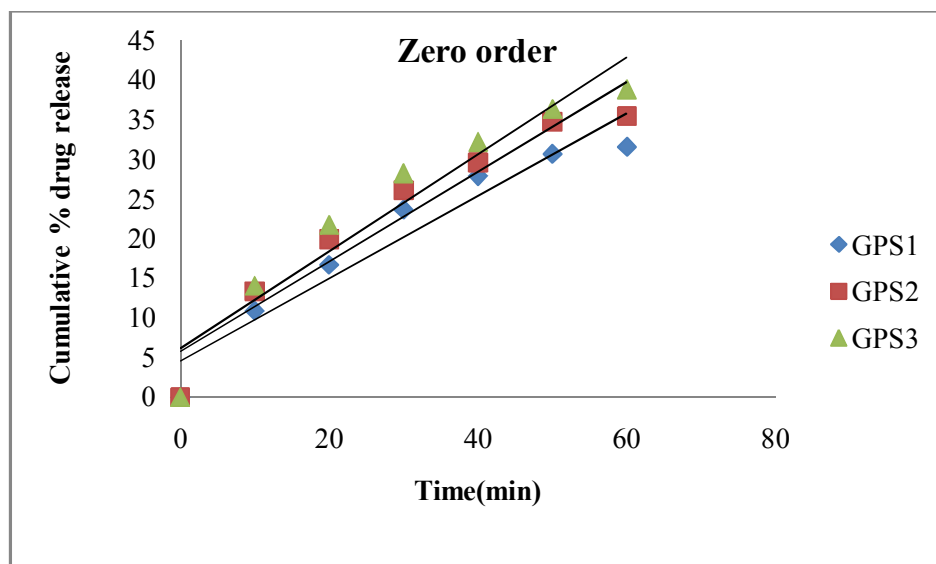
Figure 8.9: Cumulative % drug Release vs. time plot Glibenclamide solid

dispersion by Solvent evaporationwith PEG6000

Figure 8.10: Log % remaining vs. Time plot Glibenclamide solid dispersion by physical Solvent evaporationPEG6000

TableNo:8.12

In-Vitro Release of Glibenclamide Solid dispersion by Physical mixing with

UREA

Time	%Release of Glibenclamide		
(min)	1:1	1:2	1:3
0	**0**		
10	14.18	14.4	15.64
20	19.58	20.14	21.15
30	25.54	26.44	27.34
40	31.26	31.17	34.89
50	36.45	38.25	40.56
60	38.13	40.5	42.52

TableNo:8.13

Release kinetics of Glibenclamide Solid dispersion by Physical mixing with

UREA

Formulation code	Zero order	First order
	R^2	R^2
GUP1	$R^2 = 0.944$	$R^2 = 0.971$
GUP2	$R^2 = 0.955$	$R^2 = 0.979$
GUP3	$R^2 = 0.950$	$R^2 = 0.976$

Figure 8.11: Cumulative % drug Release vs. time plot Glibenclamide solid

dispersion by physical mixture with UREA

Figure 8.12: Cumulative % drug Release vs. time plot Glibenclamide solid
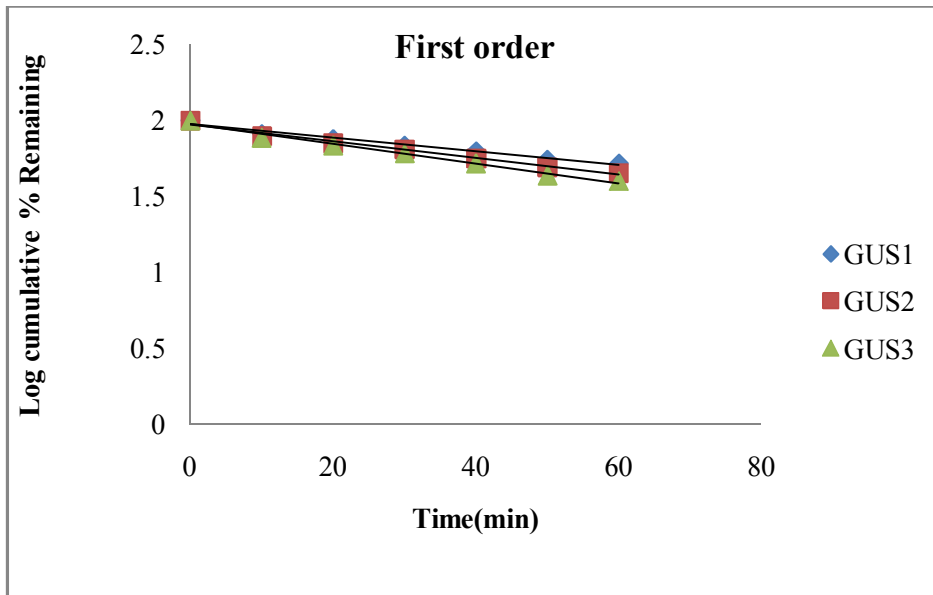
dispersion by physical mixture with UREA

Figure8.13: Log % remaining vs. Time plot Glibenclamide solid dispersion by

physical mixture UREA

TableNo:8.14

In-Vitro Release of Glibenclamide Solid dispersion by Dropping method with UREA

Time (min)	%Release of Glibenclamide		
	1:1	1:2	1:3
0		0	0
10	15.08	15.87	16.75
20	21.27	22.62	23.29
30	26.89	27.92	29.25
40	31.95	34.32	36
50	37.35	41.62	42.52
60	40.56	43.87	44.44

TableNo:8.15

Release kinetics of Glibenclamide Solid dispersion by Dropping method with UREA

| Formulation code	Zero order R^2	First order R^2
GUD1	$R^2 = 0.944$	$R^2 = 0.974$
GUD2	$R^2 = 0.952$	$R^2 = 0.979$
GUD3	$R^2 = 0.943$	$R^2 = 0.974$
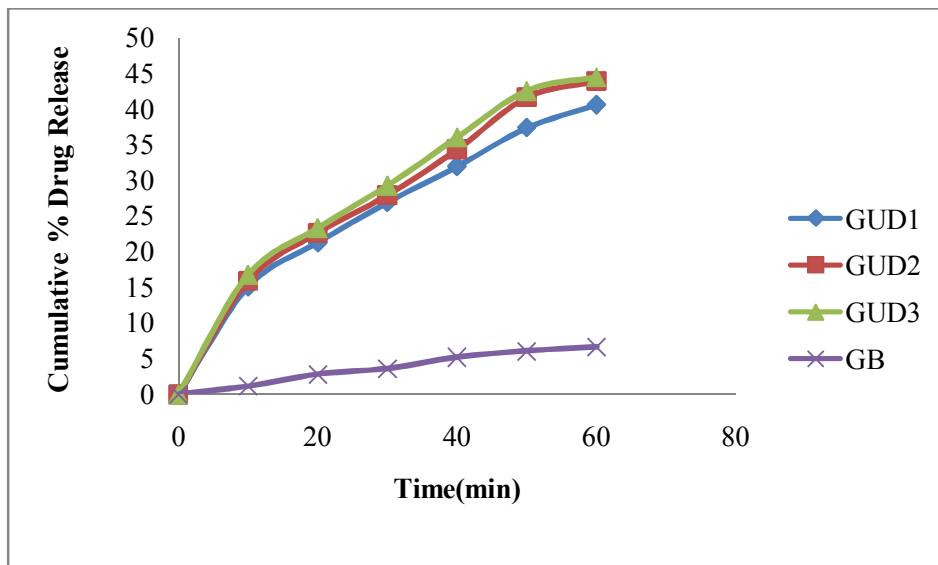
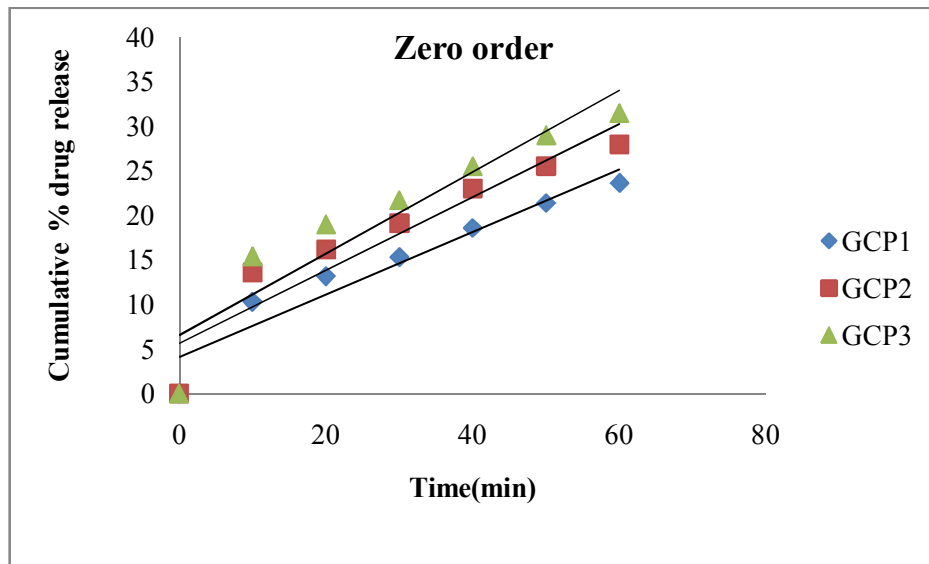Figure 8.14: Cumulative % drug Release vs. time plot Glibenclamide solid dispersion by Dropping method with UREA

Figure 8.15: Cumulative % drug Release vs. time plot Glibenclamide solid dispersion by Dropping method with UREA

Figure 8.16: Log % remaining vs. Time plot Glibenclamide solid dispersion by

physical Dropping method with UREA

Table No: 8.16

In-Vitro Release of Glibenclamide Solid dispersion by Solvent evaporation with UREA

Time (min)	%Release of Glibenclamide		
	1:1	1:2	1:3
0	0	0	0
10	18.22	20.92	22.84
20	24.75	29.14	31.5
30	31.5	35.32	39.15
40	37.12	43.87	47.82
50	44.44	50.85	56.59
60	47.82	54.78	60.05

TableNo:8.17

Release kinetics of Glibenclamide Solid dispersion by Solvent evaporation with UREA

| Formulation code	Zero order R^2	First order R^2
GUS1	$R^2 = 0.944$	$R^2 = 0.979$
GUS2	$R^2 = 0.942$	$R^2 = 0.982$
GUS3	$R^2 = 0.943$	$R^2 = 0.986$
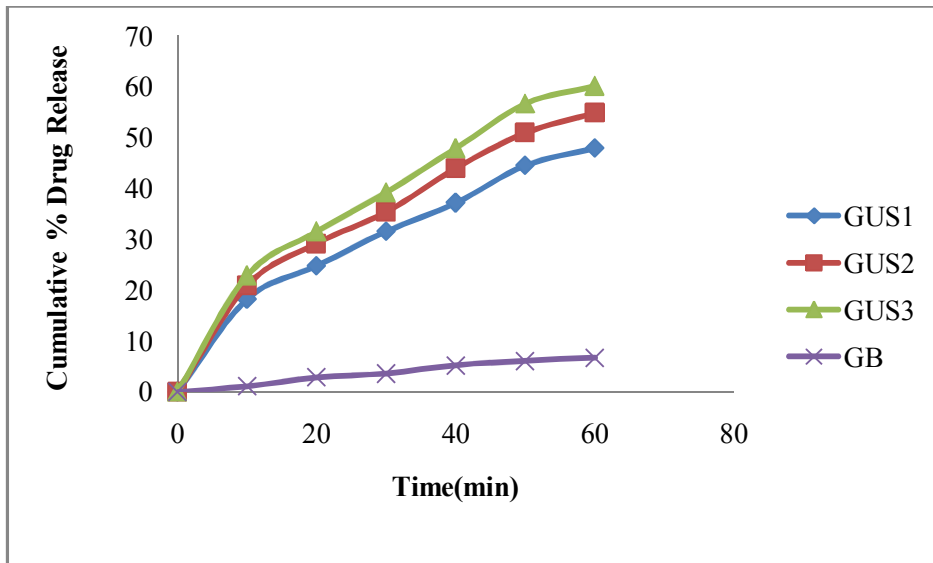
Figure 8.17: Cumulative % drug Release vs. time plot Glibenclamide solid
dispersion by Solvent evaporation with UREA

Figure 8.18: Cumulative % drug Release vs. time plot Glibenclamide solid
dispersion by Solvent evaporation with UREA

Figure 8.19: Log % remaining vs. Time plot Glibenclamide solid dispersion by

Solvent evaporation with UREA

TableNo:8.18

In-Vitro Release of Glibenclamide Solid dispersion by Physical mixing with CHITOSAN

Time (min)	%Release of Glibenclamide		
	1:1	1:2	1:3
0	0	0	0
10	10.28	13.61	15.41
20	13.16	16.2	19.01
30	15.3	19.13	21.71
40	18.56	23.06	25.54
50	21.38	25.54	29.03
60	23.63	28.01	31.5

Table No: 8.19

Release kinetics of Glibenclamide Solid dispersion by Physical mixing with CHITOSAN

Formulation code	Zero order	First order
	R^2	R^2
GCP1	$R^2 = 0.917$	$R^2 = 0.939$
GCP2	$R^2 = 0.886$	$R^2 = 0.904$
GCP3	$R^2 = 0.878$	$R^2 = 0.914$
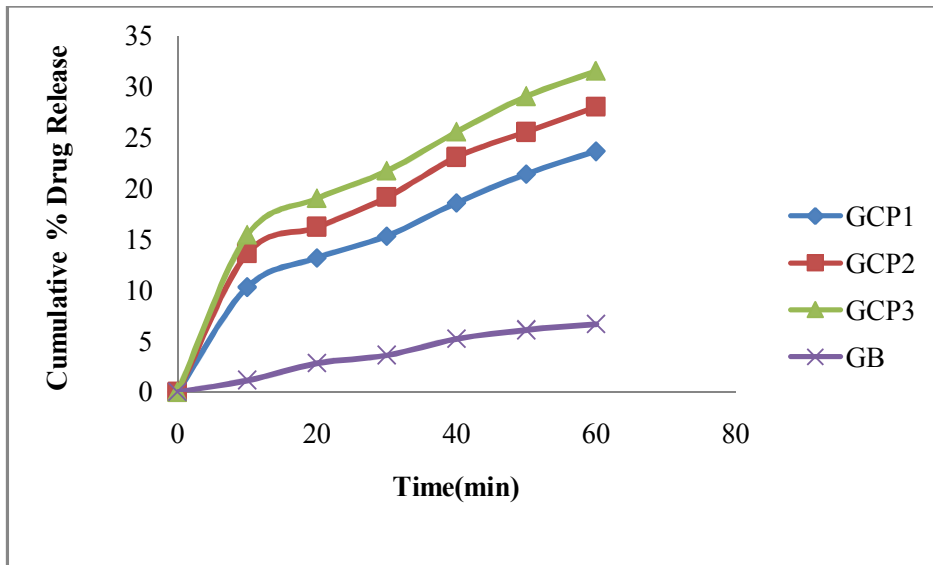
Figure 8.20: Cumulative % drug Release vs. time plot Glibenclamide solid

