



DESIGNED DEVELOPMENT AND EVALUATION OF GLIPIZIDE MICROEMULSION

**1.PIYUSH KUMAR SINHA, 2.DR. HIMANI TIWARI 3. TANYA SHARMA, 4, MD
ZULPHAKAR ALI.**

**1. Student of M pharma (Pharmaceutics) 2nd year department of pharmaceutical science,
Mewar University, Gangrar , Chittorgarh, Rajasthan 312901.**

**2. Supervisor, HOD , Department of pharmaceutical science, Mewar University Gangrar,
Chittorgarh, Rajasthan 312901.**

**3.Co-supervisor, Assistant professor and guide Department of pharmaceutical science, Mewar
University, Gangrar, Chittorgarh, Rajasthan 312901.**

ABSTRACT:-

Glipizide is a 'second generation' sulfonylurea, an oral hypoglycemic agent for the management of non-insulin dependent diabetes mellitus.

Oral delivery of glipizide shows bioavailability problems and causes hypoglycemia with gastric disturbances.

To overcome these problems, controlled release formulations as sustained release and controlled release tablets are available. Solubility of glipizide increases with increase in pH. Like any other sulfonylurea, glipizide appears to act principally by stimulating the insulin secretion from pancreatic beta-cells. Glipizide overdose symptoms include low blood sugar.

AIM:

Objective to develop more soluble and high bioavailability that's why I have done microemulsion.

INTRODUCTION:-

1.1 GLIPIZIDE:-

Glipizide is one of the most commonly prescribed drugs for treatment of type II diabetes, It comes as an oral immediate-release tablet and oral extended- release tablet.

Glipizide oral tablet is available as the brand-name drugs Glucotrol and Glucotrol XL. It's also available as a generic drug. Generic drugs usually cost less. In some cases, they may not be available in every strength or form as the brand.

it is an anti-diabetic medication of the sulfonylurea class used to treat type 2 diabetes. It is not indicated for use by itself in type 1 diabetes. It is taken by mouth and Effects generally begin within half an hour and can last for up to a day.

It may also be used with other diabetes medications. Controlling high blood sugar helps prevent kidney damage, blindness, nerve problems, loss of limbs, and sexual function problems. Proper control of diabetes may also lessen your risk of a heart attack or stroke. It lowers blood sugar by causing the release of your body's natural insulin.

it is closely related to other sulfonylureas of the same therapeutic class such as glibenclamide, blood insulin and glucose time courses differ. It also carries much lower risk of hypoglycemia

It was first introduced in 1984 and is available in various countries including Canada and the U.S According to the 2018 Clinical Practice Guidelines by Diabetes Canada, sulfonylurea drugs are considered a second-line glucose- lowering therapy following metformin Because sulfonylureas require functional pancreatic beta cells for their therapeutic effectiveness, sulfonylureas are more commonly used for early-stage type 2 diabetes when there is no progressed pancreatic failure.

Compared to the first-generation sulfonylureas, such as tolbutamide and chlorpropamide, second-generation sulfonylureas contain a more non-polar side chain in their chemical structure, which enhances their hypoglycemic potency. Compared to other members of the sulfonylurea drug group, glipizide displays rapid absorption and onset of action with the shortest half-life and duration of action, reducing

the risk for long-lasting hypoglycemia that is often observed with blood glucose-lowering agents.¹ Glipizide was first approved by the FDA in 1994 and is available in extended-release tablets under the brand name Glucotrol, as well as in combination with metformin under the brand name Metagli.

DIABETES:-

Diabetes mellitus is a chronic metabolic disorder characterized by high blood glucose concentrations (hyperglycemia) caused by insulin deficiency and it is often combined with insulin resistance.

Non Insulin Dependent Diabetes Mellitus (NIDDM) represents a heterogeneous group comprising milder form of diabetes that occur predominately in adults and a vast majority of diabetic patients possess NIDDM⁴. The analytical parameters of glipizide which will prove beneficial to researchers are shown in Table 2.

Glipizide has been in extensive use to treat NIDDM and acts by increasing the release of endogenous insulin as well as its peripheral effectiveness; but it has been associated with severe and sometimes fatal hypoglycemia and gastric disturbances like nausea, vomiting, heartburn, anorexia and increased appetite after oral therapy in normal doses.

2. REVIEW OF LITERATURE:-

Adel M.Aly et al, reported a cyclodextrin inclusion complex to enhance the dissolution rate and bioavailability of Glipizide. The α -CD was more effective than the β -CD in enhancing the dissolution rate of GZ, and the addition of NaCMC enhanced the dissolution rate of the GZ- β -CD complex more than PVP or PEG6000.

18 Mona Semalty, A Semalty, G Kumar reported mucoadhesive buccal films of Glipizide by solvent casting technique using hydroxypropylmethylcellulose, sodium carboxymethylcellulose, carbopol934P and Eudragit RL-100.¹⁹

Mark R. Burge et al, reported solid dispersions to increase the solubility of Glipizide in osmotically controlled oral drug delivery system with polyvinylpyrrolidone (PVP) in aqueous media. The Glipizide-PVP solid dispersion systems was prepared by physical mixing or spray drying method, and characterized by DSC, XRD, FT-IR and SEM. The obtained results indicated that Glipizide-PVP solid dispersion system has suitable solubility behaviour in Elementary osmotic pump tablets.

Jayvadan K. Patel et al, formulated and systematically evaluated the in vitro and in vivo performance of mucoadhesive microspheres of Glipizide. In vivo testing with albino wistar rats demonstrated significant hypoglycaemic effect of Glipizide.

Hagalvadi Nanjappa Shivakumar et al, reported a 32 factorial design to produce Glipizide lipospheres by the emulsification phase separation technique using paraffin wax and stearic acid as retardants. Results indicate that the optimized liposphere formulation developed was found to produce sustained anti-diabetic activity following oral administration in rats.

Rajan K. Verma, Sanjay Garg, developed extended release formulations of Glipizide, with techniques of thermal and isothermal stress testing (IST) used to assess the compatibility of Glipizide with selected excipients.

Srinivas Mutalik et al, reported Glipizide matrix transdermal systems using the combinations of ethyl cellulose/polyvinylpyrrolidone and Eudragit RL-100/Eudragit RS-100. Results indicated that the transdermal route exhibited negligible skin irritation and produced better improvement compared to oral administration.

Seema Thakral and A. K. Madan, reported Urea co-inclusion compounds of Glipizide for the improvement of dissolution profile. Formation of Glipizide co-inclusion compounds was confirmed by FTIR, DSC and XRD.

Garcia and E. S. Ghaly, reported delivery of Glipizide from spheres and compacts containing the natural polymer Carrageenan and prepared by extruder marumerizer technique.

Jun-Li Fenga, Zheng-WuWanga, have investigated phase diagrams of some five component systems containing poloxyl 35{EL-35} non-ionic surfactant and vitamin E, Moreover, extensive studies on the relationship between the structure of the microemulsion and the reactivity of vitamin E have been performed.

Zhong-Gao Gao, reported a microemulsion to improve the solubility and to enhance the bioavailability of poorly water-soluble cyclosporine A in addition the effects of composition on the physicochemical characteristics of each microemulsion systems were investigated for the optimization of microemulsion system.

Ljiljana Djordjevic, Marija Primorac, Mirjana Stupar, reported diclofenac diethylamine (DDA) microemulsion to determine the influence of both formulation parameters and vehicle structure on in vitro release rate. Results suggest that the obtained flux values suggested that bicontinuous microstructure hampers the release of the amphiphilic drug.

3. AIM AND OBJECTIVE:

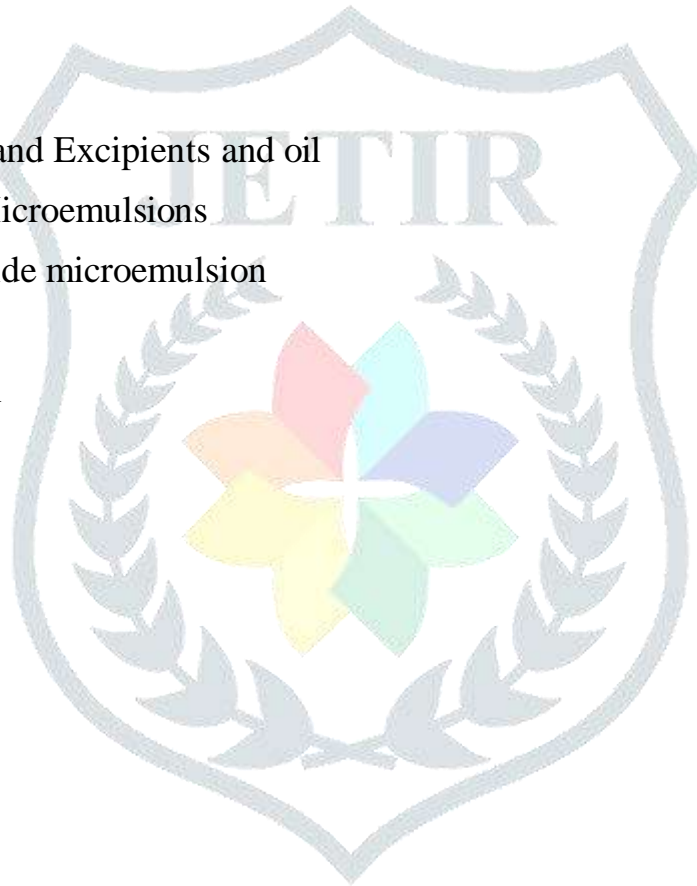
The aim of the present study is to development the formulation and evaluation a microemulsion of oral delivery of glipizide.

Glipizide is a poor water soluble & having the BCS class-II means low soluble and high permeability.

Objective to develop more soluble and high bioavailability that's why I have done microemulsion.

4. PLAN OF WORK: -

- Title selection
- Literature Review
- Procurement of drug and Excipients and oil
- Characterization of Microemulsions
- Formulation of glipizide microemulsion
- Evaluation
- Result and Discussion
- Conclusion

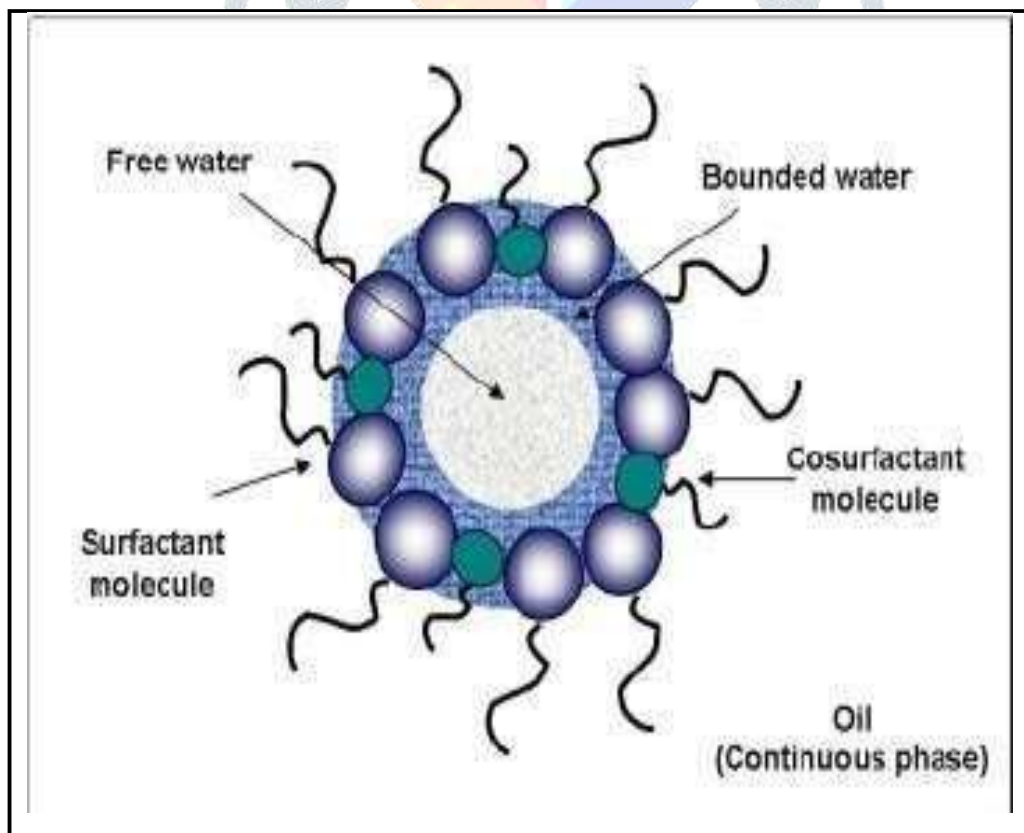


5. MICROEMULSION: -

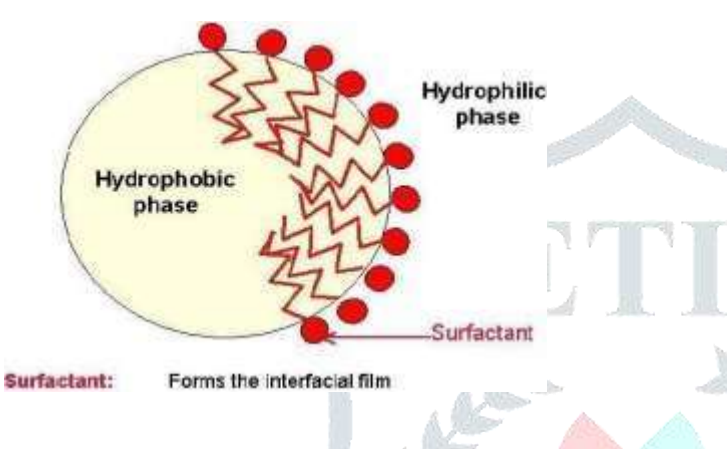
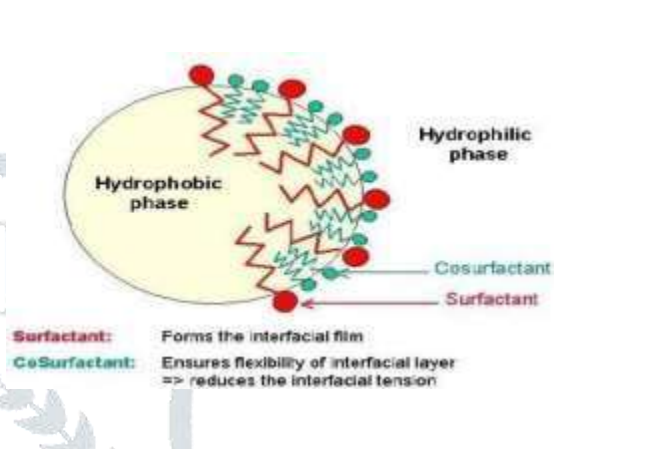
In 1943, Hour and Schulman visualized the existence of small emulsion-like structures by electron microscopy and subsequently coined the term —microemulsions

Microemulsions are isotropic, thermodynamically stable transparent (or translucent) systems of oil, water and surfactant, frequently in combination with a co-surfactant with a droplet size usually in the range of 10-100nm. whereas the diameter of droplets in a kinetically stable emulsion is >500 nm. Because the droplets are small, a microemulsion offers advantages as a carrier for drugs that are poorly soluble in water.

