Enhancement of limepiride dissolution profile by solid dispersion technique

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Submitted by

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Certificate

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CHAPTER -1

INTRODUCTION[1-9]

1 . SOLID DISPERSION SYSTEM AND ITS HISTORICALBACKGROUND

Fincher[1] reviewed in 1968 the effect of the particle size of drugs on their dissolution rates and biological availability comprehensively. The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Bioavailability can be defined as the rate and extent at which the drug is delivered to the systemic circulation from dosage form and reaches the site of action to produce the desired effect. Any new drug whose aqueous solubility is less than 0.01 µg/ml will definitely create a bioavailability problem and thereby affecting the therapeutic efficiency of a new drug. Once if we are able to increase the aqueous solubility of a drug, the disintegration and dissolution properties can be easily altered, as a result, an increase in bioavailability can be easily achieved. Methods to increase aqueous solubility of a drug are Salt formation, solubilization, particle size reduction, complexation, solvent evaporation, solid solution and solvent formation. They have been commonly used to increase dissolution rate and thereby oral absorption and bioavailability of such drugs[2]. There are practical limitations to these techniques. In 1961, Sekiguchi and Obi[2] developed a practical method whereby many of the limitations with the bioavailability enhancement of poorly water-soluble drugs just mentioned can be overcome. This method which was later termed as ‘Solid Dispersion, involved the

formation of eutectic mixtures of drugs with water-soluble carriers by the melting of their physical mixtures.

Fig. 1: Schematic representation of the bioavailability enhancement of poorly water-soluble drug by solid dispersion compared with conventional tablet or capsule.

Sekiguchi and *Obi*[2] in 1961 suggested that the drug was present in a eutectic mixture in a microcrystalline state. Later, *Goldberg et al* [3] in 1966 demonstrated that the entire drug in solid dispersions might not be necessarily present in a microcrystalline state; a certain fraction of the drug might be molecularly dispersed in the matrix, thereby forming a solid solution. In either case, once the solid dispersion was exposed to aqueous media and carrier dissolved, the drug was released as very fine and colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water-soluble drugs were expected to be high.

2. CARRIERS USED FOR SOLID DISPERSIONS

2.1. Poly Ethylene Glycols

Poly ethylene glycols are polymers of ethylene oxide a molecular weight usually falling in the range 200 - 300,000. For solid dispersions PEGs with a molecular weight of 1500 - 20,000 are usually used. As the molecular weight increases, so does the viscosity of PEG. Their solubility in water is generally good but decreases with molecular weight. A particular advantage of PEGs for the formation solid dispersions is that, they have good solubility in many organic solvents.

2.2. Poly Vinyl Pyrrolidine (PVP)

Polymerization of Vinyl Pyrrolidine leads to Poly Vinyl Pyrrolidine (PVP) of molecular weight from 2500 - 3000,000. Due to their good solubility in a wide variety of organic solvents, they are particularly suitable for solvent method. Similarly to the PEGs, the PVPs have good water solubility and can improve the wettability of the dispersed compound in many cases. The aqueous solubility of PVPs becomes poorer with increasing chain length and further much higher viscosity at a given concentration.

E.g. Poly Vinyl Alcohol, Poly Vinyl Pyrrolidine Acetate co-polymer.

2.3 HYDROXY PROPYL METHYL CELLULOSE (HPMC)

Hydroxy propyl methyl cellulose (HPMC) also known as Hypromellose of molecular weight from 10,000 – 1500000 due to their good solubility in water and in mixtures of organic solvents like Ethan and chloroform , Mixtures of methanol and dichloromethane like PEGS HPMC also have good water solubility and improving the waltability of the compounds, they are particularly suitable for solvent method.

3. CHARACTERIZATION OF SOLID DISPERSIONS

- The different methods that have been used to characterize solid dispersion are;
- Thermo analytical methods, differential thermo analysis and hot stage microscopy.
- Powder X-Ray diffraction.
- Spectroscopic methods, especially IR spectroscopy.
- Microscopic methods including polarization microscopy and scanning electron microscopy.

- Colorimetric analysis of the solution or melting enthalpy for calculation of entropy change.
- Dissolution testing.

3.1. Therrmo Analytical Methods

Thermo analytical methods include all that examine a characteristic of the systems as a function of temperature. Of this, Differential scanning calorimetry is the most highly regarded method. DSC enables the quantitative detection of all process in which energy is required or produced, i.e., endothermic and exothermic phase transition. The usual method of measurement is to heat the reference and two test samples in such a way that the temperature of two is kept identical.

If an energy requirement requiring transition occurs in the test samples, extra heat is applied to this sample so that its temperature climbs at the same rate as in the reference. The additional heat required is recorded and used to quantitate the energy or the phase transition.

Exothermic transitions, such as conversion of one polymorph to a more stable polymorph, can be also detected. Lack of a melting peak in DSC of solid dispersion indicates that the drug is present in amorphous than the crystalline form. Since the method is quantitative in nature, the degree of crystallinity can also be calculated for systems in which the drug is partly amorphous and partly crystalline. However crystallinities of fewer than 2% cannot be generally detected with DSC.

3.2. X-ray Diffraction

The principle behind X-RD is that when an x-ray beam is applied to sample, interference bands can be detected. The angle at which interference bands can be detected

can be detected depends on the wavelength applied and the geometry of the sample with respect to periodicities in the structure. Crystalline sample is reflected by a characteristic finger point region in the diffraction pattern. Owing to the specificity of the finger print, crystallinity in the drug can be separately identified from crystallinity in the carrier. Therefore, it is possible with X-Ray Diffraction to differentiate between solid dispersions, in which it is partly present in crystalline form, regardless of whether the carrier is amorphous or crystalline. However, crystallinities of under 5-10% cannot generally be detected with X-RD.

3.3. Infra Red Spectroscopy

Structural changes and lack of a crystal structure can lead to changes in bonding between functional groups which can be detected by Infra Red Spectroscopy. Since not all the peaks in the IR spectrum are sensitive to crystalline changes, it is possible to differentiate between those that are sensitive to changes in crystallinity and those that are not.

3.4. Dissolution Testing

Release rate cannot be used on a stand alone basis to determine whether a solid dispersion has been on a basis to determine whether a solid dispersion has been formed or not. However in conjunction with other physiochemical data, they provide strong evidence for the formation of a molecularly dispersed or nearly molecularly dispersed system. When the goal of preparing a solid dispersion is to improve dissolution characteristics of the drug, the results of the release rate experiments are obviously of prime importance in assessing the success of the approach. Well designed release experiments will show whether the solubility of the drug and its dissolution rate can be

enhanced, and also whether the resulting supersaturated solution is stable or tends to precipitate quickly. Comparison of results with those for pure drug powder and physical mixture can help to indicate the dissolution via solubilization and wetting which could be affected.

4. DEFINITION AND METHODS OF PREPARATION OF SOLID DISPERSIONS

4.1 Definition

The term refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent evaporation method and melting solvent method.

4.2. Methods Of Preparation

Basically there are three methods;

- Melting method.
- Solvent evaporation method.
- Melting-solvent method.

4.2.1. Melting Method

Sekiguchi and *Obi*[3] in 1961 first proposed the melting or fusion method, to prepare fast release solid dispersion dosage forms. In this method, the physical mixture of drug and water-soluble carrier is heated directly until it is melted. The melted mixture is then cooled and solidified in an ice bath under vigorous stirring. The final mass is crushed, pulverized and sieved. The dispersion can also be cooled through the process of spray congealing using spray-drying equipment. The melted material is sprayed onto cold metal surfaces, which forms pellets of the dispersion. This does not require grinding and therefore no alteration of the crystal modification of the drug occurs. In addition, the dispersion can be cooled at a controlled rate. Fusion system can also be done by a slight modification. Here the homogenous melt was poured in the form of a thin layer onto a

ferrite plate or stainless steel plate and cooled by flowing air or water onto the opposite side of the plate. The solidified masses were stored in the dessicator at ambient temperature.

Advantages

- Simplicity and economy.
- Less time consuming.
- This method is also advantageous for compounds, which do not undergo significant thermal degradation.

Disadvantages

- The main disadvantage of the melt method includes thermal degradation, sublimation, and polymeric transformation, which can affect the physicochemical properties of the drug including its rate of dissolution.
- The temperature, at which the dispersion solidifies, affects crystallization rates and may alter both the size of the crystals and the hardness of the dispersion. This may result in tacky or glossy and unmanageable dispersions, which will require storage at elevated temperature, to facilitate hardening.

Examples:

Solid dispersions of Sulphamethoxazole, Acetaminophen, Griseofulvin, Primidone, Chloropropamide, Chloramphenicol, Tolazamide, Steroids, Ketoprofen, Nimesulide.

4.2.2. Solvent Evaporation Method

This method involves dissolving the drug and carrier in a suitable organic solvent, followed by evaporation of the solvent to form solid dispersion. The mass was then stored in a dessicator, pulverized and sieved.

Solvent removal is accomplished by various means. The most common approach is the application of reduced pressure at a fixed temperature to evaporate the organic solvent. Temperatures of 125°C for 25 minutes, 115°C for one hour, –5°C and reduced pressure followed by drying for 12 hours in vacuum have been used. Spray drying is another approach by which solvent removal can be accomplished and it is probably the

fastest way of removing solvent. The freeze-drying technique is also employed to prepare solid dispersions by removal of aqueous solutions.

Advantages

The procedure is suitable for drugs that are thermolabile.

- The thermal decomposition of drugs or carriers can be prevented because of the low temperature required for the evaporation of the organic solvents.
- For aqueous systems, frozen temperature can be used to evaporate the solvent, which can enhance the integrity of the drug.

Disadvantages

- Difficulty in complete removal of the solvent.
- Finding a suitable solvent that will dissolve both the drug and carrier is very difficult.
- Plasticization of some polymers such as polyvinyl pyrrolidone has occurred with the use of some solvents.
- It is important that the rate of evaporation of a solvent is controlled so as to control the particle size of the drug, which in turn will affect the rate of dissolution of the drug in the solid dispersion.

Examples:

β-Carotene–PVP, Griseofulvin–PVP, Sulfathiazole–PVP, Steroids–PVP, Reserpine–deoxycholic acid.

4.2.3. Melting-Solvent Method

The drug is first dissolved in a suitable liquid solvent and solution is then incorporated directly into a melt of PEG obtained below 70°C without removing the liquid solvent. It was shown that 5 -10%w/w of liquid-components would be incorporated into PEG $_{4000}$ without significant loss of its solid property.

Advantages

- Possess the advantage of both melting and solvent methods.

Disadvantages

- Limited to drugs having therapeutic index below 50 mg.
- Selected solvents or dissolved solution may not be miscible with melt of PEG.

Examples:

Solid dispersion of Clofibrate, Methyl Salicylate, Benzyl Benzoate.

5. FEATURES OF SOLID DISPERSION

- Unified presentation of solid dispersion technology for drugs.

- Includes recent developments in theory and practice.
- An aid in new drug formulation and improvement of existing drugs.
- Techniques for improved dissolution rate, sustained release, altered solid-state properties and improved solubility and stability.

6. CLASSIFICATION AND FAST RELEASE MECHANISMS

6.1. Simple Eutectic Mixtures

The simple eutectic mixture is usually prepared from the rapid solidification of the fused liquid of two components, which show solid solubility. When the preparation is dissolved in aqueous medium, the carrier will dissolve rapidly, releasing very fine crystals of drug, which offers large surface area, thereby improvement in dissolution is effected. Thermodynamically, such a system is regarded as an intimately blended physical mixture of its two crystalline components.

6.2. Solid Solutions

A solid solution is made-up of a solute dissolved in a solid solvent. It is often called a mixed crystal because the two components crystallize together in a homogenous one-phase system. A solid solution achieves faster dissolution rate than eutectic mixture because, the particle size of the drug in the solid solution is reduced to a minimum state i.e. molecular size.

Solid solution can be classified according to the extent of miscibility between the two components or the crystalline structure of the solid solution. Based on this, they can be divided into four groups: continuous (or isomorphous, unlimited, complete) solid solutions, discontinuous (or limited, restricted, partial, incomplete) solid solutions, substantial solid solutions and interstitial solid solutions.

6.2.1. Continuous Solid Solutions

In this system, the two components are miscible or solid state in all proportions. The bonding strength between two components is stronger than that between the molecules of each component.

6.2.2. Discontinuous solid solution

There is a limited solubility of a solute in a solid solvent in this group of solid solutions.

6.2.3 Substitutional crystalline solid solution

In this, the solute molecules substitute for the solvent molecules in the crystal lattice of the solid solvent. It can form a continuous solid solution.

6.2.4. Interstitial Crystalline Solid Solution

The solute (guest) molecule occupies the interstitial space of the solvent (host) in the lattice; it usually forms only a discontinuous (limited) solid solution.

6.3. Glass Solutions

A Glass solution is a homogeneous, glassy system in which a solute dissolves in a glassy solvent. It is another potential modification of dosage forms in increasing drug dissolution and absorption. The familiar term "glass," however can be used to describe either a pure chemical or a mixture of chemicals in a glossy or vitreous state.

6.4. Amorphous Preparations

The amorphous form is the highest energy form of a pure drug. It should under almost all conditions, produce faster dissolution and high absorption rates than the crystalline form. In amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent. Novobiocine has been reported to have a ten-fold higher solubility than its crystalline form.

6.5. Complex Formulations

The availability of a drug depends on the intrinsic absorption rate of the complex. The water-soluble polymers have been considered as ideal carriers for the solid dispersion of poorly soluble drugs.

Advantages Of Solid Dispersions

- Solid dispersion of drugs in solid state is helpful in stabilizing unstable drugs. Many of the advantages claimed for SD are derived from their rapid dissolution rates. The increased rate of nitrazepam from the citric acid dispersion produces increase in the rate and extent of absorption.
- The PEGs may protect certain drugs example: cardiac glycosides against the decomposition by saliva and allow buccal absorption.

- Various fast release solid dispersions can be prepared by solid dispersion technique. For example: fast release solid dispersions of Lorazepam can be prepared by using urea, PEG 6000 or Mannitol as carriers.
- Solid dispersions may be a thermodynamically more active form of drug and directly influence the diffusion and release rate.
- An increased diffusion of steroid from the ointment was obtained, example: solid dispersion of prednisolone urea dispersion.
- Solid dispersion technology can be used to solidify liquid drugs, example: clofibrate and benzyl benzoate.

Disadvantages Of Solid Dispersions

- Tackiness and decommission during preparation and formulation.
- The oral administration of solid dispersions without concomitant reduction in dose may result in higher incidence of adverse effects.
- Ex: ulceration of Indomethacin–PEG 6000 dispersion.
- The physical and chemical stability of drug and vehicle.
- Reproducibility of its physicochemical properties.
- The scale up of manufacturing process.
- Its formulation into dosage forms.
- Difficulty in pulverization.
- Drug carrier incompatibility.
- Poor flow and mixing properties.
- Sifting of the dispersions, which are usually soft and tacky.

The surface modification technique can significantly improve the dissolution of hydrophobic drug, by the adsorption of very small amounts of urea at the drug particle surface. Techniques have been commonly used to improve dissolution and bioavailability of poorly water-soluble drugs, which includes micronization, the use of surfactants, and the formation of solid dispersions.

Chiou and *Riegelmann*[4] *in 1971* outlined six types of drug-carrier interactions in solid-state dispersions. Simple eutectic mixtures, solid solutions, glass solutions, glass suspensions, amorphous precipitates in a crystalline carrier and compound or complex formation. Other factors such as increased wettability, solubilization of the drug by the carrier at the diffusion layer and the reduction or absence of aggregation and agglomeration may also contribute to increased dissolution.

Fig 2: Classification And Fast Release Mechanisms

INTEL STable 1 : Solid Dispersions Of Therapeutic Agents

Drug	***Carrier***	***Method***	***Type of solid Dispersion***	***Effect of Dissolution Rate***
Triamterene	B-cyclodextrin	S, K	Not Studied	Increased
Flurbiprofen	PVP	S	Not Studied	Increased
Caffeine	Nicotinamide	M	Peritechc	Increased
Chloramphenicol	Urea	M	Solid Solution	Increased
Clofibrate	PEG 6000	M, S	Not Studied	Increased
Corticosteroids	Sugars	M	Not Studied	Increased
Diazepam	PEG 4000	M	Eutectic with solid Solution	Not Studied
Griseofulvin	Succinic acid	M	Solid Solution	Increased
	PVP	S	Not Studied	Increased
	PVP-30	Spray Embedding	Solid Solution	Increased
	PEG -4000	M, S	Not Studied	Increased
	PEG -6000	M, S	Not Studied	Increased
	PEG-2000	M, S	Not Studied	Increased
	Anhycitric acid	M	Glass suspension	Increased
Indomethacin	PEG 6000	M	Not Studied	Increased
Methyl salicylate	PEG 6000	M,S	Not Studied	Increased
Paracetamol	Urea	M	Solid solution	Increased
Mannitol	M	Eutectic	Increased	
Primidone	Citric acid	M	Glass solution	Increased

Reserpine	PVP	S	Not Studied	Increased
	Cholanic acid	S	Not Studied	Increased
	Deoxychoilic acid	S	Not Studied	Increased
Sulfathiazole	Urea	M	Simple eutectic	Not Studied
Tolubutamide	PEG-4000	S	Not Studied	Increased
	PEG-6000	S	Not Studied	Increased
	PEG 4000+6000	M, S	Not Studied	Increased
	PEG-2000	M, S	Monoacetic	Not Studied
	PVP	S	Not Studied	Increased
	Polyoxyl 40 stearate	M, S	Not Studied	Increased
	PEG-8000	M, S	Not Studied	Increased
	PVP	S	Not Studied	Increased
	PEG-6000	S	Not Studied	Increased
	PEG-4000	M	Not Studied	Increased
Allopurinol	PVP	S	Not Studied	Increased
Benzybenzoate	PEG 6000	M, S	Not Studied	Increased

*M-Melting Method, S-Solvent Method, MS- Melting Solvent Method, K-Kneading Method.

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SCHEME OF WORK

The main perspective of the present study aims at overcoming these problems with solid dispersion technology by using carriers like HPMC and peg-4000 in a view to develop fast release formulation of glimepiride and hence improve its dissolution characteristic. Glimepiride is an effective anti-diabetic, which is practically insoluble in water, hence dissolution is rate limiting.

- The research work envisaged was,
- Literature survey on solid dispersion, method and carriers for solid dispersion.
- Preparation, characterisation and evaluation of solid dispersion of Glimepiride with HPMC, and peg-4000.
- Formulation studies on solid dispersion of Glimepiride.

1. AIM

- To prepare solid dispersions of glimepiride using HPMC and peg-4000 as the inert carriers.
- To assay the solid dispersions.
- To evaluate the solid dispersions by *in-vitro* dissolution studies in phosphate buffer pH 7.4. The in-vitro release profiles of prepared solid dispersions were compared with pure drug.
- The samples were also evaluated by using various instrumental techniques.

2. EXPERIMENTAL DESIGN

- Preparation of glimepiride-peg4000 and glimepiride - HPMC solid dispersions by solvent evaporation method and fusion method.
- Assay of solid dispersions.
- Release studies on solid dispersions in phosphate buffer (pH 7.4).

3. CHARACTERISATION OF SAMPLES BY DIFFERENT METHODS

- XRD- Analysis.

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- DSC-Analysis.
- IR spectroscopic analysis.
- To study the effect of concentration and type of carrier on the release of Glimepiride from its solid dispersions.

4. FORMULATION STUDIES ON SELECTED SOLID DISPERSION

Release studies on selected solid dispersion with pure drug.