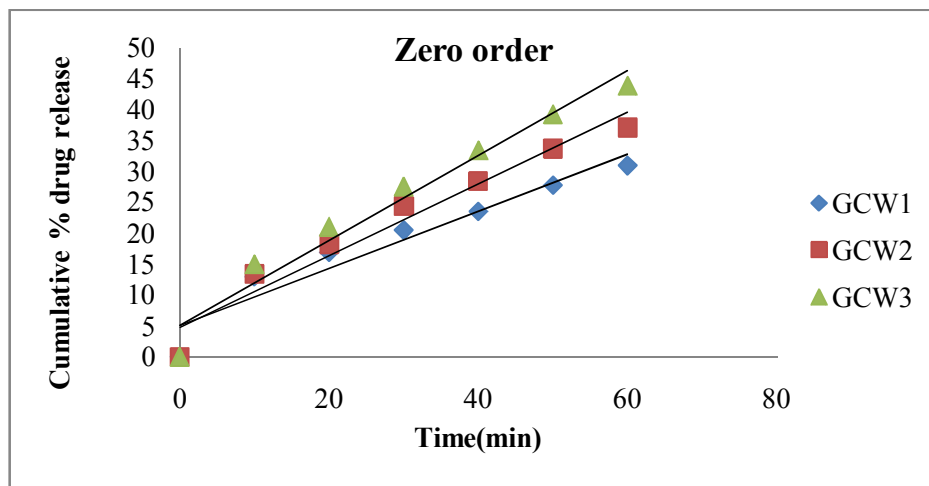dispersion by physical mixture with CHITOSAN

Figure 8.21: Cumulative % drug Release vs. time plot Glibenclamide solid
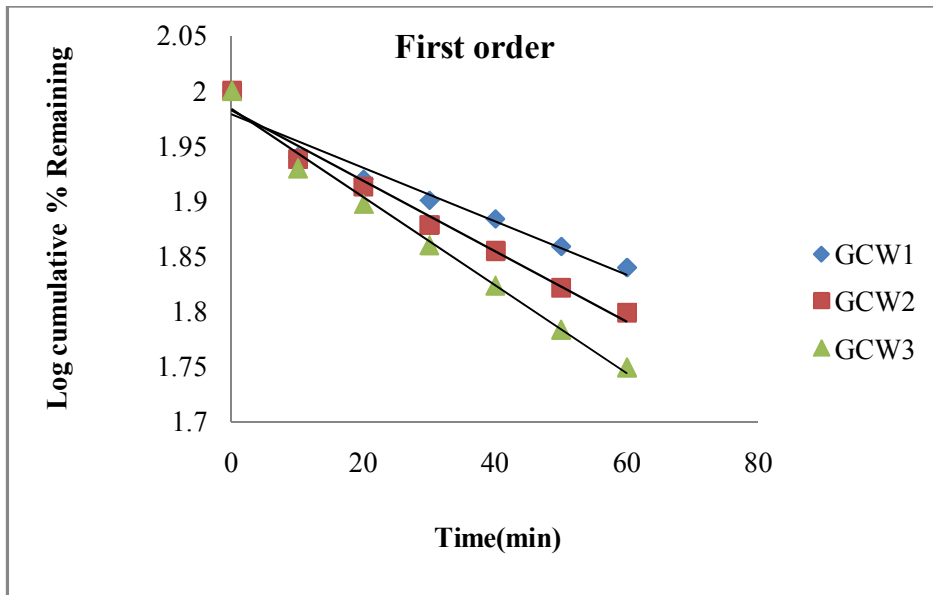
dispersion by physical mixture method with CHITOSAN
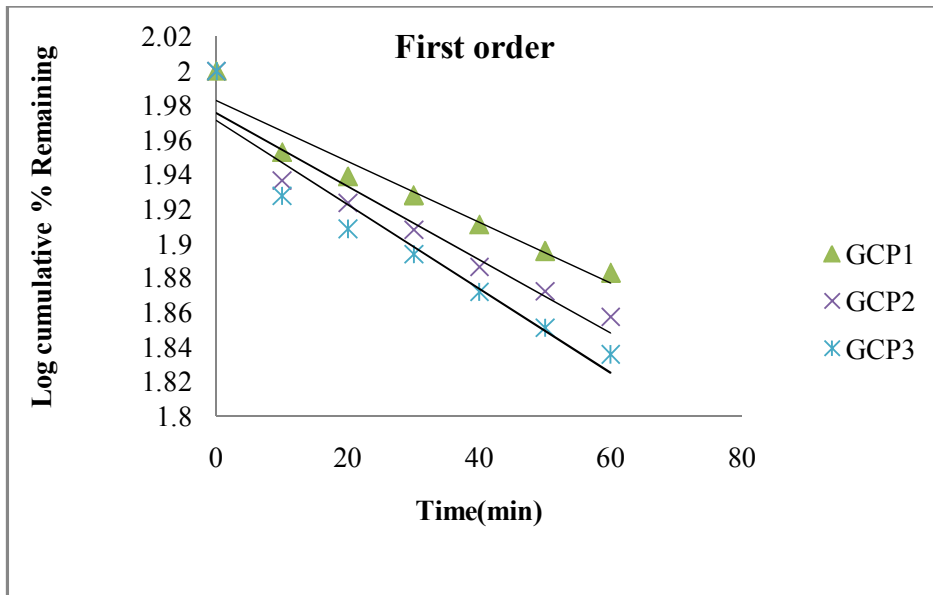
Figure 8.22: Log % remaining vs. Time plot Glibenclamide solid dispersion by

physical mixture CHITOSAN

TableNo:8.20

In-Vitro Release of Glibenclamide Solid dispersion by wetgrinding with CHITOSAN

Time (min)	%Release of Glibenclamide		
	1:1	1:2	1:3
0	0	0	0
10	12.94	13.39	14.96
20	16.88	18.22	21.04
30	20.48	24.41	27.56
40	23.51	28.46	33.41
50	27.79	33.75	39.26
60	30.94	37.12	43.87

TableNo:8.21

Release kinetics of Glibenclamide Solid dispersion by wetgrinding with CHITOSAN

Formulation code	Zero order R^2	First order R^2
GCW1	$R^2 = 0.924$	$R^2 = 0.951$
GCW2	$R^2 = 0.954$	$R^2 = 0.978$
GCW3	$R^2 = 0.963$	$R^2 = 0.987$
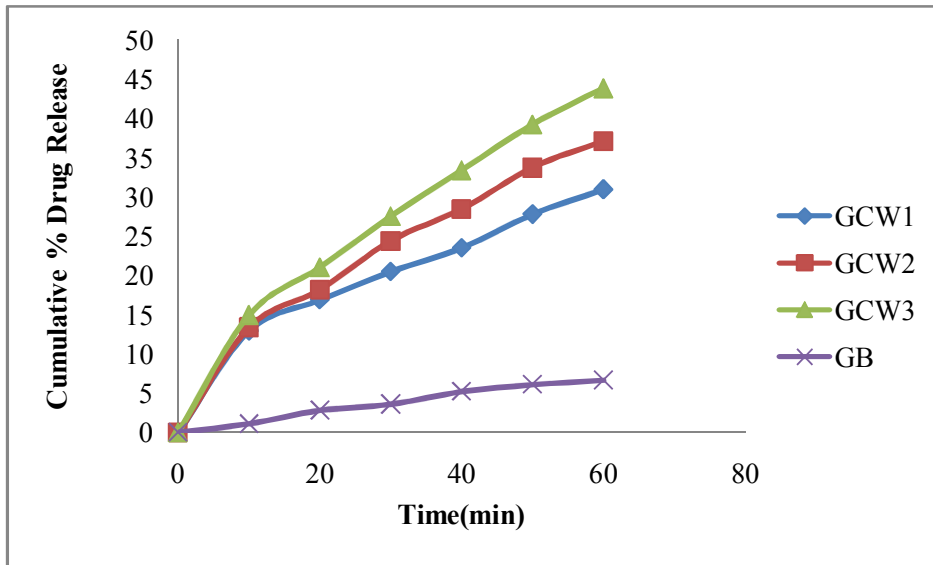
Figure8.23: Cumulative % drug Release vs. time plot Glibenclamide solid

dispersion by Wet grinding method with CHITOSAN

Figure 8.24: Cumulative % drug Release vs. time plot Glibenclamide solid

dispersion by Wet grinding method with CHITOSAN

Figure8.25: Log % remaining vs. Time plot Glibenclamide solid dispersion by Wet grinding CHITOSAN

TableNo:8.22

In-Vitro Release of Glibenclamide by nanoparticles Formulations

Time (min)	%Release of Glibenclamide			
	GMSN1	GESN2	GASN3	GSN
0	0	0	0	0
10	13.5	12.94	15	14.85
20	13.6	14.63	20.59	18.11
30	18	20.81	22.95	21.1
40	22.61	23.63	26.44	25.2
50	28.13	28.91	29.26	27.34
60	30.15	31.5	32.06	29.7

TableNo:8.23

Release kinetics of Glibenclamide by nanoparticles Formulations

Formulation code	Zero order R^2	First order R^2
GMSN1	$R^2 = 0.931$	$R^2 = 0.950$
GESN2	$R^2 = 0.941$	$R^2 = 0.962$
GASN3	$R^2 = 0.868$	$R^2 = 0.906$
GSN	$R^2 = 0.867$	$R^2 = 0.902$
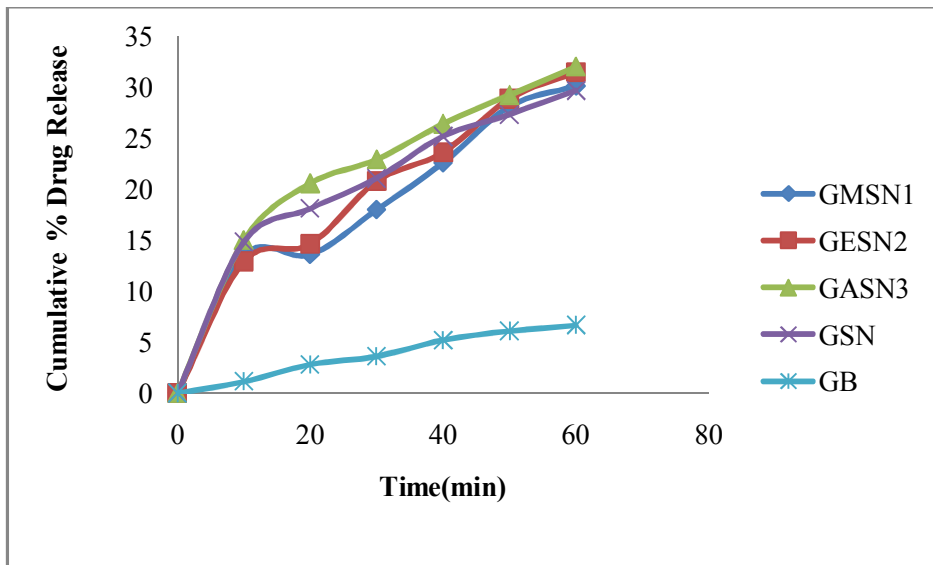
Figure 8.26: Cumulative % drug Release vs. time plot Glibenclamide by

Nanoparticles formulations
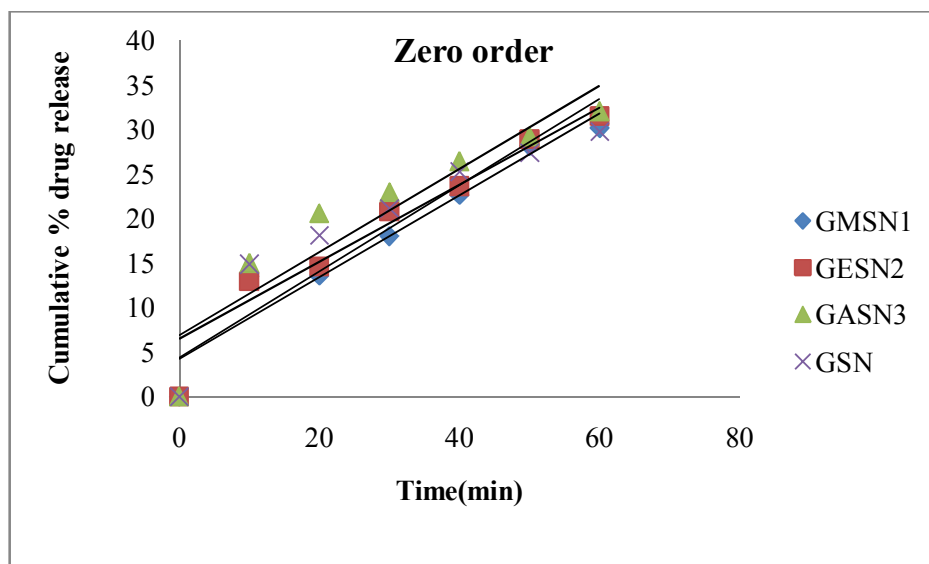
Figure 8.27: Cumulative % drug Release vs. time plot Glibenclamide by

Nanoparticles formulations
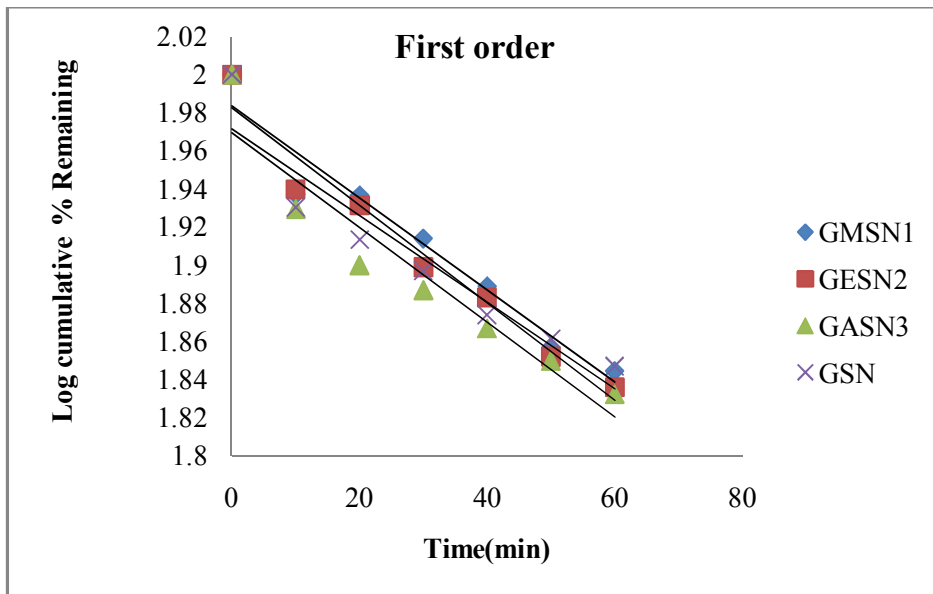
Figure8.28: Log % remaining vs. Time plot Glibenclamide by Nanoparticles

formulations

'

Chromatographic Study:

Thin layer chromatography:

The TLC studies of the ideal batches of solid dispersions, physical mixture and nanoparticles were carried out and calculated The TLC chromatography study is shown Rf value of pure Glibenclamide was (0.64), GPP3 (0.61), GUP3 (0.62) GCP3 (0.62) GSN (0.64), GMSN1 (0.63) GESN2 (0.64) GASN (0.64) the Rf value also nearby pure Glibenclamide so there is polymeric interaction may not take place in above formulations.Rf values are shown in **TableNo**: 8.24

TableNo: 8.24

Rf values ofGlibenclamide solid dispersion, physical mixture andnanoparticles.