These homogeneous systems, which can be prepared over a wide range of surfactant concentration and oil to water ratio, are all fluids of low viscosity.



(Microemulsion)**Difference between Emulsion and Microemulsion**

EMULSION	MICROEMULSION
	
<ol style="list-style-type: none"> 1. Emulsions consist of roughly spherical droplets of one phase dispersed into the other. 2. Thermodynamically unstable (Kinetically Stable) 3. Inefficient molecular packing 4. Direct oil/water contact at the interface 5. High interfacial tension 6. High viscosity 7. Droplet diameter: >500nm 8. They are lyophobic 	<ol style="list-style-type: none"> 1. They constantly evolve between various structures ranging from droplet like swollen micelles to bi-continuous structure 2. Thermodynamically stable (Long shelf-life) 3. Efficient molecular packing 4. No direct oil/water contact at the interface 5. Ultra-low interfacial tension 6. Low viscosity with Newtonian behavior 7. 10 – 100 nm 8. They are on the borderline between lyophobic and lyophilic colloids

CHARACTERISTICS OF MICROEMULSIONS:-

- Particle size 10-100 nm
- Thermodynamically stable (long shelf-life)
- Optically clear
- High surface area (high solubilization capacity)
- Small droplet size
- Enhanced drug solubilization
- Ease of formation (zero interfacial tension and almost spontaneous formation)
- Ability to be sterilized by filtration
- Long-term stability
- High solubilization capacity for hydrophilic and lipophilic drugs
- Improved drug delivery

COMPONENTS OF MICROEMULSION FORMULATIONS:

A large number of oils and surfactants are available which can be used as components of microemulsion systems but their toxicity, irritation potential and unclear mechanism of action limit their use. One must choose materials that are biocompatible, non-toxic, clinically acceptable, and use emulsifiers in an appropriate concentration range that will result in mild and non-aggressive microemulsions. The emphasis is, therefore, on the use of generally regarded as Safe (GRAS) excipients.

OIL PHASE:

The oil component influences curvature by its ability to penetrate and hence swell the tail group region of the surfactant monolayer. Short chain oils penetrate the tail group region to a greater extent than long chain alkanes, and hence swell this region to a greater extent,

resulting in increased negative curvature (and reduced effective HLB).

Saturated (e.g. lauric, myristic and capric acid) and unsaturated fatty acids (e.g. oleic acid, linoleic acid and linolenic acid) have penetration enhancing property of their own and they have been studied since a long time.

Fatty acid esters such as ethyl or methyl esters of lauric, myristic and oleic acid have also been employed as the oil phase. Lipophilic drugs are preferably solubilized in o/w microemulsions. The main criterion for selecting the oil phase is that the drug should have high solubility in it. This will minimize the volume of the formulation to deliver the therapeutic dose of the drug in an encapsulated form.

SURFACTANTS:

The surfactant chosen must be able to lower the interfacial tension to a very small value which facilitates dispersion process during the preparation of the microemulsion and provide a flexible film that can readily deform around the droplets and be of the appropriate lipophilic character to provide the correct curvature at the interfacial region. It is generally accepted that low HLB surfactants are favored for the formulation of w/o microemulsion, whereas surfactants with high HLB (>12) are preferred for the formation of o/w microemulsion. Surfactants having HLB greater than 20 often require the presence of co-surfactants to reduce their effective HLB to a value within the range required for microemulsion formation.

CO-SURFACTANTS:

In most cases, single-chain surfactants alone are unable to reduce the o/w interfacial tension sufficiently to enable a microemulsion to form.

The presence of co-surfactants allows the interfacial film sufficient flexibility to take up different curvatures required to form microemulsion over a wide range of composition.

If a single surfactant film is desired, the lipophilic chains of the surfactant should be

sufficiently short, or contain fluidizing groups (e.g. unsaturated bonds).

Short to medium chain length alcohols (C3-C8) are commonly added as co-surfactants which further reduce the interfacial tension and increase the fluidity of the interface.

ADVANTAGES OF MICROEMULSION: -

Thermodynamically stable and require minimum energy for formation

To increase the cutaneous absorption of both lipophilic and hydrophilic drugs when compared to conventional vehicles (emulsions, pure oils, aqueous solutions).

Ease of preparation and high diffusion and absorption rates when compared to solvent without the surfactant system

The formation of microemulsion is reversible. They may become unstable at low or high temperature but when the temperature to the stability range, the microemulsion reforms

Drugs that are thermo-labile are easily incorporated without the risk of degradation

Microemulsions act as super solvent of drug. They can solubilize hydrophilic and lipophilic drugs including drugs that are relatively insoluble in both aqueous and hydrophobic solvents.

This system is reckoned advantages because of its wide applications in colloidal drug delivery systems for the purpose of drug targeting and controlled release.

A large amount of drug can be incorporated in the formulation due to the high solubilizing capacity that might increase thermodynamic activity towards the skin

The surfactant and co surfactant in the microemulsions may reduce the diffusional barrier of the stratum corneum by acting as penetration

enhancer slow surface tension ensures good contact to the skin. Also, the dispersed phase can act as a reservoir making it possible to maintain an almost constant concentration

gradient over the skin for a long time

DISADVANTAGES OF MICROEMULSION: -

Use of large concentration of surfactant and co-surfactant necessary for stabilizing the nanodroplets.

Limited solubilizing capacity for high-melting substances

The surfactant must be nontoxic for using pharmaceutical applications. Microemulsion stability is influenced by environmental parameters such as temperature and pH. These parameters change upon microemulsion delivery to patients.

TYPES OF MICROEMULSIONS

1. O/W Microemulsion
2. W/O Microemulsion
3. Bi-continuous Microemulsion

1. OIL IN WATER MICROEMULSIONS:

• Oil droplets are dispersed in the continuous aqueous phase. The o/w systems are interesting because they enable a hydrophobic drug to be more soluble in an aqueous based system, by solubilizing it in the internal oil droplets. Most drugs tend to favor small/medium molecular volume oils as opposed to hydrocarbon oils due to the polarity of the poorly water-soluble drugs.

2. WATER IN OIL MICROEMULSIONS:

• Water droplets are dispersed in the continuous oil phase. Water-in-oil microemulsions are made up of droplets of water surrounded by an oil continuous phase. These are generally known as —reverse-micelles, where the polar headgroups of the surfactant are facing into the droplets of water, with the fatty acid tails facing into the oil

phase.

3. BI-CONTINUOUS MICROEMULSIONS:

- Micro domains of oil and water are interspersed within the system. A bicontinuous microemulsion system both water and oil exist as a continuous phase. Irregular channels of oil and water are intertwined, resulting in what looks like a —sponge-phase.

METHOD OF PREPARATION OF MICROEMULSION: -

1. Phase Titration Method

2. Phase Inversion Method

1. PHASE TITRATION METHOD

- Microemulsions are prepared by the spontaneous emulsification method (phase titration method) and can be depicted with the help of phase diagrams.
- Construction of phase diagram is a useful approach to study the complex series of interactions that can occur when different components are mixed.
- Microemulsions are formed along with various association structures (including emulsion, micelles, lamellar, hexagonal, cubic, and various gels and oily dispersion) depending on the chemical composition and concentration of each component.
- The understanding of their phase equilibria and demarcation of the phase boundaries are essential aspects of the study. As quaternary phase diagram (four component system) is time consuming and difficult to interpret, pseudo ternary phase diagram is often constructed to find the different zones including microemulsion zone, in which each corner of the diagram represents 100% of the particular component.

- The region can be separated into w/o or o/w microemulsion by simply considering the composition that is whether it is oil rich or water rich.

Observations should be made carefully so that the metastable systems are not included.

3. PHASE INVERSION METHOD

- Phase inversion of microemulsions occurs upon addition of excess of the dispersed phase or in response to temperature. During phase inversion drastic physical changes occur including changes in particle size that can affect drug release both *in vivo* and *in vitro*.
- This method is referred to as phase inversion temperature (PIT) method. Instead of the temperature, other parameters such as salt concentration or pH value may be considered as well instead of the temperature alone. Additionally, a transition in the spontaneous radius of curvature can be obtained by changing the water volume fraction. By successively adding water into oil, initially water droplets are formed in a continuous oil phase. Increasing the water volume fraction changes the spontaneous curvature of the surfactant from initially stabilizing a w/o microemulsion to an o/w microemulsion at the inversion locus.
- Microemulsions can be prepared by controlled addition of lower alcohols (butanol, pentanol and hexanol) to milky emulsions to produce transparent solutions comprising dispersions of either water-in-oil (w/o) or oil-in-water (o/w) in nanometer or colloidal dispersions (~ 100 nm).
- The lower alcohols are called co-surfactants; they lower the interfacial tension between oil and water sufficiently low for almost spontaneous formation. The miscibility of oil, water and amphiphile (surfactant plus co-surfactant) depends on the overall composition

which is system specific.

- Microemulsions also have industrial applications, one of them being the synthesis of polymers. Microemulsion polymerization is a complex heterogeneous process where transport of monomers, free radicals and other species (such as chain transfer agent, co-surfactant and inhibitors) between the aqueous and organic phases, takes place. Compared with other heterogeneous polymerization processes (suspension or emulsion) microemulsion polymerization is a more complicated system.

- Polymerization rate is controlled by monomer partitioning between the phases, particle nucleation, and adsorption and desorption of radicals. Particle stability is affected by the amount and type of surfactant and pH of dispersing medium

7. DRUG AND EXCIPIENT PROFILE: -

• GLIPIZIDE

➤ Chemical Structure: -

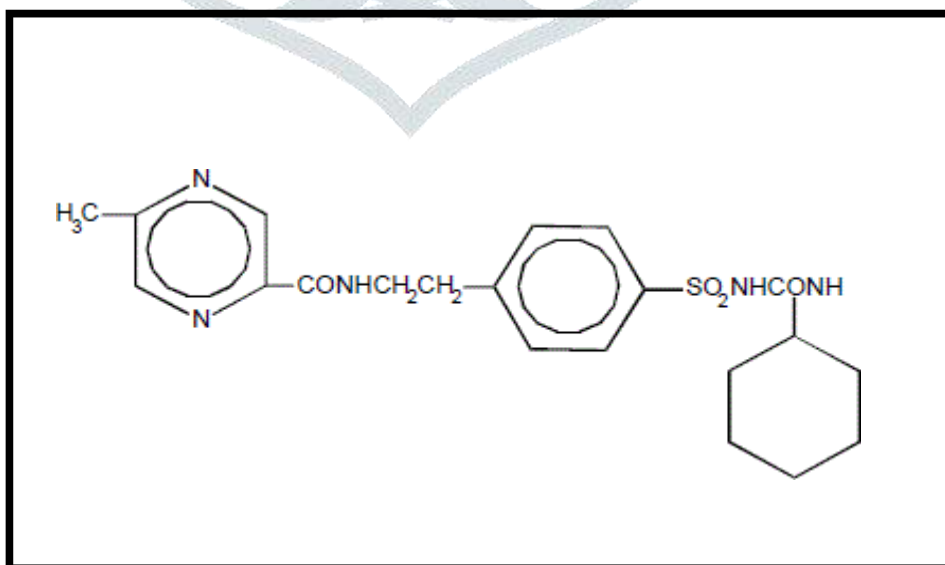
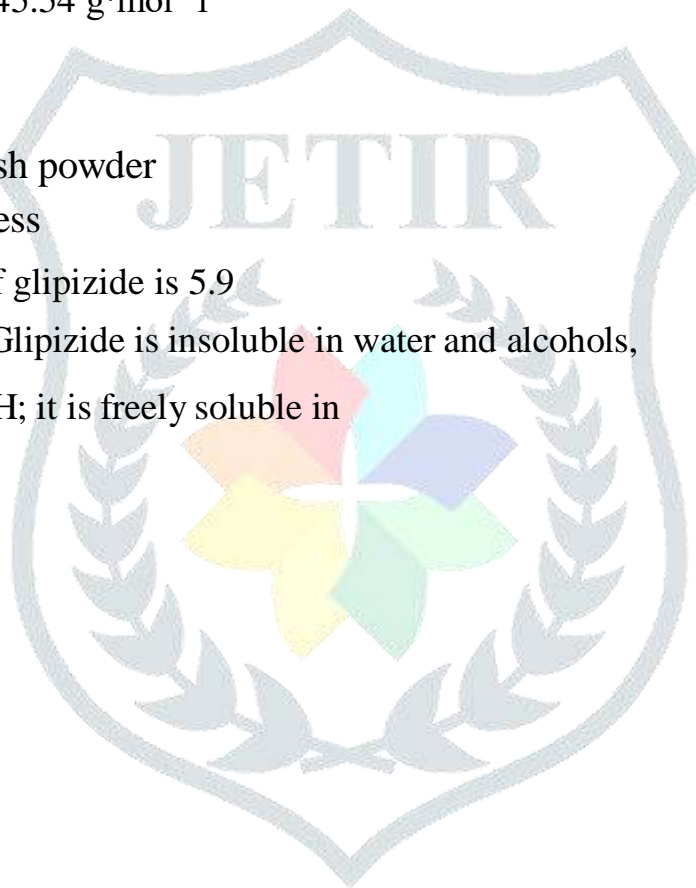


Fig-1 (Chemical structure of glipizide)

- **SYNONYMES** : Glucotrol, Glydiazinamide
- **MOLUCULAR FORMULA** : C₂₁H₂₇N₅O₄S
- **IUPAC NAME** : N-[2-(4-[[cyclohexyl carbamoyl]amino]sulfonyl)phenyl)ethyl]-5-methylpyrazine-2carboxamide
- **DRUG CLASS** : SULFONYLUREA
- **MOLAR MASS** :445.54 g·mol⁻¹

DESCRIPTION: -

- **COLOUR** : whitish powder
- **TASTE** : odorless
- **P_{ka}** : Pka of glipizide is 5.9
- **SOLUBILITY** : Glipizide is insoluble in water and alcohols, But soluble in 0.1 N NaOH; it is freely soluble in



Dimethylformamide

- **STORAGE** : Store the medicine in a closed container at room temperature away from heat, moisture, and direct light. Keep from freezing.
- **BIOAVAILABILITY** :100% (regular formulation)90% (extended release)
- **PROTEIN BINDING** :98 to 99%
- **METABOLISM** : Liver hydroxylation
- **ELIMINATION HALF-LIFE:** 2 to 5 hours
- **EXCRETION;** : Kidney and fecal

PHARMACOLOGICAL ACTIONS: -

Glipizide promotes insulin release from the pancreatic beta cells and reduces glucose output from the liver. It also improves insulin sensitivity at peripheral target sites. The extra pancreatic effect of sulfonylureas results from an increase in the deficient number of insulin receptors in the muscle, fat, or liver cells.