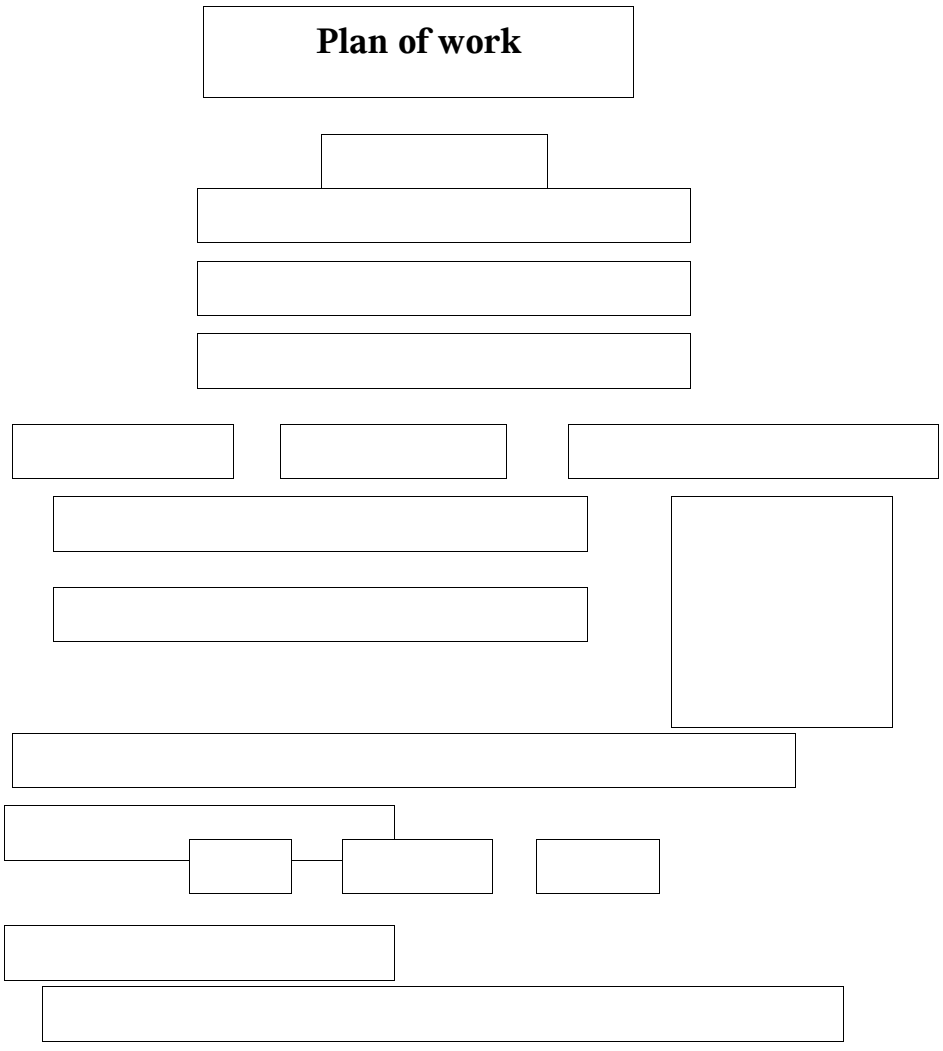

Fig 3: Plan of Work

CHAPTER - 2

DRUG PROFILE[10,13,14]

GLIMEPIRIDE, a new generation sulphonyl urea [Endocrine Journal, 2007] has several benefits: rapid and complete absorption after oral administration, a lower dose, long duration action, and possible insulin sensitizing effect. Glimepiride is an oral blood glucose lowering drug of sulfonyl urea class.

Chemical Name

Glimepiride (1–[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl] phenyl] sulfonyl]-3-(trans-4-methylcyclohexyl) urea.

The CAS registry number is 93479-97-1.

Molecular formula: $C_{24}H_{34}N_4O_5S$

Molecular Weight: 490.62

Structural formula:

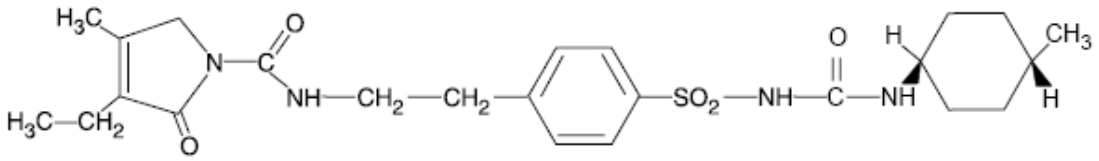

Figure 5: Structure of Glimepiride

Physical properties: Glimepiride is a white to yellowish white crystalline odorless powder.

Solubility: Glimepiride is insoluble in water, acid, base, borate and phosphate buffers but partially soluble in methanol, ethanol, acetone, and completely soluble in DMF[www.aventis.us.com].

Chemical properties: Methanolic solution of Glimepiride gives UV absorption at 229nm and aqueous solution of Glimepiride gives maximum absorption between 229 and 236nm [Indian Journal of Pharmaceutical Sciences].

Log P value: 2.5

C Log P value: 3.96 [www.tsrlinc.com]

BCS: Class 2 drug (low solubility high permeability)

Available strength: 1mg, 2mg, and 4mg

Mechanism of Action

The primary mechanism of Glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells.

In addition extra pancreatic effect may also play a role in the activity of sulfonyl urea such as Glimepiride. This is supported by both clinical and pre-clinical studies demonstrating the Glimepiride administration can lead to increased sensitivity of peripheral tissues to insulin.

Pharmacokinetics

Absorption: After oral administration, Glimepiride is completely (100%) absorbed from the GI tract. Studies with single oral doses in normal subjects and with multiple oral doses in patients with Type2 has shown significant absorption of Glimepiride with 1 hour after administration and peak drug levels at 2 to 3hours.

Distribution: After intravenous (IV) dosing in normal subjects, the volume of distribution (Vd) was 8.8L (113ml/kg), and the total body clearance (Cl) was 47.8 ml/min. Protein binding was greater than 99.5%.

Metabolism: Glimepiride is completely metabolized by oxidative biotransformation after either an IV or oral dose. The major metabolites are the cyclohexyl hydroxyl methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 2C9 has been shown to be involved in the biotransformation of Glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes. M1, but not M2, possesses about 1/3 of the pharmacological activity as compared to its parent in an animal model.

Excretion: When ^{14}C-Glimepiride was given orally, approximately 60% of the total radioactivity was recovered in the urine in 7 days and M1 (predominant) and M2 accounted for 80 – 90% of that recovered in the urine. Approximately 40% of that recovered in feces. No parent drug was recovered from urine or feces.

Pharmacokinetic Parameters

Table 2: Pharmacokinetic Parameters

Parameter	Single Dose
C_{max} (ng/ml)	
1 mg	103± 34 (12)
2 mg	177 ± 44 (12)
4 mg	308 ± 69 (12)
8 mg	551 ± 152 (12)
T_{max} (h)	1.4 ± 0.8 (48)
Cl/f(ml/min)	52.1 ± 16.0 (48)
Vd/f(l)	21.8 ± 13.9 (48)
$T_{1/2}$(h)	1.3 ± 4.1 (48)

CL/f=Total body clearance after oral dosing

Vd/f=Volume of distribution calculated after oral dosing

Adverse reactions

GASTRO INTESTINAL REACTIONS

Vomiting, gastro intestinal pain and diarrhoea have been reported.

DERMATOLOGIC REACTIONS

Allergic skin reactions, e.g. Pruritus, Erythema, Urticaria occurs.

HEAMATOLOGIC REACTIONS

Leukopenia, Agranulocytosis, Thrombocytopenia, Hemolytic Anemia, Aplastic Anemia, and Pancytopenia have been reported.

Indications and Usage

Glimepiride is indicated as an adjunct to diet and exercise to lower the blood glucose in patient with Type 2 diabetes mellitus. Hypoglycemia cannot be controlled by diet and exercise alone. Glimepiride may be used concomitantly with Metformin when diet, exercise, Glimepiride or Metformin alone do not adequate glycemic control.

Dosage and Administration [Package insert of Amaryl tablets 1, 2 and 4 mg.]

Usual starting dose of Glimepiride initial therapy is 1mg to 2mg once daily, administered with breakfast or first main meal.

Patient who may be more sensitive to Hypoglycemic drugs should be started at 1mg once daily, and should be titrated carefully.

The maximum starting dose of Glimepiride should not be more than 2mg. The usual maintenance dose is 1 to 4mg once daily. The maximum recommended dose is 8mg once daily.

CHAPTER - 3

POLY ETHYLENE GLYCOL PROFILE[15-24]

1. NONPROPRIETARY NAMES

BP: Macrogols, JP: Macrogol 400, Macrogol 1500, Macrogol 4000, Macrogol 6000, Macrogol 20000, PhEur: Macrogola, USPNF: Polyethylene glycol

2. SYNONYMS

Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; PEG; Pluriol E; polyoxyethylene glycol.

3. CHEMICAL NAME

α-Hydro-ω-hydroxypoly(oxy-1,2-ethanediyl)

4. FUNCTIONAL CATEGORY

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

5. APPLICATIONS IN PHARMACEUTICAL TECHNOLOGY

Polyetylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral, and rectal preparations. It has been used in controlled-release systems.

Polyethylene glycols are water-soluble and are easily removed from the skin by washing, making them useful as ointment bases.[2] Aqueous polyethylene glycol solutions can be used either as suspending agents or to adjust the viscosity and consistency of other suspending vehicles. When used in conjunction with other emulsifiers, polyethylene glycols can act as stabilizers.

Liquid polyethylene glycols are used as water-miscible solvents for the contents of soft gelatin capsules. In concentrations up to approximately 30% v/v, PEG 300 and PEG 400 have been used as the vehicle for parenteral dosage forms.Polyethylene glycols can also be used to

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enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions with an appropriate polyethylene glycol.

In film coatings, solid grades of polyethylene glycol can be used alone for the film-coating of tablets. Solid grades are also widely used as plasticizers in conjunction with film-forming polymers.The presence of polyethylene glycols in film coats, especially of liquid grades, tends to increase their water permeability and may reduce protection against low pH in enteric-coating films.

6. PHARMACOPEIAL SPECIFICATIONS

6.1. Typical Properties

Density	:	*1.11–1.14 g/cm^3 at 25°C for liquid PEGs; 15–1.21 g/cm^3 at 25°C for solid PEGs.*
Flash point	:	238°C for PEG 4000;
Freezing point	:	4–8°C for PEG 4000
Melting point	:	50–58°C for PEG 4000.
Moisture content	:	Liquid polyethylene glycols are very hygroscopic, hygroscopicity decreases with increasing molecular weight. Solid grades.

7. SOLUBILITY

Soluble in water, liquid PEG are soluble in acetone, alcohols, benzene, glycerin, and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol (95%), and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.

8. SURFACE TENSION

Approximately 44 mN/m (44 dynes/cm) for liquid polyethylene glycols; approximately 55 mN/m (55 dynes/cm) for 10% w/v aqueous solution of solid polyethylene glycol.

9. STABILITY AND STORAGE CONDITIONS

Polyethylene glycols are chemically stable in air and in solution, although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth, and they do not become rancid.

Polyethylene glycols should be stored in well-closed containers in a cool, dry place. Stainless steel, aluminum, glass, or lined steel containers are preferred for the storage of liquid grades.

10. INCOMPATIBILITIES

All grades can exhibit some oxidizing activity owing to the presence of peroxide impurities and secondary products formed by autoxidation. Liquid and solid polyethylene glycol grades may be incompatible with some coloring agents.The antibacterial activity of certain antibiotics is reduced in polyethylene glycol bases. The preservative efficacy of the parabens may also be impaired owing to binding with polyethylene glycols.

11. HANDLING PRECAUTIONS

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection is recommended.

12. REGULATORY STATUS

Included in the FDA Inactive Ingredients Guide (dental preparations; IM and IV injections; ophthalmic preparations; oral capsules, solutions, syrups, and tablets; rectal, topical, and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

HYPROMELLOSE (HPMC)

Nonproprietary Names

BP: Hypromellose

JP: Hydroxypropylmethylcellulose

PhEur: Hypromellosum

USP: Hypromellose

Synonyms

Benecel MHPC; hydroxypropyl methyl ether; E464; hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; merthyl hydroxypropylcellulose; Metolose ; Pharmacoat ; Spectracel 6 ; Spectracel 15; Tylopur.

Chemical Name and CAS registry number

Cellulose, 2-hydroxypropyl-methyl ether [9004-65-3]

Empirical formula molecular weight

The PhEur 2002 describes hypromellose as a partly O-methylated and O-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 20℃. Hypromellose defined in the USP 25 specifies the substitution type by appending a four-digit number to the nonproprietary name: e.g., hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH3). The second two digits refer to the approximate percentage content of the methoxy group (OCH3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group (OCH2CH (OH) CH3), calculated on a dried basis. Molecular weight is

approximately 10 000-1 500 000. The Jp 2001 includes three separate monographs for hypromellose: hydroxypropylmethylcellulose 2208, 2906, and 2910, respectively.

Functional category

Coating agent; film-former; rate – controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity – increasing agent.

Applications in pharmaceutical formulation or technology

Hypromellose is widely used in oral and topical pharmaceutions, Particularly ophthalmic preparations. Compared with methylcellulose, hypromellose produces solutions of greater clarity, with fewer undispersed fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45-1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.

Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

Description

Hypromellose is an odorless and tasteless, white or creamy white fibrous or granular powder.

Pharmacopeial specifications

Typical Properties

Acidity / alkalinity : pH = 5.5 – 8.0 for a 1% w/w aqueous solution

Ash : 1.5-3.0% depending upon the grade

Autoignition temperature: 360℃

Density (tapped) **:** 0.557 g/cm^3

Density (tapped) **:** 1.326 g/cm^3

Melting point : browns at 190-200℃; chars at 225-230℃.

Glass transition temperature is 170-180℃.

Moisture content: hypromellose absorbs moisture from the atmosphere, the amount of water absorbed depending and relative humidity of the surrounding air.

Solubility: soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents.

Specific gravity: 1.26

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Viscosity (dynamic): Wide ranges of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w. Dichloromethane and ethanol mixtures may also be used to prepare viscous hypromellose solutions. Solutions prepared using organic solvents tend to be more viscous; increasing concentration also produces more viscous solutions;

Methocel grade	Nominal	Viscosity (MPa s)
K 100LVP	100	80-120
K4M	4000	3000-5600
K15MP	15000	12000-2100
K100MP	100 000	80 000-120 000

To prepare an aqueous solution, it is recommended that hypromellose is dispersed and thoroughly hydrated in about 20-30% of the required amount of water. The water should be vigorously stirred and heated to 80-90℃, then the remaining hypromellose added. Cold water should then be added to produce the required volume.

When a water – miscible organic solvent such as ethanol, glycol, or mixtures of ethanol and dichloromethane is used, the hypromellose should first be dispersed into the organic solvent, at a ratio of 5-8 parts of solvent to part of hypromellose. Cold water is then added to produce the required volume.

Stability and storage conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying.

Solutions are stable at pH 3-11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol-gel transformation upon heating and cooling, respectively. The gel point is 80-90℃, depending upon the grade and concentration of material.

Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage.However, aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative: when hypromellose is used as a viscosity – increasing agent in ophthalmic solutions, benzalkonium chloride is commonly used as the preservative. Aqueous solutions may also be sterilized by autoclaving; the coagulated polymer must be redispersed on cooling by shaking.

Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

safety

Hypromellose is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products.

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Hypromellose is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may have a laxative effect. The WHO has not specified an acceptable daily intake fro hypromellose since the levels consumed were not considered to represent a hazard to health.

LD_{50} (mouse, IP): 5 g/kg (16)

LD_{50} (rat, IP): 5.2 g/kg

Handling precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hypromellose dust may be irritant to the eyes and eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosion. Hypromellose is combustible[63].

CHAPTER - 4

LITERATURE REVIEW [34-60]

Sethia and Squillante (2004)[58] were prepared solid dispersion of carbamazepine in PVP K30 by conventional solvent evaporation and supercritical methods. They have suggested that the best intrinsic dissolution rate (IDR) was obtained for super critically processed CBZ/PVP K30 that was four-fold higher than pure CBZ and the supercritical-based process produced augmented with amphiphilic carriers.

Eun-Jung et al., (2006)[59] has studied the dissolution rates of felodipine musing PVP and HPMC carriers by solvent wetting method. It could be shown that the dissolution rates of felodipine in PVP and HPMC solid dispersion were much faster than those for they corresponding physical mixtures. However dissolution profiles were found to depend on the carrier used; the dissolution rate of felodipine increased slowly for solid dispersions prepared using HPMC, whereas rapid initial dissolution rate were observed for solid dispersions prepared using PVP or poloxamer. Increases in dissolution rate were partly dependent on the ratios of felodipine to carrier. No significant changes in crystal form were observed by X-ray diffraction or thermal analysis, and no significant changes in dissolution rate were observed when sorbitol and mannitol were used as carriers.

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Naveen et al., (2007)[60] have studied enhancement of dissolution and mathematical modeling of drug release of a poorly water-soluble drug (rofecoxib) using water-soluble carriers viz. polyethylene glycols (PEG 4000 and 6000), polyglycolized fatty acid ester (Gelucire 44/14), polyvinylpyrollidone K25 (PVP), poloxamers (Lutrol F127 and F68), polyols (mannitol, Sorbitol), organic acid (citric acid) and hydrotropes. All the solid dispersion showed dissolution improvement vis-à-vis pure drug to varying degress, with citric acid, PVP and poloxamers as the most promising carriers. Solid-state characterization techniques revealed that distinct loss of drug crystallinity in the formulation, ostensibly accounting for enhancement in dissolution rate.

Qureshi *et al*., (1998)[34] have been studied the variability in drug dissolution testing of prednisone tablets and a marketed glibenclamide tablet product. The experiments were conducted using paddle and basket methods at 50 (calibrators) and 75 (glibenclamide) rpm. The media employed were deaerated by equilibrating at 37ºC for 24 h and by the USP recommended method. The 95% CI values for percent drug release for the USP calibrator tablets were similar to the reported tolerances for the USP *Acceptance Range*s; however, individual results from 15 of 28 laboratories suggest that the apparatus would not comply with the USP *Apparatus Suitability Criteri*a. For FDA prednisone calibrator tablets, percent drug release using equilibrated medium was different *(*P50.003) than by the USP recommended method. For the glibenclamide tablet results, a CV of 14–37% was observed, depending upon the sampling time and the type of apparatus employed. The results indicate that failure to meet the *USP*

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Dissolution Apparatus Suitability Test may not truly mean that the apparatus is 'out of compliance'. Due to the high variability in dissolution testing, in many cases the impact of formulation or manufacturing changes on drug release characteristics may not be observed, in particular with multi-point profiles.

Aceves *et al*., (1999)[35] have been studied on solid dispersion and physical mixtures were prepared and characterized by X-ray, infrared spectroscopy, electronic microscopy and dissolution rate studies. The characterization with X-ray showed a transition from the crystalline to the amorphous phase. A new phase near 50% furosemide concentration with both type of carrier was present from infrared spectroscopy strong interaction between amine and carbonyl groups from both the furosemide and the polymer were found. Electronic microscopy analysis showed that the furosemide changed its crystalline habit from needle to a new spherical phase, with diameter near to 1µm. Solid dispersion were prepared in order to modify the system characteristics. The furosemide dissolution rate was determine in order to follow the behaviour changed of the system. Scanning electron microscopy showed the present of microspheres within the polymer matrix, and the channels formed due to the frosemide dissolution inside the Eudragit, this fact modified the release pattern of the frusemide system.

Lin *et al*., (1999)[36] have been reported surface modified human serum albumin (HSA) nanoparticles with a size of approximately 150 nm in diameter were prepared from a PEG-HSA conjugate, methoxy-polyethylene glycol modified human serum albumin (HSA-mPEG) using a coacervation method and

crosslinked with glutaraldehyde. The z-potential of the surface modified nanoparticles was significantly lower than that of unmodified HSA nanoparticles. The existence of a hydrated steric barrier surrounding the nanoparticles was confirmed by electrolyte and pH induced flocculation tests. The surface modified nanoparticles showed a reduced plasma protein adsorption on the particle surface compared with unmodified particles.

