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Formulation and Evaluation of Glipizide Sustained Release Matrix Tablet

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1. INTRODUCTION

1.1 DRUG DELIVERY SYSTEM:

Oral drug delivery is the most widely utilized route of administration among all the routes that has been used for the systemic delivery of drugs via various pharmaceutical products of different dosage form. Nowadays most of the pharmaceutical scientists are involved in developing an ideal DDS, this ideal system should have advantage of single dose for whole duration of the treatment and it should deliver the drug directly at specific target site. Scientists have succeeded to develop a system that can be as near to an ideal system and it encourages the scientist to develop controlled release system. The design of oral sustained drug delivery system should be aimed to achieve the more predictability and reproducibility to control the drug release, drug concentration in the target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose. For most of the drugs, conventional methods of formulation are quite effective. However some drugs are unstable and toxic and have a narrow therapeutic range, exhibit extreme solubility problems, require localization to a particular site in the body or long-term use. In such cases a method of continuous administration of drug is desirable to maintain fixed plasma drug levels[1]. To develop the ideal drug delivery system, two prerequisites is to be required. First, it would be single dose for whole duration of treatment, whether it is for days or weeks or for the lifetime of patient, as in hypertension or diabetes. Second, it should deliver the active entity directly to the site of action, thereby minimizing or eliminating adverse effects. This may necessitate delivery to specific receptors or to localization to cells or to specific areas of the body. Ideally a drug to provide desired therapeutic action should arrive rapidly at the site of action in optimum concentration, remain there for desired time and get removed from the site. One of the interesting results of pharmaceutical research is the fact by reducing the release rate of a drug from the dosage form its absorption rate can be decreased. The products so formulated are named as sustained action, sustained release, delayed action, prolonged action, depot, repository, retarded release and time release medication [2]

1.2 The Goal In Designing Sustained Or Controlled Delivery System Is To:

The major goal set in designing sustained or controlled delivery is to:

- Reduce the frequency of dosing.
- Increase effectiveness of the drug by localization at the site of action.
- Reducing the dose required.
- Providing the uniform drug delivery.

In the past, many of the terms used to refer therapeutic systems of controlled and sustained release have been used in an inconsistent and confusing manner. Sustained release, sustained action, prolonged action, controlled release (drug release with zero order kinetics) and repository dosage forms are terms used to identify drug delivery systems that are designed to achieve prolonged therapeutic effects by continuously releasing medication over an extended period of time after administration of a single dose [2]. Sustained release describes the release of drug substance from a dosage form or delivery system over an extended period of time. The basic goal of this system is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. An important element in accomplishing this goal is to design of proper dosage regimens.

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1.3. Parmeters For Drug To Be Formulated In Sustained Release Dosage Form [4]:

There are some physicochemical parameters for the drug selection to be formulated in sustained release dosage form.

PARAMETER	PREFERRED VALUE
Molecular weight/size	<1000
Solubility	>0.1mg/ml for pH 1 to pH 7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability	From all GI segments
Release	Should not be influenced by pH and enzymes

Table 1: Physiochemical Parameters for Drug Selection

There are also some pharmacokinetic parameters for the drug selection to be formulated in sustained release dosage form.

PARAMETER	COMMENT
Elimination half-life	Preferably between 2 to 8 hrs
Total clearance	Should be dose dependent
Elimination rate constant	Required for design
Apparent volume of distribution (V_d)	The larger V_d and MEC, the larger will be the required dose size.
Absolute bioavailability	Should be 75% or more
Intrinsic absorption rate	Must be greater than release rate
Therapeutic concentration C_{ss}	The lower C_{ss} and smaller V_d , the loss among of drug required
Toxic concentration	Apart the values of MTC and MEC, safer the dosage form. Also suitable for drugs with very short half-life.

Table 2: Pharmacokinetic Parameters for Drug Selection

1.4. Sustained Release Formulatons: [8] [9]

Sustained Release:

It includes any drug delivery system that achieves slow release of drug over an extended period of time usually eight to twelve hours. Sustained Release constitutes any dosage form that provides medication over an extended time or denotes that the system is able to provide some actual therapeutic control. Sustained Release Systems generally do not attain zero order type release but try to mimic zero order release by providing drug in a slow first order.

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The ideal way of providing an exact amount of drug at the site of action for a precise time period is usually approximated by most systems. This approximation is achieved by creating a constant concentration in the body or an organ over an extended period of time; in other words, the amount of drug entering the system is equivalent to the amount of drug removed from the system. All forms of metabolism and excretion are included in the removal process urinary excretion, entero-hepatic recycling, sweat, fecal and so on. Since for most of the drugs will have a specific rate of elimination. The idea is to deliver rug at this exact rate for an extended period. This is represented mathematically as following,

$$\text{Rate in} = \text{Rate out} = \text{kelim} \times C_d \times V_d$$

Where,

C_d is the desired drug level,
V_d is the volume of distribution,
Kelim is the rate constant of drug elimination from the body.

Other such exacting delivery rates prove to be difficult to achieve through administration routes other than intravenous infusion. Noninvasive routes, for example, oral route is thus preferred**.**

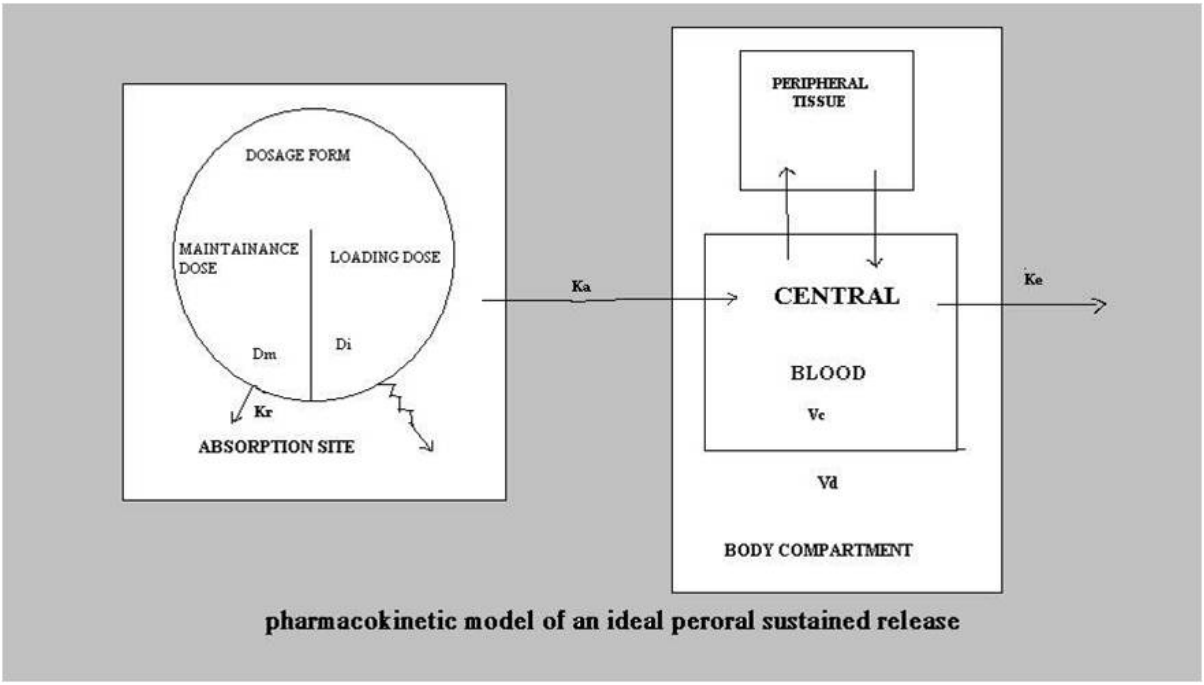

Fig 1: Pharmacokinetic Model for Sustained Release Dosage Forms

1.4.1. Merits of Sustained Release Dosage Form:

Clinical merits [4]:

1. Decreased local and systemic side effects:
2. Reduced gastrointestinal irritation.

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3. Reduced 'see-saw' fluctuation
4. Optimized therapy in treatment.
5. Improved patient compliance.
6. Economical to the health care providers and the patients.
7. Reduced total dose.
8. Improved efficiency in treatment.

Commercial merits:

1. Chances of illustration of innovative/technology leadership
2. Extension of product life-cycle
3. Differentiation of product
4. Expansion of market
5. Extension of patent.

1.4.2. Demerits of Sustained Release Dosage Form:

1. Drug with short half-life; has chances of missing the dose.
2. Dose dumping
3. The fluctuations of drug plasma level which leads to under medication or overmedication.
4. Poor patient compliance.
5. Poor in vitro-in vivo correlation.
6. Increases the possibility of dose dumping.
7. Cost of formulation is high
8. In case of toxicity, poisoning or hypersensitivity reactions retrieval of drug is difficult
9. Reduced potential for dosage adjustment of drug normally administered in varying strength
10. Increase potential for first pass metabolism
11. Education of patient for proper medication is required.
12. Decreased systemic availability in comparison to immediate release conventional dosage form.

1.4.3. Designing of Sustained Release Drug Delivery System: [4]

The oral route administration is most convenient route because of its comfortable dosage form, design and patient care. For orally administered drugs, targeting is not a primary concern and it is usually intended for drugs to penetrate to the general circulation and perfuse to other body tissues. For this reason, most systems employed are of the sustained release variety. Several parameters should be kept in mind before formulating sustain release dosage form which includes various pH in GIT, the gastrointestinal motility, the enzyme system and its effect on the dosage form and the drug. Plasma drug concentration- profiles for conventional tablet or capsule formulation, a sustained release formulation, and a zero order sustained release formulation are as follow in given figure.