The molecular mechanisms of glipizide involve a partial block of the potassium channels in the beta cells of the pancreatic islets. This potassium channel blockade results in cell depolarization, which opens up the voltage-gated calcium channels, causing insulin secretion from the pancreatic beta cells.

The second-generation sulfonylureas have a more nonpolar side chain; this results in a higher potency hypoglycemic effect. In comparison with the other sulfonylureas, glipizide has the fastest absorption and onset of action, as well as the shortest half-life and effect-duration. Thus, the risk of long-lasting hypoglycemia is minute.

The initial onset effect takes around 30 minutes, and the duration is approximately 12 to 24 hours. 99% of the drug is protein bound. Glipizide undergoes hepatic metabolism and excretion is primarily in the urine with a small percentage in the feces.

PHARMACOKINETICS: -

Gastrointestinal absorption of GLUCOTROL in man is uniform, rapid, and essentially complete. Peak plasma concentrations occur 1–3 hours after a single oral dose. The half-life of elimination ranges from 2–4 hours in normal subjects, whether given intravenously or orally. The metabolic and excretory patterns are similar with the two routes of administration, indicating that first-pass metabolism is not significant. GLUCOTROL does not accumulate in plasma on repeated oral administration.

Total absorption and disposition of an oral dose was unaffected by food in normal volunteers, but absorption was delayed by about 40 minutes. Thus GLUCOTROL was more effective when administered about 30 minutes before, rather than with, a test meal in diabetic patients. Protein binding was studied in serum from volunteers who received either oral or intravenous GLUCOTROL and found to be 98–99% one hour after either route of administration.

The apparent volume of distribution of GLUCOTROL after intravenous administration was 11 liters, indicative of localization within the extracellular fluid compartment. In mice no GLUCOTROL or metabolites were detectable autoradiographically in the brain or spinal cord of males or females, nor in the fetuses of pregnant females. In another study, however, very small amounts of radioactivity were detected in the fetuses of rats given labelled drug

The metabolism of GLUCOTROL is extensive and occurs mainly in the liver.

The primary metabolites are inactive hydroxylation products and polar conjugates and are excreted mainly in the urine. Less than 10% unchanged GLUCOTROL is found in the urine.

INTERACTIONS:-

INDICATION & USAGE:-

Consult your doctor before using this drug if you have Geriatric, Breastfeeding, or if you are allergic reaction to this medicine or any other medicine or medical problem.

Glipizide is a second-generation sulfonylurea that is FDA-approved for the treatment of adults with diabetes mellitus type 2. Its use is as an adjunct to diet and exercise.

It is usable in combination with metformin, a biguanide, to reach goal HbA1c in patients with not adequate metabolic control in 3 months, despite compliance with diet, exercise, and medication.

In a specific context, it can be a monotherapy in cases of intolerance or a contraindication to use metformin. Given its lower cost, availability, and efficacy to control type 2 diabetes, glipizide and the other sulfonylureas are common choices for physicians.

Second-generation sulfonylureas are considered to be more potent by weight when compared to the first-generation agents.

Sulfonylureas were discovered in 1942 and have enjoyed extensive use in type 2 diabetes mellitus treatment since the 1960s.

Other drug classes used in the treatment of diabetes mellitus type 2 include alpha-glucosidase inhibitors, biguanides, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, glinides, and thiazolidinediones

DRUG INTERACTION:-

□ Although certain medicines should not be used together at all, in other cases two different medicines may be used together even if an interaction might occur. In these cases, your doctor may want to change the dose, or other precautions may be necessary.

□ When you are taking this medicine, it is especially important that your healthcare professional know if you are taking any of the medicines listed below. The following interactions have been selected on the basis of their potential significance and are not necessarily all-inclusive.

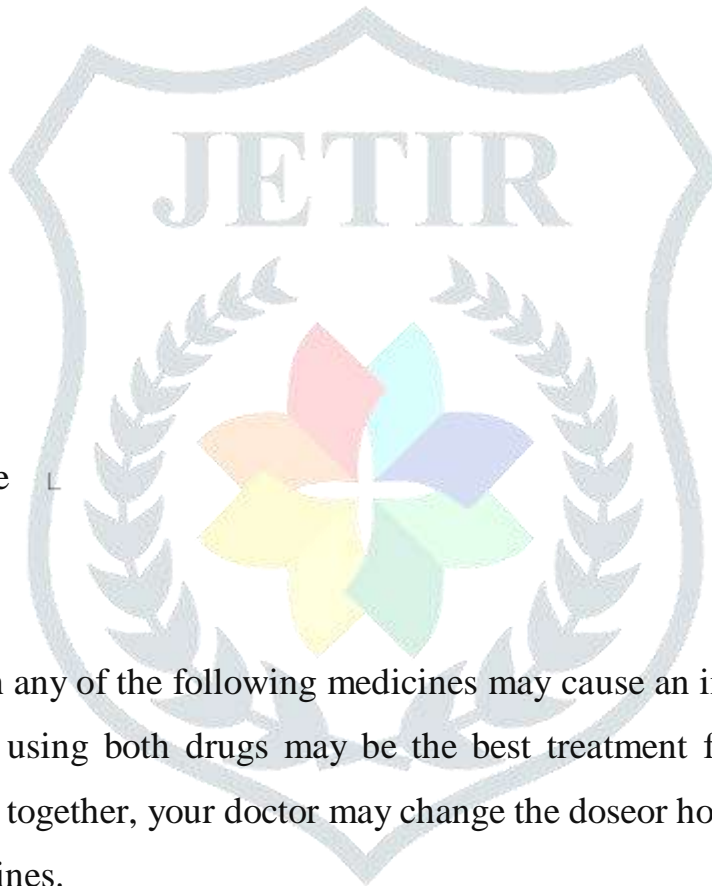
□ Using this medicine with any of the following medicines is usually not recommended, but may be required in some cases. If both medicines are prescribed together, your doctor may change the dose or how often you use one or both of the

medicines.

- └ Acarbose,Aspirin,Balofloxacin,Besifloxacin └
- Ceritinib
- └ Chloroquine └
- Ciprofloxacin └
- Desmopressin └
- Disopyramide └
- Dulaglutide └
- Enoxacin
- └ Entacapone └
- Fleroxacin └
- Flumequine └
- Gatifloxacin └
- Gemifloxacin
- └ Hydroxychloroquine └
- Lanreotide
- └ Levofloxacin

Using this medicine with any of the following medicines may cause an increased risk of certain side effects, but using both drugs may be the best treatment for you. If both medicines are prescribed together, your doctor may change the dose or how often you use one or both of the medicines.

- └ Acebutolol
- └ Aminolevulinic Acid └
- Atenolol
- └ Betaxolol
- └ Bisoprolol └



Bitter Melon

Carteolol

Carvedilol

Celiprolol

Cimetidine

Clarithromycin

Colesevelam

Cyclosporine

Esmolol

Fenugreek

Furazolidone

Glucomannan

Iproniazid

Isocarboxazid

Labetalol



OTHER MEDICAL PROBLEMS: -

The presence of other medical problems may affect the use of this medicine. Make sure you tell your doctor if you have any other medical problems, especially:

Alcohol intoxication or

Underactive adrenal glands or

Underactive pituitary gland or

Undernourished condition or

Weakened physical condition or

- ⌞ Any other condition that causes low blood sugar—Patients with these conditions may be more likely to develop low blood sugar while taking glipizide.
- ⌞ Diabetic ketoacidosis (ketones in the blood) or
- ⌞ Type I diabetes—Should not be used in patients with these conditions. ⌞ Fever or
- ⌞ Infection or ⌞
- Surgery or
- ⌞ Trauma—These conditions may cause temporary problems with blood sugar control and your doctor may want to treat you temporarily with insulin.
- ⌞ Glucose 6-phosphate dehydrogenase (G6PD) deficiency (an enzyme problem)—May cause hemolytic anemia (blood disorder) in patients with this condition.
- ⌞ Heart or blood vessel disease—Use with caution. May make this condition worse.
- ⌞ Kidney disease or
- ⌞ Liver disease—Higher blood levels of this medicine may occur, which may cause serious problems.
- ⌞ Narrowed or blocked food passages (e.g., esophagus, stomach, or intestines), severe—Use with caution. The extended-release tablet may cause obstruction in patients with this condition.

RECOMMENDED DOSAGE:

- ⌞ The dose of this medicine will be different for different patients. Follow your doctor's orders or the directions on the label. The following information includes only the average doses of this medicine. If your dose is different, do not change it unless your doctor tells you to do so.
- ⌞ The amount of medicine that you take depends on the strength of the medicine. Also,

the number of doses you take each day, the time allowed between doses, and the length of time you take the medicine depend on the medical problem for which you are using the medicine.

- For type 2 diabetes:
 - For oral dosage form (extended-release tablets):
 - Adults—At first, 5 milligrams (mg) once a day taken with breakfast. Your doctor may adjust your dose if needed. The dose is usually not more than 20 mg per day.
 - Children—Use and dose must be determined by your doctor.
 - For oral dosage form (tablets):
 - Adults—At first, 5 milligrams (mg) once a day taken at least 30 minutes before breakfast. Your doctor may adjust your dose if needed. The dose is usually not more than 40 mg per day.
 - Children—Use and dose must be determined by your doctor.

COMPARATIVE EFFICACY AND EVALUATION WITH OTHER THERAPIES:-

A) Chlorpropamide

For treatment of Diabetes mellitus Glipizide is comparable to chlorpropamide in lowering blood glucose in type II diabetes.

In a review of controlled studies in type II diabetes, glipizide is reported to be as effective as or possibly more effective than chlorpropamide and tolbutamide in controlling blood glucose.

B) Gliquidone

□ Gliquidone in a mean daily dose of 70 milligrams (mg) produced

significantly lower plasma glycosylated hemoglobin levels (HbA1) than glipizide (mean daily dose 9 mg) in a long-term (one year) study involving 39 patients with non-insulin-dependent diabetes mellitus²³ ($p < 0.01$). The dose of gliquidone is comparatively high.

C) Gliclazide

- The different comparative studies revealed the results that gliclazide is effective in controlling blood glucose levels and in reduction of glycosylated hemoglobin levels in non-insulin-dependent (type II) diabetic patients as first-generation and other second-generation sulfonylureas.
- Short term comparative studies with a small sample ($n = 47$) was performed and the results showed better control of blood glucose as compared to glyburide²⁸ though it was not confirmed in controlled studies. In another study, gliclazide showed better control of hemoglobin levels than glipizide.
- In long term studies, a randomized study was performed where $n = 247$. A significant lower secondary failure rate after 5 years of treatment was 7 % with gliclazide but 26 % with glipizide for NIDDM patients. However, the 18% secondary failure rate shown by glyburide (18%) was not significantly different from that of gliclazide.
- In this study, secondary failure was considered to be lack of achievement of postprandial blood glucose levels below 10mmol/L or glycosylated hemoglobin levels²⁵ of less than 10%. It is recommended for further studies to confirm long term efficacy of gliclazide.

D) Glipizide / Metformin Hydrochloride in Diabetes mellitus type II

- Looking into the combination therapy and taking into consideration, the fixed combination of glipizide / metformin, it is seen that this combination is more

effective than glipizide monotherapy in type II diabetic patients.

□ Fixed glipizide / metformin tablets (1.25/250 milligrams (mg), 2.5/250 mg, and 2.5/500 mg) were investigated as initial therapy in type II diabetic patients poorly controlled on diet / exercise alone (glycosylated hemoglobin 7.5 to 12.5%, fasting plasma glucose

less than 300 milligrams / deciliter (mg/dL)) in a 24-week, unpublished, active-controlled study²⁹ (n=868).

Patients were initially randomized to receive one tablet daily of the glipizide/metformin formulations, or metformin alone (500 mg) or glipizide alone (5 mg), with dose adjustments after two weeks to achieve a mean daily glucose level of 130 mg/dL or lower (maximum dose, 10/2000 mg for glipizide/metformin).

Data for the 1.25/250-mg fixed formulation were not provided. After 24 weeks, reductions in glycosylated hemoglobin in the 2.5/250- and 2.5/500-mg groups (each by about 2.1%) were significantly greater compared to glipizide monotherapy (-1.8%) or metformin monotherapy (-1.5%).

A final glycosylated hemoglobin level of less than 7% was achieved by more patients receiving either 2.5/250 or 2.5/500 mg glipizide/metformin (about 58%) than those assigned to metformin alone (35%) or glipizide alone (43%) (statistical analysis was not applied).

Fasting plasma glucose was significantly and similarly reduced in both fixed-combination dose groups (by approximately 55 mg/dL); although falls were greater compared to metformin or glipizide alone, statistical comparison was not provided. Compared to

baseline, a significantly greater reduction in the 3- hourpostprandial glucose AUC was observed with fixedglipizide/metformin relative to metformin or glipizide alone,although specific data were not presented. Fixedglipizide/metformin was reported to enhance the postprandialinsulin response, with no effect on fasting insulin levels.