Dash *et al.,* (2002)[37] reported ethylcellulose microspheres containing tolnaftate were prepared by the emulsion- solvent evaporation technique. An X-ray powder diffractometric method was developed to quantify the content of crystalline tolnaftate in these microspheres X-ray lines of tolnaftate with d-spacings of 5.5 and 4.1Aº were chosen for the quantitative analyses. Physical mixture containing various weight fraction of tolnaftate and blank (empty) microspheres were prepared and lithium fluoride (20%w/w) was added as the internal standard. The 5.5 and 4.3 lines of tolnaftate and the 2.3Aº line of lithium fluirde where used for the quantitative analysis. A plot of the intensity ratio (intensity of the 5.5Aº line of tolnaftate / intensity of 2.3 Aº line of lithium fluoride) as a function of weight percent of tolnaftate in the mixture, resulted in a straight line. The crystal line content of tolnaftate in the tolnaftate-loaded microspheres was determined using the standard curve. A second independent determination of the content of tolnaftate was possible from the intensities of the 4.3 Aº line. The enthalpy of fusion of tolnaftate, determined by differential scanning calorimetry(DSC), was also used as a measure of the crystalline content of tolnaftate in the microspheres. The X-ray and DSC methods measure the content

of crystalline tolnaftate in the microspheres in the room temperature(~ 25ºC) and at the melting point of tolnaftate (111ºC), respectively. The total content of tolnaftate microspheres was determined by HPLC. The DSC and X-ray results indicated that a substantial fraction of the incorporated tolnaftate was desoved in the ethylcellulose matrix.

Fude cui *et al.,* (2003)[38] reported to improve the bioavailability of nitrendipine microspheres, a sustained-release microspheres having solid dispersion structure were prepared in one step. Two types of polymer, i.e. solid dispersing and sustained-release polymers were employed to prepare the microspheres by the spherical crystallization technique, i.e. quasi-emulsion solvent diffusion method. The factors of effect on micromeritic properties and release profiles of the resultant microspheres were investigated. And the bioavailability of nitrendipine microspheres was evaluated in six healthy dogs. The results showed that the particle size of microspheres was determined mainly by the agitation speed. The dissolution rate of nitrendipine from microspheres was enhanced significantly with increasing the amount of dispersing agents, and sustained by adding retarding agents. The release rate of microspheres could be controlled as desired by adjusting the combination ratio of dispersing agents to retarding agents. The results of X-ray diffraction and differential scanning calorimetry analysis indicated that the crystalline form of nitrendipine was disordered, suggesting that nitrendipine was highly dispersed in microspheres, so as amorphous state. The release profiles and content of the microspheres stored at a temperature of 40ºC and a relative humidity of 75% were unchanged

during 3 months of accelerating condition of storage. And the relative bioavailability of the sustained-release microspheres compared with the Baypress_ tablets and the conventional tablets was 107.78% and 309.82%. In conclusion, the sustained-release microspheres with solid dispersion structure improved the bioavailability of the water insoluble drug and prolonged the T_{max} *value*.

***Gupta** et al., (2004)[39] studied* the solubility enhancement and enthalpy relaxation studies with respect to PVP concentration helped in a better prediction of role of carrier and optimization of concentration in the use of solid dispersions or amorphous systems. The drug release mechanism is drug-controlled rather than carrier-controlled.

Elaine Merisko-Liversidge *et al.,* (2004)[40] have studied water insoluble Zn-insulin can be formulated as a stable, biologically active nanometer-sized peptide particle dispersion using wet media milling technology, capsules differ from gelatin, which will require modification to dissolution testing methodology for certain drugs. However, for the class II BCS drug ibuprofen, the two capsule types were not statistically different when comparing AUC and C_{max} values, which suggests that the *in vitro* differences have reduced *in vivo* relevance.

Ewart et al., (2004)[41] have been studied the in vitro preformance of HPMC capsules differ from gelatin, which will require modificationto dissolution testing methodology for certain drugs. However, for the class II BSC drug ibuprofen, the two capsule type were not satistically different when comparing AUC and C_{max} values, which suggest that the *in vitro* differences have reduced *in vivo* relevance

Verma *et al.,* (2004)[42] have been worked on extended release formulation of glipizide based on osmotic technology was developed and evaluated. The effect of different formulation variables, namely, level of solubility modifier in the core, membrane weight gain, and level of pore former in the membrane, were studied. Drug release was found to be affected by the level of solubility modifier in the core formulation. Glipizide release was inversely proportional to the membrane weight but directly related to the initial level of pore former (PVP) in the membrane. Burst strength of the exhausted shells increased with the weight gain of the membrane. On the other hand, burst strength decreased with an increase in the level of pore former in the membrane. Drug release from the developed formulations was independent of pH and agitational intensity, but dependent on the osmotic pressure of the release media. Results of SEM studies showed the formation of pores in the membrane from where the drug release occurred. The numbers of pores were directly proportional to the initial level of pore former in the membrane. The manufacturing procedure was found to be reproducible and formulations were stable after 3 months of accelerated stability studies.

Rogers *et al.,* (2004)[43] studied on controlled precipitation by scalable technology that can be used to enhance the dissolution of poorly water-soluble pharmaceutical compounds.

Ould-Ouali *et al*., (2004)[44] reported the polyester diblock copolymer mmePEG750-CAP/ TMC forms spontaneously stable micelles in aqueous

medium and increases the solubility of lipophilic drugs. They are very promising vehicles for the oral delivery of poorly water-soluble drugs.

Feng-Qian Li *et al*., (2004)[45] have studied the solid dispersion of silymarin were prepared by the fusion method with the intention of improving the dissolution properties of silymarin. Polyethylene glycol (PEG 6000) was used as the inert hydrophilic matrix. The dissolution studies of the solid dispersions were performed *in vitro*. And the results obtained showed that the dissolution rate of silymarin was considerably improved when formulated in solid dispersion with PEG 6000 as compared to original drug , and the increased dissolution rate might be favorable for further oral absorption.

Verma *et al*., (2005)[46] have been studied for the development of extended release formulations of glipizide, techniques of thermal and isothermal stress testing (IST) were used to assess the compatibility of glipizide with selected excipients. Initially, differential scanning calorimeter (DSC) was used to evaluate the compatibility. IR spectrum of drug–excipient mixture was also compared with that of pure drug and excipient. Compatibility of excipients defined in the prototype formula was tested using IST. Based on the DSC results alone, magnesium stearate, meglumine, TRIS buffer, and lactose, were found to exhibit interaction with glipizide. Stressed binary mixtures (stored at 50ºC for 3 weeks) of glipizide and meglumine showed yellow coloration indicating potential incompatibility. Based on the results of DSC, IR, and/or HPLC, excipients defined in the prototype formula were found to be compatible with glipizide. The optimized formulation developed using the compatible excipients were found to

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be stable after 3 months of accelerated stability studies (40ºC and 75% RH). Overall, compatibility of excipients with glipizide was successfully evaluated using the combination of thermal and IST methods and the formulations developed using the compatible excipients was found to be stable.

Patel *et al*., (2005)[47] have been studied on formulation and evaluation of *in vitro* and *in vivo* performances of mucoadhesive microspheres of glipizide. Glipizide microspheres containing chitosan were prepared by simple emulsification phase separation technique using glutaraldehyde as a crosslinking agent. Results of preliminary trials indicate that volume of crosslinking agent, time for crosslinking,polymer-to-drug ratio,and speed of rotation affected characteristics of microspheres.Microspheres were discrete, spherical,and free flowing. The microspheres exhibited good mucoadhesive property in the *in vitro* wash-off test and also showed a high percentage drug entrapment efficiency.A 3 2 full factorial design was employed to study the effect of independent variables,polymer to drug ratio (X1),and stirring speed (X2)on dependent variables, percentage mucoadhesion,drug entrapment efficiency, and swelling index. The best batch exhibited a high drug entrapment efficiency of 75%and a swelling index of 1.42; percentage mucoadhesion after 1 hour was 78%.The drug release was also sustained for more than 12 hours.The polymer to drug ratio had a more significant effect on the dependent variables.*In vivo* testing of the mucoadhesive microspheres to albino Wistar rats demonstrated significant hypoglycemic effect of glipizide.

Shahla Jamzad *et al*., (2006)[48] reported that the depending on the dose size and solubility characteristics of low solubility drugs, a meaningful and discriminatory power of dissolution rate testing can be demonstrated. Saturation solubility of fenofibrate and glipizide in different media were determined. Solubility of fenofibrate increased directly with SLS concentration. For a 54-mg fenofibrate tablet, SLS at 0.025 M level is required for a discriminative dissolution test, while for 160-mg tablet, dissolution condition and levels of SLS should be optimized; higher con-centrations may be effective (ie, 0.052 M, ~1.5%). A pH 6.8 phosphate buffer medium is appropriate for glipizide 10-mg tablet dissolution study, when formulation ingredients include excipients with surface activity (eg, HPMC).

Aftab modi *et al*., (2006)[49] Iinvestigated the enhancement of the dissolution profile of valdecoxib using solid dispersion with PVP. The article also describes the preparation of fast –dissolving tablet of valdecoxib by using a high amount of superdisintegrant. A phase solubility method was used to evaluate the effect of various water –soluble polymer on aqeous solubility of valdecoxib. Polyvinyl pyrrolidone (PVP K-30) was selected and solid dispersion were prepared by the method of kneading. Dissolution studies using the USPpaddle method were performed for solid dispersion of valdecoxib. Infrared (IR) spectroscopy, differential scanning calorimetry (DSC), and X-ray diffractometry(XRD) were performed to indentify the physicochemical interaction between drug and carrier, hence its effect on dissolution. Tablets were formulated containing solid dispersion products and compared with commercial products. IR

spectroscopy,XRD and DSC showed no change in the crystal structure of valdecoxib. Dissolution of valdecoxib improved significantly in solid dispersion products(<85% in 5 miniutes). Tablets containing solid dispersion exhibited better dissolution perofile than commercial tablets. Thus, the solid dispersion technique can be successfully used for improvement of dissolution of valdecoxib.

Prego *et al*., (2006)[50] have been studied on chitosan nanocapsules to enhance and prolong the oral absorption of peptides. They designed a new type of nanocapsule, using chitosan chemically modified with poly(ethylene glycol) (PEG) (0.5% and 1% pegylation degree) and to investigate the cosequences of this modification on the *in vitro* and *in vivo* behaviour of the nanocapsules. Chitosan PEG nanocapsules and the control PEG-coated nanoemulsions were obtained by the solvent displacement technique. Their size was in the range of 160-250nm. Their zeta potential was greatly affected by the nature of the coating, being positive for chitosan-PEG nanocapsules and negative in the case of PEG-coated nanoemulsions. The presence of PEG, whether alone of grafted to chitosan, improved the stability of the nanocapusles in the gastrointestinal fluids. Using the caco-2 model cell line it was observed that the pegylation of chitosan reduced the cytotoxicity of the nanocapsules. In addition, these nanocapsules did not cause a significant change in the transepithelial resistance of the monolayer. Finally, the results of the *in vivo* studies showed the capacity of chitosan-PEG nanocapsules to enhance and prolong the intestinal absorption of salmon calcitonin. Additionally, they indicated that the peglyation degree affected the *in vivo* performance of the nanocapsules. Therefore, by modulating the pegylation

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degree of chitosan, it was possible to obtain nanocapsules with a good stablility, a low cytotoxicity and with absorption enhancing properties.

Fude Cui *et al*., (2006)[51] studied on biodegradation nanoparticles loaded with insulin-phospholipid complex by a novel reverse micelle-solvent evaporation method, in which soyabean phosphatidylcholine(SPC) was employed to improve the liposlubility of insulin,and biodegradable polymers as carrier materials to control drug release. Solubilization study,IR and X-ray diffraction analysis were employed to prove the complex formation. The effects of key parameters such as polymer/SPC weight ratio, organic phase and polymer type on the properties of the nanoparticles were investigated. Spherical particles of 200nm mean diameter and narrow size distribution were obtained under optimal conditions. The drug entrapment efficiency upto 90%. The *in vitro* drug release was characterized by an initial burst and subsequent delayed release in both pH 6.8 and pH 1.2 dissolution mediums. The specific modality of drug relase, i.e., free of SPC-combined, was investigated in the aid of ultracentrifugation and ultrafiltration methods. The influence of polymer type on the drug release was also discussed. The pharmacological effects on the nanopartilces made of PLGA 50/50 (Av. Mw 9500) were further evaluated to confirm their potential suitability for oral delivery. Intra gastric administrations of the 20 IU/kg nanopartilces reduced fasting plasma glucose levels to 57.4% within the first 8 h of administration and this continued for 12 h. PK / PD analysis indicated that 7.7% of oral bioavailability relative to subcutaneous injection was obtained.

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Siriporn Okonogi *et al*., (2006)[52] investigated solid dispersion system consisting of drug, carrier, and surfactant. Solid dispersions of a water insoluble ofloxacin (OFX) with polyethylene glycol (PEG) of different molecular weights, namely binary solid dispersion systems, were prepared at drug to carrier not less than 5:5. Polysorbate 80, a nonionic surfactant, was incorporated into the binary solid dispersion systems as the third component to obtain the ternary solid dispersion systems. The powder x-ray diffraction and differential scanning calorimetric studies indicated that crystalline OFX existed in the solid dispersions with high drug loading. However, a decreased crystallinity of the solid dispersions obtained revealed that a portion of OFX was in an amorphous state. The results indicated a remarkably improved dissolution of drug from the ternary solid dispersion systems when compared with the binary solid dispersion systems. This was because of polysorbate 80, which improved wettability and solubilized the non molecularly dispersed or crystalline fraction of OFX..

Kalaiselvan *et al*., (2006)[53] have been stidied the mechanism of drug release from solid dispersion of Albendazole, giving emphasis to particle size of the drug in solid dispersion. Solid dispersion were prepared using three different carriers, mixing ratios and methods in an attempt to improve solubility and dissolution rate of Albendazole. The mechanism of enhanced dissolution was investigated by a novel dissolution technique as an adjunct to face solubility study, wettability test, differential scanning calorimetry, X-ray diffractometry, infrared spectroscopy and scanning electron microscopy. The solubility of Albendazole was greater with Albendazole-poloxmer407 system, while

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polyethylene glycol dispersion showed predominant wettablilty. Physical mixture showed enhanced dissolution compared with the pure drug, due to improve wetting and solubilization of drug in the diffusion layer offering carrier-reach microenvironment. Preparation of solid dispersion further improve the dissolution compared the physical mixture, owing to increased surface area for mass transfer, thermodynamically enhance dissolution of a higher energy amorphous form from the carrier, in addition to improved wetting and solubilization. All carrier showed comparitable degree of drug particle size reduction, whereas mixing ratio and method of preparation substantially effect the particle size. Intermolecular association of drug with the carrier lead to inhibition of drug recrystallization.

Panchagnula *et al*., (2007)[54] studied the *in vitro* evaluation of modified release formulations, containing and compared their performance with a novel matrix-based multiparticulate systems. The results indicate that eventhough the marketed formualations are found to comply to the definition of modified release formulations and predicted the therapeutic blood level for a prolonged period of time, the fluctuations were expected to be found uncontrol except in the osmotic system and the matrix-based multiparticulate system. Thus, it was concluded that novel matrix-based multiparticulate system were found to be superior to any other marketed formulations with respect to the therapeutic advantage as well as manufacture fesiblility.

Srinivas Mutalik *et al*., (2007)[55] Celecoxib spherical agglomerates were prepared with polyvinyl pyrrolidone(PVP) using acetone, water and chloroform as solvent, non-solvent and bridging liquid, respectively. The agglomerates were characterized by differential scanning calorimetry(DSC), X-ray diffraction(XRD), IR

spectroscopic study and scanning electron microscopy(SEM). The IR spectroscopy and DSC results indicated the absence of any interactions between drug and additives. The XRD studies showed a decrease in crystallinity in agglomerates. The crystal exhibited significantly improved micromeritics properties compared to pure drugs. The loading efficency(% or mg drug per 100 mg crystal) was in the range of 93.9± 2.3 and 97.3± 1.3%(n=3) with all formulations. The aqueous solubility and dissolution rate of the drug from crystal was significantly ($p<0.05$) increased (nearly two times). The solubility and *in vitro* drug release rates increased with an increase in PVP concentration(from 2.5 to 10%). The SEM studies showed that the crystal posses a good spherical shape with smooth and regular surface.

Prajapati *et al*., (2007)[56] have been studied the enhancement of dissolution properties of carbamazepine by solid dispersion technique. Physical mixtures and solid dispersions of carbamazepine were prepared to enhance its water solubility. Physical mixtures and solid dispersions of carbamazepime were prepared by using polyvinyl pyrrolidone K-30, polyethylene glycol 4000 and polyethylene glycol 6000 as water-soluble carrier at various proportion (1:0.1, 1:0.2, 1:0.4, 1:0.6, 1:0.8, by weight) by employing solvent evaporation method. The drug release profile was studied according to USP XXXIII monograph in 1% sodium lauryl sulphate solution. It was found that the amount of the carrier, i.e., the higher amount of carrier used, the higher dissolution rate was obtained except for polyvinyl pyrrolidone K-30 and PEG 4000 solid dispersions. Amoung carrier studied solid dispersion of carbamazepine : PVP K 30 at 1:0.2(drug:carrier ratio) gave highest dissolution. The increase in dissolution rate of drug may be due to increase wettability, hydrophilic nature of the carrier and also possiblility due to reduction in drug crystallinity.

CHAPTER - 5

ANALYTICAL METHOD

1. THE METHODOLOGY USED IN THE PRESENT STUDY IS UV SPECTROPHOTOMETRY

1.1. Potassium Dihydrogen Phosphate, 0.2 M Solution

Take accurately weighed 27.318 gm of Potassium dihydrogen Phosphate and dissolved in 1000 ml of distilled water, this will give 0.2 M KH_2PO_4.

1.2. Sodium hydroxide 0.2 N solution

Take accurately weighed 8 gm of sodium hydroxide and dissolved in 1000 ml of distilled water, this will give 0.2 N NaOH solution.

1.3. Preparation of pH 7.4 phosphate buffer

Place 50 ml of the Potassium dihydrogen Phosphate solution in a 200 ml standard volumetric flask and add 39.1 ml of sodium hydroxide solution to this flask and make up the volume with distilled water.

2. PROCEDURE FOR STANDARD GRAPHS PREPARATION

2.1. Standard graphs preparation with phosphate buffer pH 7.4

Accurately weigh 100 mg of glimepiride and transfer to a 100 ml volumetric flask and add minimum quantity of Methanol to solubilise the drug, and then add phosphate buffer pH 7.4 to make up the volume up to 100ml, this gives the stock solution I (1000 µg/ml).

From stock solution I, pipette out 10 ml and make up the volume to 100 ml with phosphate buffer pH 7.4, this gives the stock solution II (100 µg/ml).

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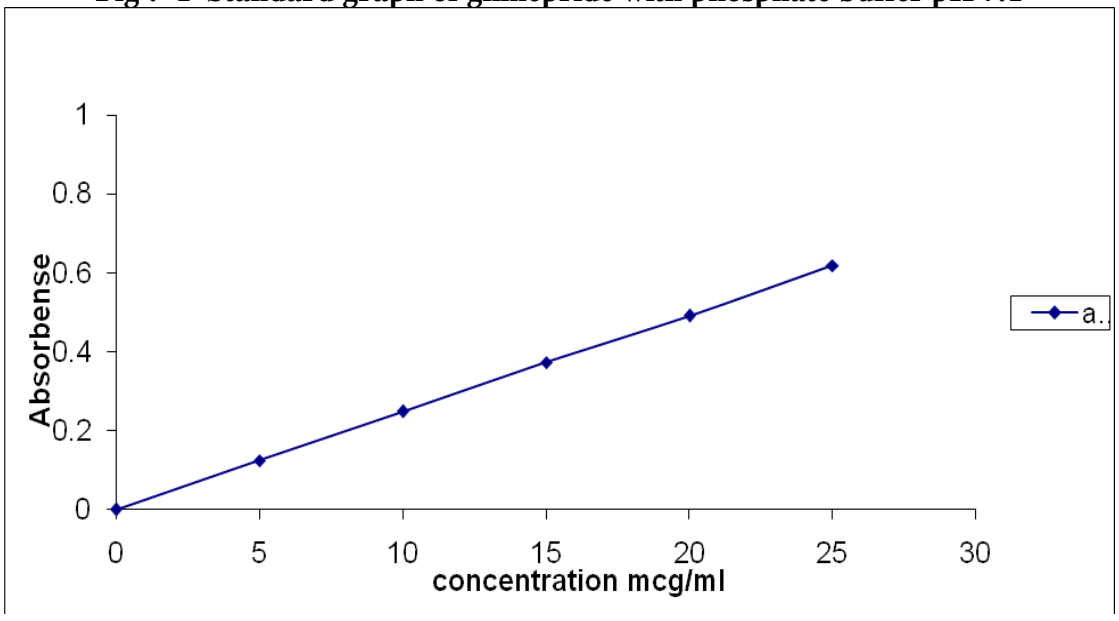
From the stock solution II, pipette out 0.5, 1.0, 1.5, 2.0, and 2.5 ml into 5 separate 10 ml volumetric flasks respectively, then make up the volume up to the mark to give 5, 10, 15, 20 and 25 µg/ml concentration solutions and the phosphate buffer pH 7.4 was taken as blank.