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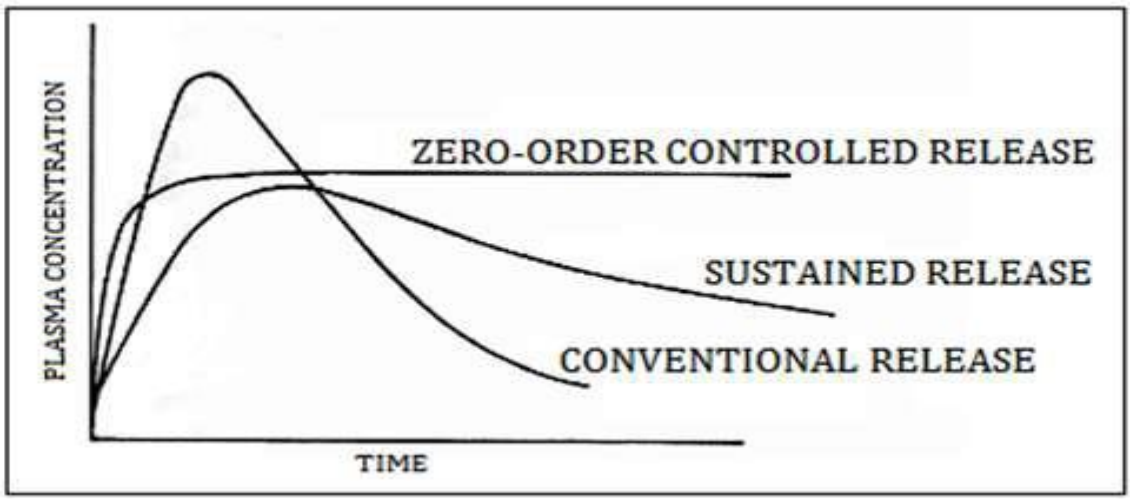

Fig 2: Plasma Drug Concentration Profile for Zero Order Controlled Release, a Sustained Release and Conventional Release Formulation

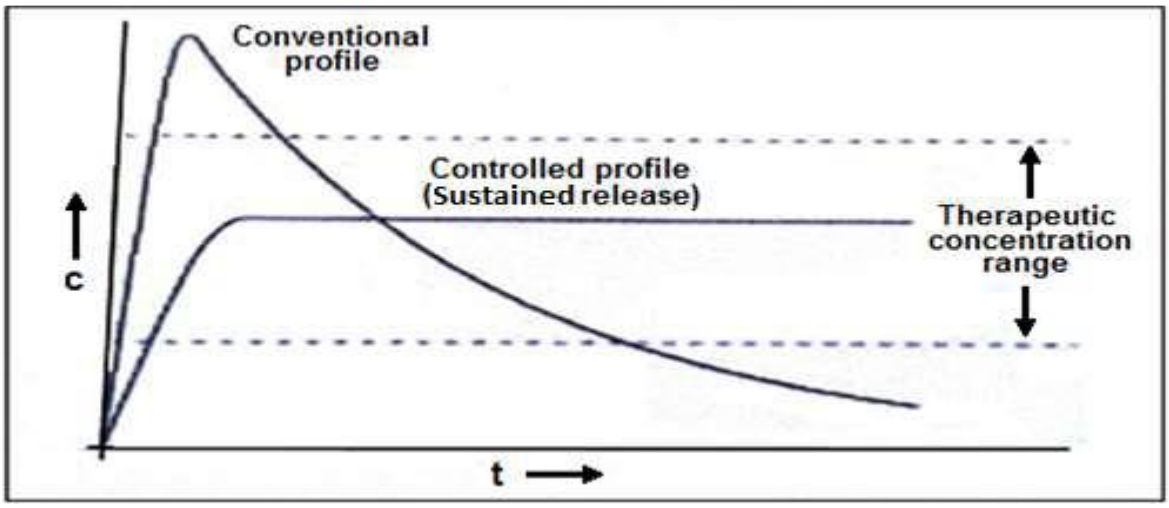

Fig 3: Comparison of Conventional and Controlled (Sustained) Release Profiles

1.4.4. Criteria to Be Met By Drug Proposed to Be Formulated in Sustained Release Dosage Forms: [1]

1. Desirable half-life
2. High therapeutic index
3. Small dose
4. Desirable absorption and solubility characteristics
5. Desirable absorption window
6. First past clearance

1.5. Approaches to Sustain Release Drug Delivery System: [2]

1. Diffusion sustained systems

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a) Reservoir type
b) Matrix type

2. Dissolution sustained systems
   a) Reservoir type
   b) Matrix type
3. Methods using Ion-exchange
4. Methods using osmotic pressure
5. pH independent formulation
6. Altered density formulation

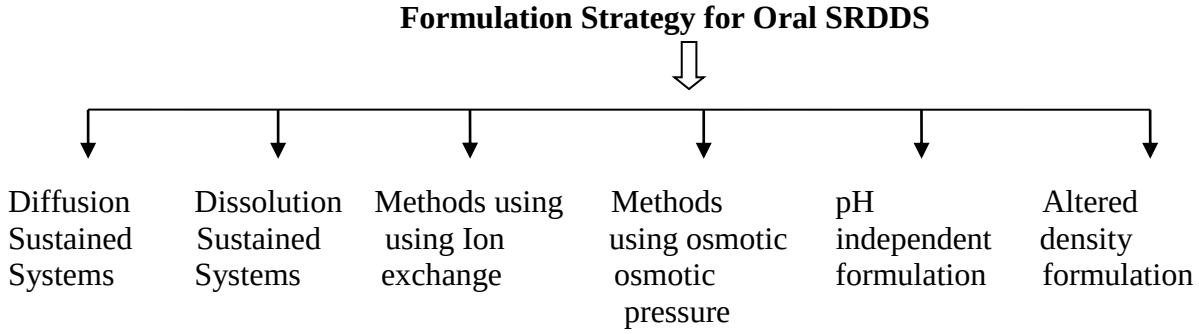

Fig 4: Formulation Strategy for Oral Sustained Release Drug Delivery System

1. Diffusion Sustained System:

The two types of diffusion controlled systems are- reservoir type and matrix type.

a) **Reservoir Type:**

These systems are hollow containing an inner core of drug surrounded in a water insoluble polymer membrane. The drug release mechanism across the membrane involves its partitioning into the membrane with subsequent release into the surrounding fluid by diffusion. In this rate controlling factors are polymeric content in coating, thickness of coating and hardness of microcapsules.

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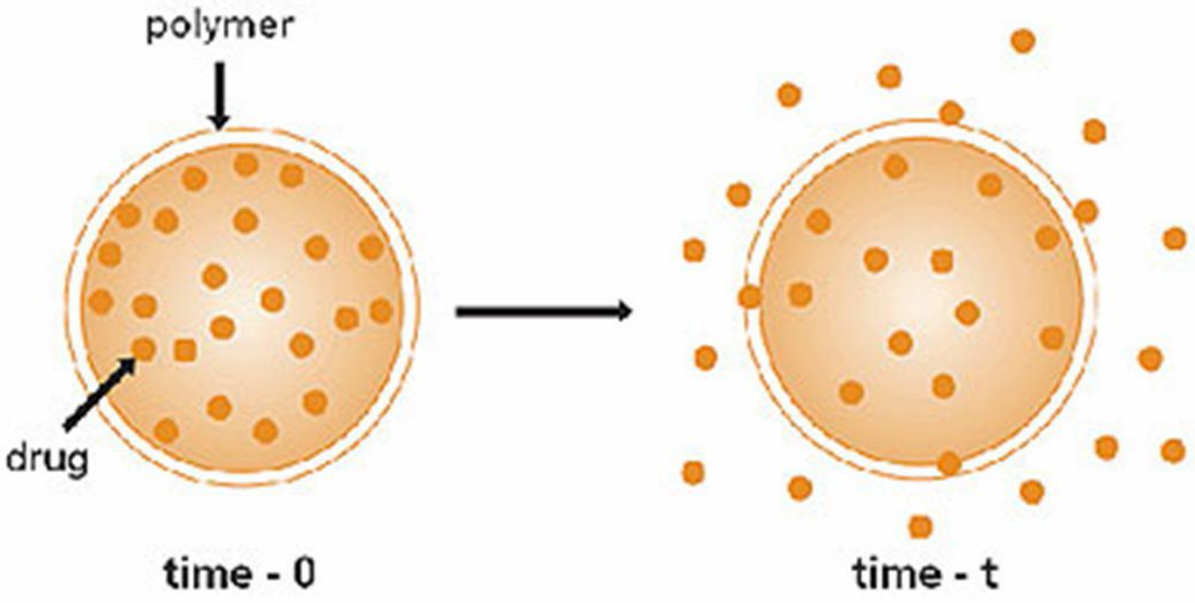

Fig 5: Schematic Representation of Diffusion Sustained Drug Release: Reservoir System

Advantages:
Zero order delivery is possible, release rates variable with polymer type.

Disadvantages:
System must be physically removed from implant sites. Difficulty in delivery high molecular weight compounds, failure of system causes potential toxicity potential toxicity.

b) Matrix type:

Here, the drug is dispersed in an insoluble matrix of rigid nonswellable hydrophobic materials or swellable hydrophobic substances. For sustaining the release of highly water-soluble drugs, swellable matrix systems are widely used. The materials used for these types of matrices are generally hydrophilic gums and may be of natural origin or semisynthetic or synthetic. The drug and the gum are granulated together with a solvent such as alcohol and compressed into tablets. As the gum swells and the drug diffuses out of it and the swollen mass devoid of drug appears transparent or glass like and therefore the system is sometimes called as glassy hydrogels. In this the rate controlling step is diffusion of dissolved drug through the matrix.