S.No	Formulation	Rf value
1.	Pure Glibenclamide(GB)	0.64
2.	GPP3	0.61
3.	GUP3	0.62
4.	GUP3	0.62
5.	GSN	0.64
6.	GMSN1	0.63
7.	GESN2	0.64
8.	GAS3	0.64

The Rf value of pure drug, soliddispersion and nanoparticles were nearly same indicating that the drug is not degraded in the solid dispersion and nanoparticles formulations.

FTIR STUDY:

The Infrared spectral analysis was carried out to the Study the Interaction between drug carriers. The IR spectrums as shown in **Figures**:8.29-8.36

The FTIR spectra of pure Glibenclamide and formulations of solid dispersion ratio 1:1 and nanoparticles were found to identical. The Absorption peak of following functional group are shown within the rang like Amide group at 1680-1630 cm^{-1},Aromatic CH group at 3000-2850cm^{-1}Sulfonamide SO group at1050cm^{-1} and Halogen Cl group at 785-540^{-1}. The above functional groups also present in the Glibenclamide. The IR spectrum of pure Glibenclamide, solid dispersion and nanoparticles of the formulations are shown peaks within the range of functional groups. This indicates that there was no chemical interaction or bonding or decomposition of Glibenclamide employed in the formulations and formulations with various carriers.

FIGURE 6.29: FTIR SPECTRUM OF PURE GLIBENCLAMIDE (GB)
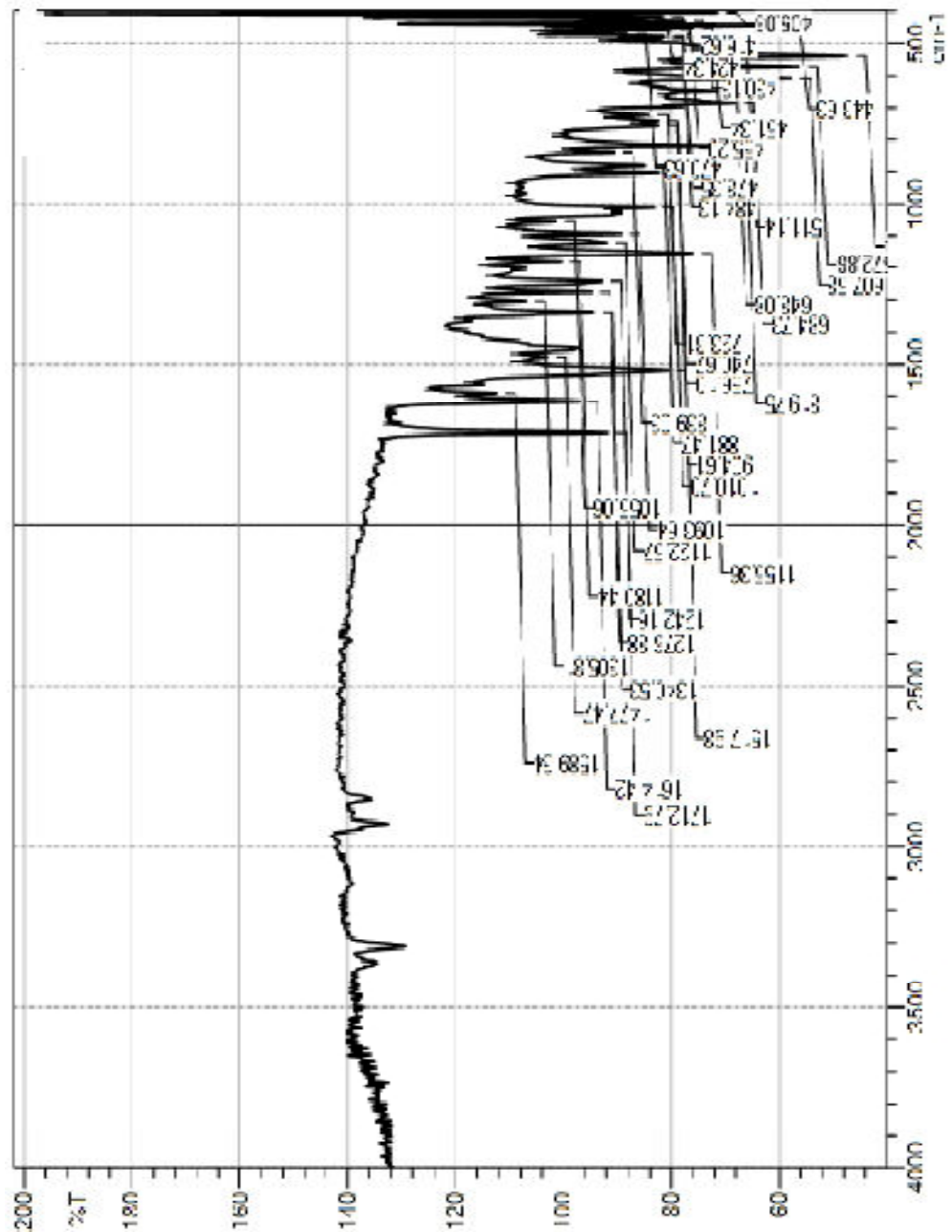
FIGURE 6.30: FTIR SPECTRUM OF GLIBENCLAMIDE SOLID DISPERSION WITH PEG6000 (GPP1)
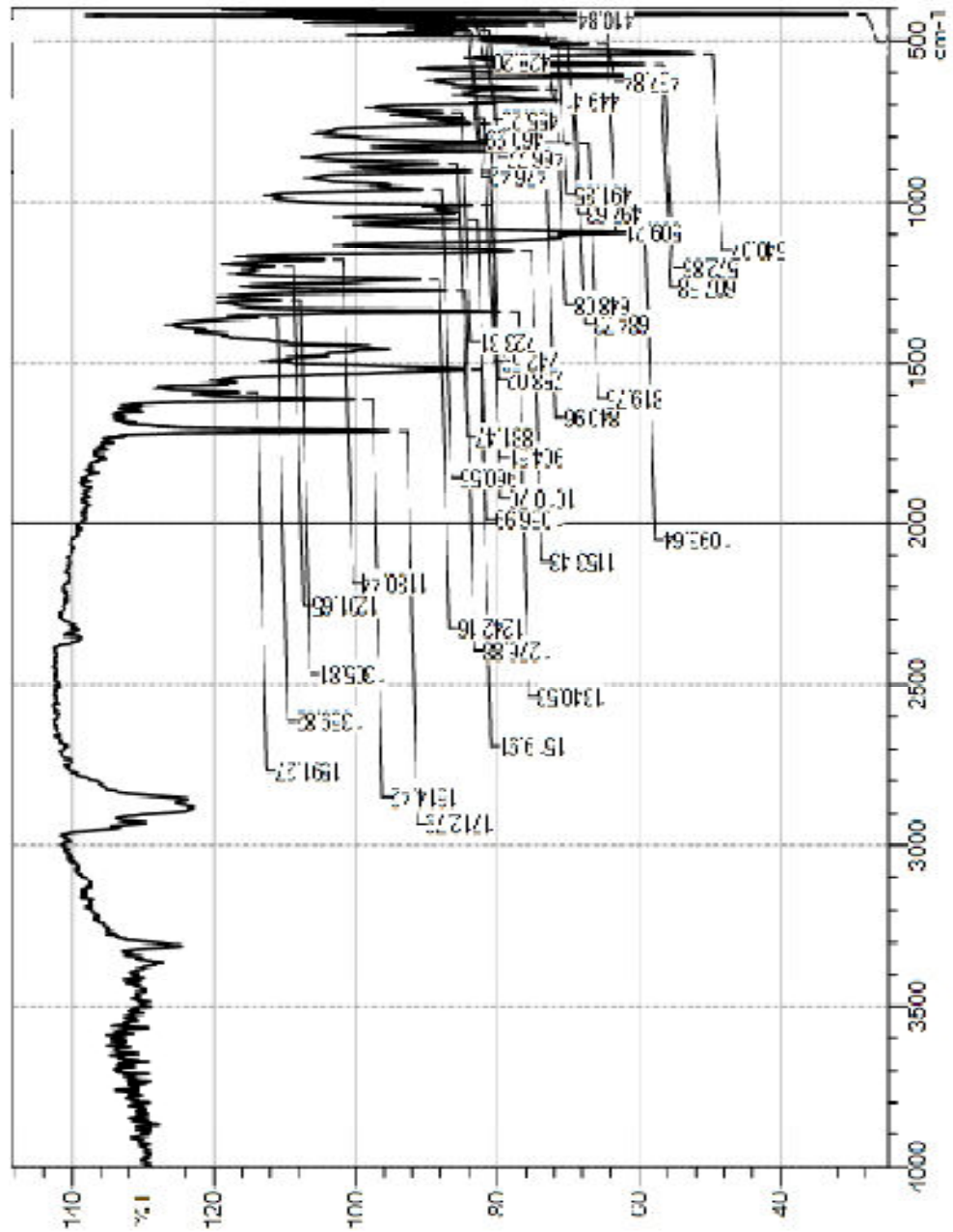
FIGURE 6.31: FTIR SPECTRUM OF GLIBENCLAMIDE SOLID DISPERSION WITH UREA (GUP1)
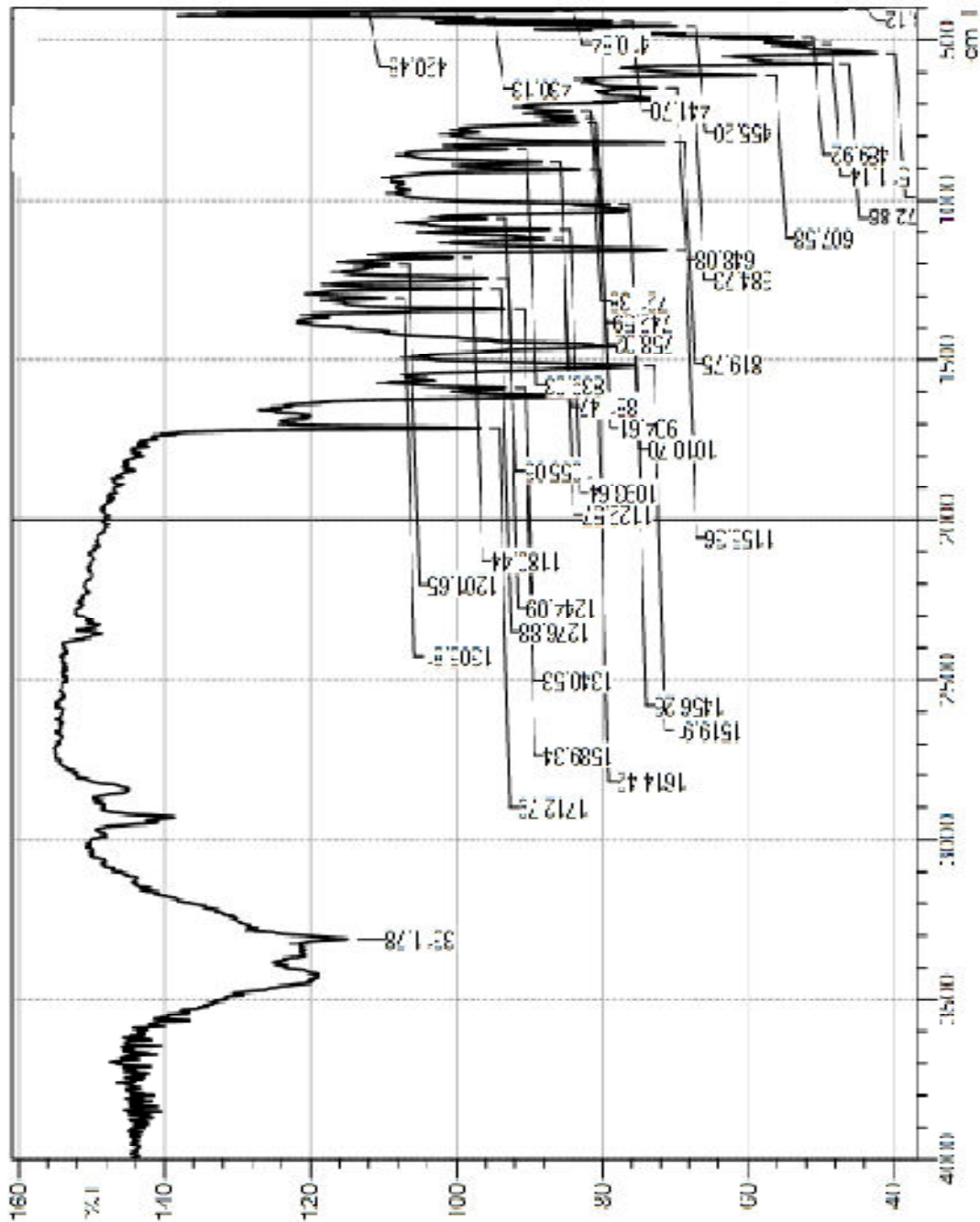
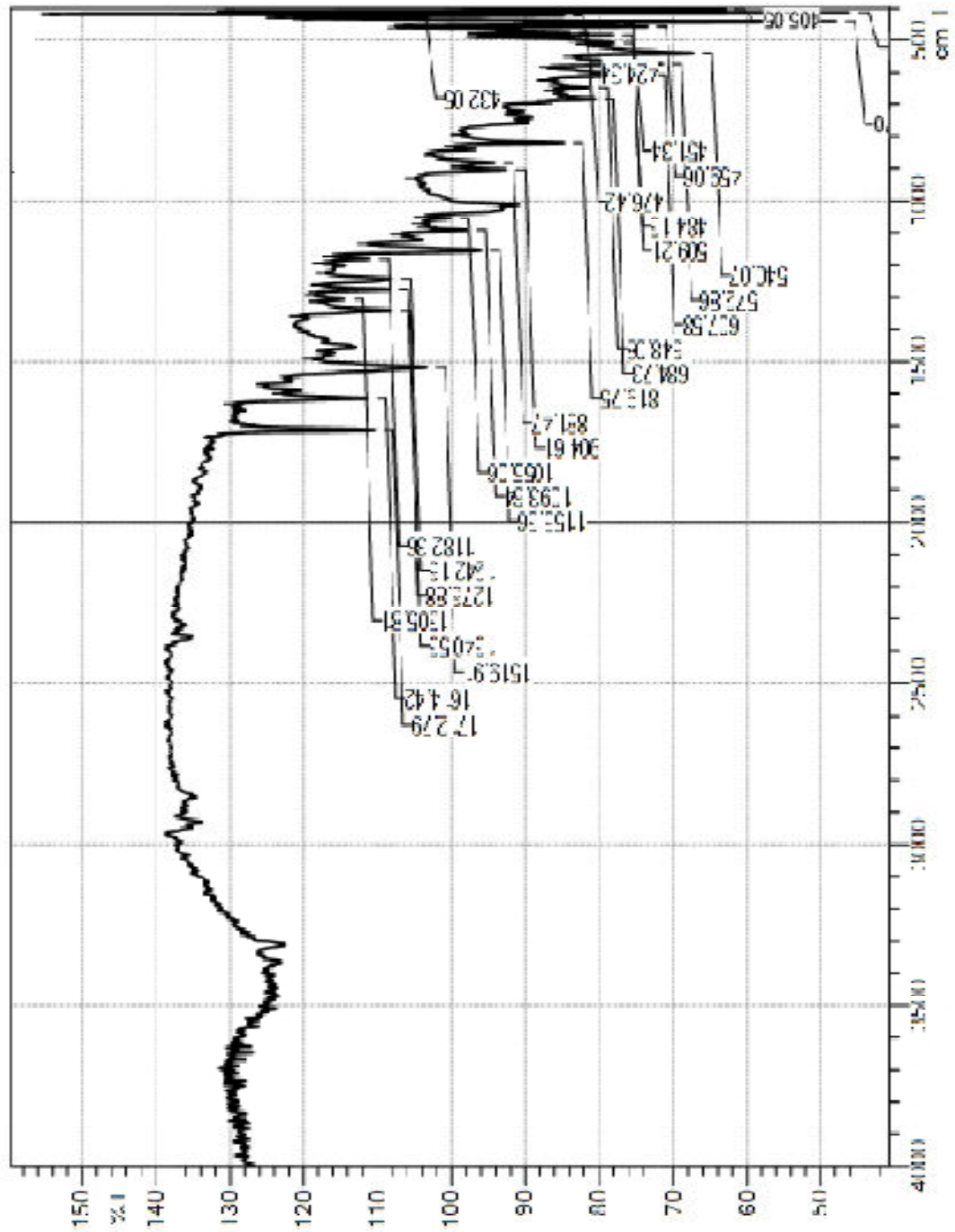**FIGURE 6.32:** FTIR SPECTRUM OF GLIBENCLAMIDE SOLID DISPERSION WITH CHITOSAN (GCP1)