The absorbance was measured at 236nm and the graph was plotted against concentration (µg/ml) Vs absorbance.

Table No. 3 : Standard Graph of Glimepiride wih phosphate buffer pH7.4.

Sl. No.	Concentration (µg/ml)	Absorbance at 236nm
1	0	0.0000
2	5	0.1249
3	10	0.2490
4	15	0.3730
5	20	0.4920
6	25	0.6202

Fig : 4 Standard graph of glimepride with phosphate buffer pH 7.4



EXPERIMENTAL SECTION

1. MATERIALS AND EQUIPMENT USED

Table 4 : Materials Used

Materials	Source
Glimepride	Aristo pharmaceuticals pvt. Ltd. mumbai Franco-indian pharmaceutical pvt.Lltd. mumbai
Methanol	Qualigens fine chemicals.,Mumbai.
SLS	Qualigens fine chemicals, Mumbai.
HPMC	Qualigens fine chemicals, Mumbai.
PEG-4000	Sisco Research laboratory .,Mumbai.
Chloroform	Qualigens fine chemicals.,Mumbai.
Ethyl acetate	Qualigens fine chemicals.,Mumbai.
Potassium dihydrogen phosphate	Qualigens fine chemicals.,Mumbai.
Sodium hydroxiode	Qualigens fine chemicals.,Mumbai.
Precoated TLC plates	Merck Pvt.Ltd., Germany.
Aluminium Foil sheet	Hindalco industries Ltd.

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Table 5 : Equipment used

Equipment	Model/Company
UV-visible spectrophotometer	JASCO V-530 & SHIMADZU 1700.
FT-IR Spectrophotometer	JASCO FT-IR 410.
Digital Balance	SHIMADZU type-BL 220H.
Balance	Dhona-200D and XP-3000.
Camera	Gel Dock.
Powder X-ray DIffractometer	Anchor.
DSC	Meffler – Toledo.
SEM	Hitachi S-450
Dissolution apparatus	Electrolab TDT- 08L.
Vaccum pump	Gelman Sciences.
Magnetic Stirrer	Remi Stirrer Equipment.
pH tester-1	Eutech & Oakton.
Hydraulic pellet press	Type-WT.
Temperature controller	Electrolab-ETC-11L.
Printer	Wipro-LQ1050+DX.
TLC viewer	CAMAG.

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2. PREPARATION AND EVALUATION OF GLIMEPIRIDE SOLID DISPERSION

Solid dispersion technology can be used to improve the *in vitro* and *in vivo* dissolution properties of poorly water soluble drugs. Glimepiride is poorly soluble in water. The dissolution rate from solid dispersion was affected by the carrier concentration. HPMC and peg-4000 were used as carriers in the preparation of glimepiride solid dispersion.

2.1. procedure for preparation of glimepiride solid dispersion by fusion method

Polymer has been taken in china disc and kept in a mantle a constant temperature programming for melting. After reaching melting point than add the drug with continuous stirring with a glass rod. After taking it out from the mantle,kept immediate for cooling in a ice bath, after cooling take it out and kept in dessicator with high vaccum more than 350Hg.

2.2. Procedure for preparation of glimepiride solid dispersion by solvent evaporation method

In solvent evaporation method solvent [methanol] is used and four different drug: carrier ratios were used(1;1, 1;2, 1;3, 1;4)to prepare solid dispersion of glimepiride.

The resulting mixture was stirred for 1h and evaporated at a temperature of 55° until dry. The dried mass was pulverized and sieved through the mesh no. 100

2.3. Procedure for preparation of glimepiride physical mixture

Drug : carrier ratio of 1:1 was used to prepare physical mixture(500mg of drug and 500 mg of carrier). The drug and the carrier were mixed thoroughly in a

mortar. This was done by geometric dilution technique to ensure homogeneous distribution.

Table 6 : Drug:carrier content ratios and respective amount taken

S. No	*Drug : carrier ratio*	*Drug content (mg)*	*Carrier content (mg)*
1	1;1	500	500
2	1;2	333	666
3	1;3	250	750
4	1;4	200	800

3. CHARACTERIZATION OF GLIMEPIRIDE SOLID DISPERSION

3.1. IR spectral analysis

Fourier transform infrared (FTIR) spectra of the samples were obtained in the range of 2000 to 400 cm^{-1} using a Jasco – FT-IR 410 PC spectrophotometer (Jasco,), by the KBr disc method. The IR spectra has been observed in the wave rance of 900, 1032, 1159, 1528, 1650 and 1690. The IR spectra has been given in the following fig 5 to 13 .

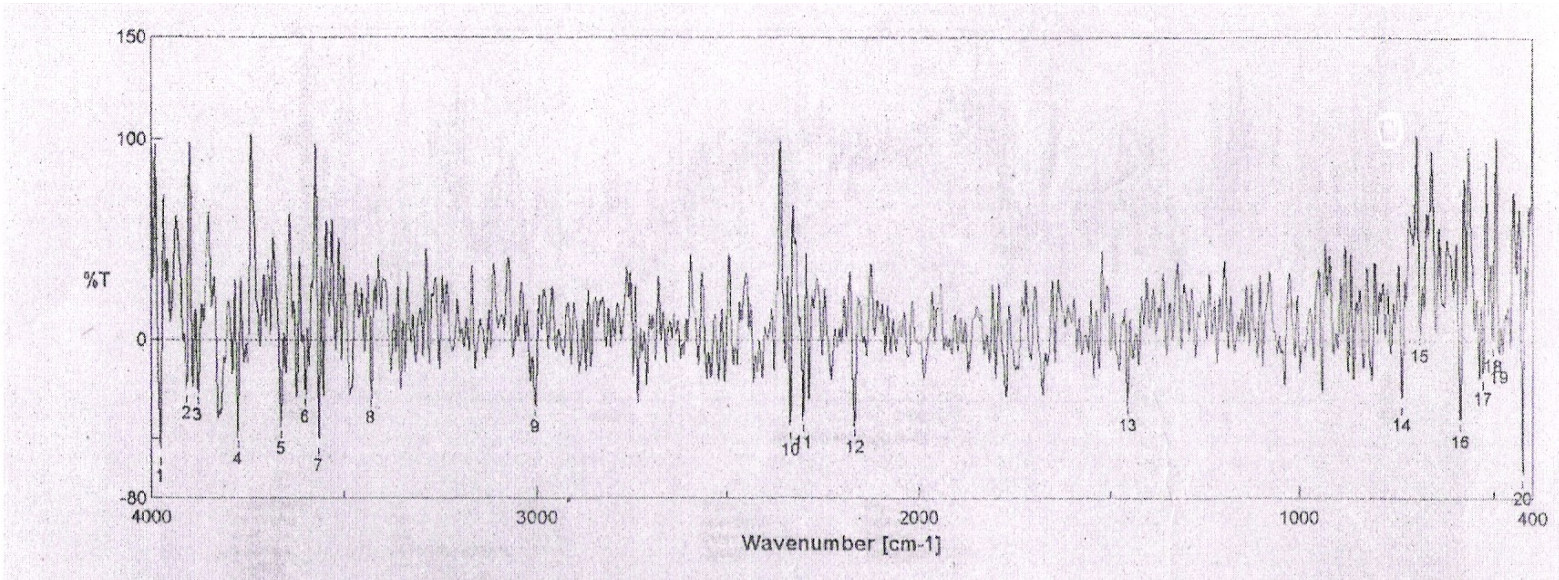
3.2. Powdered x-ray diffraction studies

The powdered X-ray diffraction patterns where recorded using Anchor diffractometer, with Cu as anode material, operated at a voltage of 30kv and a current of 15mA. The samples were analysed in the 2 theta angle range of 5°-50° and the process parameters were set as follows- sampling width of 0.010°(2θ) at scanning speed of 1°/ min and scan mode set is continuous. The X-ray diffraction spectras are given in fig

3.3. Differential scanning calorimetry

The DSC measurements were performed using Meffler – Toledo DSC 821e DSC module controlled by STARe software (Meffler-Toledo GmbH, Switzerland). All accurately weighed samples (1 mg of glipizide or its equivalents) were placed in sealed aluminium pans, before heating under dry nitrogen flow (20 ml/min) at a scanning rate of 10°C min^{-1}, over the temperature range of 25°C – 300°C. An empty aluminium pan was used as reference. The thermograms are showing below fig

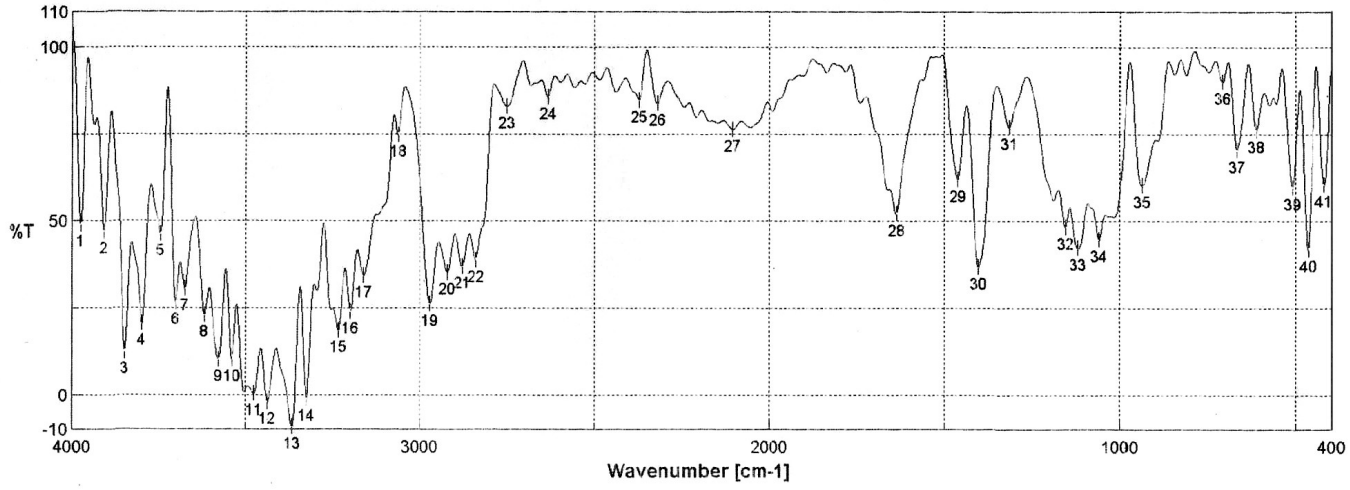
Fig. 5 : I R Spectra of PEG^{4000}



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	512	Scanning Speed	2 mm/sec
Date/Time	11/11/2006 0:03PM	Update	12/19/2006 11:01AM
Operator	govindarajan		
File Name	PEG 4000		
Sample Name	PEG 4000		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3975.53	-59.462	2	3909.97	-27.792	3	3880.08	-28.5449	4	3779.8	-50.6482	5	3666.98	-45.3821
6	3601.41	-29.5233	7	3565.74	-53.9122	8	3428.81	-29.6571	9	3004.55	-34.603	10	2333.44	-46.3586
11	2299.7	-42.4789	12	2167.6	-44.7832	13	1453.1	-33.4758	14	740.531	-33.1065	15	693.284	1.81256
16	587.218	-41.5633	17	528.4	-19.8078	18	501.401	-3.56598	19	485.974	-5.01649	20	426.191	-70.0283

Fig. 6 : I R Spectra of HPMC



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	32	Scanning Speed	2 mm/sec
Date/Time	12/6/2007 11:13AM	Update	1/4/2008 4:07PM
Operator	C.Geetha		
File Name	HPMC		
Sample Name	HPMC		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3975.53	48.907	2	3909	47.0846	3	3847.29	12.3759	4	3796.19	20.5036	5	3741.23	46.3179
6	3697.84	26.6374	7	3670.84	30.5854	8	3614.91	22.9883	9	3576.34	10.1902	10	3538.74	10.1349
11	3476.06	0.349384	12	3437.49	-2.05621	13	3365.17	-9.02671	14	3322.75	-1.21273	15	3231.15	18.5893
16	3196.43	24.0174	17	3159.79	34.2767	18	3063.37	74.701	19	2970.8	26.1814	20	2920.66	35.2191
21	2877.27	36.9449	22	2837.74	38.8857	23	2748.07	82.9002	24	2634.29	85.6128	25	2370.09	84.8049
26	2318.02	83.7781	27	2106.85	76.3214	28	1639.2	52.0126	29	1459.85	61.8941	30	1399.1	36.8657
31	1316.18	76.918	32	1157.08	48.3419	33	1120.44	42.3123	34	1058.73	44.7361	35	938.199	60.3458
36	709.676	89.9677	37	667.25	70.389	38	612.288	76.1028	39	508.151	59.6487	40	464.761	41.8312
41	421.37	60.6075												

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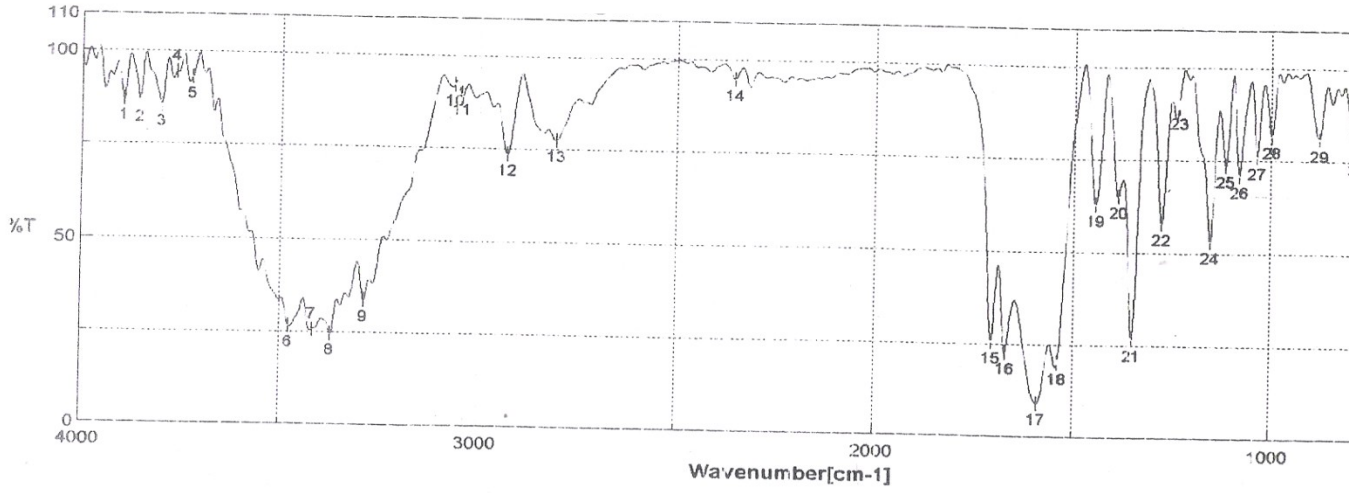
Fig. 7 : I R Spectra of Glimepiride



Accumulation	40
Zero Filling	ON
Gain	8
Date/Time	10/29/2008 0:58PM
Operator	C.Geetha
File Name	Pure drug
Sample Name	pure drug
Comment	

Resolution	4 cm-1
Apodization	Cosine
Scanning Speed	2 mm/sec
Update	10/30/2008 11:39AM

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1
1	3895.5	86.7258	2	3855.97	86.3361	3	3801.01	85.3281	4	3764.37	94.2762	5	3723.87
6	3475.1	26.6238	7	3417.24	25.7137	8	3369.03	24.5265	9	3285.14	33.7821	10	3065.3
11	3047.94	89.6521	12	2929.34	73.5423	13	2806.88	77.426	14	2353.69	94.7993	15	1704.76
16	1670.05	22.6862	17	1589.06	9.13578	18	1538.92	20.1042	19	1443.46	82.9165	20	1383.68
21	1346.07	26.6577	22	1272.79	57.9439	23	1232.29	89.2995	24	1151.29	53.2212	25	1113.69
26	1078.98	70.7579	27	1034.62	75.7824	28	997.982	81.5845	29	876.488	80.7315	30	778.136
31	686.534	70.3142	32	615.181	31.9302	33	555.398	62.0715	34	520.686	76.5492		

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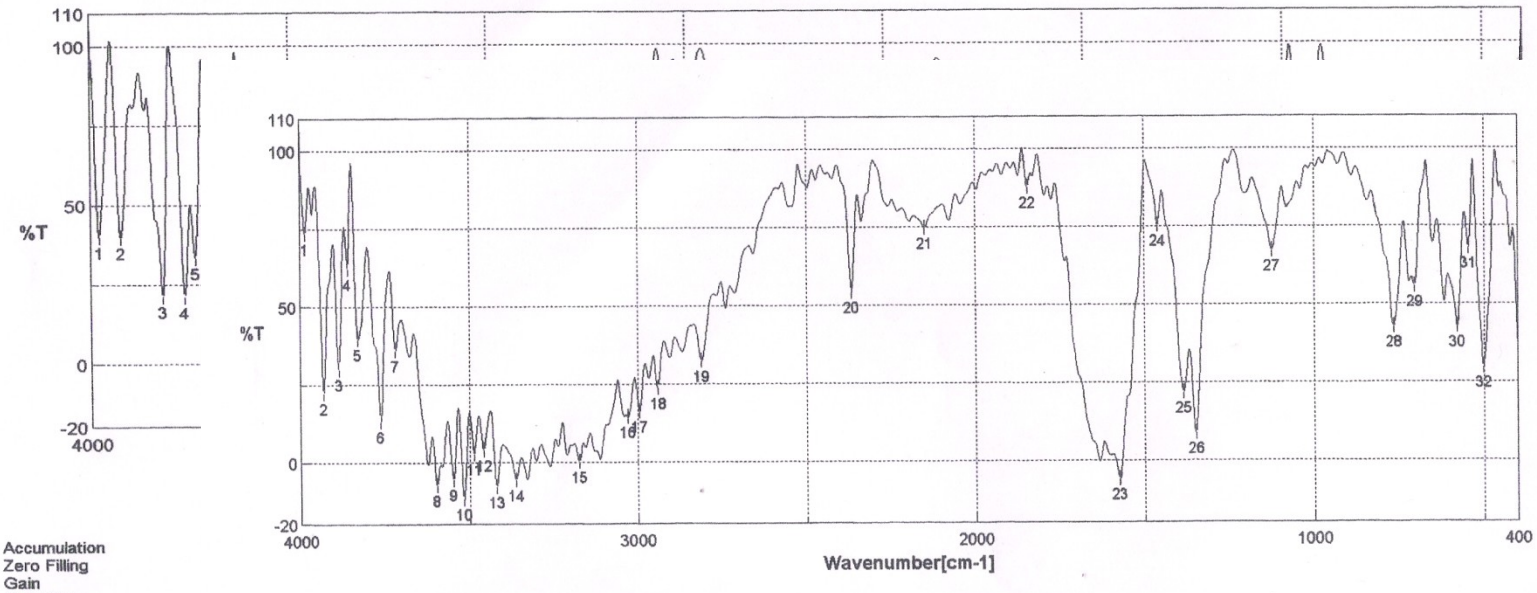
Fig. 8 : I R Spectra of Glimepiride and PEG^{4000} (by solvent evaporation method)

Fig. 9 : I R Spectra of Glimepiride and HPMC (by solvent evaporation method)



Accumulation	
Zero Filling	
Gain	
Date/Time	
Operator	
File Name	
Sample Name	
Comment	

Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	32	Scanning Speed	2 mm/sec
Date/Time	1/20/2009 11:39AM	Update	1/22/2009 10:45AM
Operator	C.Geetha		
File Name	HPMC 1,4(S)		
Sample Name	HPMC 1,4(S)		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3985.18	73.4676	2	3931.18	22.3286	3	3885.86	29.9482	4	3858.86	62.2601	5	3828.97	39.5571
6	3762.44	13.1584	7	3718.08	35.8989	8	3597.56	-7.36309	9	3549.34	-5.23129	10	3517.52	-11.7048
11	3486.67	2.81521	12	3458.71	4.12321	13	3420.14	-7.6415	14	3363.25	-5.55459	15	3175.22	0.24485
16	3028.66	14.6198	17	2995.87	16.2368	18	2941.88	23.7568	19	2811.7	32.2882	20	2367.19	54.2471
21	2149.28	74.7543	22	1844.58	87.6967	23	1575.56	-5.91847	24	1458.89	75.3197	25	1383.68	21.9207
26	1347.03	8.84236	27	1122.37	67.3291	28	764.637	42.7935	29	703.89	55.6274	30	578.54	42.7213
31	545.756	67.8549	32	501.401	29.6946									

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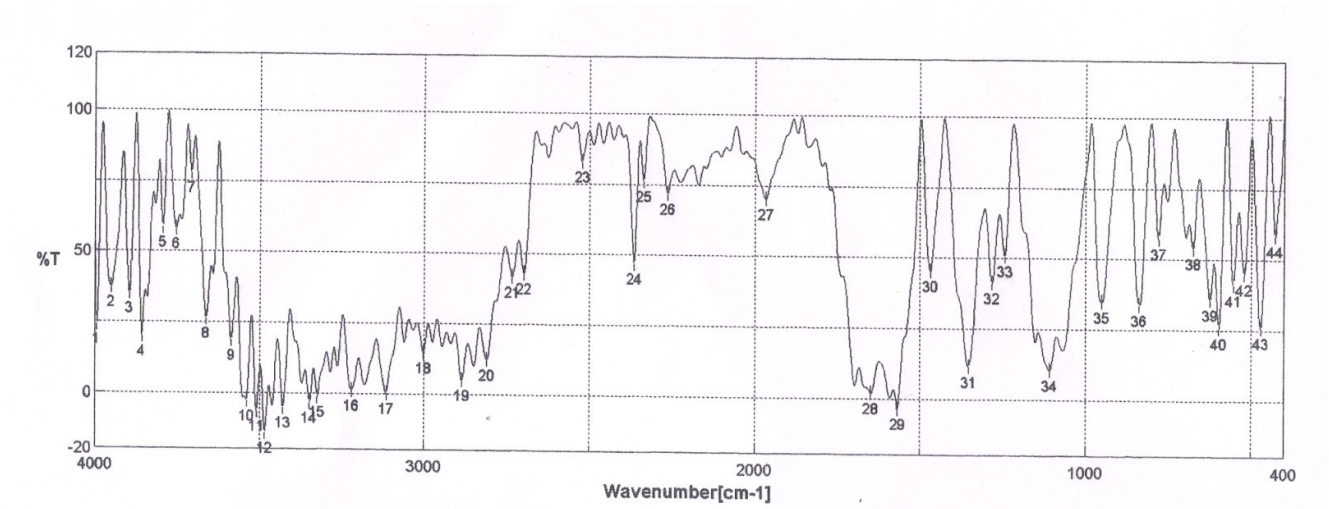
Fig. 10 : I R Spectra of Glimepiride and PEG^{4000} (Fusion method)



Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	32	Scanning Speed	2 mm/sec
Date/Time	1/20/2009 11:35AM	Update	1/22/2009 10:43AM
Operator	C.Geetha		
File Name	PEG 1,4(F)		
Sample Name	PEG 1,4(F)		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3994.82	24.3398	2	3951.43	37.5406	3	3895.5	35.2995	4	3858.86	20.1517	5	3794.26	58.6828
6	3754.73	58.2098	7	3708.44	78.0834	8	3664.09	26.6373	9	3586.95	18.9317	10	3540.67	-2.57747
11	3509.81	-6.34349	12	3484.74	-14.1206	13	3428.81	-4.87563	14	3348.78	-3.10646	15	3324.68	-1.19576
16	3222.47	1.29756	17	3116.4	0.175806	18	3003.59	14.603	19	2887.88	5.0753	20	2811.7	12.3846
21	2734.57	41.9221	22	2699.85	43.0495	23	2523.4	83.0154	24	2366.23	47.1474	25	2337.3	76.3529
26	2263.06	71.9442	27	1968	70.2592	28	1648.84	2.00812	29	1567.84	-3.53845	30	1467.56	45.3978
31	1351.86	11.6644	32	1281.47	41.2418	33	1242.9	50.9239	34	1107.9	10.4459	35	949.77	34.7431
36	836.955	33.9439	37	779.101	57.2875	38	674.963	53.9914	39	623.859	35.8842	40	595.896	25.7901
41	553.47	41.1692	42	520.686	44.9872	43	471.51	26.024	44	428.12	58.6485			

Fig. 11 : I R Spectra of Glimepiride and HPMC (Fusion method)

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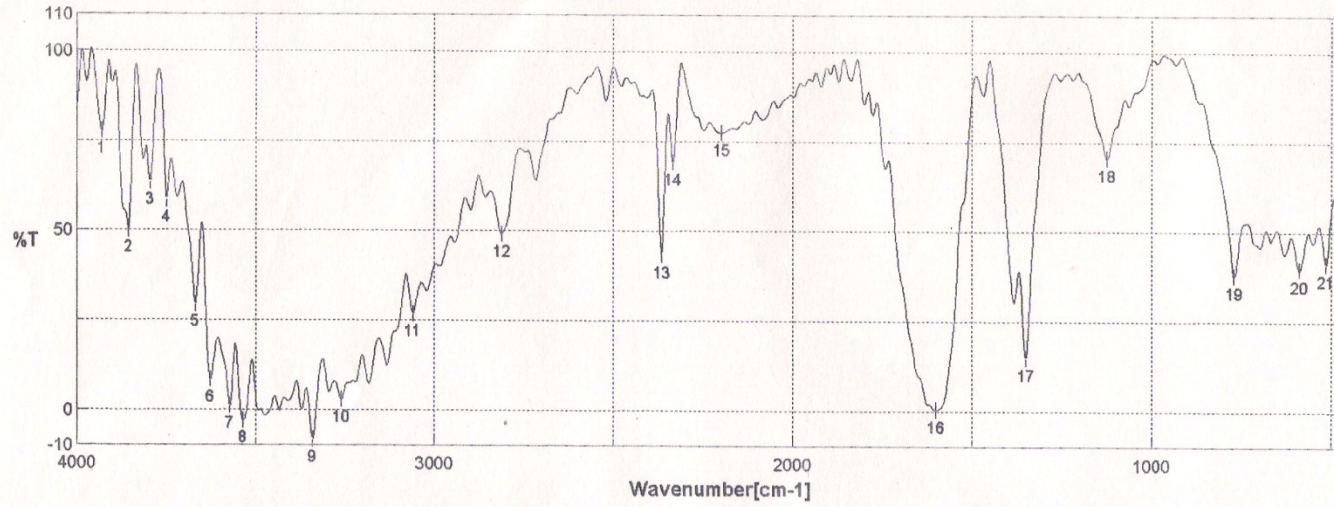

Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	16	Scanning Speed	2 mm/sec
Date/Time	1/20/2009 11:37AM	Update	1/22/2009 10:53AM
Operator	C.Geetha		
File Name	HPMC 1,4(F)		
Sample Name	HPMC 1,4(F)		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3931.18	77.544	2	3856.93	50.0633	3	3794.26	63.3788	4	3747.98	58.4963	5	3667.94	29.4444
6	3626.48	8.42972	7	3572.48	1.1839	8	3534.88	-2.94531	9	3340.1	-8.16941	10	3261.04	2.8246
11	3061.44	26.8851	12	2813.63	49.0412	13	2366.23	43.2558	14	2334.41	69.1164	15	2198.45	77.399
16	1601.59	0.33092	17	1348	14.9449	18	1122.37	70.4522	19	768.494	37.885	20	587.218	39.606
21	513.936	41.2265	22	415.585	87.6937									

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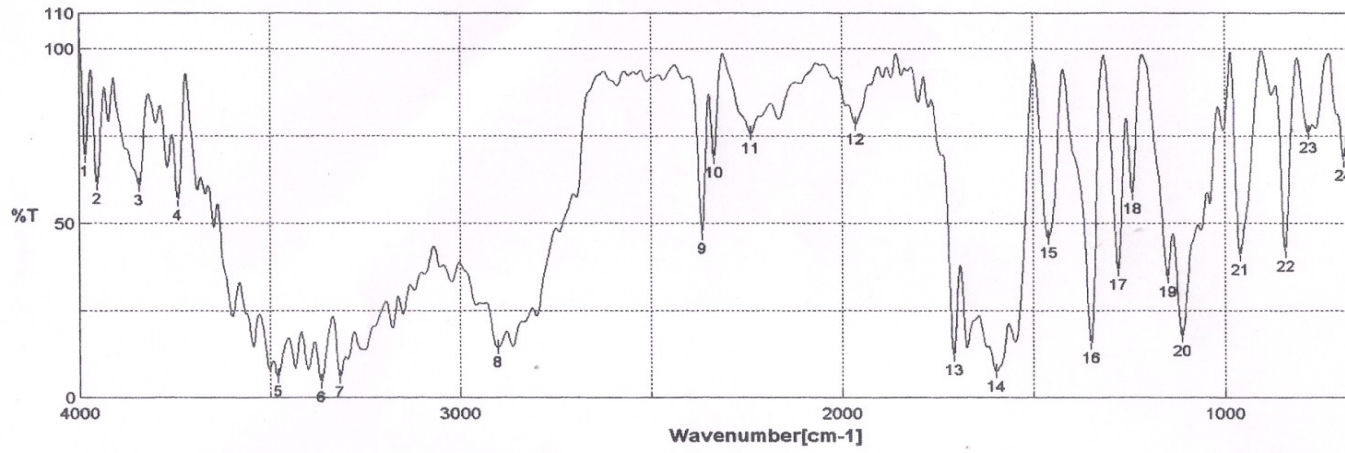
Fig. 12 : I R Spectra of Glimepiride and PEG^{4000} (Physical mixture)



Accumulation	40
Zero Filling	ON
Gain	16
Date/Time	1/20/2009 11:33AM
Operator	C.Geetha
File Name	PEG 1,4(P)
Sample Name	PEG 1:4(P)
Comment	

Resolution	4 cm-1
Apodization	Cosine
Scanning Speed	2 mm/sec
Update	1/22/2009 10:41AM

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1
1	3984.21	69.2534	2	3953.36	61.3238	3	3842.47	61.0912	4	3740.26	56.7149	5	3478.95
6	3365.17	4.75234	7	3316	6.14591	8	2904.27	14.6011	9	2366.23	47.1451	10	2335.37
11	2237.02	75.7774	12	1965.11	78.4476	13	1707.66	12.3949	14	1597.73	7.63477	15	1459.85
16	1348	15.7762	17	1277.61	36.7361	18	1240.97	58.5494	19	1150.33	34.8575	20	1112.73
21	959.412	41.0074	22	840.812	42.1842	23	781.029	76.1313	24	688.463	68.0752	25	617.109
26	464.761	60.2841											

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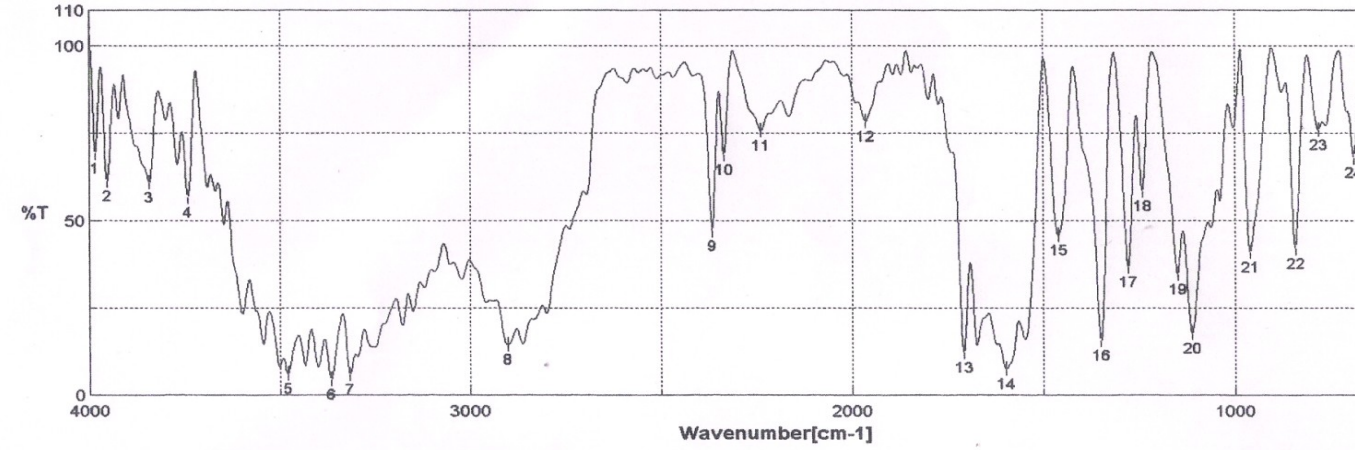
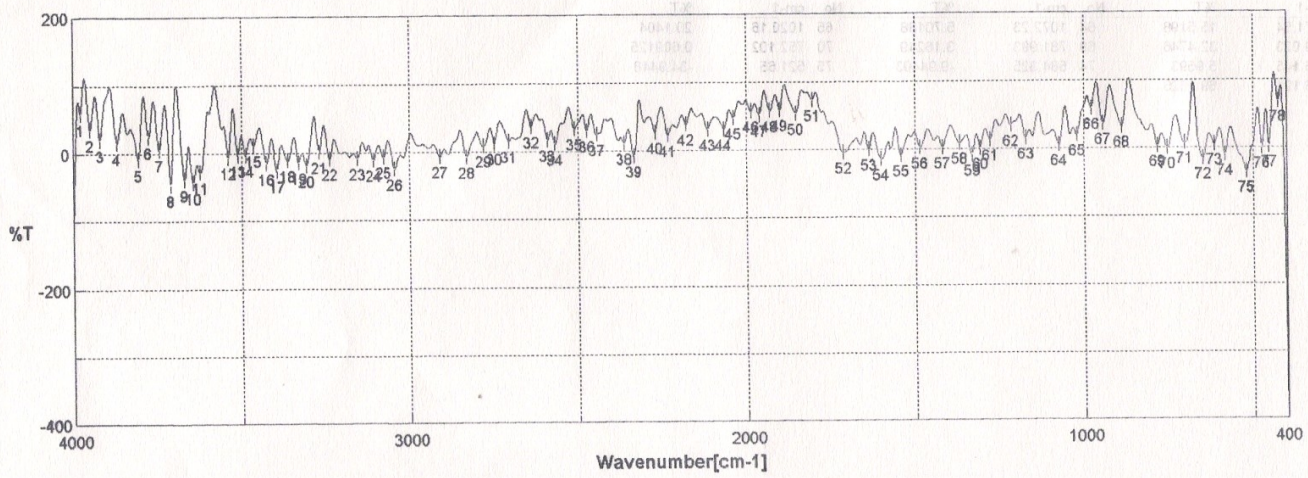


Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	16	Scanning Speed	2 mm/sec
Date/Time	1/20/2009 11:33AM	Update	1/22/2009 10:41AM
Operator	C.Geetha		
File Name	PEG 1,4(P)		
Sample Name	PEG 1:4(P)		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1
1	3984.21	69.2534	2	3953.36	61.3238	3	3842.47	61.0912	4	3740.26	56.7149	5	3478.95
6	3365.17	4.75234	7	3316	6.14591	8	2904.27	14.6011	9	2366.23	47.1451	10	2335.37
11	2237.02	75.7774	12	1965.11	78.4476	13	1707.66	12.3949	14	1597.73	7.63477	15	1459.85
16	1348	15.7762	17	1277.61	36.7361	18	1240.97	58.5494	19	1150.33	34.8575	20	1112.73
21	959.412	41.0074	22	840.812	42.1842	23	781.029	76.1313	24	688.463	68.0752	25	617.109
26	464.761	60.2841											

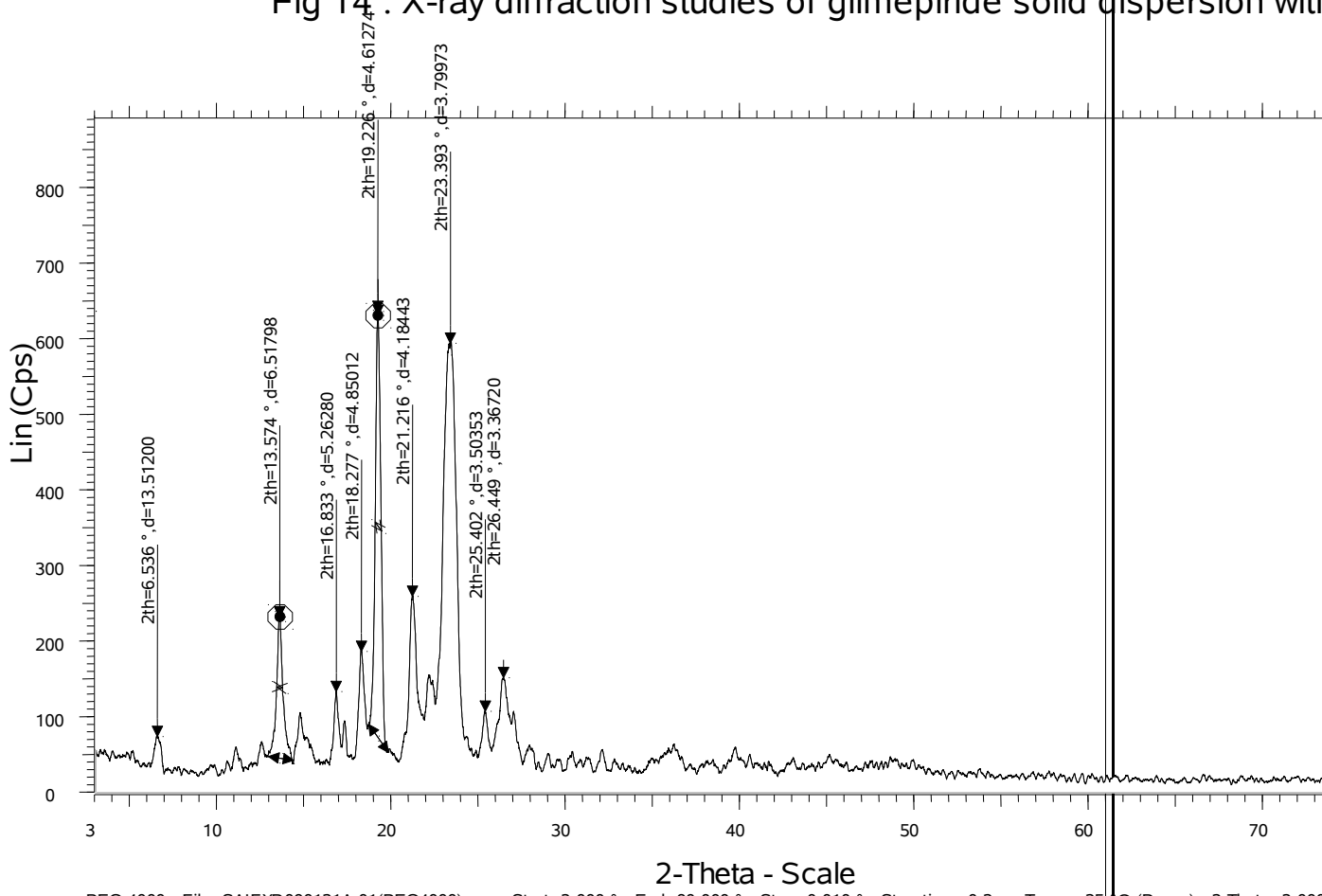
Fig. 13 : I R Spectra of Glimepiride and HPMC (Physical mixture)



Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	256	Scanning Speed	2 mm/sec
Date/Time	1/20/2009 11:41AM	Update	1/22/2009 10:50AM
Operator	C.Geetha		
File Name	HPMC 1,4(P)		
Sample Name	HPMC 1,4(P)		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3978.43	59.0282	2	3950.46	35.8583	3	3920.57	19.9539	4	3870.43	16.1184	5	3807.76	-8.9552
6	3776.9	24.5695	7	3745.08	5.68007	8	3711.33	-46.6624	9	3670.84	-38.6489	10	3644.8	-42.8815
11	3623.59	-27.8743	12	3539.7	-6.06054	13	3511.74	-2.77695	14	3487.63	-2.98586	15	3464.49	11.6446
16	3425.92	-14.8264	17	3396.99	-26.0892	18	3364.21	-10.9104	19	3331.43	-13.7467	20	3309.25	-18.102
21	3270.68	1.60017	22	3240.79	-9.02416	23	3155.94	-8.07553	24	3107.72	-10.373	25	3078.8	-5.83322
26	3044.09	-24.2592	27	2911.99	-6.8136	28	2830.99	-6.96718	29	2781.81	8.93128	30	2747.1	12.3113
31	2704.67	15.8138	32	2639.11	37.077	33	2590.9	17.1826	34	2568.72	11.3468	35	2511.83	33.6126
36	2474.22	30.2959	37	2446.26	24.824	38	2363.34	11.7855	39	2335.37	-7.61277	40	2270.77	27.2151
41	2232.2	22.5573	42	2178.2	38.6851	43	2115.53	31.7732	44	2067.32	31.6605	45	2039.35	48.0972
46	1986.32	57.9912	47	1962.22	51.8192	48	1929.43	58.3418	49	1900.5	58.768	50	1852.29	54.0753
51	1804.08	73.974	52	1712.48	-4.47193	53	1637.27	-0.167414	54	1600.63	-13.6469	55	1541.81	-8.98747
56	1484.92	2.76827	57	1418.39	2.95793	58	1369.21	8.69869	59	1331.61	-8.91614	60	1306.54	1.90333

Fig 14 : X-ray diffraction studies of glimepiride solid dispersion with



PEG 4000 - File: SAIFXR090121A-01(PEG4000).raw - Start: 3.000 ° - End: 80.000 ° - Step: 0.010 ° - Step time: 0.2 s - Temp.: 25 °C (Room) - 2-Theta: 3.000

1) PEG 4000 - Left Angle: 12.920 ° - Right Angle: 14.380 ° - FWHM: 0.331 ° - Net Area: 80.94 Cps x deg.