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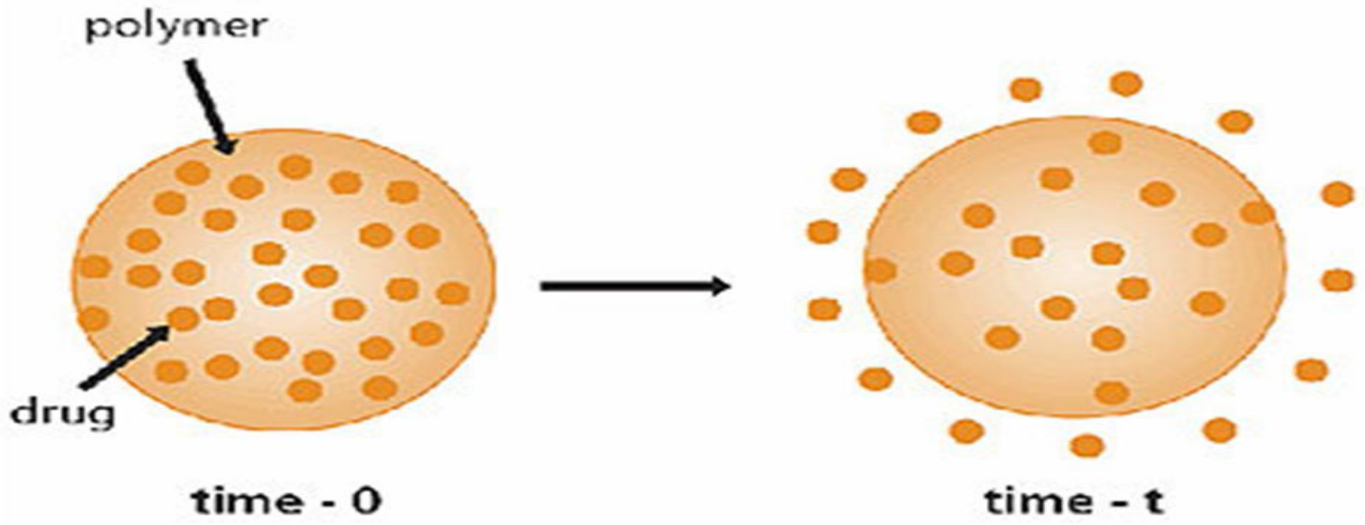

Fig 6: Schematic Representation of Diffusion Sustained Drug Release: Matrix System

Advantages:
High molecular weight compounds can be delivered

Disadvantages:
For implanted system, removal of remaining matrix is necessary; it cannot provide zero order release.

2. **Dissolution sustained systems:**
   Such systems are easiest to design. These systems are of two types-reservoir type and matrix type

   a) **Reservoir Type:**
   Here, the drug particles are coated or encapsulated by one of the several microencapsulation techniques with slowly dissolving materials like cellulose, PEGs, polymethacrylates, waxes etc. The resulting pellets may be filled as such in hard gelatin capsules or compressed into tablets. The dissolution rate of coat depends upon the solubility and thickness of the coating which may range from 1 to 200 microns.

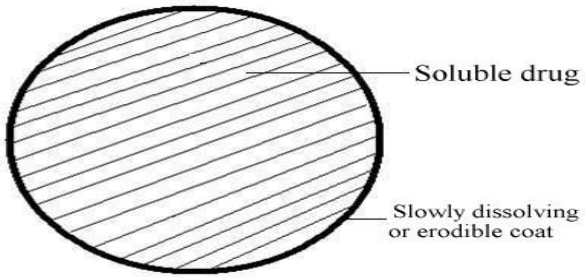

Fig 7: Schematic Representation of Dissolution Sustained Drug Release: Reservoir System

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b) Matrix Type:

These are also called monoliths since the drug is homogenously dispersed throughout a rate-controlling medium. They are very common and employ waxes such as beeswax, carnauba wax, hydrogenated castor oil etc. which control drug dissolution by controlling the rate of dissolution fluid penetration into the matrix by altering the porosity of tablet, decreasing its wettability or by itself getting dissolved at a slower rate.

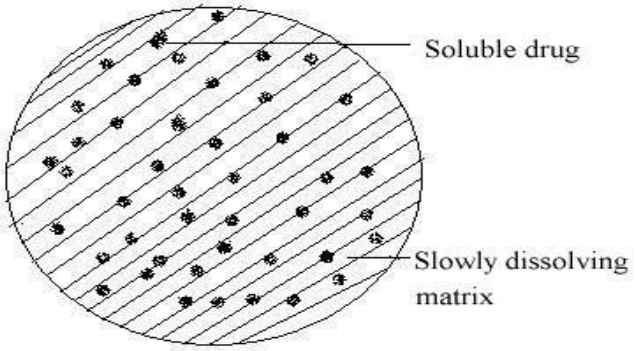

Fig 8: Schematic Representation of Dissolution Sustained Drug Release: Matrix System

3. Methods Using Ion Exchange:

Controlled delivery of ionizable acidic and basic drugs can be obtained by complexing them with insoluble nontoxic anion exchange and cation exchange resins. The drug is released slowly by diffusion through the resin particle structure. The complex can be prepared by incubating the drug-resin solution or passing the drug solution through a column containing ion-exchange resin. The drug-resin complex can be coated with cellulose or hard paraffin and formulated as ion free suspension for padiatric use.

4. Methods Using Osmotic Pressure:

Unlike the solution-diffusion mechanism for most systems, an oral osmotic pump, popularly called as oros, works on the principle of osmotic pressure to release the drug at a constant zero-order rate. A core comprising of drug and an osmotically active substance such as KCl or mannitol is surrounded by a rigid Semi-permeable.

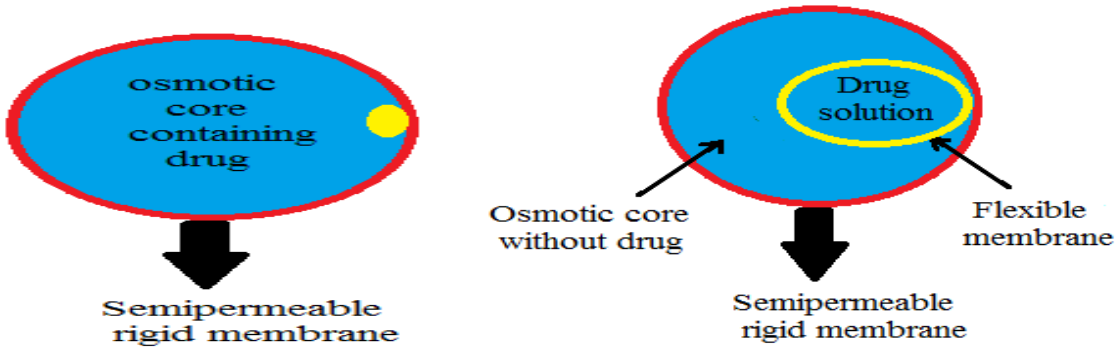

Fig 9: Type – A Osmotic System Type- B Osmotic System

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The ODDS can be conveniently classified into following types:

A. Single chamber osmotic pump
- Elementary osmotic pump (EOP)

B. Multi chamber osmotic pump
- Push pull osmotic pump
- Osmotic pump with non expanding second chamber

C. Specific types
- Controlled porosity osmotic pump
- Monolithic osmotic systems
- Osmotic bursting osmotic pump
- OROS- CT
- Multi Particulate Delayed Release Systems (MPDRS)
- Liquid Oral Osmotic System (L- OROS)

5. pH- Independent Formulations:

Such systems are designed to eliminate the influence of changing GI pH on dissolution and absorption of drugs by formulating them with sufficient amount of buffering agents that adjust the pH to the desired value as the dosage form passes along the GIT and permit drug dissolution and release at a constant rate independent of GI pH.

6. Altered density formulations:

The transit time of GI contents is usually less than 24 hrs. This is the major limiting factor in the design of oral controlled release formulation which can reduce the frequency of dosing to a time period little more than the residence time of drug. However, if the residence time of drug in the stomach/ intestine is prolonged in same way, the frequency of dosing rate can be further reduced.

High Density Approach:

The density of GI fluids is around 1.4 g/cc. use of drug pellets having density greater than this value, preferably above 1.6 g/cc, results in prolonged GI residence that is unaffected by food.

Low Density Approach:

Also called as hydrodynamically balanced systems, such pellets, having density less than that of GI fluids floats on the gastric juice for an extended period of time while slowly releasing the drug.

1.6. Factors affecting the formulation of oral Sustained release drug delivery system: [6]

1) Physicochemical factors

1.1.Aqueous Solubility:

Most of the drugs are weak acids or weak bases. High water solubility drug can dissolve in water or gastrointestinal fluid readily and tends to release its dosage form rapidly and thus is absorbed quickly which

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leads to increase in the blood drug concentration compared to less soluble drug. The biopharmaceutical classification system (BCS) follows the three major factors solubility, dissolution and intestinal permeability which affect the oral absorption.

1.2) Partition coefficient [P (o/w)]:

Partition coefficient is defined as the fraction of drug in an oil phase to that of an adjacent aqueous phase. Drugs that have lower partition coefficient are not suitable for oral CR drug delivery system and drugs that have higher partition co-efficient are also not suitable for oral SR drug delivery system because they will not passes out of the lipid membrane once it gets in the membrane

1.3) Drug pKa and ionization at physiological pH:

Drugs existing largely in ionized form are poor candidates for oral Sustained release drug delivery system. An important assumption is that only unionized form of the drug is absorbed and permeation of the ionized drug is negligible since its rate of absorption is 3 to 4 times less than that of unionized drug. Drug shall be unionized at the site to an extent 0.1-5.0%.

1.4) Drug stability:

Drugs undergo both acid/base hydrolysis and enzymatic degradation when administered oral route. A drug for oral use may destabilize either during its shelf-life or in the GIT. Drugs having poor bioavailability when administered orally, there may be two major stability problems. They are- first the degradation of the drug into inactive form, and second is the interaction with one or more different components either of the dosage form or those present in the GIT to form a complex that is poorly soluble or is unabsorbable.

1.5) Molecular size and diffusivity:

Diffusivity depends on size & shape of the cavities of the membrane. Almost all drugs having molecular weight less than 500 to 600 Daltons easily cross the capillary membrane to diffuse into the extracellular interstitial fluids. For drugs having molecular weight > 500 Daltons, are restricted to enter the cell through aqueous filled channels unless a specialized transport system exists for them.

2) Biological factor:

2.1) Half-life:

It is defined as the time taken for the amount of drug in the body as well as plasma concentration to decline by one-half or 50% of its initial value.. If the drug has short half life (less than 2 hours) the dosage form may contain a prohibitively large quantity of the drug. Ideally, the drug should have half-life of 3-4 hours for formulation of drug delivery system.