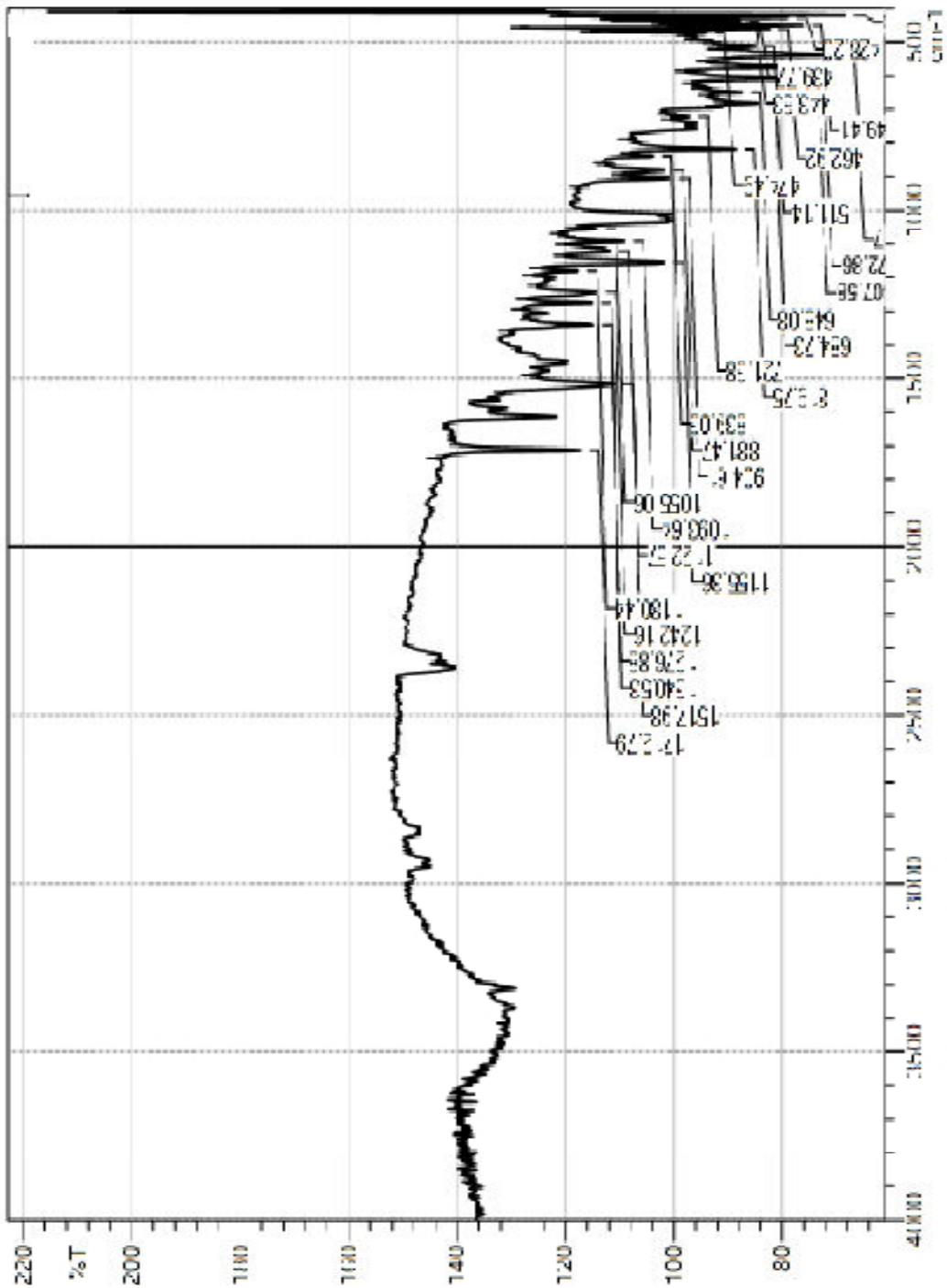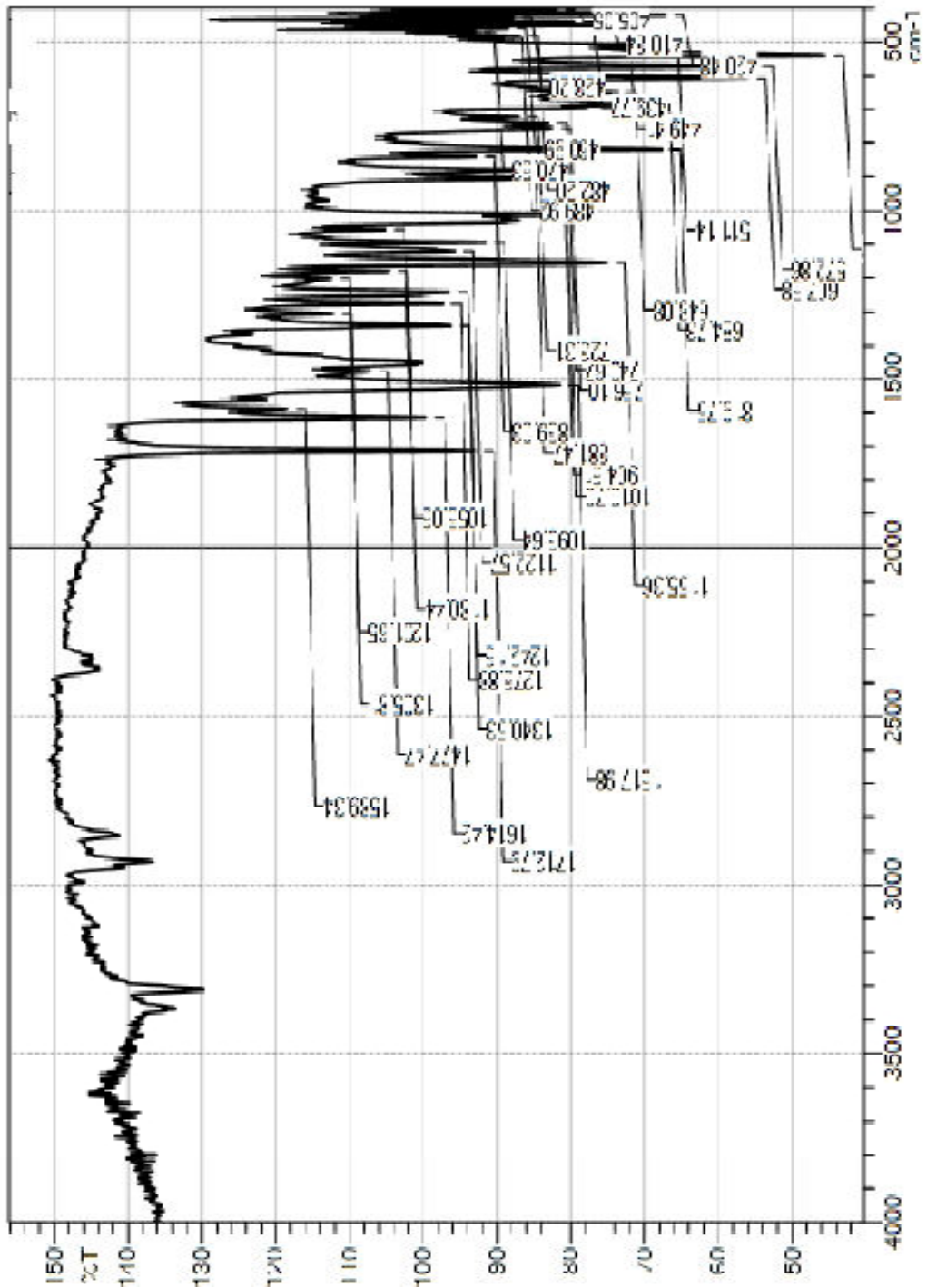**FIGURE 6.34:** FTIR SPECTRUM OF GLIBENCLAMIDE NANOPARTICLES BY USING ETHANOL

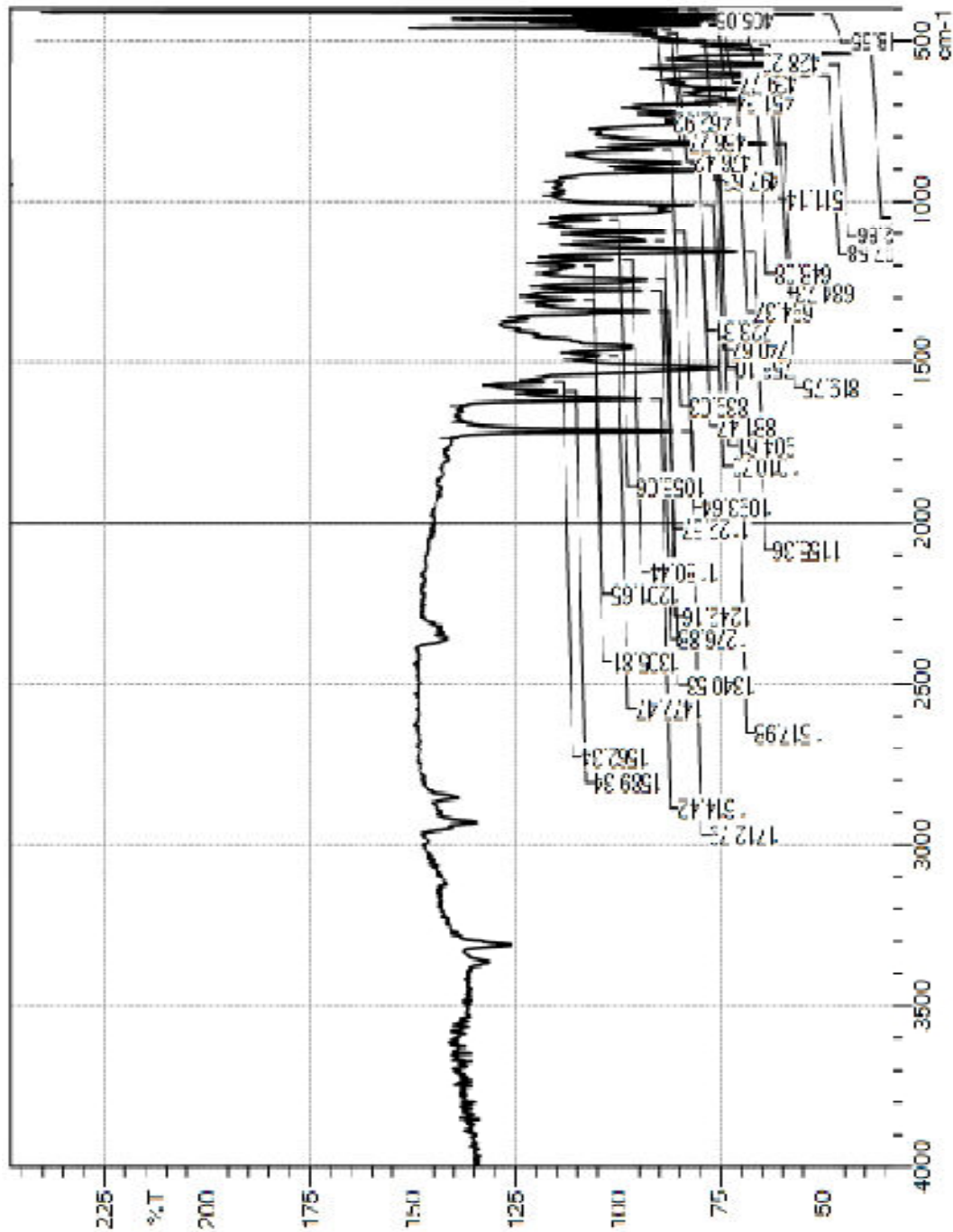**FIGURE 6.35:** FTIR SPECTRUM OF GLIBENCLAMIDE NANOPARTICLES BY USING ACETONE
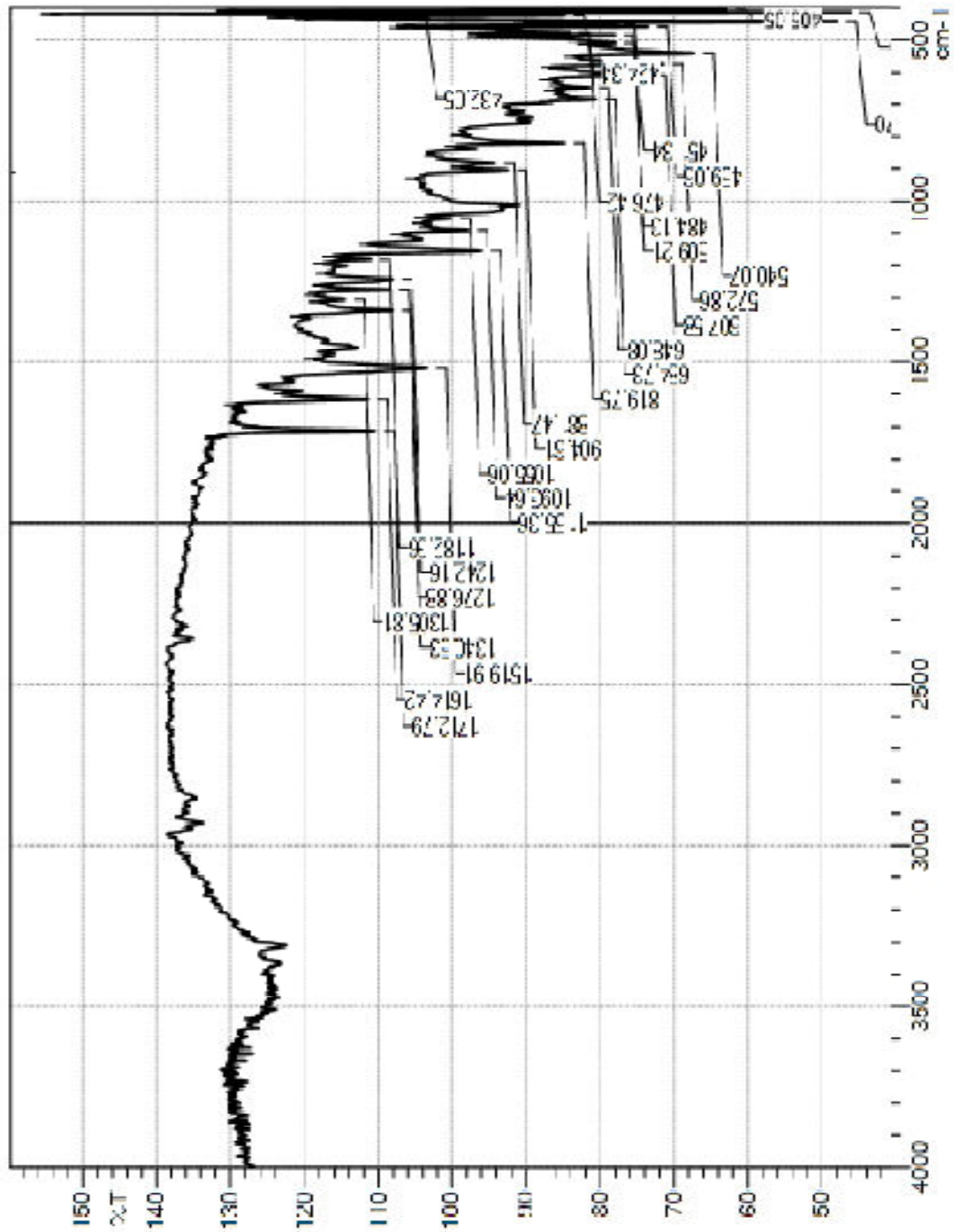
FIGURE 6.36: FTIR SPECTRUM OF GLIBENCLAMIDE NANOPARTICLES BY ULTRASONICATION METHOD