2) PEG 4000 - Left Angle: 18.710 ° - Right Angle: 19.830 ° - FWHM: 0.355 ° - Net Area: 211.0 Cps x deg.

Operations: Smooth 0.150 | Import

Fig 15 : X-ray diffraction studies of glimepiride solid dispersion with H

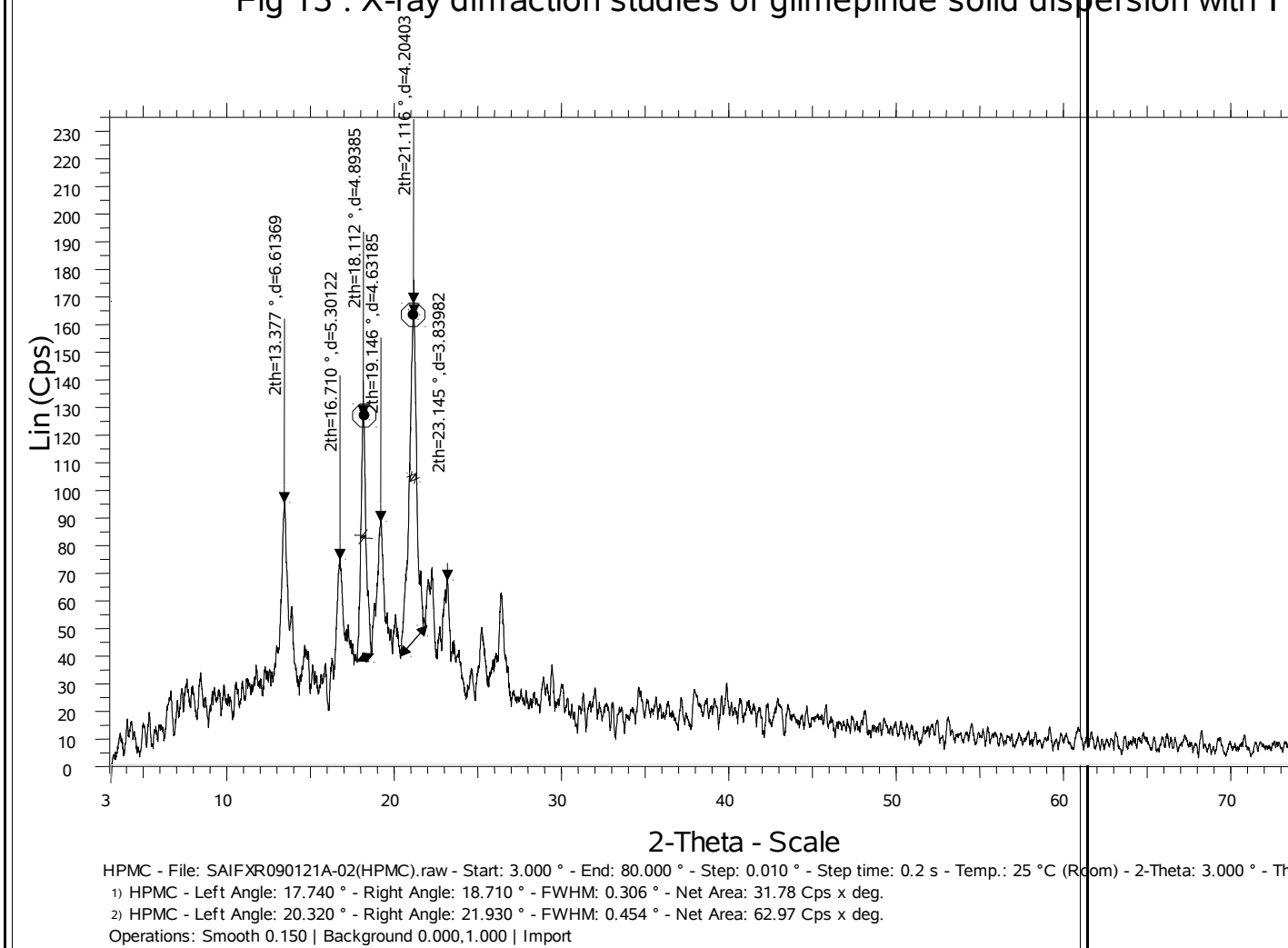


Fig 16 : X-ray diffraction studies of glimepiride

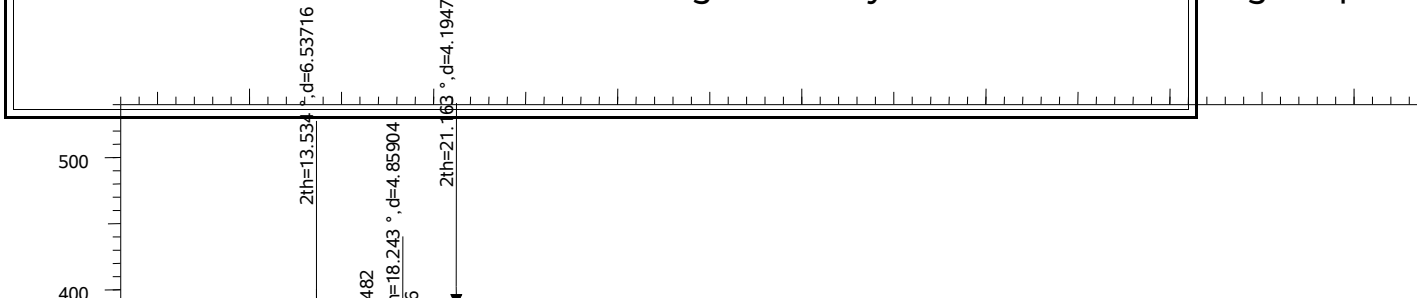
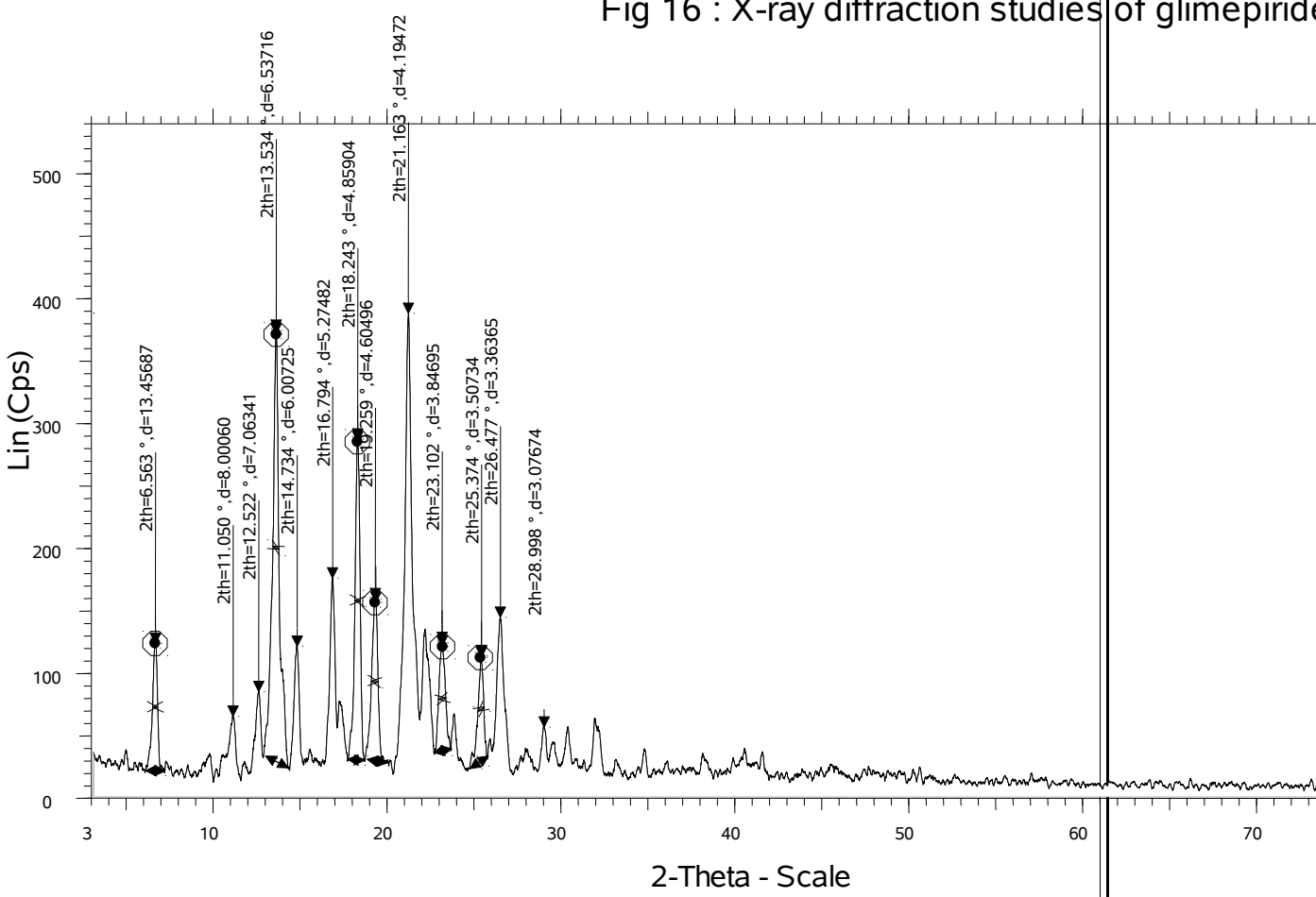


Fig 16 : X-ray diffraction studies of glimepiride



GLIMEPIRIDE - File: SAIFXR090121A-03(Glimepiride).raw - Start: 3.000 ° - End: 80.000 ° - Step: 0.010 ° - Step time: 0.2 s - Temp.: 25 °C (Room) - 2-Theta:

1) GLIMEPIRIDE - Left Angle: 12.920 ° - Right Angle: 14.240 ° - FWHM: 0.333 ° - Net Area: 154.8 Cps x deg.
2) GLIMEPIRIDE - Left Angle: 17.670 ° - Right Angle: 18.640 ° - FWHM: 0.310 ° - Net Area: 87.35 Cps x deg.
3) GLIMEPIRIDE - Left Angle: 24.720 ° - Right Angle: 25.770 ° - FWHM: 0.341 ° - Net Area: 31.88 Cps x deg.
4) GLIMEPIRIDE - Left Angle: 18.780 ° - Right Angle: 19.970 ° - FWHM: 0.396 ° - Net Area: 54.07 Cps x deg.
5) GLIMEPIRIDE - Left Angle: 6.000 ° - Right Angle: 7.120 ° - FWHM: 0.291 ° - Net Area: 35.05 Cps x deg.
6) GLIMEPIRIDE - Left Angle: 22.620 ° - Right Angle: 23.670 ° - FWHM: 0.425 ° - Net Area: 36.74 Cps x deg.

Operations: Smooth 0.150 | Import

Fig 17 : DSC Studies of PEG^{4000}

Fig 18 : DSC Studies of HPMC

Fig 19 : DSC Studies of Glimepiride

4. EVALUATION OF SOLID DISPERSION

4.1. Drug content uniformity

The glimepiride solid dispersions, which were prepared and tested for drug, content uniformity. From each batch of solid dispersions (prepared in different ratios) equivalent to 10 mg of glimepiride were taken and analyzed for drug content uniformity.

4.2. Estimation of solid dispersion by uv spectrophotometry

Accurately weighed amount of solid dispersion were dissolved in 0.2M, pH 7.4 buffer solution in 10 ml of volumetric flask which was previously cleaned and dry. This solution after suitable dilution was measured at 236 nm in a JASCO V-530 UV/Vis spectrophotometer. The results are shown in Table No.

Table 7 : Drug Content Uniformity

Solid Dispersion	Drug : Carrier	Amount of SD taken (mg)	Expected Amount of drug in SD (mg)	% of Glimepiride (by solvent evaporation) estimated by UV spectrophotometer	% of Glimepiride (by fusion) estimated by UV spectrophotometer
Glimepiride – PEG^{4000}	1 : 1	10	5	98.4	97.21
	1 : 2	10	3.3	99.8	96.21
	1 : 3	10	2.5	97.2	96.12
	1 : 4	10	2	99.2	92.21
Glimepiride - HPMC	1 : 1	10	5	99.4	98.91
	1 : 2	10	3.3	98.21	99.81
	1 : 3	10	2.5	97.21	94.28
	1 : 4	10	2	99	94.21

DISSOLUTION RATE STUDIES OF DIFFERENT SOLID DISPERSIONS OF GLIMEPIRIDEDE

The dissolution studies are most important part of the evaluation of solid dispersions, where the dissolution of pure drug and solid dispersions were carried out, by using dissolution apparatus, which is shown in figure

Dissolution rate studies of various solid dispersions were carried out in 0.2M, pH 7.4 phosphate buffer using USP XXIV dissolution rate apparatus (Electro Lab).

Dissolution method

900 ml. of 0.2 M, pH 7.4 phosphate buffer was used as dissolution medium. SD equivalent to 40 mg of Glimepiride was taken in a hard gelatin capsule. The paddle type stirrer was adjusted to 70 rpm and the temperature was maintained at 37°±5°C. 5 ml aliquot dissolution media was withdrawn at different time intervals and volume withdrawn was replaced with fresh quantity of dissolution media.

The samples were analyzed for Glimepiride after suitable dilution by measuring absorbance at 236nm using Jasco V-530, UV/Vis. spectrophotometer. 0.2M, pH 7.4 phosphate buffer was used as blank solution. The dissolution experiment work was conducted in triplicate. The percentage of Glimepiride dissolved at various time intervals was calculated and plotted against time.

Table 8 : Dissolution of glimepiride solid dispersion (solvent evaporation) by PEG 4000 at different drug : carrier ratios

MEDIUM : 0.2M Phosphate Buffer pH 7.4

TEMPERATURE : 37ºC±5ºC

RPM : 70

Time (Min)	Percentage Glimepiride dissolved					
	Pure Drug (4 mg)	Physical Mixture (1:1)	1:1	1:2	1:3	1:4
0	0	0	0	0	0	0
5	1.36	1.9	3.2	5.2	3.0	2.4
10	2.03	2.8	5.1	7.5	4.3	4.0
15	4.54	6.1	10.1	15.1	12.3	11.1
30	5.87	9.4	27.9	28.3	26.1	25.2
45	7.13	10.8	38.7	40.5	30.6	30.3
60	10.81	12.3	50.3	52.4	42.7	39.1
90	16.19	18.9	57.3	63.7	50.4	48.2
120	19.99	27.3	65.4	76.57	61.2	58.7

Fig. No 20

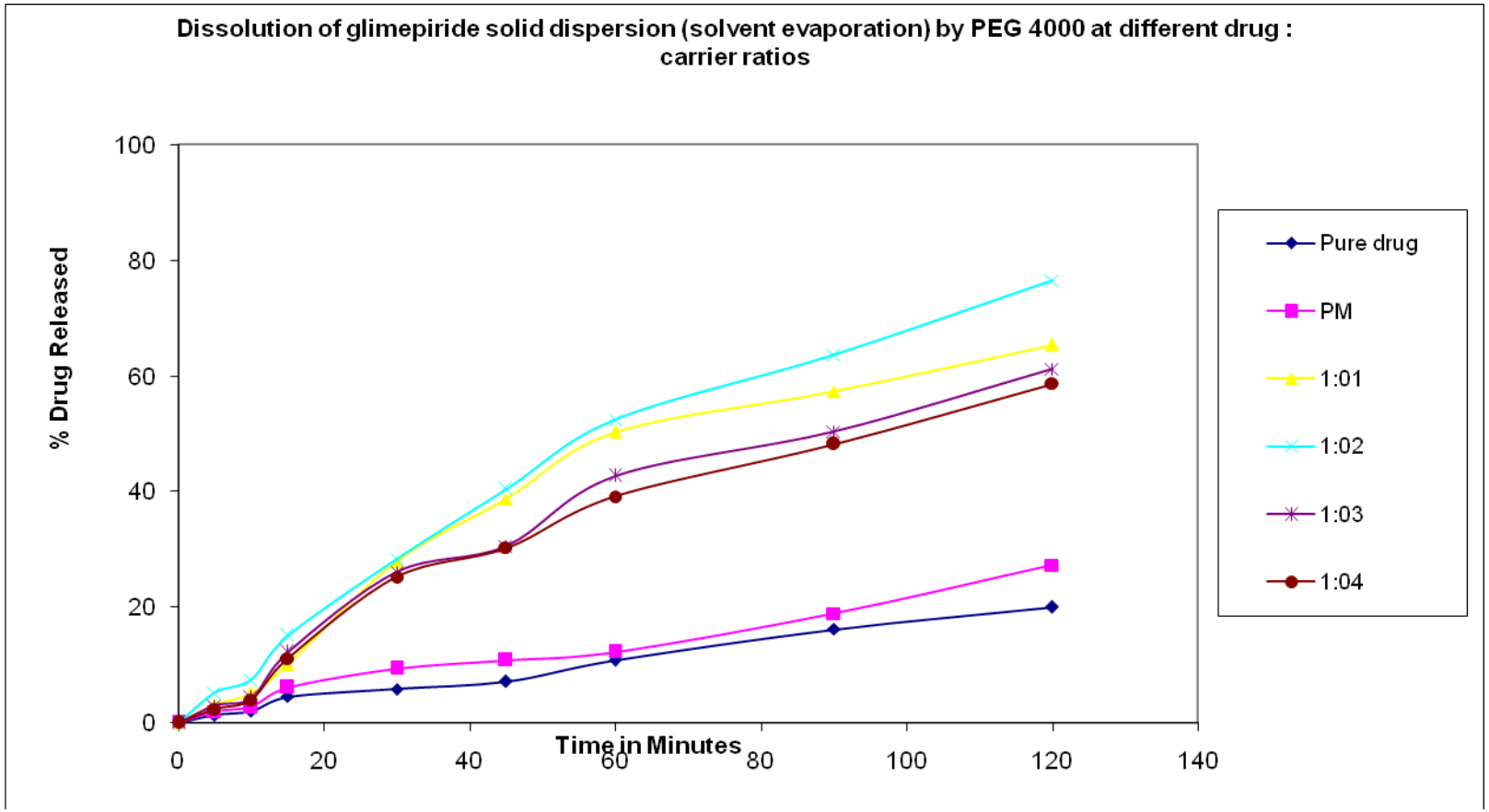

Dissolution of glimepiride solid dispersion (solvent evaporation) by PEG 4000 at different drug : carrier ratios
% Drug Released
Time in Minutes
0
20
40
60
80
100
120
140
Pure drug
PM
1:01
1:02
1:03
1:04