E) INSULIN

Treatment with sulfonylureas or exogenous insulin results in equivalent improvement in insulin action in patients with noninsulin-dependent diabetes mellitus. Eight patients were studiedbefore and after three months treatment with each agent, using arandomized crossover design.

- Decreases in mean glycosylatedhemoglobin were similar as well as lowering of postabsorptiveglucose production rates. Glucose utilization at supraphysiologicinsulin concentrations was increased, while neither agent alterederythrocyte insulin binding at physiologic insulin concentrations. The authors suggest that both agents operate by modifying a postbinding defect. In a placebo-controlled, double-blinded, randomized, crossoverstudy, the use of glipizide was evaluated in combination with insulin.
- Ten patients with type II diabetes mellitus, but requiring insulin,were studied. After 8 weeks on combined glipizide and insulin therapy, no significant difference was found in fasting blood glucose, glycosylated hemoglobin and plasma lipoproteins when comparedto insulin alone.
- Pre-treatment with insulin before instituting therapy with glipizide was evaluated in patients with type II diabetes mellitus. The study group consisted of 69 Mexican American type II diabetics who wereobese, had poor glycemic control, and had previously

failed therapeutically on a first-generation sulfonylurea.

- The study subjects were randomized to receive either glipizide or a short course (10 weeks) of insulin prior to switching to glipizide. After 10 weeks, insulin was found to provide a more rapid decrease in fasting blood glucose, two-hour postprandial glucose and glycosylated hemoglobin than glipizide.
- However, by the end of the study (10 months) no significant differences were found between the group receiving the insulin pretreatment and the group that had been simply started on glipizide.
- The combination of insulin and glipizide was compared to insulin and placebo in 20 type II diabetics who previously failed on oral hypoglycemic agents. Overall, there was no significant change in diabetic control in either group; however, the median fasting plasma glucose fell in the glipizide group, but not in the placebo group.
- There was no significant change in fasting C-peptide and no increase in C-peptide response to glucagon. However, an increase in fasting insulin concentration was noted in the glipizide group as compared to the placebo group.

F) NATEGLINIDE

Glipizide immediate release (IR), glipizide gastrointestinal therapeutic system (GITS), and nateglinide provided control of postprandial glucose levels in patients with type II diabetes mellitus (DM).

In a small, randomized, placebo-controlled, cross-over study, 15 adult patients with type II DM (body mass index less than 40 kilogram/squared meter (kg/m^2)) and glycosylated

hemoglobin(HbA1c) less than 8%), received glipizide IR twice daily, nateglinide 120 mg four times daily, and glipizide GITS once daily for 7 to 10 days.

A cross-over design was used with a 48 hour washout period. Glipizide dosage was titrated to a fasting capillary glucose level below 6 millimoles/liter (mmol/L). Glipizide IR was given 30

minutes before breakfast and dinner, glipizide GITS 30 minutes before breakfast, and nateglinide 10 minutes before meals and bedtime snack.

At day 7 to 10 of each study period patients returned for laboratory testing at which time, study medication was administered before test meals in a placebo- controlled, double-blind fashion.

Overall postprandial hyperglycemia, the primary endpoint, was determined by the glucose area-under-the-curve (AUC) at 11 hours post breakfast and peak postprandial glucose. Significantly lower plasma glucose levels compared to placebo (p less than 0.05) occurred with all drug regimens. However, between group comparisons are difficult to access because the authors choose to report standard error of the mean rather than the mean, itself. **CONTRAINDICATIONS :-**

Glipizide is contraindicated in patients with: 1. Known hypersensitivity to glipizide or any excipients in the GITS tablets. 2. Type 1 diabetes mellitus, diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.

Contraindications to glipizide include patients with hypersensitivity to sulfa drugs and patients with type 1 diabetes mellitus, diabetic ketoacidosis, and hyperosmolar hyperglycaemic state (HHS).

The administration of sulfonylureas reportedly correlates with a slight increase in adverse cardiac events as compared to patients treated with insulin and diet. This caution is not

unique to glipizide, but also several classes of oral hypoglycemic agents (e.g., tolbutamide) studied in the University Group Diabetes Program.

If a patient is to initiate glipizide therapy, they should receive information regarding the potential risks, benefits, and possible complications.

Glipizide and sulfonylureas cross the placenta and have correlations in some cases with neonatal hypoglycemia. It is suggested to discontinue this drug two weeks before expected delivery.

Limited information suggests that levels of glipizide are low in lactation; results are not conclusive. In some instances, an alternative drug may be preferable, particularly while nursing preterm or a newborn.

The recommendation is to monitor for hypoglycemia symptoms in breastfed infants whose mother is taking glipizide or other sulfonylureas. In some cases, a newborn with clinical symptoms of hypoglycemia needs the supervision of blood glucose during the time the mother is taking sulfonylureas.

SIDE EFFECTS

Rare

Along with its needed effects, a medicine may cause some unwanted effects. Although not all of these side effects may occur, if they do occur they may need medical attention. Check with your doctor immediately if any of the following side effects occur

Anxiety

blurred vision

burning, crawling, itching, numbness, prickling, "pins and needles", or tingling feelings

cold sweats confusion

cool, pale skin depression

dizziness

fast heartbeat headache

increased hunger joint pain

leg cramps

muscle pain or stiffness nausea

nervousness nightmares

pain in the joints

problems in urination or increase in the amount of urine sweating

└ Abdominal or stomach pain

└ body aches or pain

└ burning, dry, or itching eyes ┘

congestion

┘ constipation └

cough

└ dark urine └

diarrhea └ fever

└ heartburn └

indigestion └ itching

└ loss of appetite ┘ pain in



the eye

Other Effects

It has been shown that GLUCOTROL therapy was effective in controlling blood sugar without deleterious changes in the plasma lipoprotein profiles of patients treated for NIDDM.

In a placebo-controlled, crossover study in normal volunteers, GLUCOTROL had noantidiuretic activity, and, in fact, led to a slight increase in free water clearance.

EXCIPIENT PROFILE:-

✚ OLEIC ACID

- **Chemical structure:**

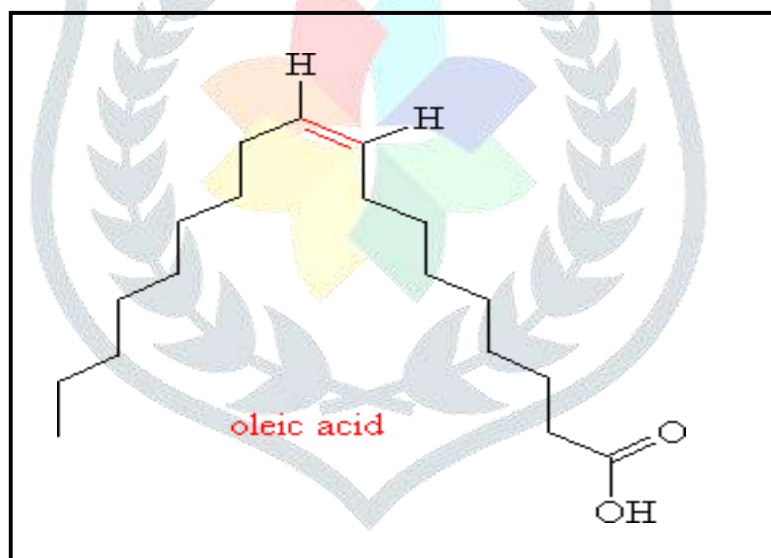


Fig-2(oleic acid)

□ **Molecular Formula**

:C₁₈H₃₄O₂

Synonyms

:Ethyl 9-octadecenoate, Kessco

EO Chemical name

:(Z)-9-Octadecenoic acid, ethyl

ester Molecular Weight

:282.4614 g/mol

Functional Category

:Skin penetrant, Emulsifying agent

Description :

- **Colour** :Pale yellow or brownish yellow oily liquid with lard-like odor
- **Solubility** :Soluble in acetone, chloroform, ether, Insoluble in water.

SPECIFIC PROPERTIES:-

Melting point : 13-14 °C

(286 K) **Flash point** : 175.3°C **Freezing point** : ~×-×32°C

Moisture content : 0.08% (at 20°C and 52%RH) **Surface**

tension : 32.3 dynes/cm at 25°C **Viscosity**

(dynamic) : 3.9 cP at 25°C **Viscosity (kinematic)** : 4.6 cSt at 25°C

PHARMACEUTICAL APPLICATION:

Oleic acid is used as an emulsifying agent in foods and topical pharmaceutical formulations. It has been used as a penetration enhancer in transdermal formulations, to improve the bioavailability of poorly watersoluble drugs in tablet formulations, and as part of a vehicle in soft gelaticapsules.

Oleic acid has been reported to act as an ileal ‘break’ that slows down the transit of luminal contents through the distal portion of the small bowel.

Oleic acid is used as a vehicle for certain parenteral preparations which are to be administrated by the intramuscular route.

It has also been used as a solvent for drugs formulated as biodegradable capsules for subdermal implantation and in the preparation of microemulsions containing cyclosporine.

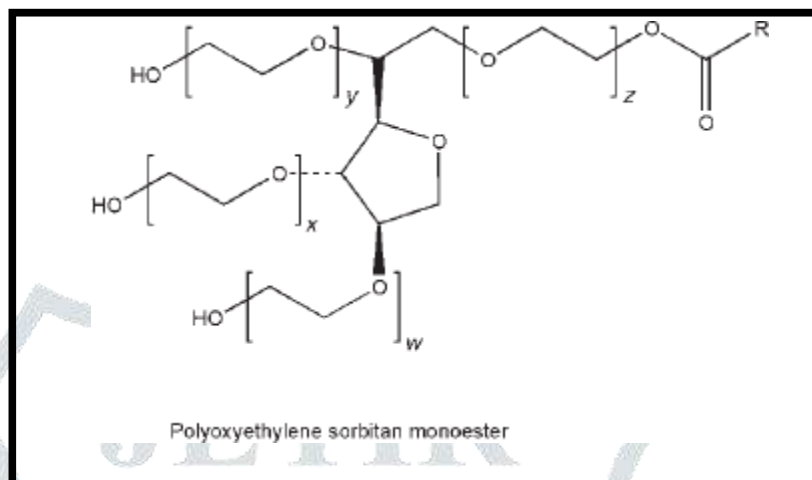
Oleic acid labeled with ¹³¹I and ³H used in medical imaging

STABILITY & STORAGE:-

Oleic acid should be stored in a cool, dry place in a small, well- filled, well- closed container, protected from light.

✚ TWEEN-20

Chemical Structure:



Synonyms : Armotan PML 20; Tween 20.

Chemical Name : Polyoxyethylene 20 sorbitan monolaurate

Molecular formulae : $C_{58}H_{114}O_{26}$.

Molecular weight : 1128g/mol

Functional category : Nonionic surfactant;
suspending agent; wetting agent.

DESCRIPTION:

- **Colour** : Yellow oily liquid at 25°C
- **Odour and Taste** : Polysorbates have a characteristic odor and a warm, bitter taste.

INCOMPATIBILITIES:

Discoloration and/or precipitation occur with various substances, especially phenols, tannins, tars, and tarlike materials.

STABILITY AND STORAGE CONDITIONS:

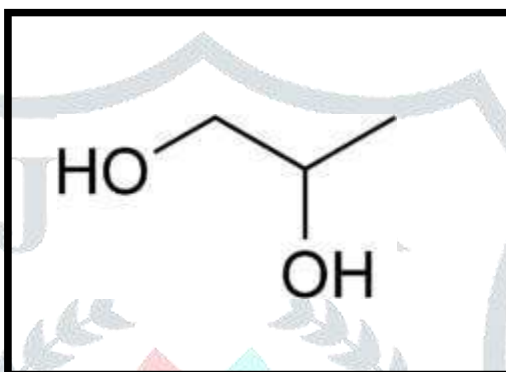
Polysorbates are stable to electrolytes and weak acids and bases; gradual saponification occurs with strong acids and bases. The oleic acid esters are sensitive to oxidation.

Polysorbates are hygroscopic and should be examined for water content prior to use

and dried if necessary. Also, in common with other polyoxyethylene surfactants, prolonged storage can lead to the formation of peroxides. Polysorbates should be stored in a well-closed container, protected from light, in a cool, dry.

✚ PROPYLENE GLYCOL

Chemical Structure:



□ **Molecular Formula**

: C₃H₈O₂

Synonyms

: propylene glycol, α-propylene glycol, 1, 2-propanediol,

Chemical Name

: propane-1, 2-diol

Molecular Weight

: 76.09g/mol

Functional Category

disinfectant; humectants

: Antimicrobial preservative;

DESCRIPTION :

1. A clear and colorless
2. Viscous and practically odorless
3. Sweet, slightly acrid taste
4. Resembling glycerol

TYPICAL PROPERTIES:

Boiling point

: 188°C

Flash point

: 99°C

Freezing point	: -59°C
Surface tension	: 40.1 dyne/cm at 25°C
Density	: 1.038 g/cm ³ at 20°C
Specific heat	: 2.47 J/g (0.590 cal/g) at 20°C
Vapor density (relative)	: 2.62 (air = 1)
Vapor pressure	: 9.33 Pa (0.07 mmHg) at 20°C
Viscosity (dynamic)	: 58.1 mPa s (58.1 cP) at 20°C

SOLUBILITY:

Miscible with acetone, chloroform, ethanol (95%), glycerin, and water; soluble at 1 in 6 parts of ether; not miscible with light mineral oil or fixed oils, but will dissolve some essential oils.

SAFETY:

Propylene glycol is used in a wide variety of pharmaceutical formulations and is generally regarded as a relatively nontoxic material.

STABILITY AND STORAGE CONDITIONS:

At cool temperatures, propylene glycol is stable in a well-closed container, but at high temperatures, in the open, it tends to oxidize, giving rise to products such as propionaldehyde, lactic acid, pyruvic acid, and acetic acid.

Propylene glycol is chemically stable when mixed with ethanol (95%),

glycerin, or water; aqueous solutions may be sterilized by autoclaving. Propylene glycol is hygroscopic and should be stored in a well-closed container, protected from light, in a cool, dry place.