2.2) Absorption:

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Absorption rate of a sustained formulation depends upon the release rate constant of the drug from the dosage form, and for the drugs that are absorbed by active transport the absorption is limited to intestine.

2.3) Distribution:

It is defined as the reversible transfer of a drug between the blood and the extravascular fluids and tissues. Since it not only lowers the concentration of circulating drug but it also can be limiting in its equilibrium with blood and extra vascular tissue depending on the time course of drug deposition. Thus for design of sustain release products, one must have information of disposition of drug.

2.4) Metabolism:

The metabolic conversion of a drug is defined as the chemical conversion of one form to another. A successful sustain release product can be developed, if the location, rate and extent of metabolism are known.

2.5) Therapeutic index:

Drugs with low therapeutic index are unsuitable for in Sustained release formulations. If the system fails in the body, dose dumping may occur, which leads to toxicity.

2.6) Absorption window:

Drugs when administered orally are absorbed only from a specific part of gastrointestinal tract. This part is referred to as the *'*absorption window'. These drugs are also unsuitable for SRDDS.

1.6.1. Characteristics of drugs unsuitable for oral sustained release forms:

- Not effectively absorbed in the lower intestine e.g. riboflavin, ferrous salts.
- Absorbed and excreted rapidly; short biologic half-lives (< 1 hr) e.g. penicillin G, furosemide.
- Long biologic half-lives (> 12 hr.) e.g. diazepam, phenytoin
- Large doses required (> 1g) e.g. Sulfonamides.
- Cumulative action and undesirable side effects, drugs with low therapeutic indices e.g. Phenobarbital, digitoxin
- Precise dosage titrated to individual is required e.g. anticoagulants, cardiac glycosides.
- No clear advantage for sustained release formulations e.g. Griseofulvin.

1.7. MATRIX TABLETS [11]

Two classes of retardant material used to formulate matrix:

- Soluble, inert Polyethylene, Polyvinylchloride, Ethyl cellulose.
- Insoluble, erodible Carnauba wax, Stearic acid, Polyethylene glycol.

Hydrophilic matrix tablet: [12]

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Hydrophilic matrix can be utilized as a means to control the drug release rate. To activate the release mechanism, the hydrophilic matrix requires water and thus having several advantages, including ease of manufacture and excellent uniformity of matrix tablets. Upon immersion in drug release is controlled by a gel diffusion barrier that is formed and tablet erosion. The matrix building material with fast polymer hydration capability is the best choice to use in a hydrophilic matrix tablet formulation. The polymers used in the preparation of hydrophilic matrices are divided into three broad groups as follows:

- **Cellulose derivatives:** HEC, HPMC, Ethyl cellulose, Cellulose acetate, Cellulose acetate propionate, HPC

- **Non- cellulose natural or semi synthetic polymers:** Agar-agar, Carob Gum, Alginates, Molasses, Polysaccharides of Mannose and Galactose, Chitosan and Modified starches.

- **Polymers of acrylic acid:** Polymers which are used in acrylic acid category is Carbopol 934P, other hydrophilic materials used for preparation of matrix tablet are Alginic acid, Gelatin and Natural Gums.

Fat –wax matrix tablet:

The drug can be incorporated into fat-wax granulations by spray congealing in air, blend congealing in an aqueous media with or without the aid of surfactant and spray-drying techniques. In the bulk congealing method, a suspension of drug and melted fat-wax is solidify and is then prepared for sustained-release granulations. The mixture of active ingredients, waxy materials and fillers are converted into granules. The drug is sprayed into a melt of fats and waxes are released by leaching or hydrolysis as well as dissolution of fats under the influence of enzymes and pH change in the gastrointestinal tract. The addition of surfactants to the formulation can also influence both the drug release rate and the proportion of total drug that can be incorporated into a matrix.

Plastic matrix tablet (Hydrophobic matrices): [3]

Sustained release tablets based upon an inert compressed plastic matrix have been used extensively. Release is usually delayed because the dissolved drug has to diffuse through capillary network. Polymers used are as follows: Polyvinyl chloride, Ethyl cellulose, Cellulose acetate and Polystyrene.

Biodegradable Matrices:

These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. Examples are natural polymers such as proteins, polysaccharides and modified natural polymers, synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

Mineral matrices:

These consist of polymers which are obtained from various species of seaweeds. Example is alginic acid which is obtained from species of brown seaweeds (Phaephyceae) by the use of dilute alkali. Matrix systems can also be classified according to their porosity and these are macro porous, micro porous and non- porous systems.

2. DRUG AND POLYMER PROFILE

2.1. GLIPIZIDE

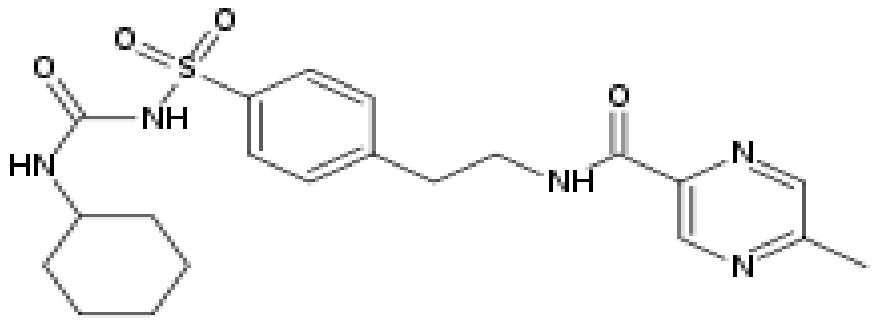

Figure 10: General Structure of Glipizide

Sl..No	Parameter	Observation
1.	Color	White
2.	Odor	Odorless
3.	Taste	Tasteless
4.	Texture	Crystalline powder

Table 3: Physical Properties of Glipizide

Chemical Formula	C_{21} H_{27} N_5 O_4 S
IUPAC Name	1-cyclohexyl-3-[[4-[2-[[(5-methylpyrazine-2-yl)carbonyl]amino]ethyl]phenyl]sulphonyl]urea
Route of administration	Oral
pka value	5.9
Log P	1.37
Protein binding	97-99%

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Volume of distribution	11 L
Metabolism	Hepatic
Dose	5-10 mg
Half-life	2-4 hours
Melting point	201-202ºC
Molecular weight	445.5 g/mol
Route of elimination	Approximately 90% of dose is excreted as biotransformation products in urine (80%) and faeces (10%). It is eliminated primarily by hepatic biotransformation, less than 10% of a dose is excreted as unchanged.
Toxicity	Low blood sugar, tingling of lips and tongue, nausea, yawning, confusion, agitation, tachycardia, sweating, convulsions, stupor and coma. Intoxication with sulfonylureas can cause hypoglycemia and patients are best managed with glucose administration.

Table 4: Pharmacokinetic Parameters of Glipizide

Pharmacology:

Glipizide, a second generation sulfonyl urea is used to lower blood glucose in patients with diabetes mellitus type II. The primary mode of action of glipizide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. Fasting insulin levels are not elevated even on long-term glipizide administration, but the post prandial insulin response continues to be enhanced after at least 6 months of treatment.

Mechanism of Action:

Glipizide acts by partially blocking potassium channels among beta cells of pancreatic islets of Langerhans. By potassium channels, the cell depolarizes which results in the opening of voltage-gated calcium channels. The resulting calcium influx encourages insulin released from beta cells. Sulfonyl urea's may also cause the decrease of serum glucagon and potentiate the action of insulin at the extra pancreatic tissues.

Drug Interactions:

Alcohol is reported to prolong but not increase the hypoglycemic effect of glipizide. A disulfiram-like reaction (characterized primarily by flushing of the face, neck and arms) can occur but with sulphonylureas like

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glipizide, gliclazide, glibenclamide etc. Sodium bicarbonate significantly increased the absorption of glipizide and enhanced its effects to some extent, but the total absorption was unaltered. Magnesium hydroxide also considerably increased the rate of absorption of glipizide. Glipizide may significantly increase the plasma concentration of cyclosporine by reducing its metabolism, dose reduction of cyclosporine may be necessary.Trimethoprim may augment glipizide induced hypoglycemia and patients should be closely observed, when using these drugs simultaneously. One case of acute hypoglycemia was reported when glipizide was administered with co-trimoxazole.

Adverse Effects:

Cardiovascular - Edema, Syncope

Central Nervous System - Anxiety, Depression,

Headache, Insomnia,

Nervousness

Gastrointestinal - Anorexia, Nausea, Vomiting,

Constipation, Flatulence

Hepatic - Cholestatic jaundice, hepatic

Porphyria.

Ocular - Blurred vision

Renal - Diuretic effect (minor)

2.2 ETHYL CELLULOSE

Ethyl cellulose is a derivative of cellulose in which some of the hydroxyl groups on the repeating glucose units are converted into ethyl ether groups.