Table 9 : Dissolution of glimepiride solid dispersion (solvent evaporation) by HPMC at different drug : carrier ratios

MEDIUM : 0.2M Phosphate Buffer pH 7.4

EMPERATURE : 37ºC±5ºC

RPM : 70

Time (Min)	Percentage Glimepiride dissolved					
	Pure Drug (4 mg)	Physical Mixture (1:1)	1:1	1:2	1:3	1:4
0	0	0	0	0	0	0
5	1.36	2.3	2.0	2.1	1.8	1.5
10	2.03	3.8	3.0	3.20	2.7	2.0
15	4.54	5.3	10.1	10.0	9.8	9.0
30	5.87	6.8	19.2	19.4	17.6	15.6
45	7.13	8.6	28.8	30.2	26.4	22.1
60	10.81	10.1	30.4	39.5	38.1	36.4
90	16.19	15.2	46.3	52.4	49.2	40.8
120	19.99	21.0	61.9	69.3	56.2	54.3

Fig. 21

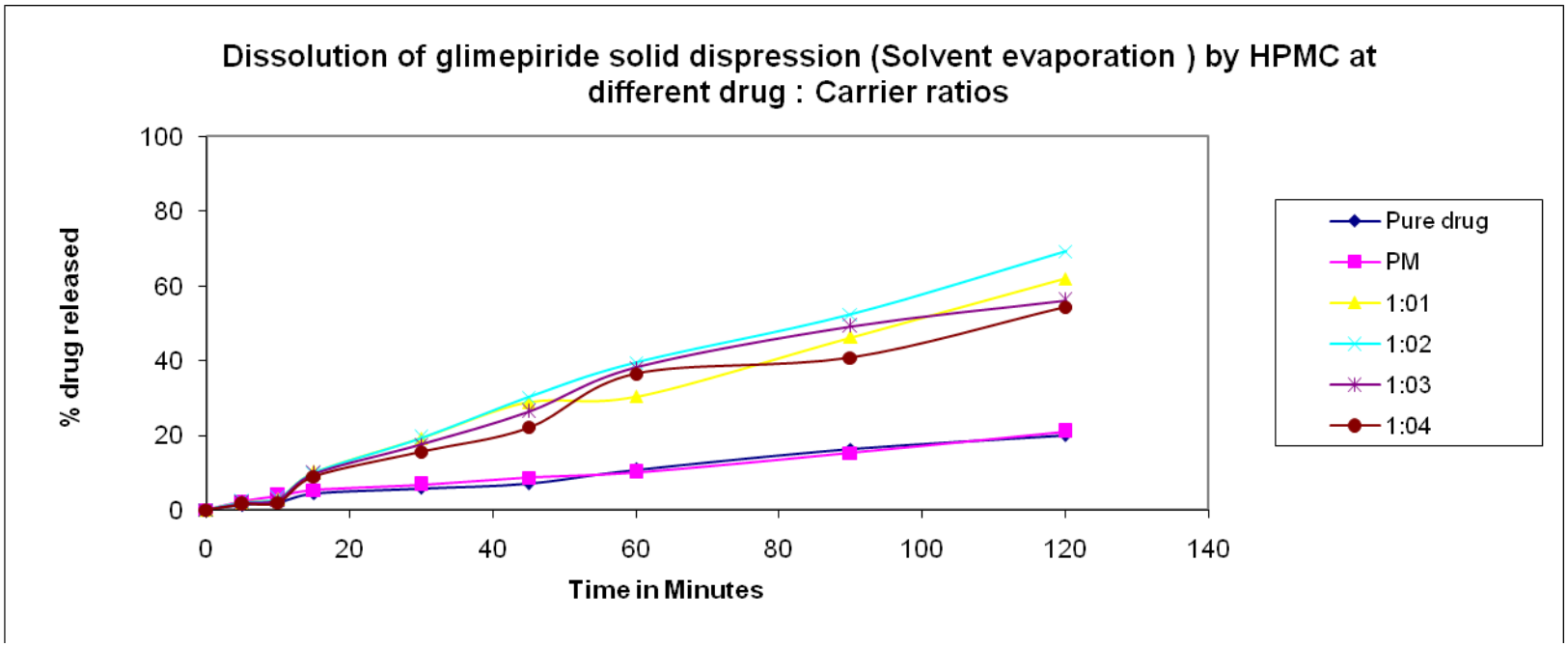

Dissolution of glimepiride solid dispression (Solvent evaporation) by HPMC at different drug : Carrier ratios
% drug released
Time in Minutes
0
20
40
60
80
100
120
140
Pure drug
PM
1:01
1:02
1:03
1:04

Table 10 : Dissolution of glimepiride solid dispersion (Fusion method) by PEG 4000 at different drug : carrier ratios

MEDIUM : 0.2M Phosphate Buffer pH 7.4

EMPERATURE : 37ºC±5ºC

RPM : 70

Time (Min)	Percentage Glimepiride dissolved					
	Pure Drug (4 mg)	Physical Mixture (1:1)	1:1	1:2	1:3	1:4
0	0	0	0	0	0	0
5	1.36	1.9	2.9	3.8	2.0	2.3
10	2.03	2.8	4.0	5.4	3.7	3.2
15	4.54	6.1	9.2	11.0	8.6	7.7
30	5.87	9.4	21.9	23.7	10.7	10.6
45	7.13	10.8	33.3	35.6	28.3	26.4
60	10.81	12.3	41.2	47.8	40.1	30.2
90	16.19	18.9	50.1	55.2	49.5	40.5
120	19.99	27.3	62.6	71.4	58.1	55.4

Fig. : 22

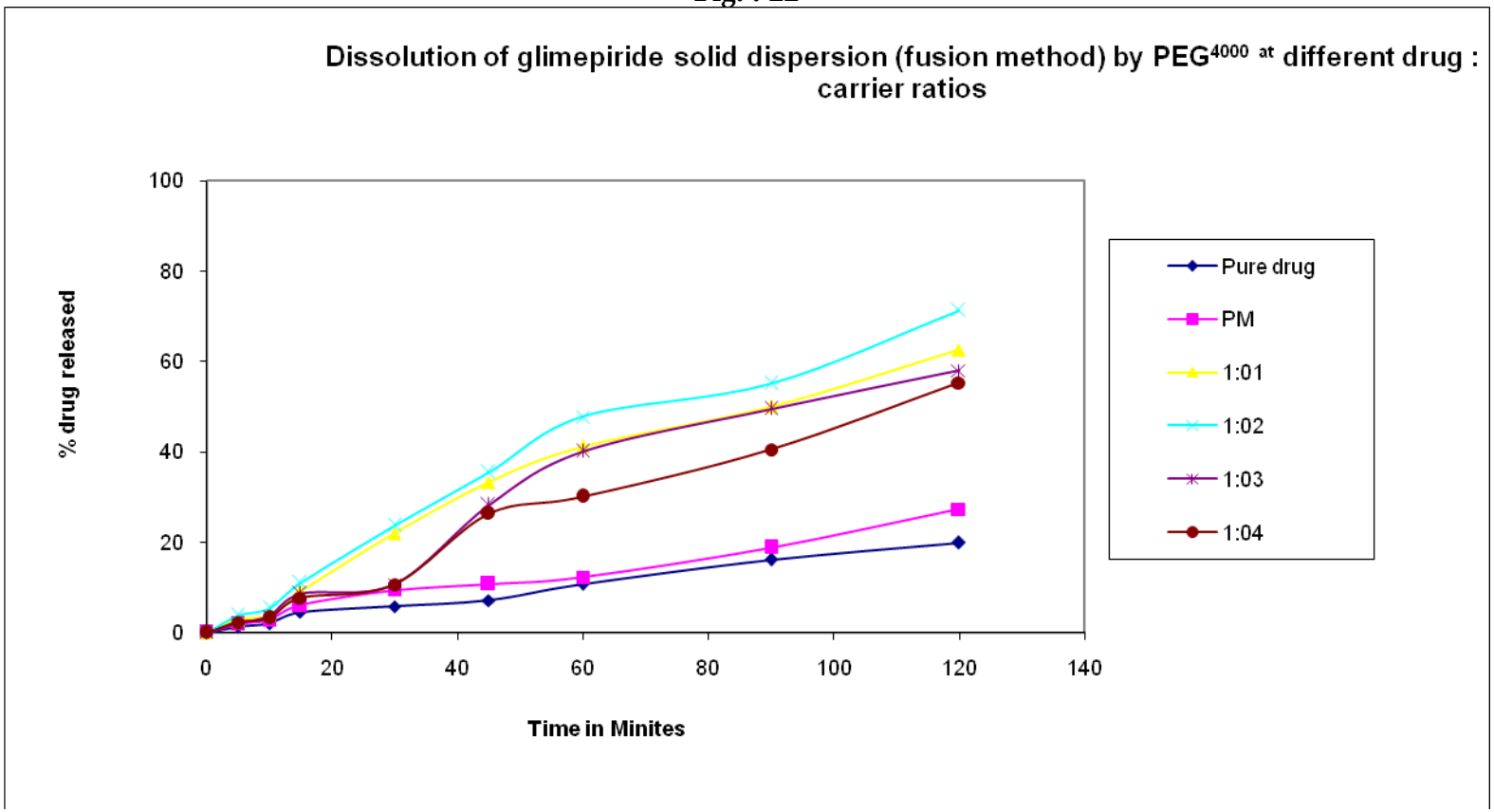

Dissolution of glimepiride solid dispersion (fusion method) by PEG4000 at different drug : carrier ratios
% drug released
Time in Minites
0
20
40
60
80
100
120
140
Pure drug
PM
1:01
1:02
1:03
1:04

Table 11: Dissolution of glimepiride solid dispersion (Fusion method) by HPMC at different drug : carrier ratios

MEDIUM : 0.2M Phosphate Buffer pH 7.4

EMPERATURE : 37ºC±5ºC

RPM : 70

Time (Min)	Percentage Glimepiride dissolved					
	Pure Drug (4 mg)	Physical Mixture (1:1)	1:1	1:2	1:3	1:4
0	0	0	0	0	0	0
5	1.36	2.3	1.7	1.8	1.5	1.3
10	2.03	3.8	2.5	2.9	2.6	2.0
15	4.54	5.3	8.6	9.1	8.8	7.9
30	5.87	6.8	14.3	16.4	14.5	12.4
45	7.13	8.6	21.0	28.7	21.4	19.0
60	10.81	10.1	29.4	37.3	32.7	28.7
90	16.19	15.2	45.0	50.4	46.1	39.6
120	19.99	21.0	57.8	66.1	54.8	52.9

Fig. 23

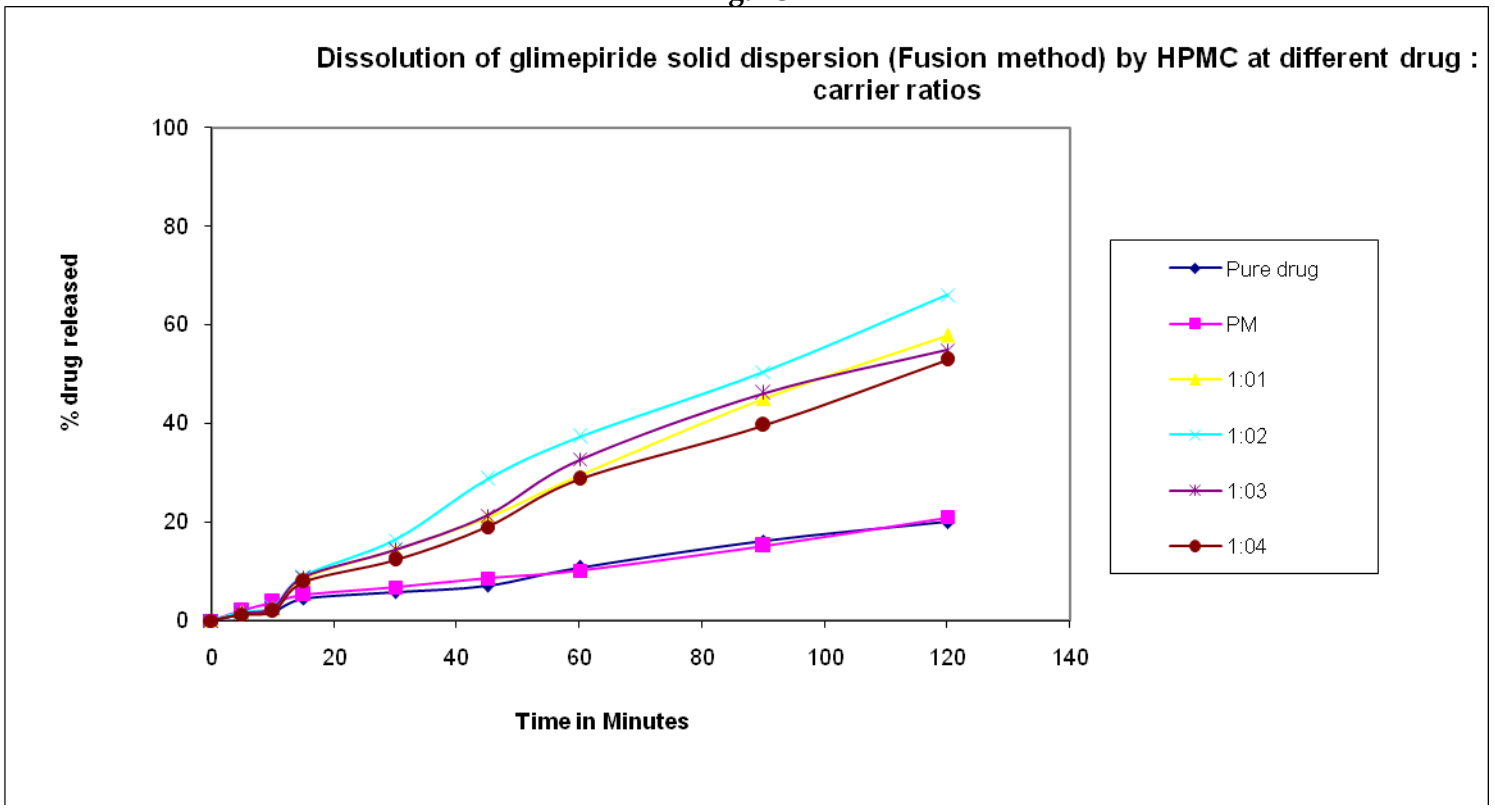

Dissolution of glimepiride solid dispersion (Fusion method) by HPMC at different drug : carrier ratios
% drug released
Time in Minutes
0
20
40
60
80
100
120
140
Pure drug
PM
1:01
1:02
1:03
1:04

Table 12. Dissolution of glimepiride solid dispersion (Physical mixture) with various carriers

Table 13 : DISSOLUTION OF GLIMEPIRIDE IN PURE FORM AND FROM SOLID DISPERSION (SOLVENT EVAPORATION) WITH VARIOUS CARRIERS AT DRUG : CARRIER RATIO OF 1:2

MEDIUM : 0.2M Phosphate Buffer pH 7.4

TEMPERATURE : 37ºC±5ºC

RPM : 70

Time (Min)	Percentage Glimepiride dissolved		
	PURE DRUG (4 MG)	SE (PEG 4000)	SE (HPMC)
0	0	0	0
5	1.36	5.2	2.1
10	2.03	7.5	3.20
15	4.54	15.1	10.0
30	5.87	28.3	19.4
45	7.13	40.5	30.2
60	10.81	52.4	39.5
90	16.19	63.7	52.4
120	19.99	76.57	69.3

Fig. 25

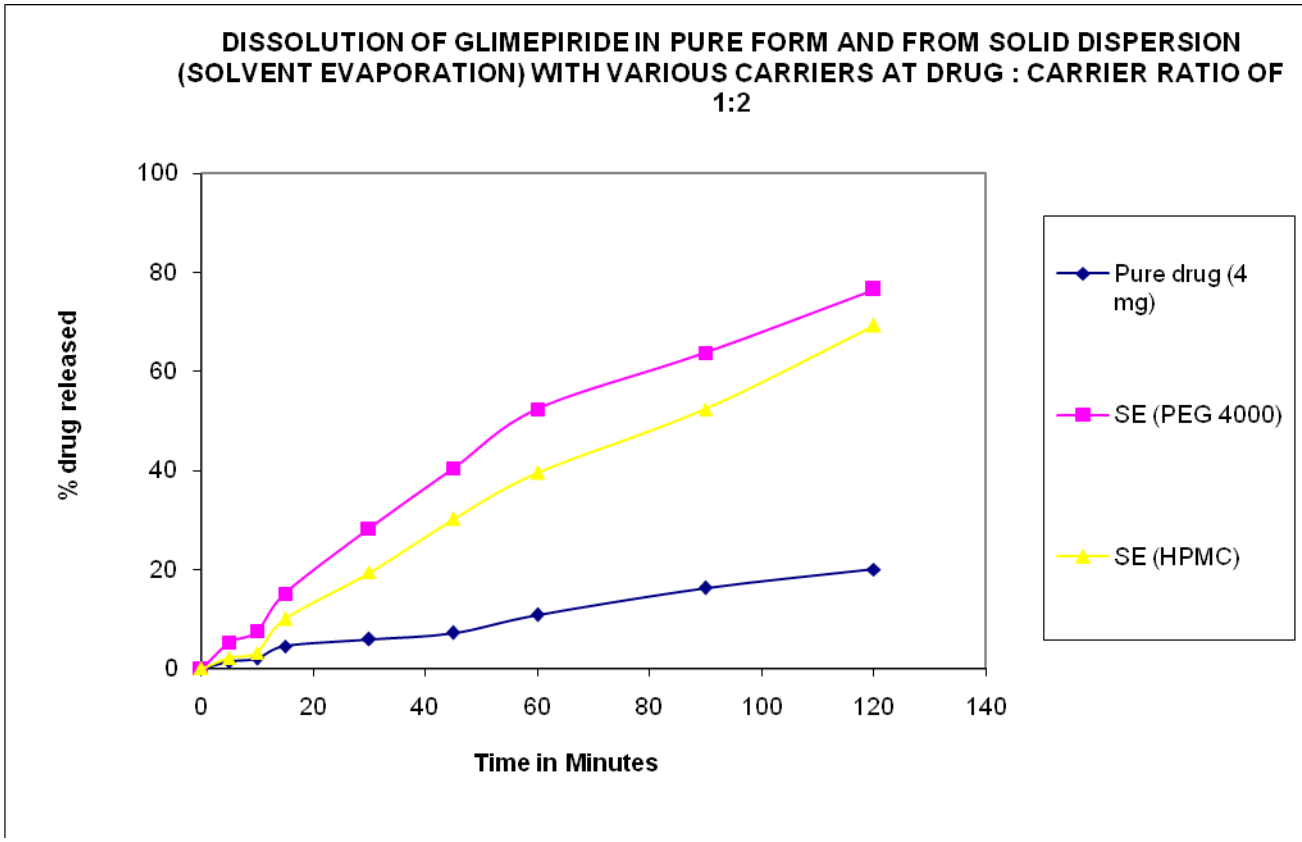

DISSOLUTION OF GLIMEPIRIDE IN PURE FORM AND FROM SOLID DISPERSION (SOLVENT EVAPORATION) WITH VARIOUS CARRIERS AT DRUG : CARRIER RATIO OF 1:2
% drug released
Time in Minutes
0
20
40
60
80
100
120
140
Pure drug (4 mg)
SE (PEG 4000)
SE (HPMC)