ISOPROPYL ALCOHOL:-

Chemical Structure

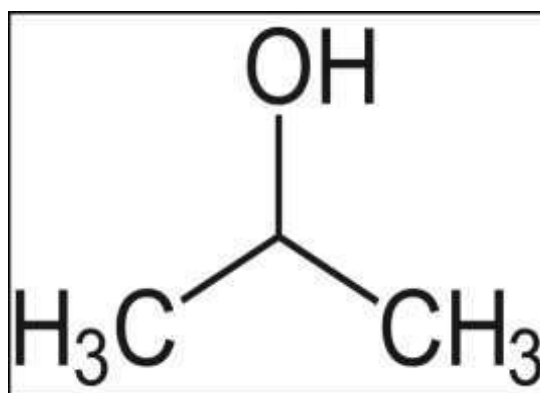


Fig-3

Molecular Formula : C_3H_8O

Synonyms : 2-Propanol, Isopropanol

Chemical Name : propan-2-ol

Molecular Weight

:

60.1 g/mol

DESCRIPTION :- It is a colorless liquid having disinfectant properties. It is used in the manufacture of acetone and its derivatives and as a solvent

PHYSICO PROPERTIES:-

Colour]

: Colourless **Boiling point** :

82.5°C **Melting point** : 89.5°C

Flash point : 11.7°C (closed cup)

17°C (open cup)

Relative density: 0.785 (Water = 1)

Vapour pressure: 4399.62 Pa at 20°C

Viscosity : 0.00243 Poises (2.43 cP) at 20°C

Ph : N/A

Odour □ : Slight odour resembling a mixture of ethanol and acetone.

Taste □ : Slightly bitter taste

□ **SOLUBILITY** : In water in all proportions at 20°C In alcohol in all proportions at 20°C In ether in all proportions at 20°C

FORMULATION AND EVALUATION OF GLIPIZIDE MICROEMULSION:-

During the recent decades, various colloidal systems have been investigated as suitable pharmaceutical vehicles for oral delivery of the active substance. Microemulsions are thermodynamically stable isotropically clear systems in which two immiscible liquids (i.e., water and oil) are mixed to form a single phase with an appropriate surfactant or its mixture.

Hoar and Schulman introduced the word microemulsion, which they defined as a transparent solution obtained by titrating a normal coarse emulsion with medium-chain alcohols.

The short to medium chain alcohols are generally considered as co-surfactants in the microemulsion system. The presence of surfactant and co-surfactant in the system makes the interfacial tension very low.

A microemulsion is considered as a suitable candidate for the oral delivery of poorly water-soluble drugs.

It has the ability to improve drug solubilization, protection against enzymatic hydrolysis and enhance the potential for absorption of hydrophilic, hydrophobic and amphiphilic substances in the gastrointestinal tract (GI), caused by surfactant-induced permeability changes.

After oral administration, it readily disperses in the stomach to a small droplet of the microemulsion, which promotes a wide distribution of the drug throughout the GI tract. Microemulsion comprises structures such as water in oil (w/o), oil in water (o/w) and bicontinuous systems. These help in the release of the drug.

The microemulsion can also sustain the release the drug if the partitioning of the drug between water and oil phases strongly affects the drug release. It can be formulated as an oil in water and water in oil microemulsion. Oil in water microemulsion is considered as a promising approach to improve the

solubility and oral bioavailability of hydrophobic drugs such as cyclosporine and also to sustain the release.

Hydrophobic drugs will be solubilized in surrounds the dispersed phase helps in sustaining

the release of the drug. On the other hand, water in oil microemulsion is considered as an approach to improve the bioavailability and to sustain the release of hydrophilic drugs across the intestinal mucosa

Therefore, it is important in our study to formulate oil in water microemulsion to improve the oral delivery of a hydrophobic drug, glipizide.

MATERIALS AND METHODS:-

Microemulsion systems composed of oleic acid, isopropyl myristate as oils; tween 80, span 20 and cremophor EL as surfactants; propylene glycol, isopropyl alcohol as cosurfactants were investigated as potential drug delivery vehicle for delivery for glipizide. Pseudo-ternary phase diagram of the investigated system at constant surfactant concentration and varying oil/water or oil/cosurfactant ratios was constructed at room temperature by titration method. This allowed studying structural inversion from oil-in-water to water-in-oil microemulsion. Furthermore, electrical conductivity, *in vitro* dissolution studies, pH, centrifugation, % transmittance, viscosity, particle size, polydispersity index, zeta potential, DSC and accelerated stability studies were conducted.

SAMPLE COLLECTION

Glipizide was provided as a gift sample from Aurobindo laboratories Ltd, Hyderabad, India. Cremophor EL was obtained from Signet chemical corporation, Mumbai, India.

Oleic acid, isopropyl myristate, isopropyl alcohol, propylene glycol, ethanol, tween 80, span 20, sodium chloride were obtained from SD fine chemicals Private Limited, Gujarat, India. Solvents and all the reagents were of analytical grade

PREPARATION OF GLIPIZIDE MICROEMULSIONS:-

Construction of phase diagram:-

Phase diagrams were used to construct different regions of microemulsion formation, from which a large number of potential microemulsions could be determined.

The pseudo-ternary phase diagram was constructed by titration of homogeneous liquid mixtures of oil, surfactant, and water with a cosurfactant at room temperature. Oil, glipizide, surfactant and water blend were prepared and cosurfactant was added drop by drop, under mechanical stirring.

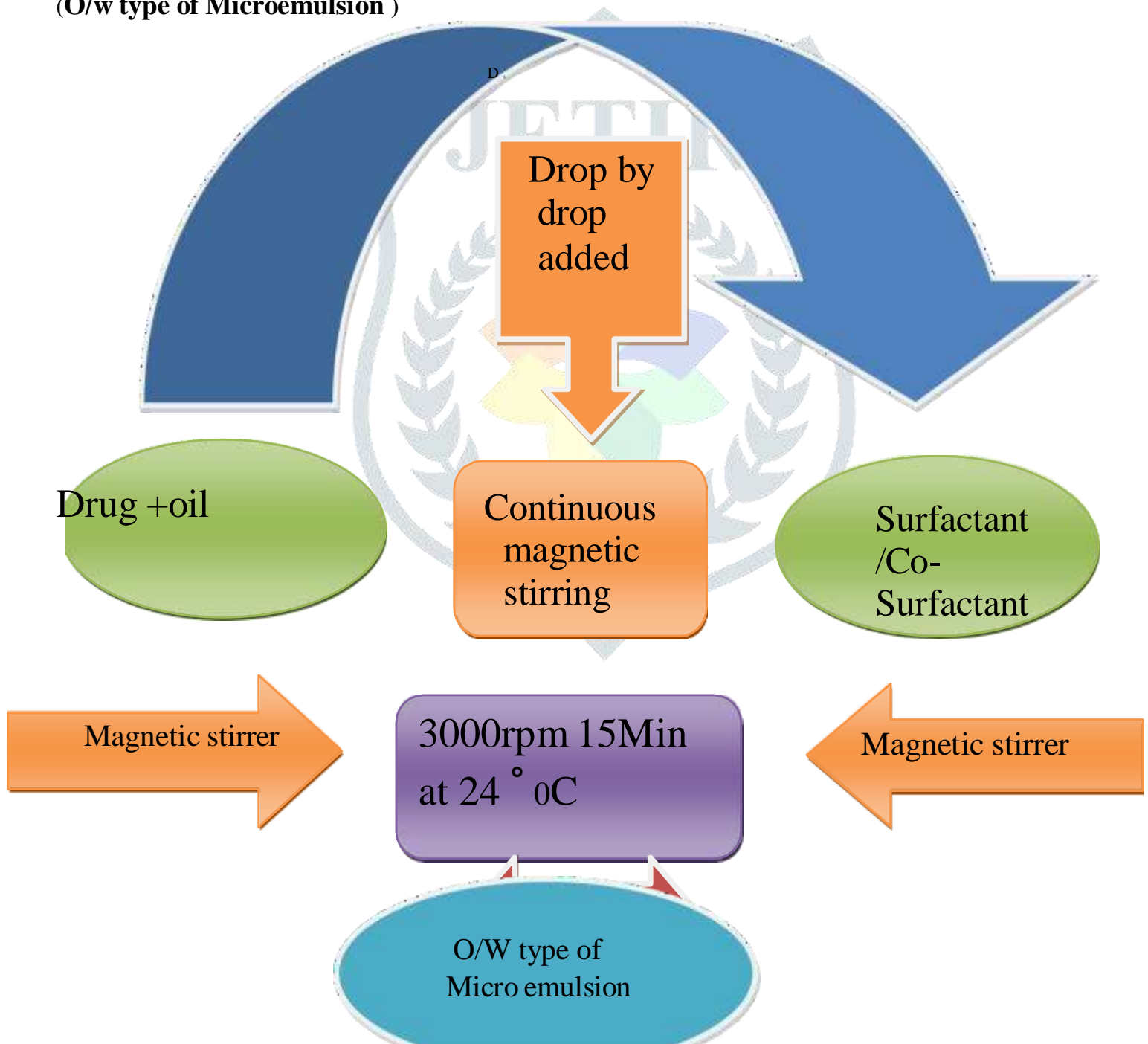
In this experiment, the contents of oil and water were varied in the ratio of 90:10 to 10:90.

Transparent, single-phase, low viscous mixtures were designated as a microemulsion.

After the cosurfactant titration, in order to establish the microemulsion regions, phase diagrams were constructed for the following 3 systems.

- ✓ System I-Oleic acid: Tween 80: Propylene glycol.
- ✓ System II-Isopropyl myristate: (Tween80-Span20): Isopropyl alcohol.
- ✓ System III-Oleic acid: Cremophor EL: Isopropyl alcohol.

(O/w type of Microemulsion)



PREPARATION:-

□ Microemulsions were prepared by cosurfactant titration method. In this method about 2.5 mg of glipizide for 5 ml formulation was accurately weighed and taken in a beaker. It was dissolved in an appropriate amount of oil. To this required amount of surfactant and water were added. The preparation was then gently stirred with a mechanical stirrer until all the components were mixed properly. Cosurfactant was then added dropwise to this preparation until the solution was clear. The samples were then stirred for 15 min to allow equilibration.

CHARACTERIZATION OF MICROEMULSION :-

Conductivity measurements:-

□ The electrical conductivity of the samples was measured using a Digital pH/conductivity meter (model DI-707, Digisun electronics, Hyderabad). Conductivity was measured by using 0.01N sodium chloride solution instead of using water. The measurements were performed in triplicate at 25 °C

In vitro drug release studies:-

- Dialysis tube method was used for performing the dissolution process. In this method, a boiling tube was taken which was opened at both the ends.
- To this tube, a cellophane membrane was attached at one end, which was previously soaked in 7.4 pH buffer for 24 h. 5 ml of microemulsion was taken from the other end of the tube. This setup was attached to the paddle of the dissolution apparatus.
- The dissolution medium consisted of 50 ml of freshly prepared phosphate buffer of pH 7.4. The release study was performed at 37 ± 0.5 °C, with a rotation speed of 50 rpm.
- Samples of 3 ml were withdrawn at 1, 2, 3 up to 8 h at regular one-hour intervals and replaced with fresh medium. Dissolution of placebo microemulsion was performed in the same manner and samples were utilized as blank for the respective drug loaded microemulsion. The samples were analyzed by UV-Visible spectrophotometer at 276 nm. The release studies were performed in triplicate.

Ph Determination:-

The pH values of the samples were measured by a Digital pH meter (model DI-707, Digisun electronics, Hyderabad) at 37 ± 1 °C.

Centrifugation:-

In order to eliminate metastable systems, the selected drug-loaded microemulsions were centrifuged (Research Centrifuge, R-24, Remi Instruments Limited, Mumbai) at 4000 rpm for 4 h.

Rheological Studies:-

The viscosity of the samples was measured using Brookfield Viscometer LV DV-II+P (Brookfield Engineering Laboratories, Inc. Middleboro, United states) fitted with an S-32 spindle. A Sample volume of 15 ml was used. All the microemulsions studied were subjected to shear stress of 0-20 Pa at different rpm (3, 6, 12, 30 and 60) and the rheological behavior of the disperse systems were examined by constructing rheograms of shear stress vs. shear rate.

Particle Size, Polydispersity Index And Zeta Potential Measurement:-

Measurements were made on a Zetasizer Nano ZS instrument at 25 °C at a wavelength of 633 nm and incorporate non-invasive backscatter optics (NIBS). At a detection angle of 173 °C measurements were made.

Differential Scanning Calorimetry Measurements (DSC):-

DSC measurements were performed with DSC TA Q100 instrument equipped with a refrigerated cooling system.

Nitrogen with a flow rate of 50 ml/min was used as purge gas. Approximately 4 to 13 mg of sample was weighed precisely into hermetic aluminum pans. An empty hermetically sealed pan was used as a reference.

Samples were cooled from 25 °C to -50 °C at a cooling rate of 5 °C/min, held for 3 min at -50 °C and then heated to 25 °C at a heating rate of 10 °C/min. All measurements were performed in triplicate.

Stability Studies Of Optimized Formulation:-

Stability studies were carried out for optimized formulation for 6 mo at 37±2 °C and 04±2 °C according to ICH guideline in a controlled chamber. The sample was analyzed periodically for physical appearance, rheological properties, pH and percentage release by UV-Visible spectrophotometer at 276 nm.

Pseudo-ternary phase diagram

A pseudo ternary phase diagram was constructed to determine the composition of the aqueous phase, oil phase, and surfactant: a co-surfactant phase that will yield a microemulsion. Among the various phases formed by these four components a field with clear and transparent liquid microemulsions was identified.

A pseudo ternary phase diagram of microemulsions prepared with system I was represented in fig. 1(a).

At low concentrations of water, clear microemulsions were obtained. But at concentrations >18%, gel-like preparation was formed. Replacement of water with 0.01N sodium chloride solution produced the same microemulsions as that obtained with water.