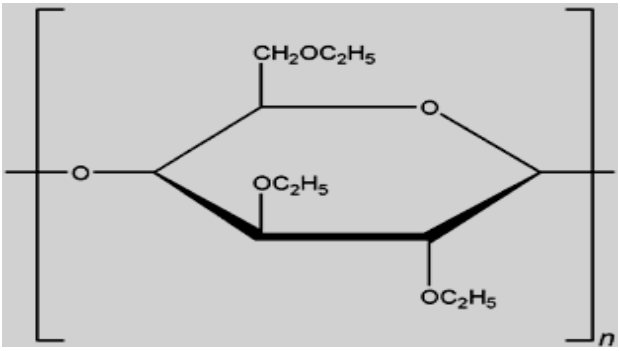

Figure 11: General Structure oF Ethyl Cellulose

IUPAC Name	2-[4,5-diethoxy-2-(ethoxymethyl)-6-methoxyoxan-3-yl]-6-(hydroxymethyl)-5-methoxyoxane-3,4-diol
Physical properties	❖ White or yellowish-white powder or granular. ❖ Powder, odorless or almost odorless.
Form of Product	Powder
Dissolution	Dissolution above pH 6.0
Characteristics	❖ Availability in a wide range of viscosity or molecular weight grade. ❖ Solubility in a variety of organic solvents. ❖ With various water soluble materials that permit the permeability characteristics of matrix film to be readily changed. ❖ Coast is comparatively less than other polymer.
Weight average molar mass	Variable
Glass Transition Temperature (Tg)	133.4ºc
Molecular weight	454.50912 g/mol
Empirical Formula	C_{12} H_{23} O_6 (C_{12} H_{22} O_5) n C_{12} H_{23} O_5
Density	0.4 g/cm^3

Table 5: Polymer Profile of Ethyl Cellulose

Application in Pharmaceutical Formulation or Technology:

- Ethyl cellulose is widely used in oral and topical pharmaceutical formulation.
- It is used as hydrophobic coating agent for tablets and granules.
- It is used as modify the release of drug and used as taste masking of drugs.
- It is used as thickening agents in creams, gels or lotions.
- Drug release can be controlled by diffusion, through the film coating of Ethyl cellulose

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2.3 XANTHAN GUM

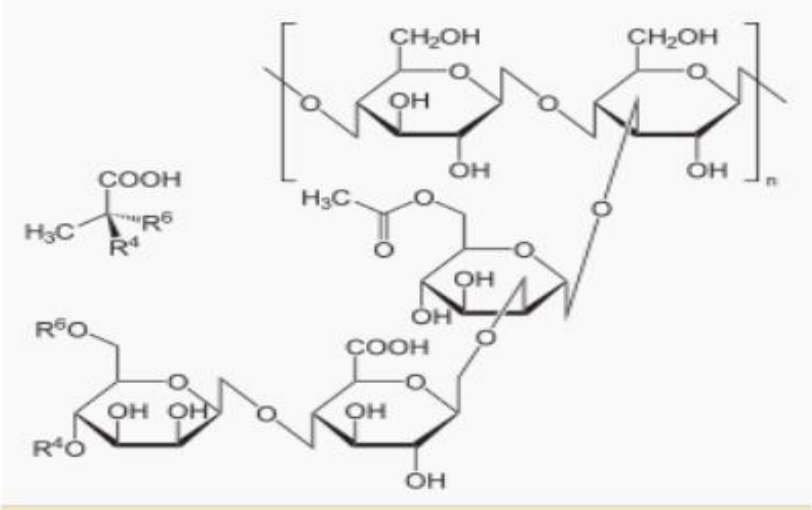

Figure 12: General Structure of Xanthan Gum

Synonyms	❖ Corn sugar gum,Keldent, Grindsted ❖ Rhodicare, Rhodigel, Xantural
Chemical Name and CAS Registry Number	Xanthan gum [11138-66-2]
Empirical Formula	$(C_{35}H_{49}O_{29})_n$
Molecular weight	1×10^6
Functional category	Gelling agent; stabilizing agent; suspending agent; sustained-release agent; viscosity-increasing agent.
Description	Xanthan gum occurs as a cream- or white-colored, odorless, free flowing, fine powder.
Acidity/ Alkalinity	pH = 6.0–8.0 for a 1% w/v aqueous solution.
Stability	❖ Xanthan gum is a stable material. Aqueous solutions are stable over a wide pH range (pH 3–12), although they demonstrate maximum stability at pH 4–10 and temperatures of 10–60ºC. ❖ Xanthan gum solutions of less than 1% w/v concentration may be adversely affected by higher than ambient temperatures.

	❖ It ensures excellent freeze–thaw stability.
Solubility	Practically insoluble in ethanol and ether; soluble in cold or warm water
Specific gravity	1.600 at 25ºc
Incompatibilities	❖ Xanthan gum is an anionic material and is not usually compatible with cationic surfactants, polymers, or preservatives, as precipitation occurs. ❖ Anionic and amphoteric surfactants at concentrations above 15% w/v cause precipitation of Xanthan gum from a solution.
Storage condition	Xanthan gum provides the same thickening, Stabilizing, and suspending properties during long-term storage at elevated temperatures as it does at ambient conditions.

Table 6: Polymer Profile of Xanthan Gum

Application in Pharmaceutical Formulation or Technology:

- It is widely used in oral and topical pharmaceutical formulations, and stabilizing agent.
- It has also been used as a suspending agent for conventional, dry and sustained –release suspensions.
- It is also used as a thickening and emulsifying agent.
- It is non-toxic, compatible with most other pharmaceutical ingredients has good stability and viscosity properties over a wide pH and temperature range.
- Although primarily used as a suspending agent, Xanthan gum has also been used to prepare sustained-release matrix tablets

2.4 PECTIN

Pectin is a complex polysaccharide comprising mainly esterified D-galacturonic acid residues in a α-(1–4) chain. The acid groups along the chain are largely esterified with methoxy groups in the natural product. The hydroxyl groups may also be acetylated.

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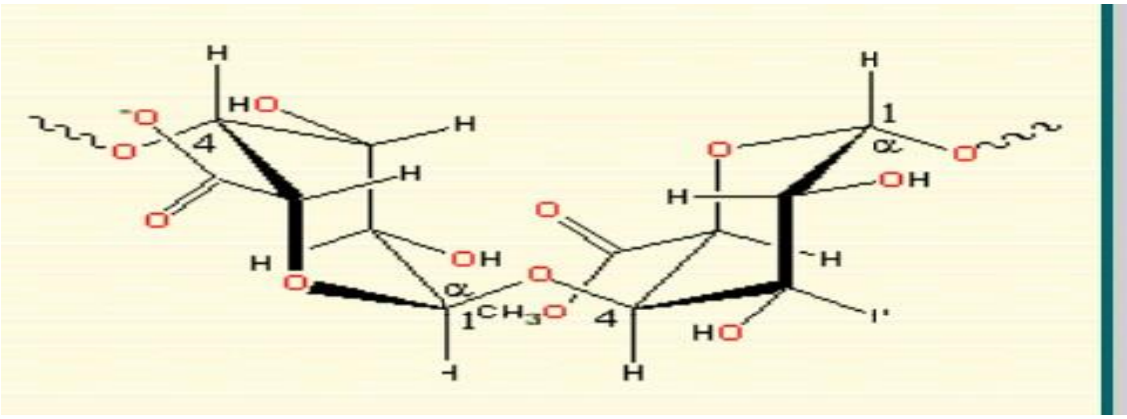

Figure 13: General Structure of Pectin

Synonyms	❖ Citrus pectin; E440; Genu; methopectin; ❖ Methyl pectin; methyl pectinate; mexpectin; pectina; pectinic acid.
Chemical Name and CAS Registry Number	Pectin [9000-65-5]
Functional Category	Adsorbent; emulsifying agent; gelling agent; thickening agent; stabilizing agent.
Empirical Formula	Pectin is a high-molecular-weight, carbohydrate-like plant constituent consisting primarily of chains of galacturonic acid units linked as 1, 4-a-glucosides.
Molecular Weight	30000-100000
Description	Pectin occurs as a coarse or fine, yellowish-white, odorless powder that has a mucilaginous taste.
Acidity/ Alkalinity	pH = 6.0–7.2
Stability	Pectin is a nonreactive and stable material.
Solubility	Soluble in water; insoluble in ethanol (95%) and other organic solvents.
Storage condition	It should be stored in a cool, dry place.

Table 7: Polymer Profile of Pectin

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Application in Pharmaceutical Formulation or Technology:

- Pectin has been used as an adsorbent and bulk-forming agent, and is present in multi-ingredient preparations for the management of diarrhea, constipation and obesity.
- It has also been used as an emulsion stabilizer
- Pectin has been used in gel formulations for the oral sustained delivery of ambroxol.
- It has also been used in a colon-biodegradable pectin matrix with a pH-sensitive polymeric coating which retards the onset of drug release, overcoming the problems of pectin solubility in the upper GI tract.

2.5 Hydroxy propyl methylcellulose K 15 M:

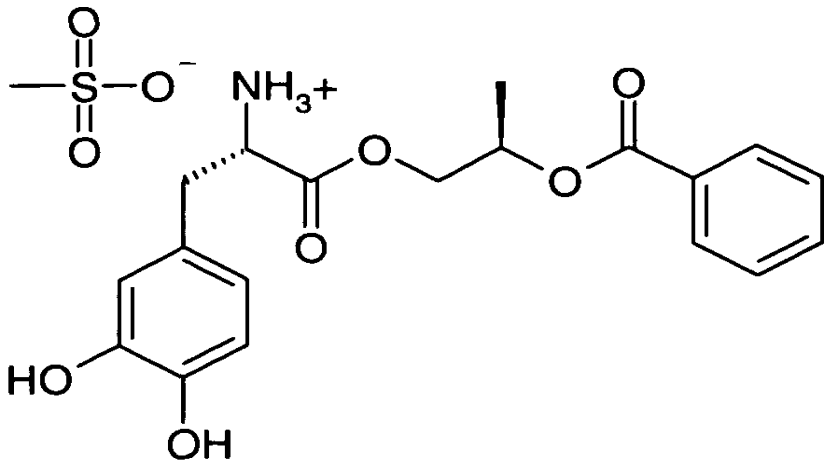

Figure 14: General Structure of HPMC K 15 M

Synonyms	❖ Benecel MHPC, hydroxy propyl methylcellulose, Hypromellose, methocel ❖ Methylcellulose propylene glycol ether, methyl hydroxypropylcellulose, Metolose, Tylopur.
Empirical Formula	O- Methylene
Chemical Name	Cellulose hydroxy propyl methyl ether
Molecular weight	10000- 1500000
Functional category	Dispersing agent, dissolution enhancer, emulsion stabilizer, Bioadhesive material, coating agent, controlled-release agent, viscosity increasing agent.