Table 14. DISSOLUTION OF GLIMEPIRIDE IN PURE FORM AND FROM SOLID DISPERSION (FUSION METHOD) WITH VARIOUS CARRIERS AT DRUG : CARRIER RATIO OF 1:2

MEDIUM : 0.2M Phosphate Buffer pH 7.4

TEMPERATURE : 37ºC±5ºC

RPM : 70

Time (Min)	Percentage Glimepiride dissolved		
	PURE DRUG (4 MG)	**SE (PEG 4000)**	**SE (HPMC)**
0	0	0	0
5	1.36	3.8	1.8
10	2.03	5.4	2.9
15	4.54	11.0	9.1
30	5.87	23.7	16.4
45	7.13	35.6	28.7
60	10.81	47.8	37.3
90	16.19	55.2	50.4
120	19.99	71.4	66.1

Fig. 26

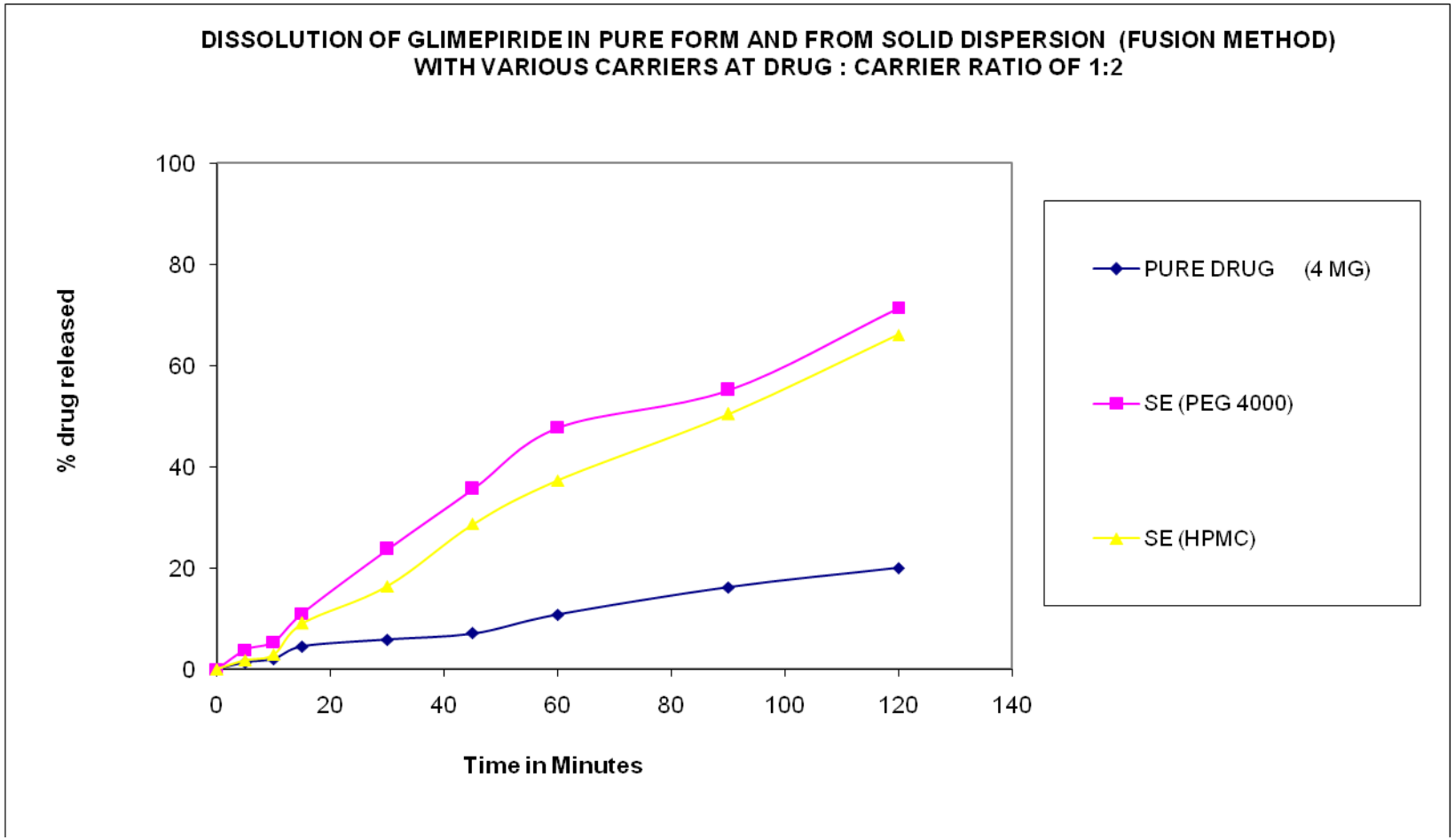

DISSOLUTION OF GLIMEPIRIDE IN PURE FORM AND FROM SOLID DISPERSION (FUSION METHOD) WITH VARIOUS CARRIERS AT DRUG : CARRIER RATIO OF 1:2
% drug released
100
80
60
40
20
0
0
20
40
60
80
100
120
140
Time in Minutes
PURE DRUG (4 MG)
SE (PEG 4000)
SE (HPMC)

Table 15.

DISSOLUTION OF GLIMEPIRIIDE IN PURE FORM ,PHYSICAL MIXTURE AND SOLVENT EVAPORATION WITH PEG 4000 AT DRUG : CARRIER RATIO OF 1:2

Time (min)	Percentage Glmepiride dissolved		
	Pure drug (4mg)	PHYSICAL MIXTURE (1:1)	SE PEG 4000 (1:2)
0	0	0	0
5	1.36	1.9	5.2
10	2.03	2.8	7.5
15	4.54	6.1	15.1
30	5.87	9.4	28.3
45	7.13	10.8	40.5
60	10.81	12.3	52.4
90	16.19	18.9	63.7
120	19.99	27.3	76.57

Fig. 27

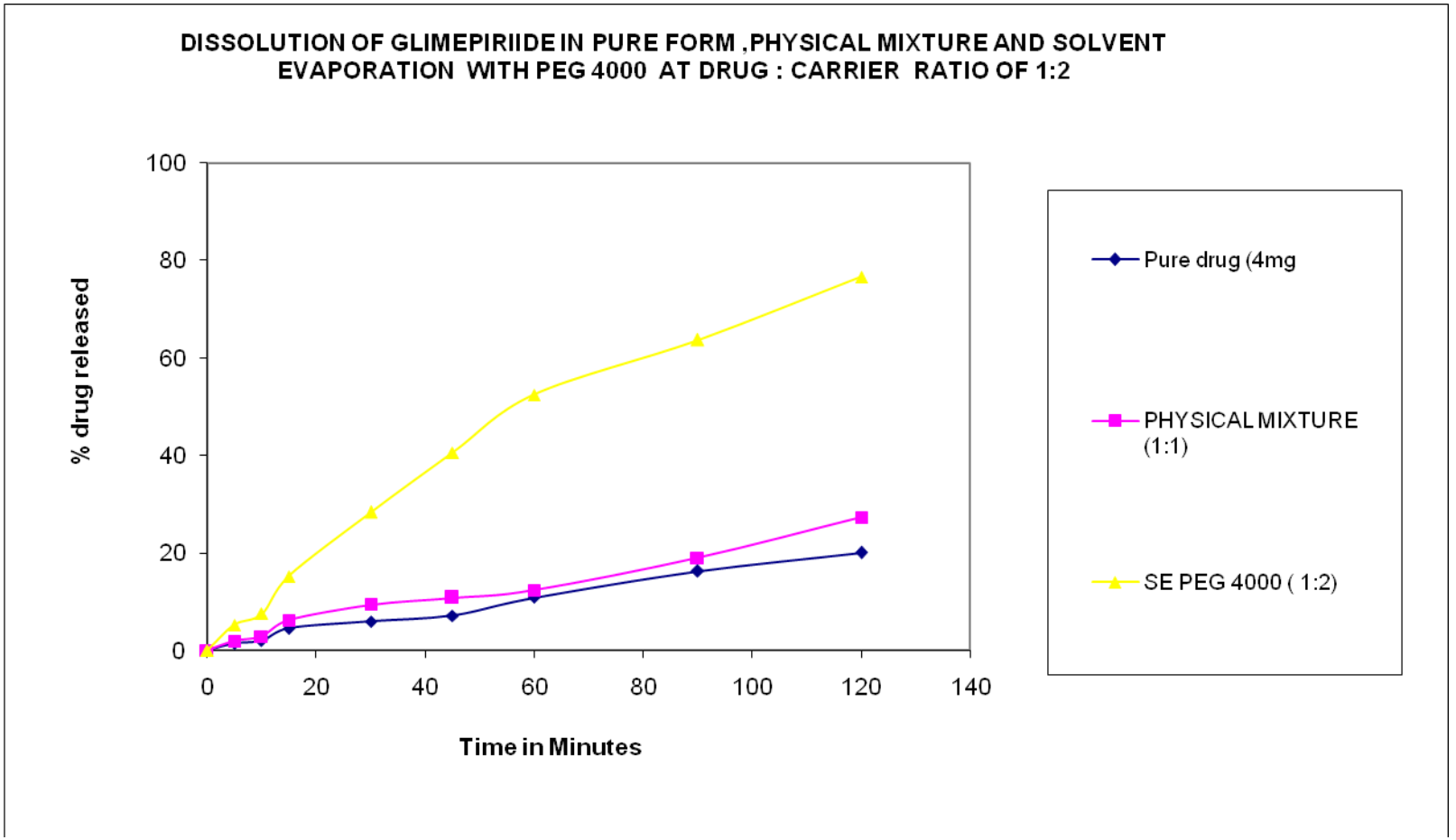

DISSOLUTION OF GLIMEPIRIIDE IN PURE FORM ,PHYSICAL MIXTURE AND SOLVENT EVAPORATION WITH PEG 4000 AT DRUG : CARRIER RATIO OF 1:2
% drug released
100
80
60
40
20
0
0
20
40
60
80
100
120
140
Time in Minutes
Pure drug (4mg
PHYSICAL MIXTURE (1:1)
SE PEG 4000 (1:2)

Table 16 : Log percentage glimepiride un dissolved from pure form and from PEG 4000 solid dispersions (solvent evaporation method) of 1:2 ratio.

S.No	Time (mins)	Percentage Glimepiride undissolved from solid dispersions (Log percentage Glimepiride undissolved)		
		Pure drug	Physical mixture	(SE)PEG 4000
1	0	0	0	0
2	5	98.64 (1.994)	98.10 (1.991)	94.8 (1.976)
3	10	97.97 (1.991)	97.22 (1.987)	92.5 (1.966)
4	15	95.46 (1.979)	93.91 (1.972)	84.90 (1.928)
5	30	94.13 (1.973)	90.63 (1.957)	71.70 (1.855)
6	45	92.87 (1.967)	89.22 (1.950)	59.5 (1.774)
7	60	89.19 (1.950)	87.72 (1.942)	47.60 (1.677)
8	90	83.81 (1.923)	81.12 (1.909)	36.3 (1.559)
9	120	80.01 (1.903)	72.77 (1.861)	23.43 (1.369)

Fig. 28

Log percentage glimepiride un dissolved from pure form and from PEG 4000 solid dispersions (solvent evaporation method) of 1:2 ratio.

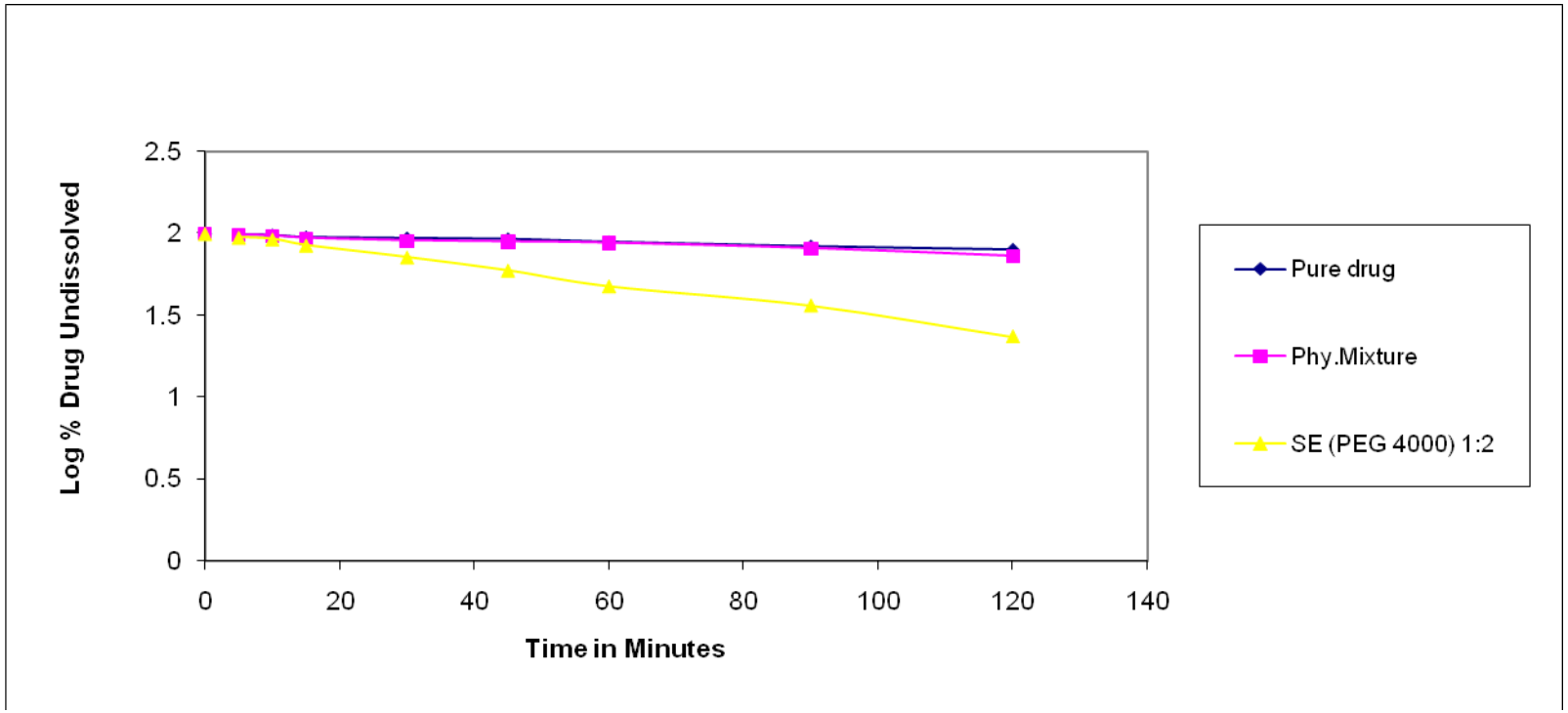

Log % Drug Undissolved
2.5
2
1.5
1
0.5
0
0
20
40
60
80
100
120
140
Time in Minutes
Pure drug
Phy.Mixture
SE (PEG 4000) 1:2

Table 17: First order rate constant for glimepiride.
By Solvent evaporation method

Solid Dispersion	***K (min^{-1})***
PURE DRUG	0.0010
PHYSICAL MIXTURE	0.0012
GLIIMEPIRIDE : PEG 4000 (SE) 1 : 2	0.0050

CHAPTER - 7

RESULTS AND DISCUSSION

Glimepiride is an effective anti diabetic which is practically insoluble in water, hence, dissolution is rate limiting. The present aim of this study is to develop a fast release formulation of glimepiride by solid dispersion technology using different carrier, such as PEG^{4000} and HPMC.

- **PREPRATION OF SOLIDDISPERSION**

The solid dispersion of glimepiride were prepared by different techniques such as fusion method, solvent evaporation method and physical mixture method. The method of preparation for all the three method were all ready mentioned in material and method. In all methods the various drug and carrier ratios 1:1, 1:2, 1:3, and 1:4 had been used. The resultant produce were characterized by X-ray, DSC, in vitro dissolution studies.

- **COMPATIBILITY STUDIES**

FTIR Spectroscopy

Fourier transform infrared (FTIR) spectra of the samples were obtained in the range of 2000 to 400cm^{-1} using JASCO FTIR 410 Pc Spectrophotometer by using KBr disc method. The IR spectra of the solid dispersion and pure samples are given in the fig – to fig-from the IR spectra this study found that there were no incompatibility between drug and carrier such as PEG^{4000} and HPMC .

- **CHARACTERIZATION**

Powder X-ray diffraction

The fig 16 showed a numerous distinctive peaks indicating a high crystallinity of pure drug of glimepiride. A solid dispersion containing glimepiride with HPMC (fig 15) showed reduction intensive peaks. The X-ray of solid dispersion with PEG ^{4000} (fig 14) showed very less distinctive peaks. That indicates confirmation of changing the nature of the compound from crystalline to amorphous nature. From this X-ray studies it conclude that PEG^{4000} is a best carriers for increasing solubility of poorly soluble glimepiride.

- **DIFFERENTIAL SCANNING CALORIMETRY**

The DSC of pure drug, polymer and all solid dispersion formulations were performed using Meffler – Teledo DSC 831e (Meffler - TeldoGmbh, Switzerland). From the DSC thermogram of glimepiride solid dispersion containing drug and PEG^{4000} the metting was found to be and 215^{0}C which is different from the pure drug(Metting point of glimepiride (207^{0} C)) from the DSC thermo gram of glimepiride solid dispersion with HPMC (1:2) which is prepared by solvent evaporation method was found to be 200^{0}C which shows that the crystalline nature of compound getting changed. From the DSC studies of solid dispersions conclude that there was a

change in nature of the compound. The DSC spectras are given in Fig 17,18 & 19.

- **INVITRO ANALYSIS:**

The *invitro* dispersion studies of pure drug and all solid dispersion formulation with different ratios 1:1, 1:2, 1:3, and 1:4 by using two different carriers such as PEG ^{4000} and HPMC. The prepared solid dispersions of glimepiride equivalent to 4mg of pure drug was filled in hard gelation capsule and dissolution studies were carried out in dissolution apparatus electro lab TDT – 08L containing 900ml of PH 7.4 in at 37± 5^0c with rpm 70. The samples were taken at different interval of time. Omin, 5min, 10min, 15min, 30min, 45min, 60min, 90min and 120min. also absorbance were recorded at 236nm. From this *in vitrostudies* the solid dispersion containing drug and PEG^{4000} (1:2) released maximum 76.57% W/V (Solvent evaporation method). The solid dispersion containing drug and HPMC (1:2) showed 69.3% (w/v) (solvent evaporation method). From this *invitro* studies it conclude that the solid dispersion containing glimepiride and PEG^{4000} (1:2) (Solvent evaporation method) showed high release. The studies proved that one of the fast releasing dosage form for poorly water soluble glimepiride by using solid dispersion technology.

CHAPTER - 8

SUMMARY AND CONCLUSION

Studies were under taken on the preparation and evaluation of solid dispersion of glimepiride with a view to develop fast release formulation of glimepiride. In the prepration of solid dispersion carries such as PEG ^{4000} and HPMC were used. In this present study solid dispersions were prepared by solvent evaporation and fusion methods.

The solid dispersions prepared were Interaction to be fine and free flowing powders. Interaction studies like IR spectra were shown and there was no interaction between drug and carriers used. All the solid dispersions prepared were found to be uniform in drug content.

X-ray diffraction studies revealed that crystalline nature of glimepiride in pure form was reduced in the solid dispersions. This might be the reason for improved dissolution, it was also indicates the amorphous character of the solid dispersions, DSC thermo gram showed no interaction between drug and polymer and confirmed the amorphous nature of the solid dispersions.

Pure drug Good correlation was observed between percentage carries in the dispersions. The dissolution of glimepiride from all dispersions followed first order kinetics. Among the carriers used PEG^{4000}

gave the fastest dissolution rate and the order of dissolution of glimepiride from the various solid dispersions. Glimepiride solid dispersions in PEG^{4000} prepared at drug: carrier ratio of 1:2 was formulated in to capsule and evaluated for dissolution characteristics. The dissolution of glimepiride capsule solid dispersions were found to be fast and rapid when compared to the pure drug formulation.

The solid dispersion containing drug: PEG^{4000} (1:2) considered as a fast release dosage form of glimepiride when compared to pure drug and ration of glimepiride solid dispersions.

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