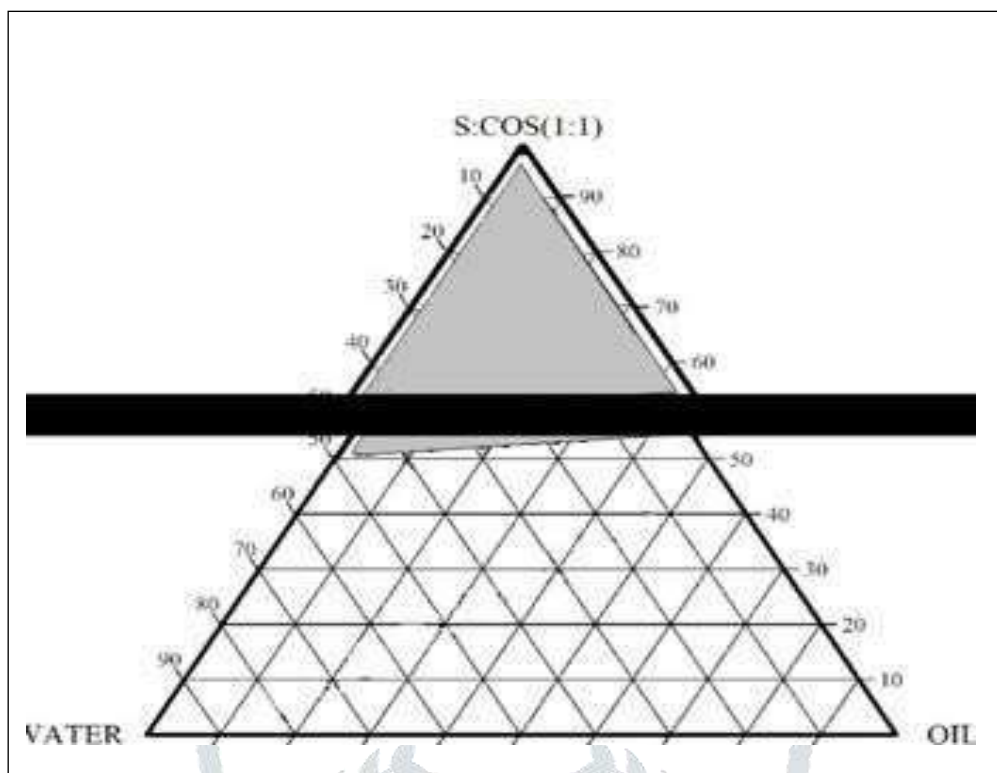
This was not surprising, as the various components of microemulsion were non-ionic and thus unaffected by the ionic strength of the dispersed aqueous phase.

It was clear from the pseudo-ternary phase diagram that, microemulsions in this system was formed with less than 18% of water, 2.84-32.73% of oleic acid, 45% of tween 80 and 17% of propylene glycol.

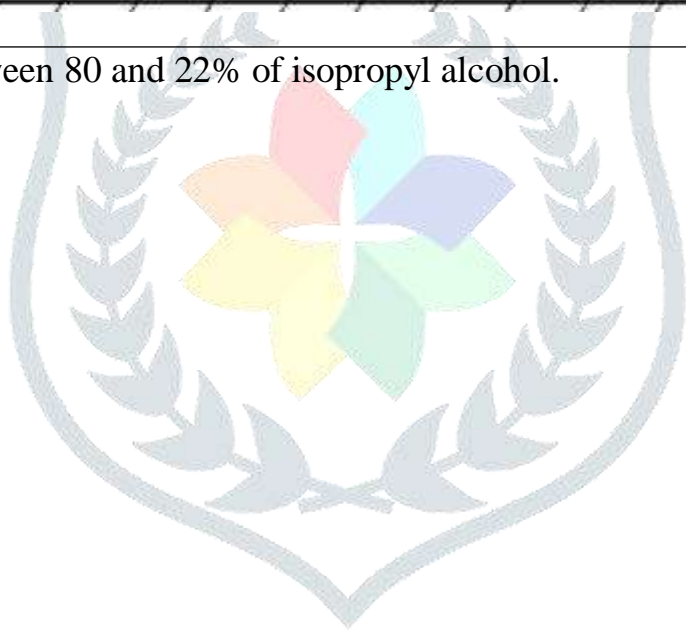
The pseudo-ternary phase diagram of system II was shown in fig. 1(b). In this system the ratio of tween 80:span20 was 1:1. This combination of surfactant produced a broader range of microemulsions as compared with the other microemulsion systems. It appears that stable microemulsions were formed with 3-47% of water, 3-42% of isopropyl myristate, 27% of tween80: span20 (1:1) and 25% of isopropyl alcohol. A representative phase diagram of system III was shown in fig. 1(c).

Water concentration of up to 32% was used. Above this concentration, gel-like preparation was observed.

Stable microemulsions were formed with <32% of water, 2-28% of isopropyl myristate,



45% of cremophor EL: tween 80 and 22% of isopropyl alcohol.



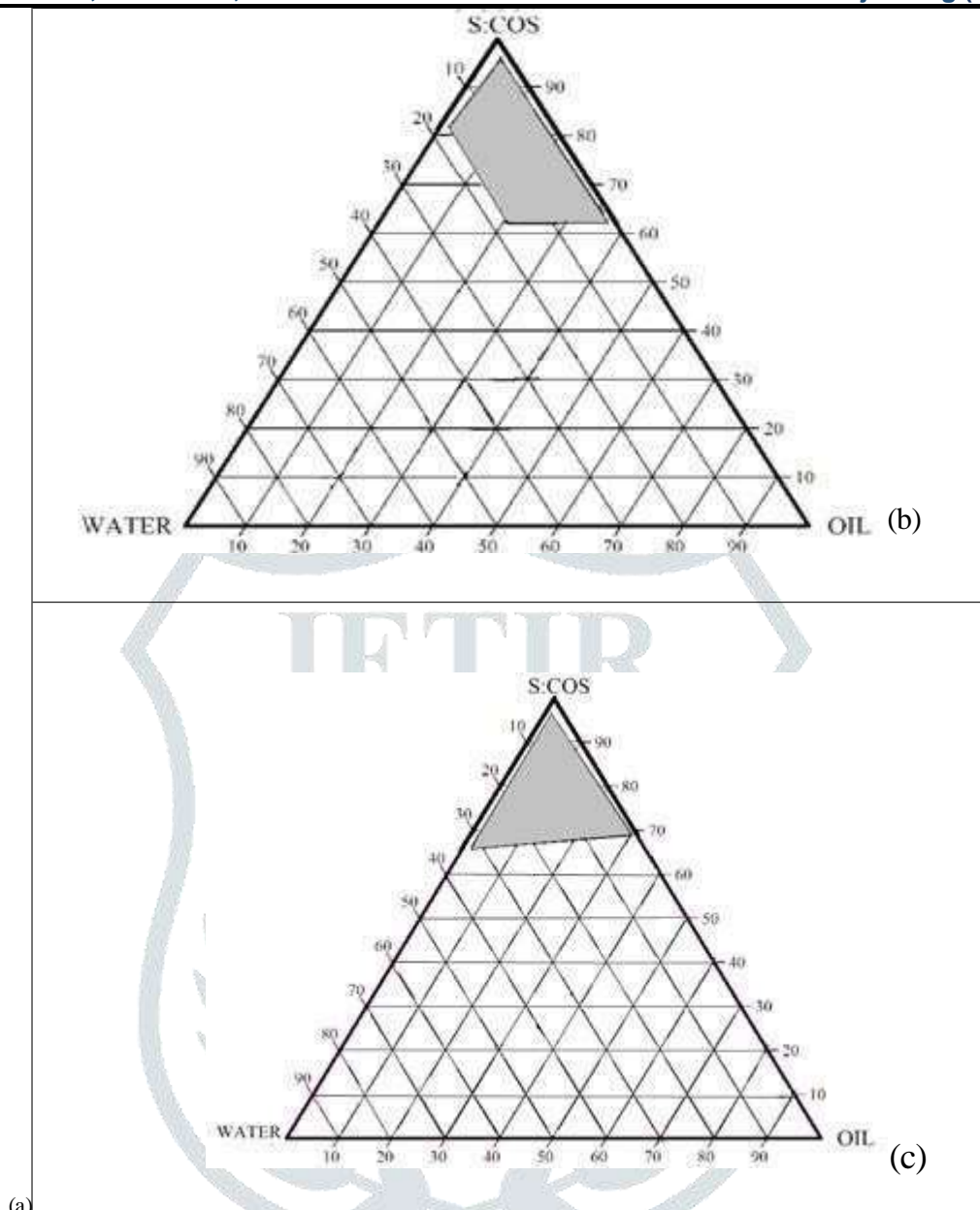


Fig. 1: Pseudo-ternary phase diagrams of a) system I b) system II c) system III

CHARACTERIZATION OF MICROEMULSION

Conductivity studies

Conductivity studies were performed by including sodium chloride solution in microemulsion instead of water.

The electrical conductivity (σ) of the system I, as a function of percentage water content (Φ_w), was presented in fig. 2 (a).

At concentrations of water $< 5\%$ the conductivity of system I was 126mv. During water titration of $> 5\%$, the conductivity was suddenly increased to 176 mv. From Φ_w 6.66-

17.75% (w/w), the conductivity of the system was not significantly affected by the further addition of water.

After 17.75% there was no addition of water, a further addition of water lead to the formation of a gel. The increase in water incorporation was because of the presence of propylene glycol.

When the volume of water increases, the electrical conductivity slightly increases until the critical Φ_w was reached where a sudden increase in conductivity was observed. This phenomenon was called as percolation, and the threshold (Φ_p).

The percolation threshold was observed at 13.2% water, where a network of conductive channels exists, which corresponds to the formation of water cylinders or channels in an oil phase due to the attractive interactions between the spherical microdroplets of the water phase in the w/o microemulsion.

The Percolation threshold of up to 20% was observed in piroxicam microemulsion . For the $\Phi_w > 16.64\%$ (w/w) the conductivity data can be explained by the dilution of microemulsion with the added water, which decreased the concentration of the dispersed oil droplets and increased conductivity.

Thus, this σ - Φ_w curve illustrates the occurrence of the three structural regions: W/O ($\Phi_w < 13.2\%$ (w/w)), nonspherical W/O-bicontinuous-non-spherical O/W ($13.2\% (w/w) < \Phi_w < 16.64\% (w/w)$), and O/W ($\Phi_w > 16.64\% (w/w)$).

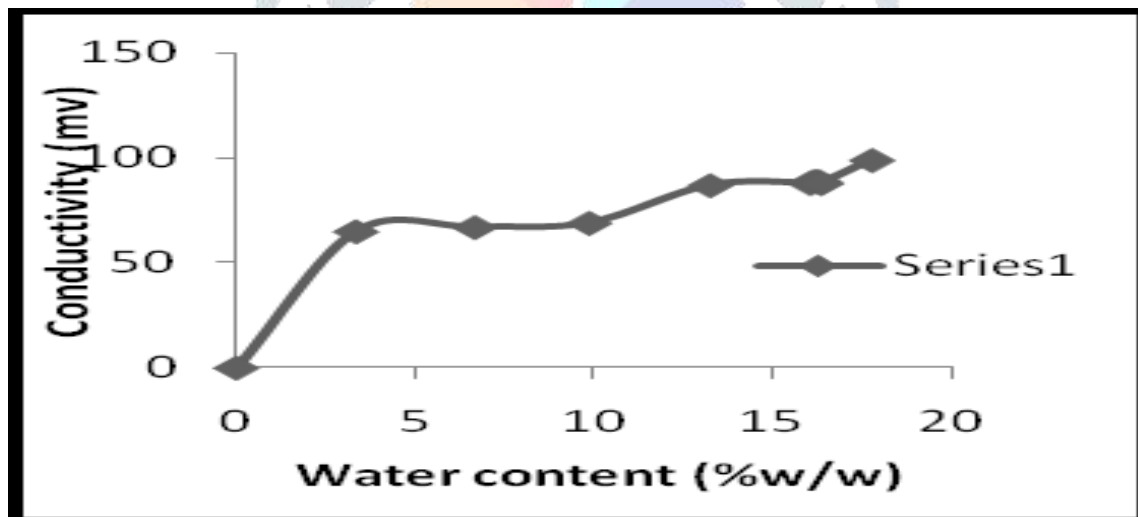


Fig-(a)

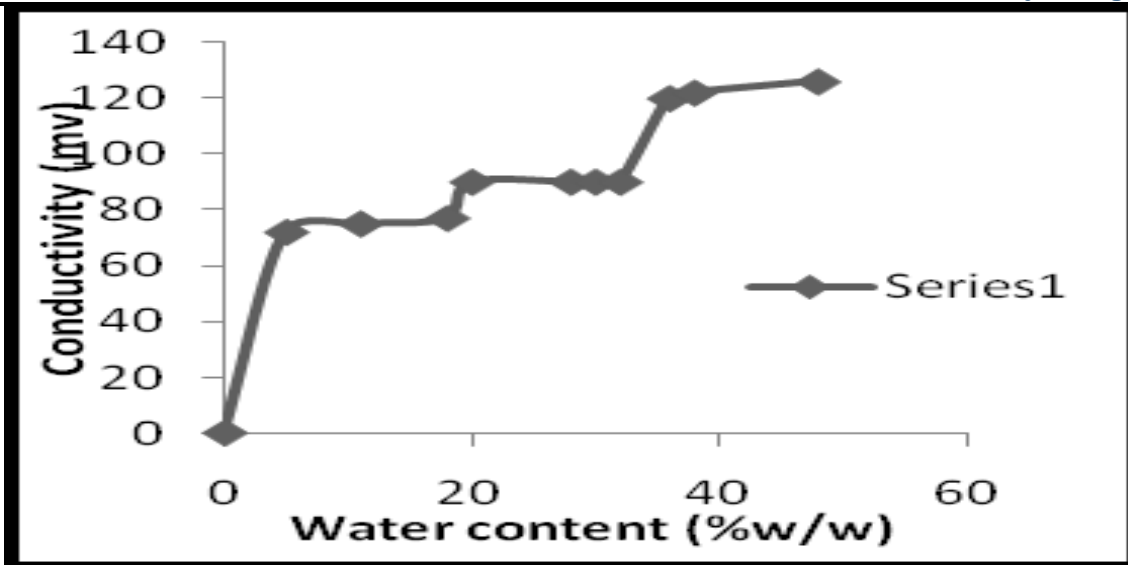


Fig-2(b)