XRD Studies:

The XRD of pure Glibenclamide with various carriers of solid dispersion and nanoparticles were studied. The XRD spectrums are shown **figure 8.37-8.44.** In this study the crystalline nature of pure Glibenclamide was reduced in form of solid dispersion and Nanoparticles of Glibenclamide.

In the study   a pure drugshowedmore   peak intensity the drug showed more crystalline nature. The solid dispersions of PEG600, Chitosan and Urea were showed less peak intensity compared to pure Glibenclamide .Its indicates the nature of crystalline property was decreased orit'sbecome amorphous form. The nanoparticles were showed less peak intensity of pure Glibenclamide But its less in solid dispersions .The solid dispersion of Urea were showed veryless peak intensity of other formulations of solid dispersion and nanoparticles. So the solid dispersion of Urea has been showed more soluble in other formulations.

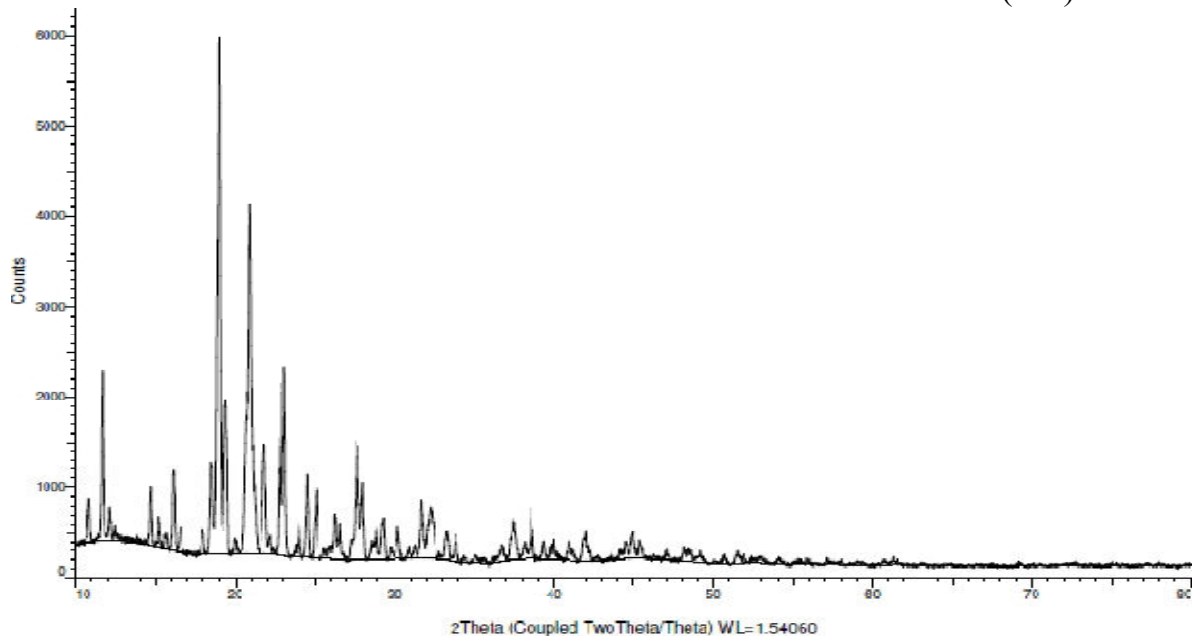**FIGURE 8.37:**XRD SPECTRUM OF PURE GLIBENCLAMIODE(GB)

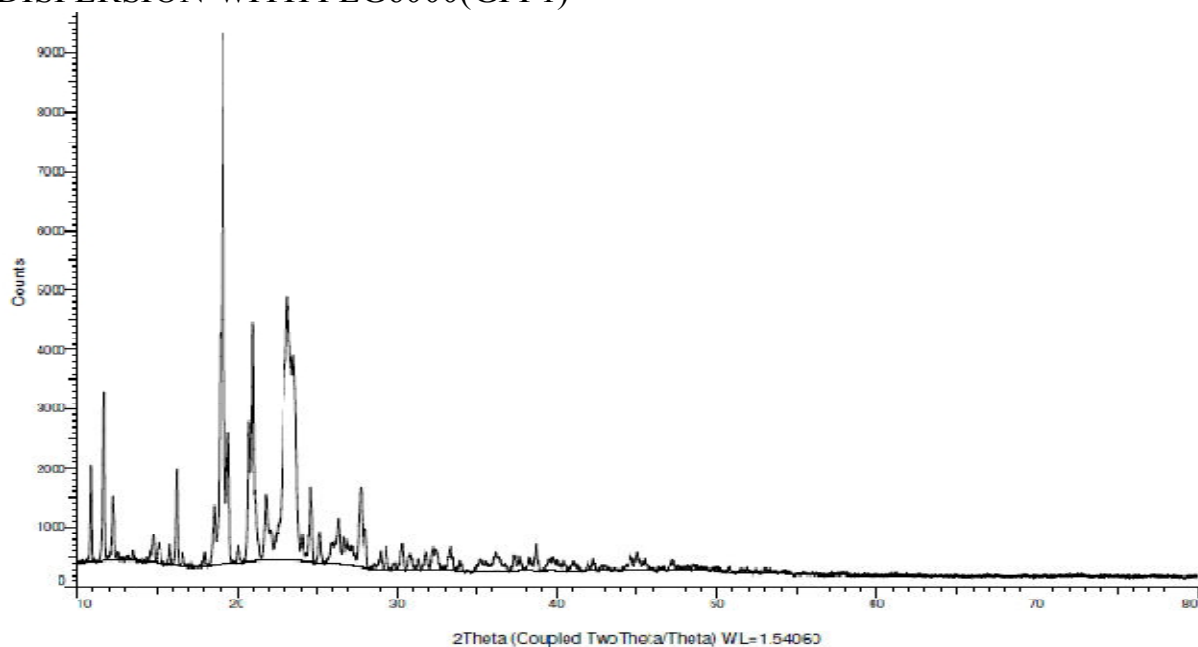**FIGURE 8.38:** XRD SPECTRUM OF GLIBENCLAMIODE SOLID DISPERSION WITH PEG6000(GPP1)

FIGURE 8.39: XRD SPECTRUM OF GLIBENCLAMIODE SOLID DISPERSION WITH UREA(GUP1)

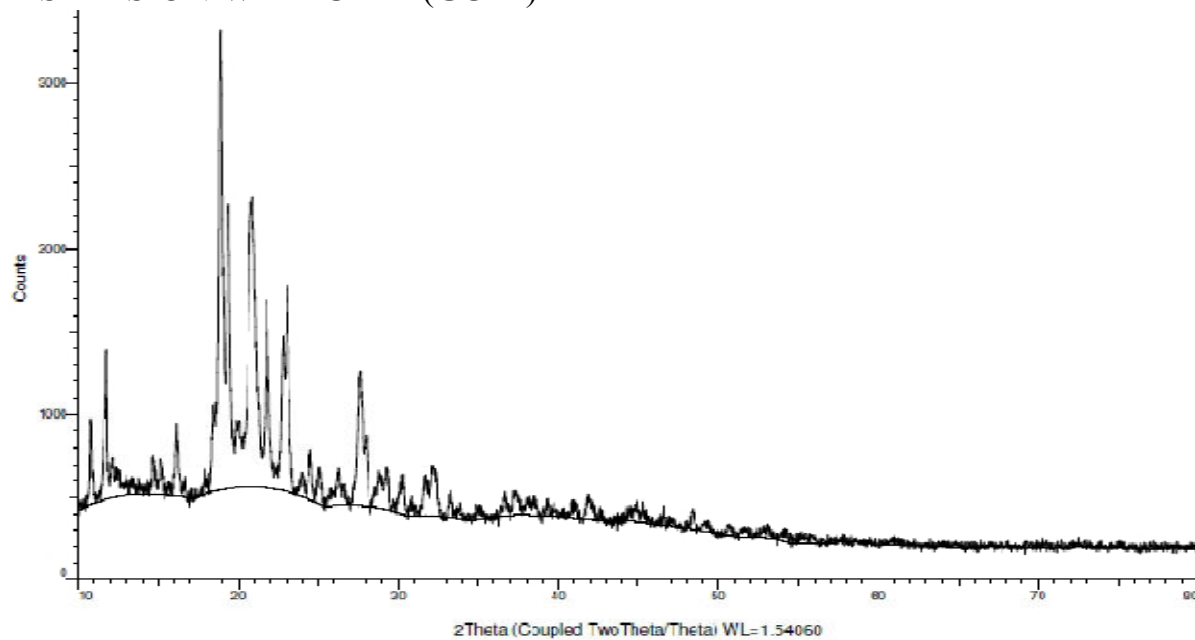**FIGURE 8.40:**XRD SPECTRUM OF GLIBENCLAMIODE SOLID DISPERSION WITH CHITOSAN(GCP1)
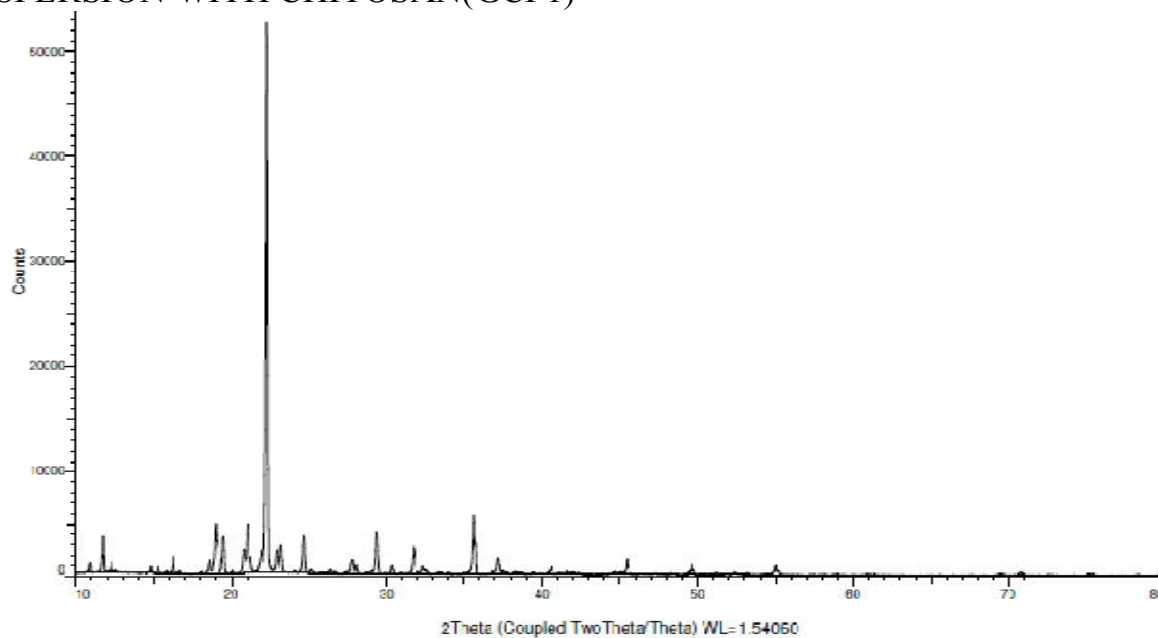
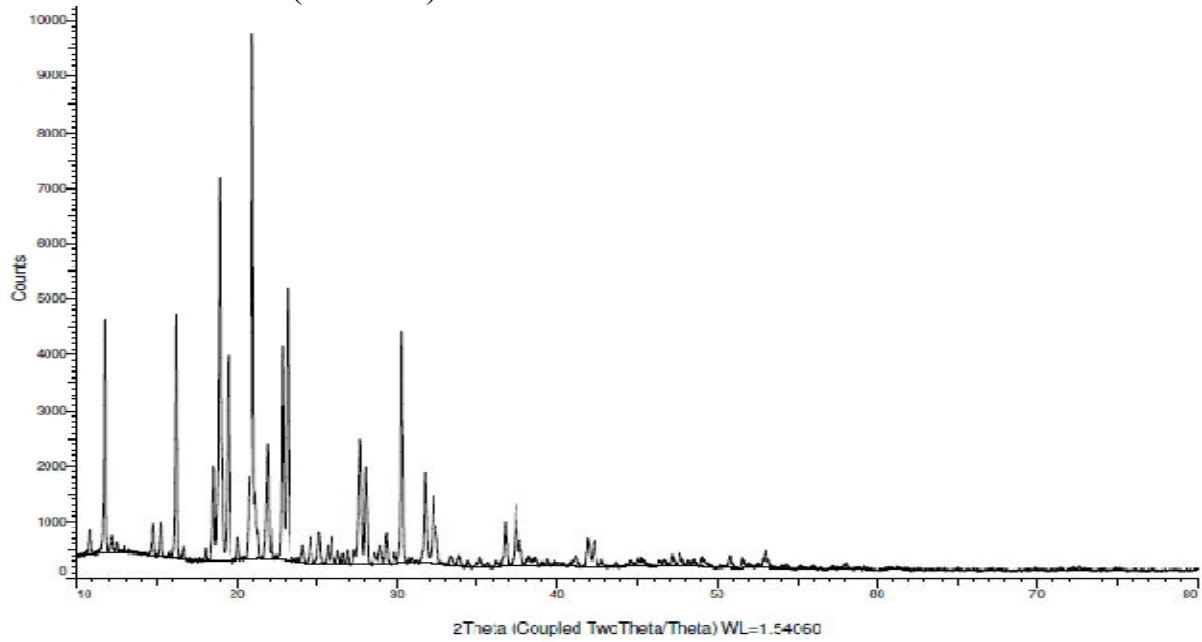**FIGURE 8.41:**XRD SPECTRUM OF GLIBENCLAMIODE NANOPARTICLES WITH METHANOL(GMSN1)