Acidity / Alkalinity	pH= 5.0 – 8.0 for a 2% w/w aqueous solution
Ash	41.5%
Density (bulk)	0.341 g/cm^3
Specific gravity	1.26 g/cm^3
Stability	❖ Usually powder is a stable material, although it is hygroscopic after drying. ❖ Solutions are stable at pH 3-11
Storage condition	It should be stored in a well-closed container, in a cool, dry place

Table 8: Polymer Profile of HPMC K 15 M

Applications in Pharmaceutical Formulation or Technology:

- It is widely used in ophthalmic, oral, nasal and topical pharmaceutical formulations.
- It is used as a tablet binder, in film-coating, and as a matrix for use in extended release tablet formulations.
- High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10- 80% w/w in tablets and capsules.
- It is also used in liquid oral dosage forms as a suspending agent and / or thickening agent at concentration ranging from 0.25-5.0%.

2.6 GUAR GUM

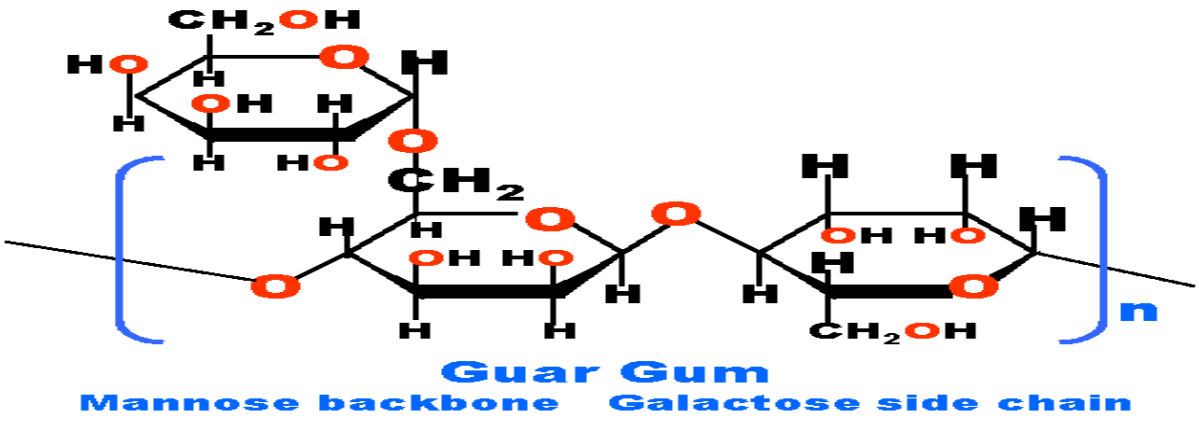

Figure 15: General Structure of Guar Gum

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Synonyms	E412; Galactosol; guar flour; guar galactomannanum; jaguar gum; ❖ Meyprogat; Meyprodor; Meyprofin
Chemical Name and CAS Registry Number	Galactomannan polysaccharide [9000-30-0]
Empirical Formula	$(C_6H_{12}O_6)_n$
Molecular weight	≈220 000
Functional Category	Suspending agent; tablet binder; tablet disintegrant; viscosity increasing agent
Description	The USP32–NF27 describes guar gum as a gum obtained from the ground endosperms of Cyamopsis tetragonolobus (L.) Taub. (Fam. Leguminosae). It consists chiefly of a high-molecular-weight hydrocolloidal polysaccharide, composed of galactan and mannan units combined through glycoside linkages, which may be described chemically as a galactomannan. The main components are polysaccharides composed of D-galactose and D-mannose in molecular ratios of 1: 1.4 to 1: 2. The molecule consists of a linear chain of b-(1!4)-glycosidically linked manno-pyranoses and singlea-(1!6)-glycosidically linked galactopyranoses.
Acidity / Alkalinity	pH = 5.0–7.0 (1% w/v aqueous dispersion)
Solubility	Practically insoluble in organic solvents. In cold or hot water, guar gum disperses and swells almost immediately to form a highly viscous, thixotropic sol. The optimum rate of hydration occurs at pH 7.5–9.0.
Density	1.492 g/cm3
Stability	Aqueous guar gum dispersions have a buffering action and are stable at pH 4.0–10.5. However, prolonged heating reduces the viscosity of dispersions
Incompatibilities	❖ Guar gum is compatible with most other plant hydrocolloids such as tragacanth. ❖ It is incompatible with acetone, ethanol (95%), tannins, strong acids, and alkalis. Borate ions, if present in the dispersing water, will prevent the

	hydration of guar gum.
Storage condition	It should be stored in a well-closed container in a cool, dry place.

Table 9: Polymer Profile of Guar Gum

Application in Pharmaceutical Formulation or Technology:

- It is commonly used in cosmetics, food products and pharmaceutical formulations.
- It also used in the preparation of sustained-release matrix tablets in the place of cellulose derivatives such as methylcellulose.
- It is also used in solid- dosage forms as a binder and disintegrant.
- In oral and topical products as a suspending, thickening and stabilizing agent and also as a controlled-release carrier.
- Therapeutically, guar-gum has been used as a part of the diet of patients with diabetes mellitus.

2.7 EUDRAGIT RS 100

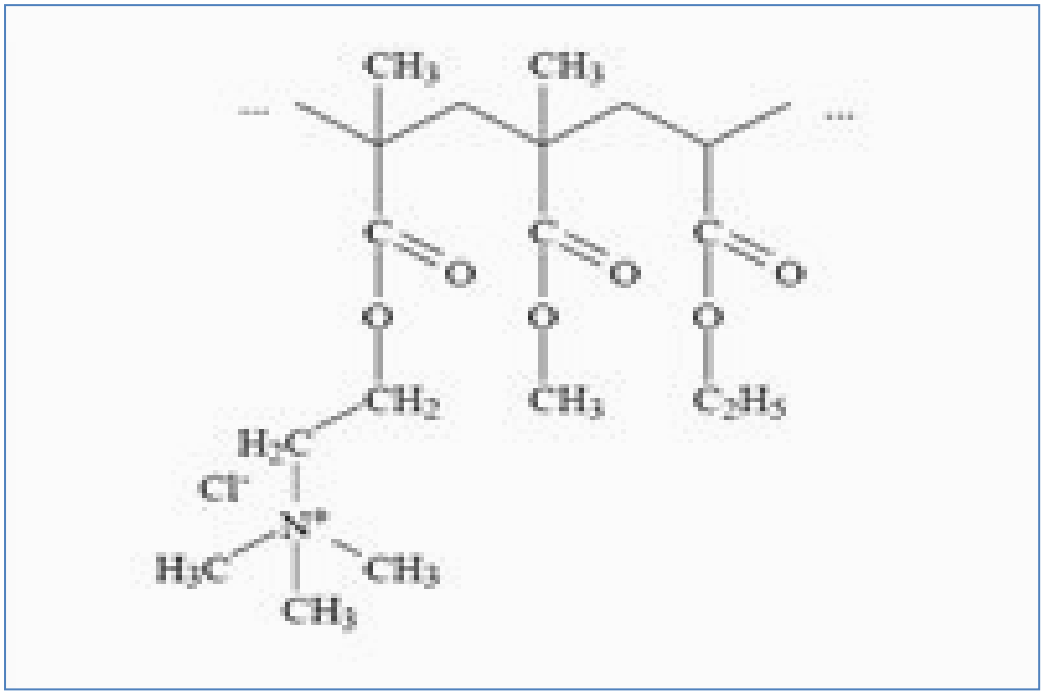

Figure 16: General Structure of Eudragit RS 100

Nonproprietary Name	Ethacrylic acid copolymers (USP)
Chemical Name	Poly (ethyl acrylate-co-methyl methacrylate-corimethylammonioethyl methacrylate chloride) 1:2:0.1.
Product form	Granules
Average Molecular Mass	32000 g/mol
Functional Category	Eudragit RS 100 used as bioadhesive material, emulsifying agent, suspending agents, controlled-release agents, film former and tablet binders etc.
Description	Eudragit RS 100 is a copolymer of methyl methacrylate, ethyl acrylate and quaternary ammonium groups with a low content of methacrylic acid ester. The ammonium groups are make the polymers permeable.
Solubility	Practically insoluble in petroleum ether, 1 N sodium hydroxide and water.
Storage Condition	It should be stored in a well closed container in a cool, dry place.

Table 10: Polymer profile of Eudragit RS 100

Application in Pharmaceutical Formulation or Technology:

- **Ophthalmic drug delivery**
  Eudragit RS100 has positive charge and no toxicity with good bioadhesive strength which make it suitable for ophthalmic controlled release drug delivery.

- **Buccal and sublingual drug delivery**
  It provides good adhesive strength with good drug release barrier, due to good adhesive strength it retained in the mouth with desired duration.

- **Gene drug delivery**
  It is used as gene delivery; antisense oligodeoxy nucleotides were successfully delivered by nano particle of Eudragit RS 100.

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3. PREPARATION OF SUSTAINED RELEASE TABLET OF GLIPIZIDE

Tablets were prepared by wet granulation technique. The composition of formulation is given in Table 11 .All the powders were passed through 80 mesh. Required quantities of drug and polymer were mixed thoroughly, and a sufficient volume of binder was added slowly. After enough cohesiveness was obtained, the mass was half dried and after that sieved through 22 mesh. The half dried granules again fully dried and then sieved through 22/44 mesh. Once dry, the granules retained on 44 mesh were mixed with 15% of fines (granules that passed through 44 mesh). Microcrystalline cellulose as a diluent, Talc and magnesium Stearate were finally added as glidant and lubricant. Granules thus obtained were compressed into tablets on a 16 station single punch rotary tablet compression machine (Cadmach). A flat-faced punch 8 mm in diameter was used for tableting. Compression force of the machine was adjusted to obtain the hardness of 4-6 kg/cm2 for different batches.