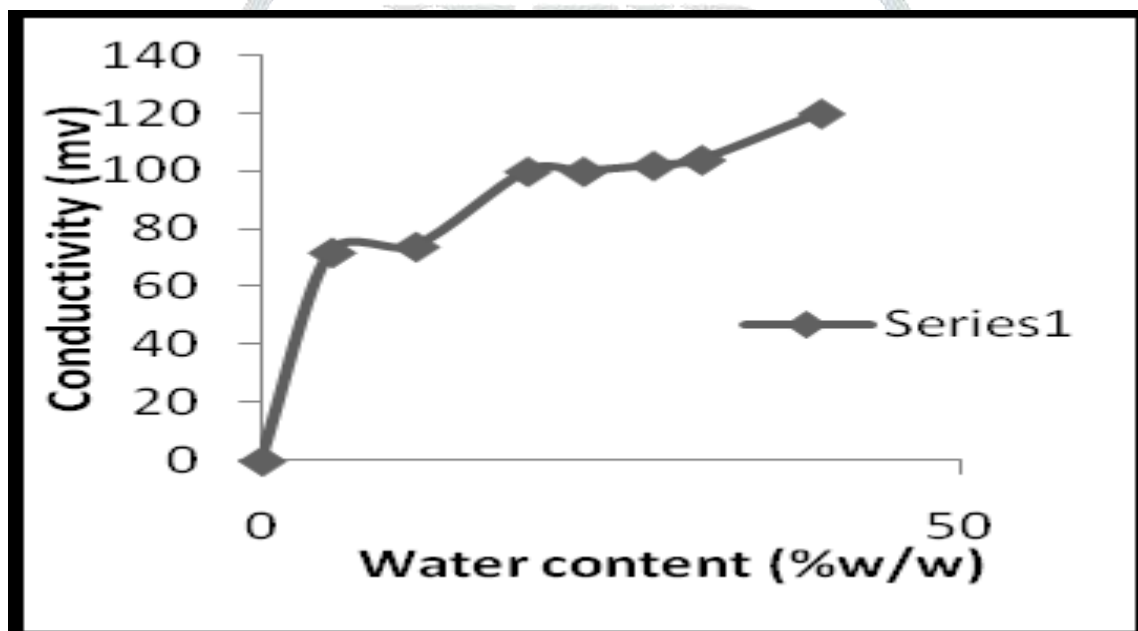


Fig-2(c)

Fig. 2: Conductivity vs Φ_w profile of a) system I b) system II c) system III

The electrical conductivity of system II was presented in fig. 2 (b). At low fractions of water, i.e. <math>\Phi_w < 18\%</math>, the conductivity slowly increased from 72mv to 77mv. After $\Phi_w \sim 18\%$ there was an increase in conductivity.

From $18\% < \Phi_w < 32\%$ there was no significant increase in conductivity with the addition of water. At $\Phi_w > 32\%$ there was again a raise in the curve. Further addition of water caused no significant increase in the conductivity of water.

Thus, this $\sigma - \Phi_w$ curve illustrates the occurrence of the three structural regions: W/O ($\Phi_w < 18\%$ (w/w)), nonspherical W/O-bicontinuous-nonspherical O/W ($18\% < \Phi_w < 32\%$ (w/w)), and O/W ($\Phi_w > 32\%$ (w/w)).

The electrical conductivity of system III was illustrated in fig.2 (C). At low levels of

$\Phi_w < 19\%$ (w/w), there was a slow increase in the conductivity of water.

After $\Phi_w > 19\%$, there was a steep increase in the conductivity of the formulation. After that, there was a slow increase in the conductivity of water until $\Phi_w \sim 31.45\%$. Then a sudden increase in the conductivity observed with the added water.

Thus, this $\sigma-\Phi_w$ curve illustrates the occurrence of the three structural regions: W/O ($\Phi_w < 19\%$ (w/w)), nonspherical W/O-bicontinuous-nonspherical O/W ($19\% < \Phi_w < 31.45\%$ (w/w)), and O/W ($\Phi_w > 31.45\%$ (w/w)).

The observed conductivity curves of the 3 investigated systems as a function of water content enumerates the use of conductivity to measure the structural changes in microemulsions.

From the conductivity studies, O/W microemulsions were selected for carrying out *in vitro* dissolution studies [table 1].

IN VITRO DISSOLUTION STUDIES :-

The dissolution studies of these microemulsions were compared with the dissolution profile of the plain drug. The release percentages at regular intervals were calculated and represented below in fig. 3.

Formulations	Oleic acid (%w/w)	IPM* (%w/w)	Tween 80 (%w/w)	Span 80 (%w/w)	CEL* (%w/w)	IPA* (%w/w)	PG* (%w/w)	Water (%w/w)
F1	2.84	—	44.81	—	—	—	34.37	17.75
F2	5.71	—	45.02	—	—	—	32.22	17.03
F3	11.53	—	45.45	—	—	—	26.79	16.26
F10	—	2.98	14.6	14.6	—	22.04	—	46.36
F11	—	9.09	14.77	14.77	—	22.27	—	39.07
F12	—	12.18	14.85	14.85	—	22.39	—	35.7
F20	2.90	—	—	—	43.6	21.95	—	31.53
F21	5.99	—	—	—	43.84	22.06	—	28.10
F22	9.03	—	—	—	44.06	22.17	—	24.71

Table 1: O/W microemulsions of glipizide selected from conductivity studies

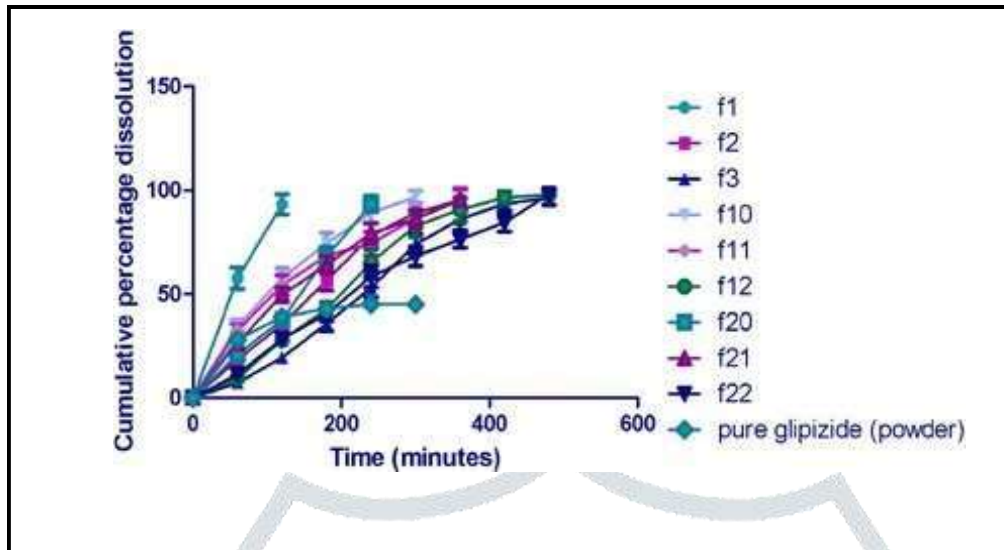


Fig. 3: In vitro release profile of o/w microemulsions data

Dissolution studies of pure glipizide have shown only 40% release owing to its poor dissolution and solubility in water. Formulation f1 have shown 93% release within 2 h, but not able to sustain the release. The fast release may be because of more amount of propylene glycol in the formulation which enhances the permeability of drug and also the presence of less oil content.

This formulation can be suggested as immediate release formulation of glipizide. Formulations f2, f10, f11, f20, f21 showed good percentage release but are not capable of sustaining the release. However the formulations f3, f12, f22 showed >95% release and also sustained the release for 8 h.

This may be because of the more internal oil phase and more solubilization of the drug in the oil phase. So, it takes time for the drug to diffuse through oil phase, surfactants, enter into the water phase and then reach the surrounding buffer.

Hence, the formulations f3, f12, f22 were chosen taken for further studies.

S. N. Deepak has shown similar dissolution profile for guaifenesin and phenylephrine microemulsion (100% drug release in 6 h), where oleic acid, tween 80, water and 2-propanol were used as formulation ingredients.

- The cumulative percentage release of each optimized formulation at different time periods was fitted in various kinetic models [table 2]. The The value of $n > 0.8$ indicates super case II transport of glipizide from microemulsion. This shows that the rate-limiting step in the release of glipizide was dissolution controlled release and not diffusion controlled release.

Formulation code		Zero order	First order	Hixson crowell (Q - Qt)	Koresmeyer peppas (n)
F3	slope r	0.125 0.9760	0.961 -0.0001	3.736 0.970	0.825 0.977
F12		0.141 0.979	0.923 -0.001	4.122 0.930	1.031 0.892
F22		0.137 0.994	0.865 -0.001	4.003 0.936	0.922 0.992

Table 2: Release kinetics of microemulsions selected

- pH studies were performed for the three formulations and found that the formulations have a pH near to neutrality. This indicates that they are not too acidic nor too basic, thus safe to take it orally.
- Centrifugation studies were done at 4000 rpm for 4 h and no phase separation was observed in all the optimized formulations which show that the samples were not metastable forms, which undergo phase separation easily, but were stable. Percentage transmittance studies were performed at 560 nm by using UV-Vis spectrophotometer. The results have shown >99.90% transmittance, which indicates that the microemulsions were transparent which is considered as the primary property of a microemulsion [table 3].

The rheological studies of chosen formulations were investigated at 4 different shear rates at 303 °K which was shown in fig. 4.

It was observed that viscosity was constant with an increase in the shear rate for all the compositions. This indicates that the sample follows the Newtonian flow.

The results of the rheological study also have shown low viscosity values. So, it is considered that the other characteristic property of microemulsion, i.e., the low viscosity was met. Hence, Newtonian flow and lower viscosity values help in easy packaging, handling of the microemulsion and also helps to increase patient compliance upon oral administration.

Out of the three formulations, f12 has viscosity very much lower than the other two formulations. Particle size analysis indicates that the size and polydispersity index (PDI) of f12 is much lower than formulations f3 and f22 [fig. 5]. Lower the particle size; greater is the permeation of microemulsions through the gastrointestinal tract and greater will be the bioavailability. PDI values of f12 indicate that droplet size in the formulation was uniform.

The results of zeta potential showed that all the optimized formulations have good physical stability. The values confirm a net negative charge on the surface of the globule. From the above results of viscosity, particle size, PDI and zeta potential f12 formulation was optimized as a final microemulsion. Further differential scanning calorimetric studies (DSC) were performed to determine its stability and drug entrapment.

Formulations	pH	% Transmittance	Viscosity (cps)	Particle size (nm)		PDI	Zeta potential
					Peak2	Peak	

				Peak1	3			
F3	6.87±0.05	99.93±0.01	210±2.3	10±0.2	25±0.31	315.3±2.9	0.608±0.04	-27.2±0.2
F12	6.72±0.15	99.99±0.01	30±0.67	10±0.09	83.3±0.45	-	0.120±0.01	-29.8±0.1
F22	6.98±0.04	99.98±0.2	150±0.45	30±0.11	183±1.6	-	0.452±0.02	-25.7±0.4

Table 3: Evaluation studies of selected o/w formulations

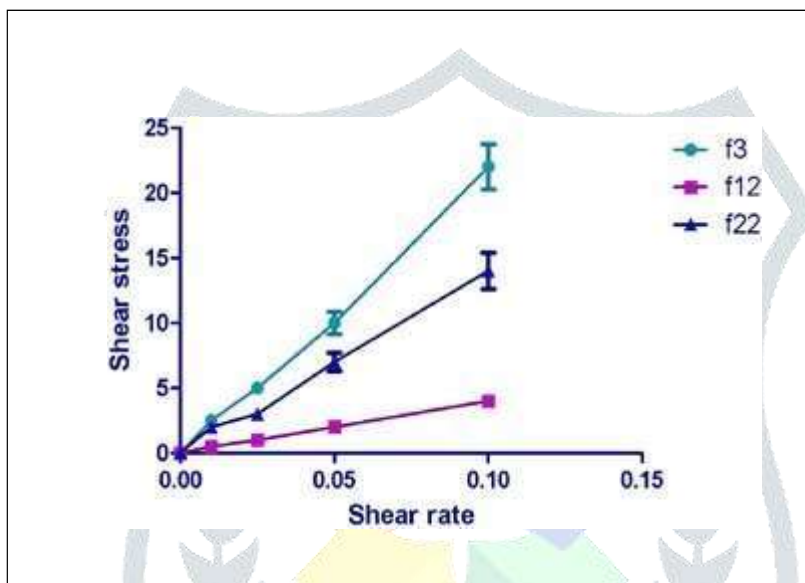
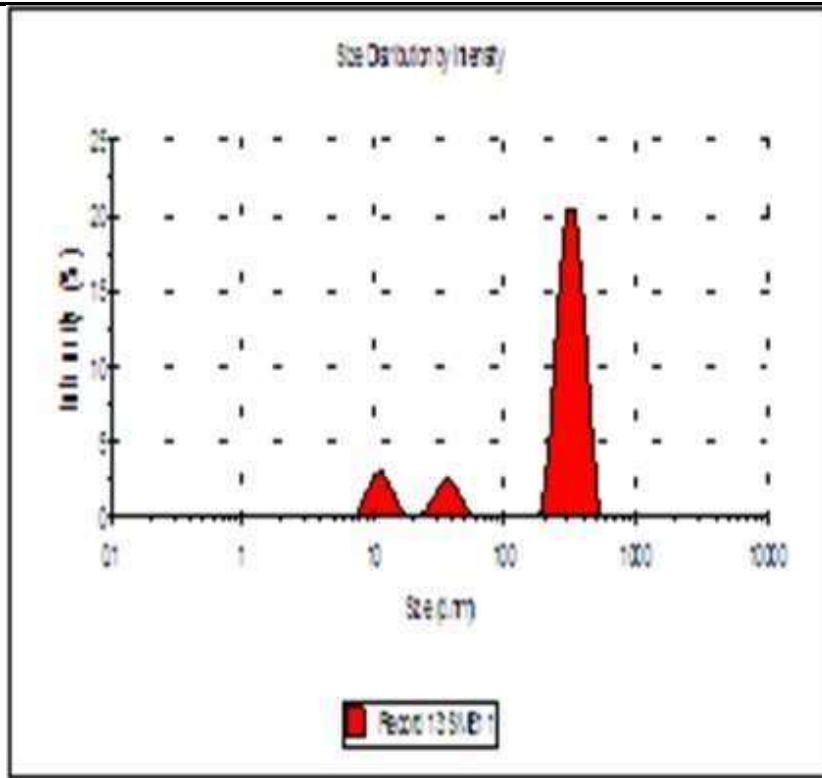
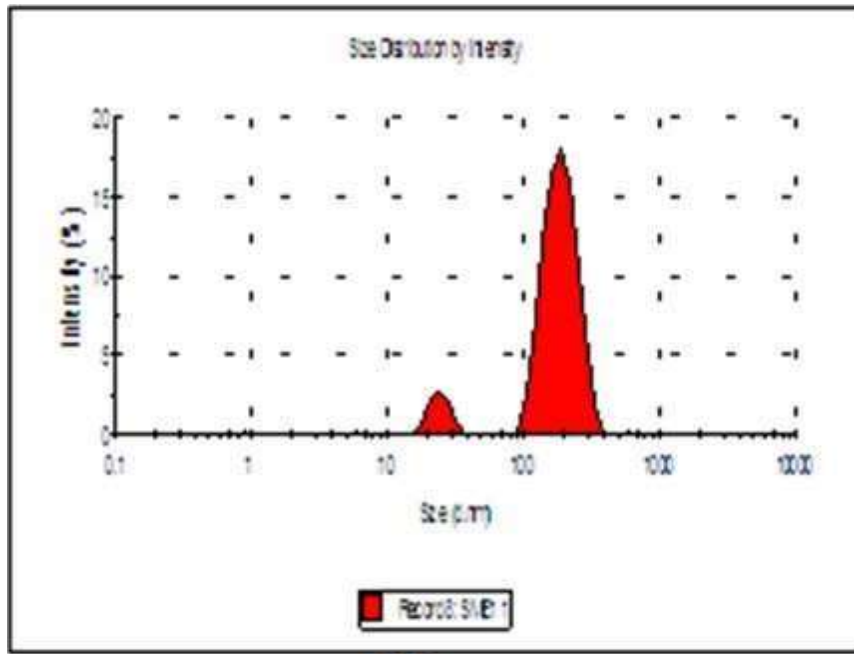