FIGURE 8.42:XRD SPECTRUM OF GLIBENCLAMIODE NANOPARTICLES WITH ETHANOL(GESN2)
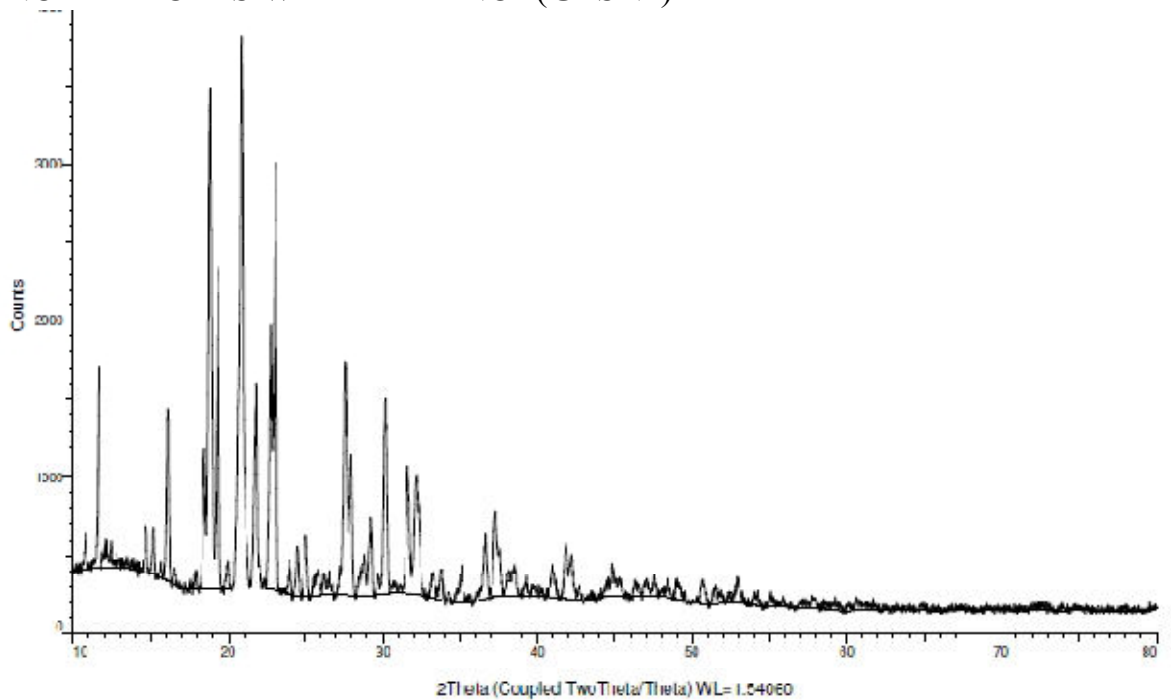
FIGURE 8.43: XRD SPECTRUM OF GLIBENCLAMIODE NANOPARTICLES WITH ACETONE(GASN3)
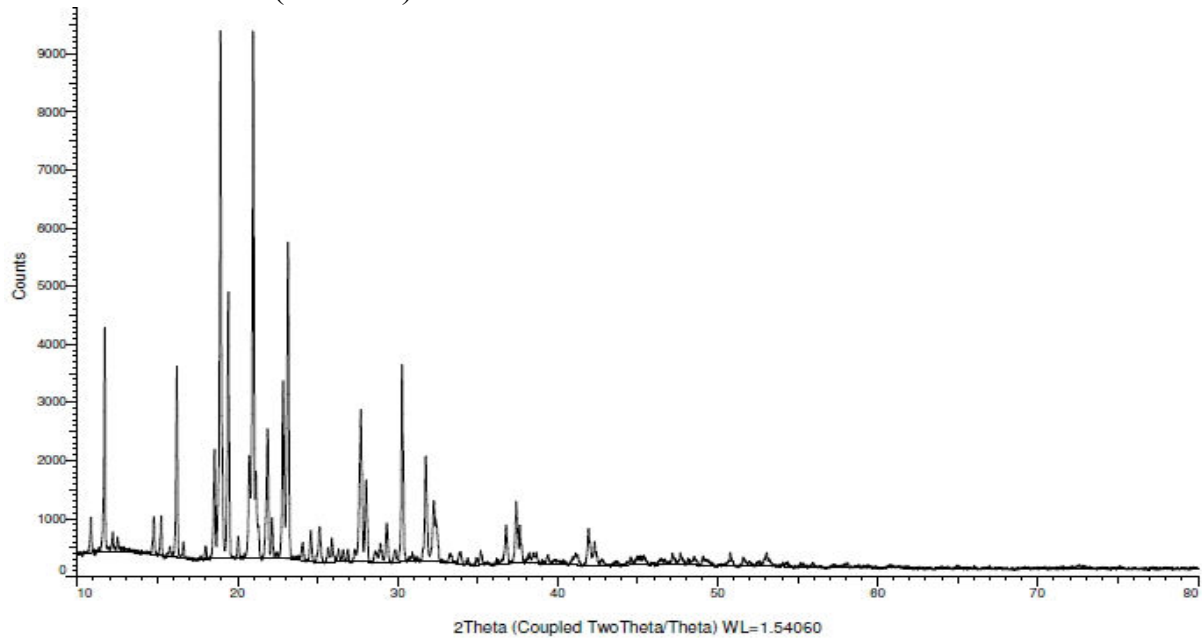
FIGURE 8.44: XRD SPECTRUM OF GLIBENCLAMIODE NANOPARTICLES BY ULTRASONICATION METHHOD
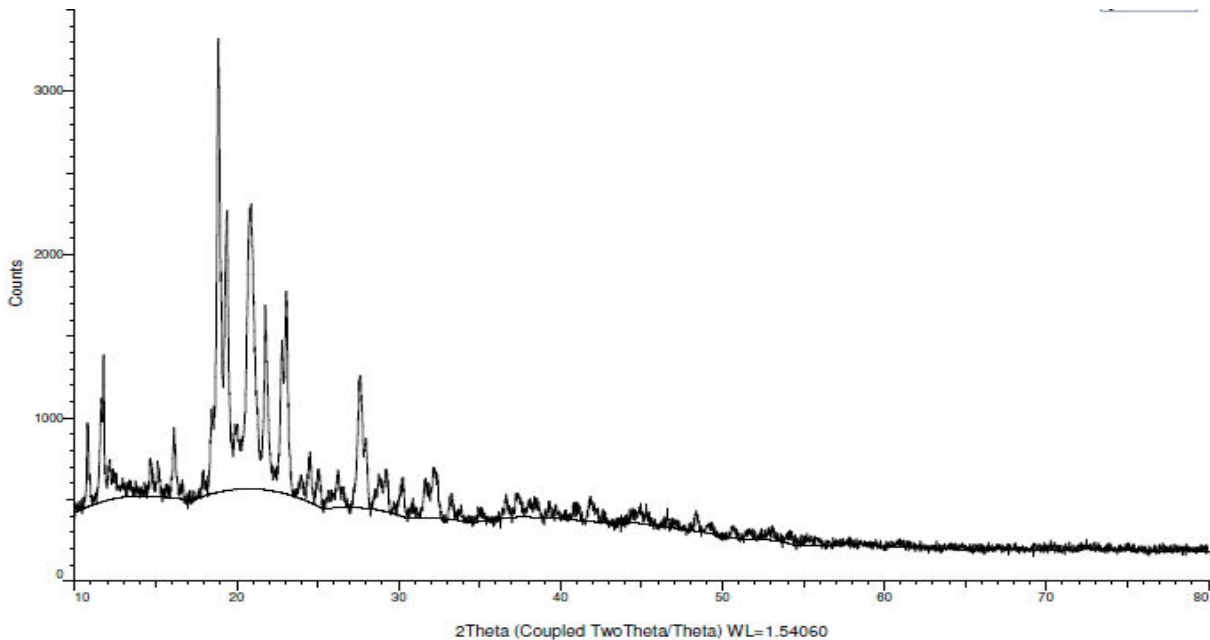
Particle Size Analysis: Solid dispersion

Particle size of best releasing formulations were analyzed by using compound microscope the obtained values can be followed: GPP3 (165.64μ), GPD3 (179.53μ), GPS3 (143.89μ), GUP3 (158.42μ), GUD3 (164.56μ), GUS3 (139.82μ), GCP3 (162.93μ), GCW3 (178.34μ).

Results are shown in**TableNo: 8.25**

Table No: 8.25

Particle size if Ideal Batches of best releasing solid dispersion formulations

Formulations	Average particle size(μ)
GPP3	165.64
GPD3	179.53
GPS3	143.89
GUP3	158.42
GUD3	164.56
GUS3	139.82
GCP3	162.93
GCW3	178.34

Particle Size Analysis: nanoparticles

Particle size of best releasing formulations were analyzed by using MALVERN particle sizeAnalyzer the results can be followed: GMSN1 {225.5(d.nm)}, GESN2 {28.20(d.nm)}, GASN3 {1076 and 283.7 (d.nm)} and GSN {141.8 (d.nm)}.

Were,

d.nm is diameter in nanometer.

The results are shown in**Table No: 8.26**

Table No: 8.26

Particle size if Ideal Batches of best releasing nanoparticle formulations

Formulations	Average particle size(d.nm)
GMSN1	225.5
GESN2	28.20
GASN3	1076
	283.7
GSN	141.8

Particle size if Ideal Batches of best releasing nanoparticle formulations

Figure 8.45:
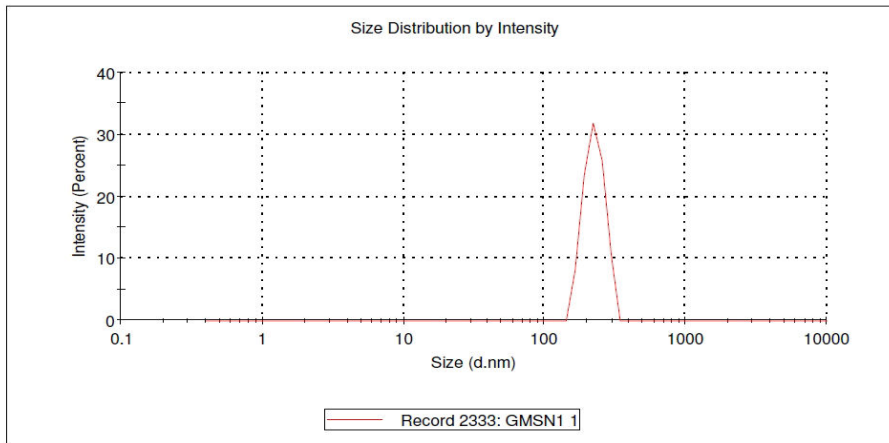
Figure 8.46:
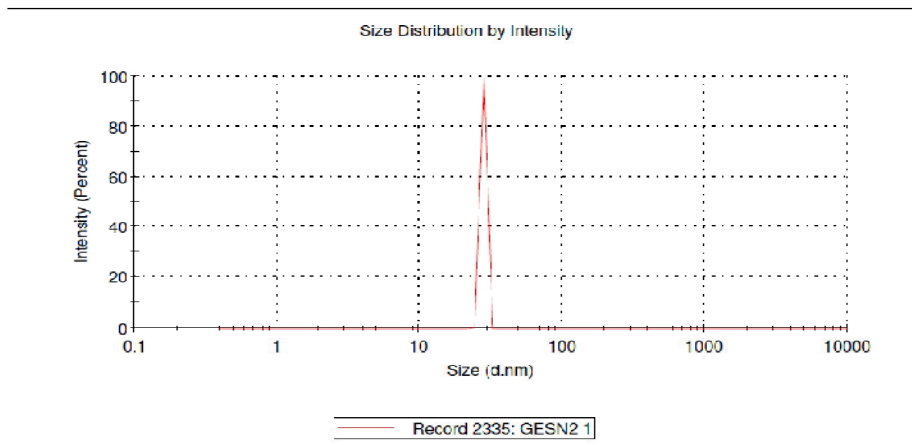
Figure 8.47:
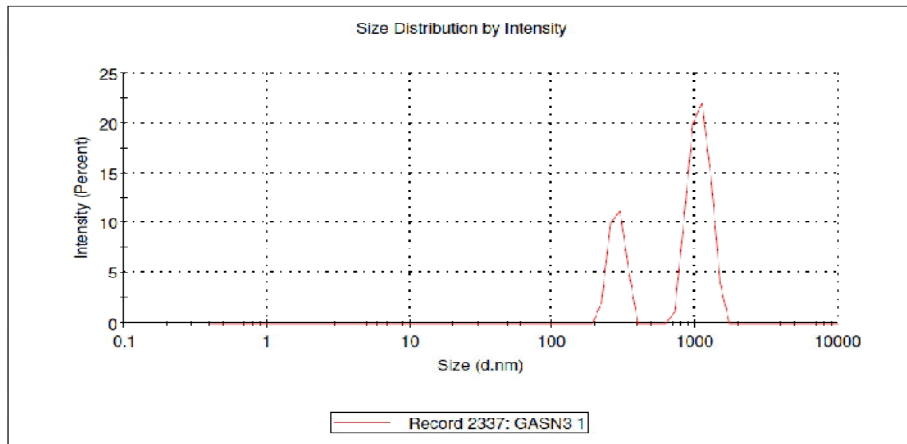
Figure 8.48:
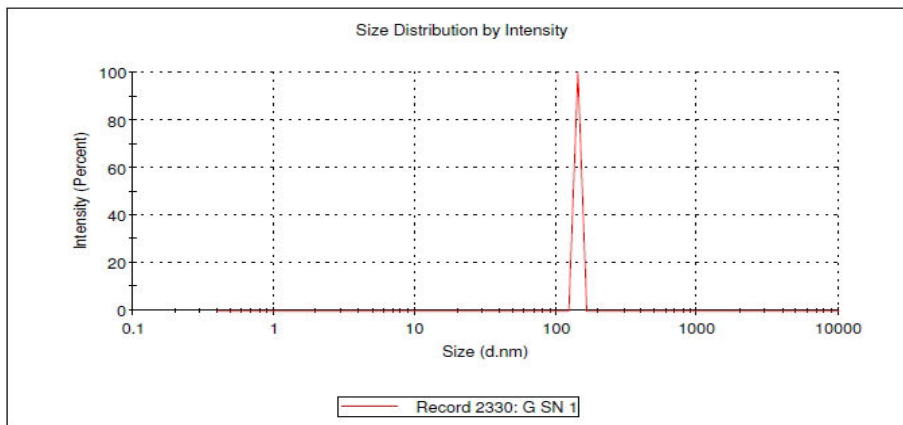
Preparation and characterization of tablets:

Glibenclamide solid dispersions in GUS3 formulatedinto tablets. The tablets containing 5mg of Glibenclamide were prepared by directcompression method as per the formula given in the table. Theprepared tablets were stored in screw capped glass bottles. Theprepared tablets were evaluated for drug release characteristics

Table No: 8.27

Si No	Ingredients	Formulations (mg)	
		GB	**GUS3**
1	Glibenclamide	5	-
2	Glibenclamide-Urea solvent evaporated (1:3)	-	5
3	Lactose	25	25
4	Micro crystalline cellulose	157.5	157.5
5	Talc	5	5
6	Magnesium stearates	5	5

Evaluation of tablets

Tablet formulations are evaluated for the following

Weight variation test

Individual weight of 20 tablets was taken and the average weight was calculated by using following formula.

$$\text{Weight variation} = \frac{(\text{Weight of tablet} - \text{Average weight})}{\text{Average weight of tablet}} \times 100$$

Weight variation should not be more than 5.5%.

Friability

Friability of the tablets was calculated by the use of friabilator. Friability should be less than 1.

Disintegration time

Disintegration time of the tablet was observed with the help of Disintegration apparatus.

Physical parameter studies

Table No: 8.28 Physical parameter studies of different tablet formulations

Parameter	GB	GUS3
Thickness (mm)	3.2	3.4
Hardness (kg/cm^3)	2.6	2.5
Disintegrating time(min)	1-4	1-3
Friability in (in %)	0.421	0.396
Weight Variation		
S.no	Wt (mg)	Wt (mg)
1	**210.2**	212
2	**212.8**	210.4
3	**213**	211
4	**212.5**	214
5	**212.8**	212.3
6	**213.4**	212.5
7	**214.7**	213
8	**211.8**	210.8
9	**216.3**	211.2
10	**212.8**	213.2
11	**213.9**	211.5

12	**212.6**	214
13	**214**	212.6
14	**213.4**	212.6
15	**212.5**	213
16	**211.3**	212.1
17	**210**	212.4
18	**214.2**	213
19	**214**	212.4
20	**215**	213.6
Average	213.6	212.38

The results in table No: 8.28 indicates that tablets are within the limits

TableNo:8.29

Dissolution of Glibenclamide from tablet formulations

Time	Percentage of Glibenclamide dissolved		
(min)	GB TABLET	GUS3 TABLET	MARKETED TABLET
0	0	0	0
10	3.67	12.67	12.79
20	7.82	28.19	27.43
30	11.46	41.43	40.21
40	14.87	55.74	51.46
50	17.64	69.30	65.67
60	20.76	81.83	76.82

In this study the best release solid dispersion and pure Glibenclamide was converted in to tablet form and it wascompared to marketed available same dose of Glibenclamide the result shows the 81.83% of drug release. So the solid dispersion formulation was better than marketed available formulation.

STABILITY STUDIES

Formulations were stored at40^0C$\pm$ 2^0C/75% RH $\pm$ 6% (Accelerated testing) and 30^0C$\pm$ 2^0C/60% RH $\pm$ 5% (Alternate testing).After 30 days of storage,the formulations were observed physically and no colorchanges occurred. The content of Glibenclamide in all best formulations at various intervals of 10, 20, and 30 days was calculated. The result proved that the percentage of Glibenclamide was not less than 2-3 % in all best formulationsas shown in **TableNo: 8.30**.

TableNo: 8.30

Stability Analysis of ideal formulations

Formulation code	Temperature(^{o}C)	% of Glibenclamide			
		0 Days	10 Days	20 Days	30 Days
GB	$40^0C \pm 2^0C$/75% RH $\pm$ 6%	98.98	98.94	98.96	98.76
	$30^0C \pm 2^0C$/60% RH $\pm$ 5%	98.98	98.99	98.96	98.97
GPP3	$40^0C \pm 2^0C$/75% RH $\pm$ 6%	98.20	98.23	98.21	98.22
	$30^0C \pm 2^0C$/60% RH $\pm$ 5%	98.20	98.19	98.24	98.21
GPD3	$40^0C \pm 2^0C$/75% RH $\pm$ 6%	98.60	98.58	98.63	98.62
	$30^0C \pm 2^0C$/60% RH $\pm$ 5%	98.60	98.65	98.64	98.58
GPS3	$40^0C \pm 2^0C$/75% RH $\pm$ 6%	96.40	96.48	96.44	96.38
	$30^0C \pm 2^0C$/60% RH $\pm$ 5%	96.40	96.42	96,47	96.47
GUP3	$40^0C \pm 2^0C$/75% RH $\pm$ 6%	98.40	98.39	98.43	98.37
	$30^0C \pm 2^0C$/60% RH $\pm$ 5%	98.40	98.42	98.42	98.39
GUD2	$40^0C \pm 2^0C$/75% RH $\pm$ 6%	98.20	98.30	98.17	98.24
	$30^0C \pm 2^0C$/60% RH $\pm$ 5%	98.20	98.19	98.13	98.24
GUS3	$40^0C \pm 2^0C$/75% RH $\pm$ 6%	98.60	98.69	98.57	98.63
	$30^0C \pm 2^0C$/60% RH $\pm$ 5%	98.60	98.62	98.58	98.64
GCP3	$40^0C \pm 2^0C$/75% RH $\pm$ 6%	96.60	96.89	96.80	96.79
	$30^0C \pm 2^0C$/60% RH $\pm$ 5%	96.60	96.73	96.79	96.58
GCW3	$40^0C \pm 2^0C$/75% RH $\pm$ 6%	98.00	98.12	98.02	97.97
	$30^0C \pm 2^0C$/60% RH $\pm$ 5%	98.00	98.16	98.09	98.03
GASN3	$40^0C \pm 2^0C$/75% RH $\pm$ 6%	98.40	98.35	98,42	98.48
	$30^0C \pm 2^0C$/60% RH $\pm$ 5%	98.40	98.42	98.42	98.42

SUMMARY

Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in solid state in order to achieve increasing dissolution rate, to sustain in the release of drugs, to alter solid state properties and to improve and enhance the release of drugs from ointment and suppository bases and improve the solubility and stability. Nanotechnology is a technique to decreases the particle size of materials. Whether increases specific surface area of a drug subsequently to increases the absorption of drug from site of administration.

The study was performed in the following phases,

All the above phases of investigation brought out several factors, which lead to following conclusions.

1. Preliminary investigation of the effect of carriers in the solubility of Glibenclamide, various formulation methods can be followed as like physical mixture, dropping, solvent evaporation and wet grinding of Glibenclamide with suitable carriers.The nanoparticles were prepared by ultra Sonication and anti solvent method.

2. Studies on drug – polymer interactionby using FTIR and TLC chromatography study in FTIR spectral analysis shows there are no interaction of pure Glibenclamide spectrum. The solid dispersion and nanoparticles spectrum are same like pure Glibenclamide spectrum. The TLC chromatography study is shown Rf value of pure Glibenclamide was(0.64), GPP3 (0.61), GUP3 (0.62) GCP3 (0.62) GSN (0.64), GMSN1 (0.63) GESN2 (0.64) GASN (0.64) the Rf value also nearby pure Glibenclamide so there is polymericinteraction may not placein above formulations.

3. Study about nature of drug; in the study the pure drugshowed more peak intensity.The drug showed more crystalline nature. The solid dispersions of PEG6000, Chitosan and Urea were showed less peak intensity compared to pure Glibenclamide. It indicates the nature of crystalline property was decreased or its converts to amorphous form. The nanoparticles were showed less peak intensity of pure Glibenclamide But its more than in solid dispersions .The solid dispersion of Urea were showed veryless peak intensity of other formulations of solid dispersion and nanoparticles. So we are concluded the solid dispersion of Urea have been more soluble in compared to other formulations.

4. Study about particle size.The prepared solid dispersion formulations were studied under the by microscopy method by usingcompound microscopy the obtained values can be followed: GPP3 (165.64μ), GPD3 (179.53μ), GPS3 (143.89μ), GUP3 (158.42μ), GUD3 (164.56μ), GUS3 (139.82μ), GCP3 (162.93μ), GCW3 (178.34μ). Particle size of best releasing formulations were analyzed by using MALVERN particle size Analyzer obtained values can be followed: GMSN1 {225.5(d.nm)}, GESN2 {28.20(d.nm)}, GASN3 {1076 and 283.7 (d.nm)} and GSN {141.8 (d.nm)}.were d.nm is diameter in nanometer.

5. Solubility study.The water soluble carriers can be in solid dispersion techniquesignificance increases in the solubility of Glibenclamide. Among these carriers urea was found to possess highest solubilizing characters and dissolutions in solvent evaporation method of preparation.All the Glibenclamide nanoparticles were found to increases the solubility of Glibenclamide significantly, but lesser then solid dispersion of Glibenclamide.

6. Dissolution study. The dissolution rate of pure drug was compared with various solid dispersions at different ratios of all the polymers showed significant increases in the rate of dissolution in solid dispersion and nanoparticles. The dissolution rate of urea was greater

than the other polymeric and nanoparticle formulations because the rate of dissolution of solid dispersion urea was 60.05%, while pure drug showed only 6.64% dissolution rate at the end of 60 minutes.

Dissolution profile of drugformulation produced by different methods is compared:

The dissolution profile of solvent evaporation method was more than wet grinding. Wet grinding method was comparable to greater than dropping method and lesser then solvent evaporation method.Thedropping method was comparable to greater thanPhysical mixture and lesser thansolvent evaporation method,wet grinding method.Physical mixture was comparable to lesser then Solvent evaporation,wet grinding and Dropping method. The decreasing order of Dissolution profile of drug formulation is followed.

Solvent evaporation > Wet grinding> Dropping method> Physical mixture

7. Stability studies of prepared best formulations

Drug degradation was tested after storing ideal batches of solid dispersion and nanoparticles different temperature and Relative humidityat $40^0C \pm 2^0C/75\%$ RH $\pm$ 6% (Accelerated testing) and $30^0C \pm 2^0C/60\%$ RH $\pm$ 5% (Alternate testing). There was no degradation of drug after storing for 30 days at only 2-3% of drug was degraded after 30 days.

8. Comparison of marketed available drug:

In this study the best release solid dispersion and pure Glibenclamide was converted in to tablet form and its compared to marketed available same dose of Glibenclamide the result shows the release of solid dispersion better than marketed available drug

CONCLUSION

Form the present research work, it is concluded that the preparation of solid dispersion of poorly soluble drugs like Glibenclamide with suitable carriers like PEG 6000, UREA, CHITOSAN, and Nanoparticles to enhance the dissolution rate. The robust formulation in solid dispersion is with solvent evaporation by urea shows higher *in-vitro* dissolution rate.

The dissolution characteristics of Glibenclamide were improved by formulation of solid dispersion with PEG 6000, UREA, CHITOSAN and Nanoparticles in decreases in the crystallinity of the drug substance is decisive for the increases dissolution profile.

The stability study was carried out in best prepared solid dispersion formulations and nanoparticles Glibenclamide. The accelerated stability study was conducted over the 30 days. As per results no physical changes takes place at the end of stability studyand there was no degradation of drug after storing for 30 days at only 2-3% of drug was degraded after the end stability studies. .

The dissolution profile of marketed available formulation was compared to the prepared best solid dispersion Glibenclamide. The release pattern prepare best solid dispersion Glibenclamide can be better than the marketed available formulation.

Finally it is proven that the solid dispersion by solvent evaporation technique is a promising technique to improve dissolution rate of poorly soluble drugs and the technique used for the preparation of solid dispersion was simple, cost effective, stable, and easy to scale up.

LIST OF REFERENCES:

1. Aremanda, Sindhu P .Improving solubility of poorly water soluble drug indomethacin by incorporating porous material in solid dispersion. The Brooklyn Center 2010;14:110.

2. Tiwari v , Kinikar J D, Pillai K Gokulan D P. Preparation and evaluation of fast dissolving tablets of celecoxib. *J Pharm Res* 2010;04:4-11.

3.Sekiguchi, K.; Obi, N. Studies on absorption of eutectic mixture. I. A comparison of the behavior of eutectic mixtureof sulfathiazole and that of ordinary sulfathiazole in man.*Chem.   Pharm. Bull.*1961, 9, 866-872.

4.Christian Leuner, Jennifer Dressman;"Improving drug solubility for oral delivery using solid dispersions"; *Eur. J.Pharm.*,2000,vol50,P 47-60.

5. Khuvana R,Ahuja A,Khar RK. Polymers and polymeric systems; Applications in pharmaceutical field*The Eastern pharmacist*. 1998;XL1b (488):65-70.

6.English JP, Dang W.Fabrication of controlled delivery devices Mathiowitz E,editor. Encyclopedia of controlled drug delivery vol 1*New York. John Wiley*;1999;351-356.

7.Vogelson CT.*Mod Drug Discovery*.2001;4;49-52.