3.1 SCHEMATIC REPRESENTATION

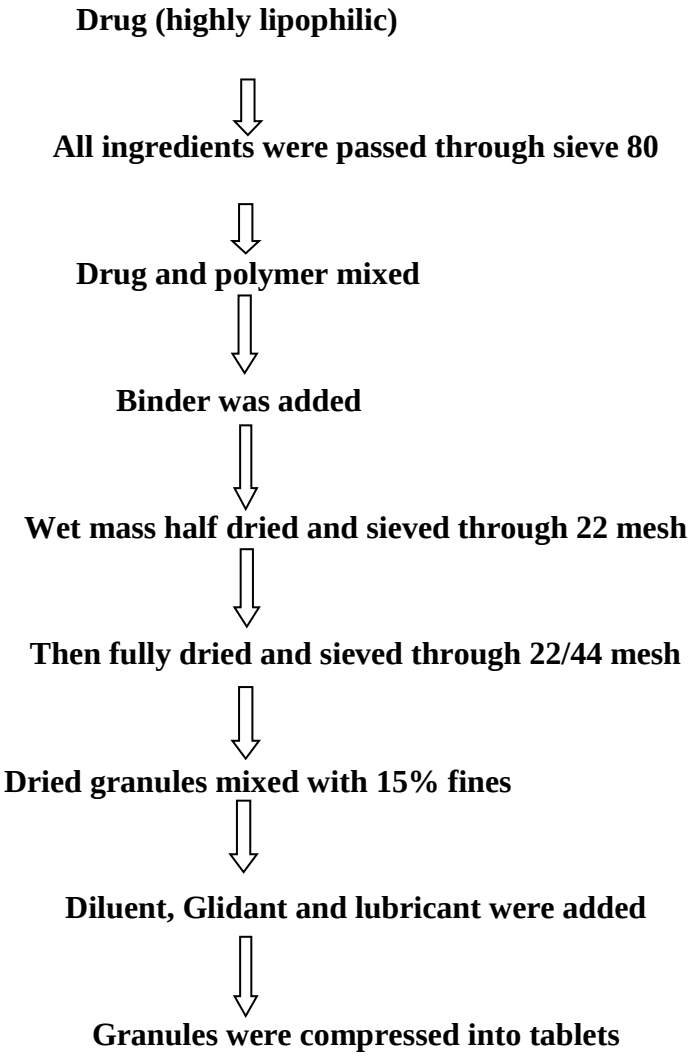

Fig 17: Schematic Representation of Preparation of Sustained Release Matrix Tablet of Glipizide

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3.2 Formulation of Glipizide Sustained Release Matrix Tablet

Ingredients	Quantity (mg)					
	FP_1	FP_2	FP_3	FP_4	FP_5	FP_6
Drug	5	5	5	5	5	5
HPMC K 4 M	-	-	-	-	-	40
HPMC K 15 M	-	40	-	-	-	-
Ethyl Cellulose	-	20	-	-	-	20
Guar gum	-	-	-	25	-	-
Xanthan gum	25	-	-	-	50	-
Eudragit RS 100	25	-	25	25	-	-
Pectin	-	-	25	-	-	-
MCC	45	54	45	45	119	54
Lactose	77	50	77	77	-	50
Starch	20	25	20	-	20	25
PVP K-30	-	-	-	20	-	-
Magnesium stearate	3	3	3	3	3	3
Talc	-	3	-	-	3	3
Total Weight	200	200	200	200	200	200

Table 11: Composition of Sustained Release Tablet of Glipizide

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4. EVALUATION

4.1 QUANTITATIVE ESTIMATION OF DRUG

Preparation of calibration curve of Glipizide in different solvent media like distilled water, Phosphate buffer pH 6.8, Phosphate buffer pH 7.4, 0.1 N HCl.

100 mg of Glipizide was weighed accurately and dissolved in small volume of methanol. The volume of solution was made up to 100 ml. the solution was marked as stock solution- I, the 10ml of stock one was taken and volume of solution was made up to 100ml (stock-II).

- From stock-II, dilutions having concentration 5µg/ml, 10µg/ml, 15µg/ml, 20µg/ml, 25µg/ml were prepared.
- Above prepared solution were observed in double beam UV- Spectrophotometer (Shimadzu, Model No.1700) to measure the absorbance, in increasing order of concentration.

Sl.No.	Concentration(µg/ml)	Absorbance (λ_{max} 274 nm)
1	5	0.029
2	10	0.035
3	15	0.046
4	20	0.068
5	25	0.087

Table 12: Preparation of Calibration Curve of Glipizide in Distilled Water At Λ_{Max} 274nm

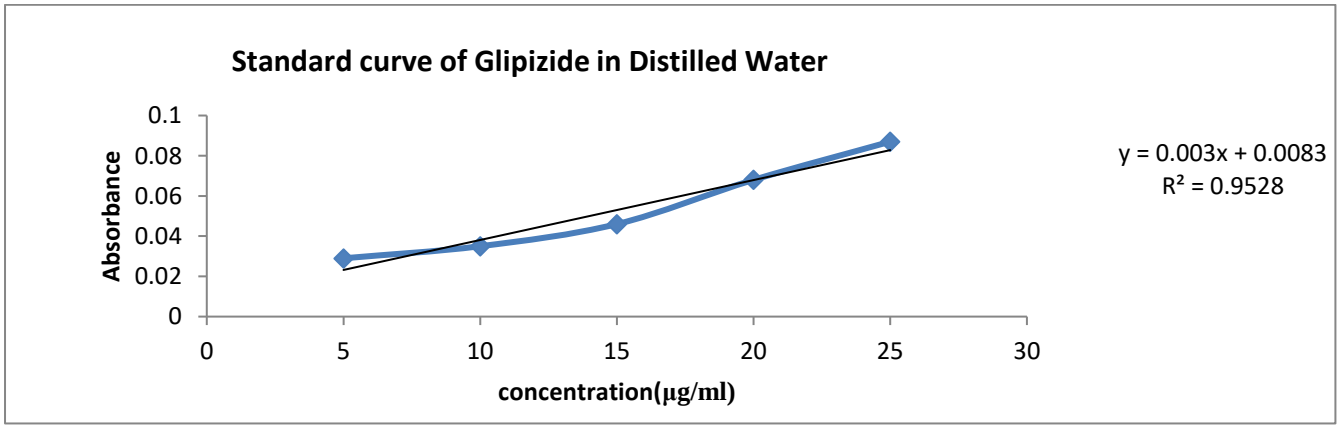

Figure 19: Calibration Curve of Glipizide in Distilled Water

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S.NO.	Concentration (µg/ml)	Absorbance (λ_{max} 276 nm)
1	5	0.071
2	10	0.120
3	15	0.188
4	20	0.257
5	25	0.332

Table 13: Preparation of Calibration Curve of Glipizide in Ph 6.8 Phosphate Buffer At Λ_{Max} 276 Nm

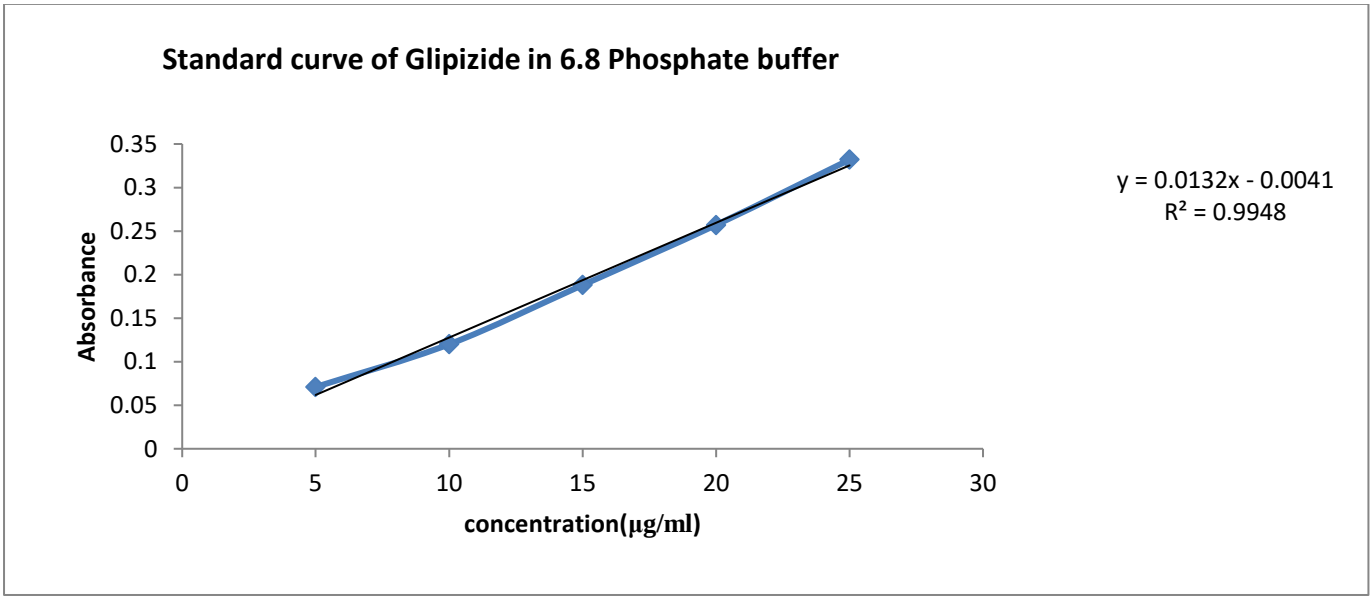

Figure 20: Calibration Curve of Glipizide In Ph 6.8 Phosphate Buffer

S.NO.	Concentration (µg/ml)	Absorbance (λ_{max} 276 nm)
1	5	0.120
2	10	0.231
3	15	0.302
4	20	0.423
5	25	0.525

Table 14: Preparation of Calibration Curve of Glipizide in Ph 7.4 Phosphate Buffer at Λ_{max} 276 Nm