Fig. 4: Effect of shear stress on different rates of shear. Data represents mean±SD (n=3)

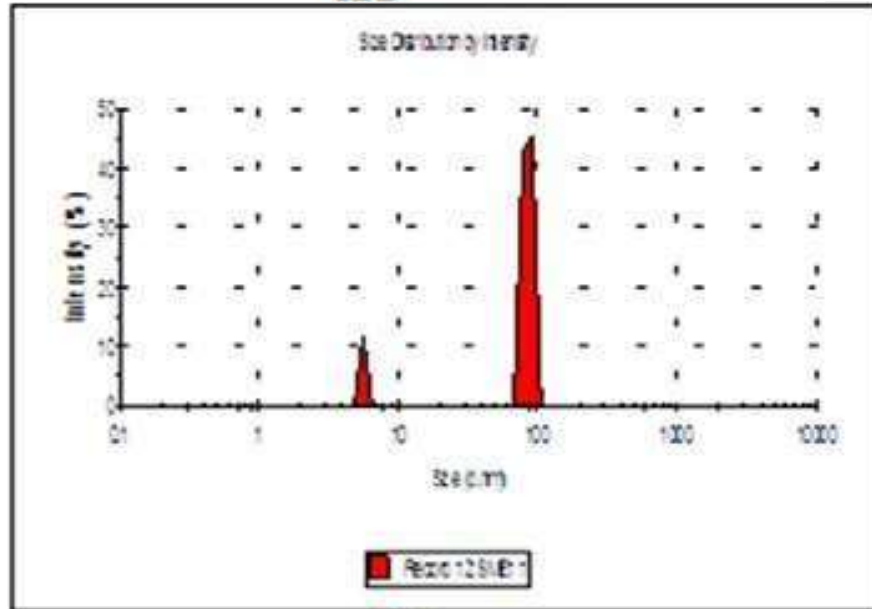


f3





f22



f12

Fig. 5: Particle size distribution of selected formulations

DIFFERENTIAL SCANNING CALORIMETRIC STUDY :-

Formulation f12 showed endotherms at 124.4 °C and 247 °C. Formulation f12 placebo showed endotherms at 128.6 and 254.2 °C [fig. 6]. Isopropyl myristate (IPM) oil showed endotherm at 212 °C.

The endotherm of f10 at 247 °C and endotherm of placebo at 254.2 °C was due to the presence of IPM in the formulations. In f12, no peak for the drug was observed indicating that the drug was completely solubilized in the formulation. Further, stability studies were carried out for optimized formulation as per ICH guidelines at 37 ± 2 °C, 4 ± 2 °C in a controlled chamber.

In periodic time intervals samples were withdrawn and retested for physical appearance, viscosity, pH and *in vitro* release for 6 mo. The physical appearance of the preparation was good without any phase separation or turbidity. The average pH of 6.8, viscosity of 40 cps and no considerable change in the percentage release, i.e., 95% was observed for 6 mo.

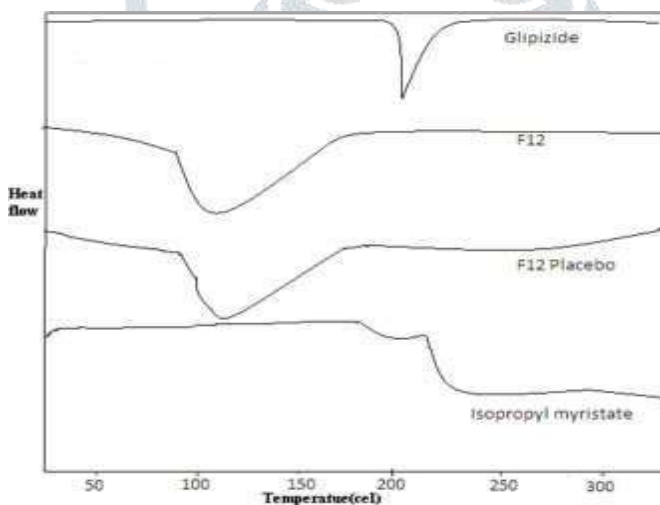


Fig. 6: DSC thermogram of glipizide, isopropyl myristate, f12 and f12 placebo

RESULTS AND DISCUSSION

Oleic acid, isopropyl myristate were lipophilic permeation enhancers and can be used to improve the membrane permeability of microemulsion [16, 17]. Tween 80, span 20, cremophor EL were nonionic surfactants and categorized as generally recognized as safe (GRAS) excipients, which were widely used in pharmaceutical preparations [18-20]. Surfactants were used in microemulsion preparation such that their hydrophilic lipophilic balance value is greater than 10. Cosurfactants propylene glycol, isopropyl alcohol were used in the concentration which was safe for oral use

□ The results of electrical conductivity clearly indicated the structural inversion. Based

on these values oil/water microemulsions were selected. The plain drug has shown only 40% of dissolution, while the drug from all the o/w microemulsions has shown >90% dissolution. Based on *in vitro* release studies f3, f12, f22 formulations were chosen. Particle size values of f3, f12, f22 formulations are 202.4 nm, 83.3 nm, 315.3 nm respectively. Viscosity results showed that the formulations follow the Newtonian flow

CONCLUSION:

The 3 formulations f3, f12 and f22 were successful in increasing the dissolution of glipizide in GIT and capable of sustaining the release of the drug for 8 h. From the viscosity, particle size, polydispersity index values, f12 was considered as the optimized formulation. Further, centrifugation, zeta potential and accelerated stability studies also indicated that the formulations were stable. DSC studies revealed no drug-excipient interaction in the optimized formulation. Owing to the above results microemulsion can be thus considered as a suitable oral delivery system for glipizide.

REFERANCE:-

1. Melander A, Wahlin-Boll E: Clinical pharmacology of glipizide. Am J Med. 1983 Nov 30;75(5B):41-5
2. Skillman TG, Feldman JM: The pharmacology of sulfonylureas. Am J Med. 1981 Feb;70(2):361-72.
3. Quianzon CC, Cheikh IE: History of current non-insulin medications for diabetes mellitus. J Community Hosp Intern Med Perspect. 2012 Oct 15;2(3). pii: 19081. doi: 10.3402/jchimp.v2i3.19081. Print 2012.
4. Sola D, Rossi L, Schianca GP, Maffioli P, Bigliocca M, Mella R, Corliano F, Fra GP, Bartoli E, Derosa G: Sulfonylureas and their use in clinical practice. Arch Med Sci. 2015 Aug 12;11(4):840-8. doi: 10.5114/aoms.2015.53304. Epub 2015 Aug 11.
5. Giustini MS, Murgia G, Palazzo. Does The Schulman's Titration Of Microemulsions Really Provide Meaningful Parameters? Langmuir, 2004;20(18):7381-4..
6. Lawrence MJ, Rees GD. Microemulsion-Based Media As Novel Drug Delivery Systems, Adv Drug Deliv Rev, 2000; 45(1): 89-121.. Googman and Gilman's The Pharmacological Basis of Therapeutics, 11th Edition, 2005. P. 1415, Unit II, —Disease Of Organ System|| 1304-1309.
7. Tripathi Kd, Essentials Of Medical Pharmacology. 5th Ed. Published By Jaypee Brother's Medical Publisher's Pvt. Ltd., New Delhi: 2003:167-184.
8. . Jadupatimalakar, Suma OS, Amit KN. Development and Evaluation Of microemulsions For Transdermal Delivery Of

Insulin, Research Article, 201:1-7.

9. . Bhavika H. Zala, Radhik BP, Manali DP, Ramkishan. Formulation And Development of Microemulsion Drug Delivery System Of Acyclovir For Enhancement of Permeability, Journal of Pharmacy Research, 2011:4(3),930-933.
10. Manish K Singh, Vikas Chandel, Vandana Gupta and Suman Ramteke Formulation Development and Characterization Of Microemulsion For Oral Delivery Of Glipizide, Scholars Research Library, Der Pharmacia Lettre, 201: 2(3), 33-42.
11. Gupta S, Moulik SP, Lala S, Basu MK, Sanyal SK And Datta S. Designing and Testing Of An Effective Oil-In-Water Microemulsion Drug Delivery System For In Vitro Application. Drug Delivery. 2005; 12(5):267-273.
12. Arulanantham K, Genel M. Central nervous system toxicity associated with ingestion of propylene glycol, J Pediatr 1978; 93:515–516.
13. E.A. Rawlins, Bently's Text book of pharmaceuticals, Bailliere Tindall, London, 8th ed, 663.
14. Martin's physical pharmacy pharmaceutical sciences. 5th ed. India: Wolters Kluwer; 2007:448.
15. Bourne DW, Pharmacokinetics, In: Banker GS, Rhodes CT,—Modern Pharmaceuticals, 4th ed, New York, NY: Marcel Dekker Inc; 2002:67-92.
16. Trotta M, Morel S, Gasco MR. Effect of oil phase composition on the skin permeation of felodipine from oil in water microemulsions. Pharmazie 1997;52:50-3.
17. Vandana P, Hirenkumar K, Rajshree M, Naazneen S, Surjyanarayan Ml. Development of microemulsion for solubility enhancement of clopidogrel. Iran J Pharm Res 2010;9:327–34.
18. Sarkhejiya Naimish A, Nakum Mayur, Patel Vipul P, Atara Samir A, Desai Thusarbindu R. Emerging trend of the microemulsion in formulation and research. Int Bull Drug Res 2012;1:54-83.
19. Bolzinger MA, Carduner TC, Poelman MC, Bicontinuous sucrose ester microemulsion: a new vehicle for topical delivery of niflumic acid. Int J Pharm 1998;176:39-45.
20. Kreilgaard M, Pedersen EJ, Jaroszewski JW. NMR characterisation and transdermal drug delivery potential of microemulsion systems. J Controlled Release 2000;69:421–33.
21. Kumar P, Mital KL. Handbook of Microemulsion: Science and Technology. Marcel Dekker, New York, Basel; 1999.
22. Kibbe AH. Handbook of Pharmaceutical Excipients. 3rd ed. Pharmaceutical Press: London; 2000.
23. Ritschel WA. Microemulsion technology in the reformulation of cyclosporine: the reason behind the pharmacokinetic properties. Neoral Clin Transplant 1996;10:364–73.
24. Eskandar M, Anayatollah S, Fatemeh L. Preparation and evaluation of tretinoin microemulsion based on the pseudo-ternary phase diagram. Adv Pharm Bull 2012;2:141–7.
25. Henri LR, John LC, David LC, James HW. Microemulsions: a commentary on their

preparation. *J Soc Cosmet Chem* 1988;39:201-9.

26. Phalka PN, Sherikar AV, Dhadke PM. Direct spectrophotometric analysis of glipizide and phenformin hydrochloride in pharmaceutical dosage forms. *Indian J Pharm Sci* 1997;59:18-21.

27. Gui SY, Wu L, Peng DY, Liu QY, Yin BP, Shen JZ. Preparation and evaluation of a microemulsion for oral delivery of berberine. *Pharmazie* 2008;63:516-9.

28. Carlucci A, Vidal MC, García R, Bregni C. O/W microemulsions for oral drug delivery. *Boll Chim Farm* 2003;142:324-9.

29. S Peltola, P Saarinen-Savolainen, J Kiesvaara, TM Suhonen, A Urtili. Microemulsions for topical delivery of estradiol. *Int J Pharm* 2003;254:99–107.

30. N Subramaniam, S Ray, SK Ghosal, R Bhadra, SP Moulik. Formulation design of self-micro emulsifying drug delivery systems for improved oral bioavailability of celecoxib. *Biol Pharm Bull* 2004;27:1993–9.

31. Lv FF, Zheng LQ, Tung CH. Phase behavior of the microemulsions and the stability of the chloramphenicol in the microemulsion-based ocular drug delivery system. *Int J Pharm* 2005;301:237–46.

32. Ramadan E, Borg TH, Abdelghani GM, Saleh Bull NM. Formulation and evaluation of acyclovir microemulsions. *Bull Pharm Sci* 2013;36:31-47.