8.Batycky RP, Hanes J,Langer R,Edwards DA.A theoretical model of erosion and macromolecular drug release from biodegrading microspheres, *J Pharm Sci*.1997;86(12);1464-1477.

9.Leuner C and Dressman V: *Eur. J. Pharm. Biopharmaceutics* 2000; 50:47- 60.

10. Pouton CW (2006). *Eur. J. Pharm. Sci.*, 29: 278-287.

11. Karavas, E. *Eur. J. Pharm. Biopharm.*2006, 64, 115–126.

12. Vasconcelos T, Sarmento Costa B, P. *Drug Discover Today*.2007; 12(23- 24): 1068-1075.

13. Ghaderi R, Artursson P and Carifors J (1999). *Pharm. Res*., 16: 676-681.

14. Pokharkar VB, Leenata P Mandpe, Mahesh N Padamwar, Anshuman A. Ambike, Kakasaheb R. Mahadik andAnant Paradkar (2006). *Powder Technol.,* 167: 20-25.

15. Dhirendra K, Lewis S, Udupa N And Atin K *Pak. J. Pharm. Sci.,* Vol.22, No.2, April 2009, pp.234-246.

16. Chiou, W. L.; Riegelman, S.; *J. Pharm. Sci*.; 1971; 60:1281-1302.

17. H. Karanth, V. S. Shenoy, and R. R. Murthy,"Industrially feasible alternative approaches in the manufacture of solid dispersions: A technical report," *AAPS PharmSciTech*., vol. 7 issue 4, Article 87, 2006, pp. E31-38, doi: 0.1208/pt070487

18. Sekiguchi K, Obi N, "Studies on absorption of eutectic mixtures. I. A comparison of the behavior of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man*", Chem. Pharm. Bull*., 1961; 9; 866-872.

19. Goldberg A, Gibaldi M, Kanig L, "Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures II experimental evaluation of a eutectic mixture: urea-acetaminophen system", *J. Pharm. Sci*. 1966; 55; 482-487

20. Goldberg H, Gibaldi M, Kanig L, "Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures I - theoretical considerations and discussion of the literature", *J. Pharm. Sci*.,1965; 54;1145-1148.

21. Hume-Rotherly W, Raynor G V, "The Structure of Metals and Alloys", Institute of Metals, London , 1954.

22. Reed-Hill R E, "Physical Metallurgy Principles", Van-Nostrand, Princetown, *NJ*, 1964.

23. Chiou W L, Riegelman S, "Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin", *J. Pharm*. Sci. 1969; 1505-1510.

24. Goldberg A, Gibaldi M, Kanig J L, "Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures III - experimental evaluation of griseofulvin- succinic acid solid solution", *J. Pharm. Sci.,*1966;55; 487-492

25. Serajuddin A., "solid dispersion technique", *J.Pharm.Sci.*1999; 88(10); 891-900.

26. Narang A., Shrivastava A. "Melt extrusion solid dispersion technique", *Drug Dev. Ind. Pharm.*, 2002;26(8);111-115

27. Breitenbach J. "Melt extrusion: from process to drug delivery technology.*"Eur J Pharm Biopharm.* 2002;54;107-117.

28. Chokshi R, Hossein Z. "Hot –Melt Extrusion Technique: A Review", *Int J Pharm Res.,* 2004;3;3-16.

29. Perissutti B, Newton JM, Podezeck F, Rubessa F. "Preparation of extruded Carbamazepine and PEG 4000 as a potential rapid release dosage form", *Eur J Pharm Biopharm.*, 2002;53; 125-132.

30. Tsinontides S C, Rajniak P, Hunke W A, Placek J, "Freeze drying-principles and practice for successful scale-up to manufacturing", *Int. J. Pharm.*, 2004;280(1); 1-16.

31. Vilhelmsen T, Eliasen H, Schaefer T. "Effect of a melt agglomeration process on agglomerates containing solid dispersions" *Int. J. Pharm.*, 2005; 303(1- 2); 132-142.

32. Seo A, Schaefer T., "Melt agglomeration with polyethylene glycol beads at a low impeller speed in a high shear mixer" *Eur. J. Pharm. Biopharm.,* 2001; 52(3); 315-325.

33. Ghebremeskel A N, Vemavarapu C and Lodaya M., "Use of surfactants as plasticizers in preparing solid dispersions of poorly soluble API: Selection of polymer surfactant combinations using solubility parameters and testing the processability", *Int. J. Pharm.*,2007;308; 119-129.

34. Zhang R, Somasundaran P, "Advances in adsorption of surfactants and their mixtures at solid/solution interfaces. Advances in colloid and interface science", *Int. J. Pharm*, 2006;123; 213-229.

35. Hohman M M, Shin M, Rutledge G, Michael P, "Brennera electrospinning and electrically forced jets. II Applications", Physics *of fluids,* 2001; 13(8); 2221-2236.

36. Neamnark A, Rujiravanit R, Supaphol P, "Electrospinning of hexanoyl Chitosan Carbohydrate polymers", *Int. J. Pharm,* 2006;66; 298-305.

37. Zhang W, Yan E, Huang Z, Wang C, Xin Y, Zhao Q, Tong Y, "Preparation and study of PPV/ PVA nanofibers via electrospinning PPV precursor alcohol solution", *European polymer*,2007;43;802-897.

38. Muhrer G, Meier U, Fusaro F, Albano S, Mazzotti M, "Use of compressed gas precipitation to enhance the dissolution behavior of a poorly water-soluble drug: generation of drug microparticles and drug-polymer solid dispersions", *Int. J. Pharm,* 2006;308; 69-83.

39. Majerik V, Charbit G, Badens E, Horv´ath G, Szokonya L, Bosc N , "Bioavailability enhancement of an active substance by supercritical antisolvent precipitation", *J of Supercritical Fluids*,2007;40; 101 110.

40. Taki S, Badens E, Charbit G, "Controlled release system formed by supercritical anti-solvent coprecipitation of a herbicide and a biodegradable polymer", *J of Supercritical Fluids*, 2001;21; 61 70.

41. Manna L, Banchero M, Solta D, Ferri A, Ronchetii S, Sicrdi S, "Impregnation of PVP microparticles with ketoprofen in the presence of supercritical CO2", J of *Supercritical Fluids*, 2006;78; 67-69

42. Dohrn R, Bertakis E, Behrend O, Voutsas E, Tassios D, "Melting point depression by using supercritical CO2 for a novel melt dipersion micronization process", *J of Molecular Liquids,* 2007;131-132; 53-59.

43.Sushama R, Desai MS, Loyd V, Robert B,Greenwood ML. Effervescent soliddispersions of prednisone, griseofulvin and primidone. *Drug Dev Ind Pharm*.1989; 15:671-677.

44. Ho HO, Shu HL, Tsai T, Sheu MT. The preparation and characterization of solid dispersions on pellets using a fluidized bed system. *Int J Pharm*. 1996; 139:223-229.

45.Subramaniam B, Rajewski RA and Snavely K (1997). *J. Pharm. Sci.,* 86(8): 885-890.

46.Serajuddin AT, *J. Pharm, Sci*, 88, 1999, 1058–1066.

47.Serajuddin ATM, Sheen PC and Augustine MA (1990). *J. Pharm. Sci.,* 79: 463-464.

48.Walker SE, Ganley JA, Bedford K and Eaves T (1980).. *J. Pharm. Pharmacol.,* 32: 389-393.

49. Vadnere MK. Co-precipitates and Melts. In: Swarbrick J, Boylan JC, editors. Encyclopedia of pharmaceutical technology. *New York: Marcel Dekker Inc*; 1990.

50 .http://en.wikipedia.org/wiki/Nanoparticle

51. http://www.understandingnano.com/medicine.html

52.D.M.Patel, R.R.Shah: *Indian Journal of Pharma. Sci.* May-June 2003, 264-266

53.M.Gopalrao, R.. Suneetha: *Indian Journal of Pharma. Sci.* Jan-Feb 2005, 26-29

54.M.M.Soniwala, P.R. Patel: *Indian journal of Pharma. Sci.* Jan-Feb 2005, 62-65

55.K.P.R.Choudhary, Shaikh Srinivasa: *Indian Journal of pharma. Sci.*Sep-Oct 2001. 438-444

56.Nagarsenker M. S, Musale J.M.: Indian Journal of Pharmaceutical Science, Apr-may, 1997.34-42.

57.K.P.R.Choudhary, R.Hymin: *Indian Journal of Pharma. Sci.* Mar-Apr.2001, 150-153

58. *International Journal of Current Pharmaceutical Research*Vol 2, Issue 3, 2010*14-17*

59. K.P.R.Choudhary, G. Kamalkara: *Indian journal of pharma. Sci.* Mar-Apr 2002. 142-145

60. V.Kusum Devi, P.Vijayalaxmi: *Indian Journal of Pharma. Sci.* Sept.- Oct. 2003 .542-545

61. Neelam Seedher: *American Association of Pharmaceutical Sciences*-2003, article 33, 185-194

62. Taneja L.N., Khopade A. J. And Jain N. K.: *Indian Drugs* 34(2), 72, 1997.

63. R. Kaliselvam, G. S. Prasas: *Indian Journal of Pharma. Sci.* Nov.-Dec.2003, 605-608.

64. Kuchekar B. S. And Yadav A.V: *Eastern Pharmacist,* 38(Sep), 149, 1995.

65. Swati Rawat, Laila F: *Indian Journal of Pharma. Sci.* 200 July-Aug 267-370

66. *Der Pharmacia Lettre*, 2013, 5 (4):310-319.

67. U. Ubalidulla, B. Senthilkumar*,: Indian Journal of pharma, Sci*. July-Aug. 2005,422-427.

68. Parikh R.K., Mansuri N.S.,: *Indian Drugs*, 4 (3) March 2005,149-154.

69. Ganesh V., Sandhy K.G,: *The Indian Pharmacist*, Sept. 1997, 129-132

70. Mukta Khadilkar, Jasmine Avari: *The Eastern Pharmacist,* Sept. 1997, 19-132

71. Sanjula Baboota, Suraj P. Agarwal: The Indian Pharmacist, may. 2005,62-68.

72. Kashappa Goud H. Desai,: *Graduate School of Biotechnology, Korea university,* Jul.2004.

73. Cehngsheng Lili.: Life Science College, *Ocean University of China,* Aug.2004.

74. Pan R. N., Chon J. H.: School of pharmacy, National Taiwan University, China.

75. F.Cilurzo, P. Mingheti., et,al.: *International Journal of Pharmaceutics,* (242), 2002, pg.no.313-327.

76. Duncam Q.M. Craig.: *International Journal of Pharmaceutics,* (231), 2002, 131-144

77. S. Verneyen, N. Balton., *International Journal of Pharmaceutics*,(249), 2002, 45-58.

78. Sudha R.Vippogunta: *International Journal of Pharmaceutics,* (236), 2002, 111-123.

79. Ahmad M. Abdul Fatteha,: *International Journal of Pharmaceutics*, (235), 2002, 17-35.

80. F.Damian, N. Blaton,: *International Journal of Pharmaceutics,* (244), 2002, 87-98.

81. Omar Saeed et al., Knowledge of modifiable risk factors of Coronary Atherosclerotic Heart Disease (CASHD) among a sample in India. *BMC International Health and Human Rights* 2009;9:2.

82. Laurent P, Mike R, Coralie G, JeanMarie D, Francoise Q, Philippe L. New solid lipid microparticles for controlled ibuprofen release: Formulation and characterization study.*Int J Pharm* 2012; 422: 59-61.

83. RosannaT, GeraldineP, Luc D, SantoScalia .Solidlipid microparticles containing the sunscreen agent, octal dimethylaminobenzoate: Effect of the vehicle. *Eur J Pharm Biopharm 2007*; 66: 483-7.

84. Severine J, Pascal B , Geraldine P, Jean-Michel D,Luc D, Brigitte E.Solid lipid microparticles as a sustained release system forPulmonary drug delivery. *Eur J Pharm Biopharm* 2007; 65: 47-56.

85. Helmut R, Joachim H, Achim G. Development and characterization of lipid microparticles as a drug carrier forsomatostatin. *Int J Pharm* 2001;218: 133-143.

86. Giovannelli L, Bellomi P F, Albertin B. Characterizationof nifedipine microparticles prepared by Hot Air Coating technique.*Int J Pharm* 2005; 293: 225-234.

87. Sudhir SC, Sinjan D, Donald WM, Dennis HR .Comparison of anti-tumor efficacy of paclitaxel delivered in nano and microparticles.*Int J Pharm* 2010; 383: 37-44.

88. Nicoleta B, Christian A S, Michelangelo Foti,Olivier J , Reid.Dexamethasone-containing PLGA super paramagneticmicroparticles as carrier for the local treatment of arthritis.*Biomater* 2009; 30: 1772–80.

89. Formulation and characterization of Glibenclamide micro- andnano-particles using acrylic polymers

90. Raymond C Row, Paul J Shekey & marin E Quinn; "*Hand book pharmaceutical excipients*";The pharmaceutical press London., 6th ed., 2009,p 129-134.

91. *Hand book pharmaceutical excipients*, 6th edition,159-161.

92. *Indian pharmacopeia*, 1996, Vol II, Published by controller of publications India. Appendix: 4.5, 4.6, 5.4, 7.3, 13.1(A_147).

93. Apparao.b,m,r. Shivalingam , Y. E. Kishorereddy. *International journal of pharmaceutical sciences and drug research* 2010; 2(2): 146 – 150.

94. Vinothapooshan.G JSS College of pharmacy,2000.

95. *AAPS PharmScTec.Jun* 2010; 11(2): 518-527

96. Dhirendra K, Lewis S, Udupa N et al. Solid Dispersions: A Review. *Pak. J. Pharm. Sci.* 2009; 22(2):234-246.

97. Serajuddin ATM, Sheen PC and Augustine MA (1990).*J.Pharm.Sci.* 79: 463-464.

98. V.Van Toi And , T.H.Lien Phuons(eds), 5th International Conference on Biomedical Engineering in Vietnam, IFMBE Proceeding 46, DOI: 10. 1007/978_3_319-11776_8_74.

99. *R.M. Mainardes, R.C. Evangelista / International Journal of Pharmaceutics 290 (2005) 137–144.*

100. *Int Pharm Pharm Sci,* Vol 6, Issue 1, 838-851.

101. *Der Pharmacia Lettre,*2013, 5 (4):310-319.

102. M.A.HASSAN,NM NAJIB M.S.SULEIMAN: characterization of glibenclamidglassystate .*Int.J.Pharm* 67,131-137(1991).

103. H H Willerd; L L Merrit (Jr.); J A Dean. Instrumental method of analysis 4th Edition, CBS Publishers and Distributors, New Delhi, 1986,287-320

104. *International journal of Current Pharmaceutical Research* Vol 2,Issue 3,2010.

105.Remington: The Science and Practice of Pharmacy. 19th Edition 1995, Vol I,640.