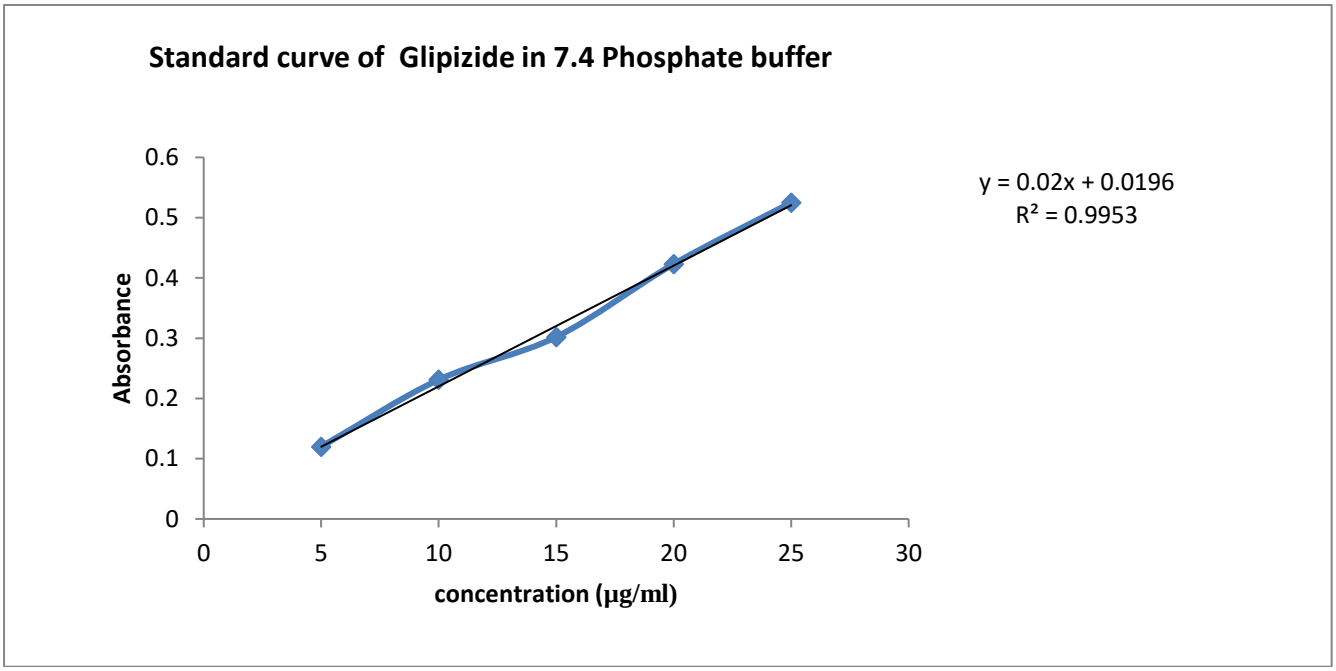

Figure 21: Calibration Curve of Glipizide In Ph 7.4 Phosphate Buffer

S.NO	Concentration (µg/ml)	Absorbance (λ_{max} 278.5 nm)
1	5	0.124
2	10	0.211
3	15	0.301
4	20	0.404
5	25	0.511

Table 15: Preparation of Calibration Curve of Glipizide In 0.1 N Hcl At Λ_{max} 278.5 Nm

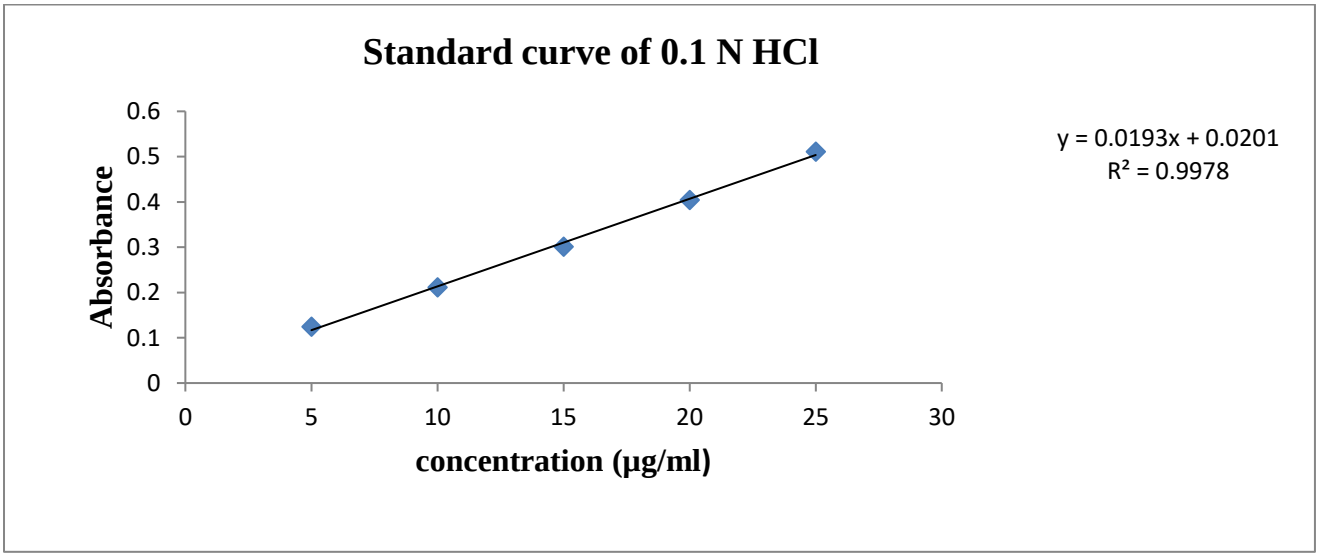

Figure 22: Calibration Curve of Glipizide In 0.1 N Hcl

4.2 EVALUATION OF RHEOLOGICAL PARAMETERS

1. Angle of Repose

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The granules were allowed to flow through the funnel freely onto the surface.

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The height and diameter of the powdered cone was measured angle of repose was calculated by using the following formula,

$$\tan \Theta = h/r, \text{ therefore, } \Theta = \tan^{-1} h/r$$

Where,

Θ = angle of repose
h = height of the cone in cm
r = radius of the cone base in cm

Angle of Repose	Type of Flow
< 25	Excellent
25 – 30	Good
30 – 40	Possible
>40	Very poor

2. Bulk Density

An accurately weighed granules of powder was introduced into a 100 ml measuring cylinder, the initial volume was observed and bulk density was calculated by using the following formula,

Bulk density = weight of the powder / bulk volume of the powder

3. Tapped Density

An accurately weighed granules of powder was introduced into a 100 ml measuring cylinder. Now the cylinder was allowed to tap at regular interval until no further change in the volume was observed and tapped density was calculated by using the following formula,

Tapped density = weight of the powder / tapped volume of the powder

4. Carr's Index

The compressibility index of the granules was determined by Carr's compressibility index.

Carr's index % = (Tapped density – Bulk density) / tapped density × 100

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Carr's Index	Type of Flow
5 – 15	Excellent
15 – 18	Good
18 -23	Fair to possible
23 – 35	Poor
35 – 38	Very poor

5. Hausner's Ratio

Hausner's ratio is a number that is correlated to the flow ability of a powder

Hausner's ratio = (Tapped density / Bulk density) × 100

4.3 EVALUATION OF SUSTAINED RELEASE MATRIX TABLET

Tablets were subjected to evaluation of properties including weight variation, tablet hardness, friability, size and shape, thickness and in-vitro release with different media.

1. Weight Variation

The weight of the tablet being made routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weight to the average.

2. Tablet Hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by Monsanto hardness tester. The hardness was measured in terms of kg/cm^2; three tablets were chosen randomly and tested for hardness

3. Friability

Friability was determined using Roche friabilator and expressed in percentage (%). 5 tablets from each batch were weighed separately and placed in the friabilator, which was then operated for 100 revolutions

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at 25 rpm. The tablets were reweighed and the percentage friability was calculated for each batch using formula,

$$\% \text{ Friability} = \frac{\text{Initial weight of tablet} - \text{Final weight of tablets}}{\text{Initial weight of tablet}} \times 100$$

4. Tablet Thickness

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier caliper. It was determined by checking the thickness of ten tablets of each formulation. The extent to which the thickness of the each tablet deviated from ± 5% of the standard value was determined.

5. Content Uniformity:

The tablets were tested for their drug content uniformity. At random 20 tablets were weighed and powdered. The powder equivalent to 100 mg of drug was weighed accurately and dissolved in 100ml of phosphate buffer of pH 6.8. The solution was shaken thoroughly and subjected for sonication. The undissolved matter was removed by filtration through Whatman's filter paper No.41. Then dilutions were carried out (if required). The absorbance of the diluted solutions was measured at 276 nm. The concentration of the drug was computed from the standard curve of glipizide in phosphate buffer of pH 6.8 and the drug content was calculated using formula,

$$\text{Drug content} = \frac{\text{Conc.} \times \text{vol.} \times \text{DF}}{100}$$

6. In-Vitro Dissolution Study

In- vitro drug release studies were carried out using USP Dissolution testing apparatus Type II, paddle method. The tablets were placed in the 0.1 N HCl for first 2 hours and pH 6.8 phosphate buffer for next 4 hours and pH 7.4 phosphate buffer for next 2 hours respectively, then the apparatus was run at 37ºC ± 0.5ºC and a rotating speed of 50 rpm in a 900 ml dissolution medium. The 5 ml aliquots were withdrawn at intervals of 30 mins and done for 8 hours and replacement of withdrawn was done each time with equal amounts of fresh dissolution medium maintained at same temperature and tested for drug release. Process was repeated for 3 times, for each formulation [n=3].

7. Drug release kinetic study

To study the release kinetics of in-vitro drug release, data was applied to kinetic models such as Zero order, First order, Higuchi, Korsmeyer-Peppas and Hixson Crowell. The kinetics of drug release was calculated by using BIT-soft 1. 12.

4.3.1. Physical Appearance

Sl.No	Parameter	Observation
1	Color	White
2	Odour	Odourless
3	Taste	Tasteless
4	Texture	Crystalline

Table 13: Physical Parameter of Glipizide

4.3:2 Melting Point

Sl.NO.	Average (ºC)	Melting Point ±S.D
1.	199	200.6 ± 1.52
2.	202	
3.	201	

Table 14: Melting Point Of Glipizide

The mean melting point was found to be 200.6ºC and the standard deviation was found to be 1.52 which was in between the value stated in literature.

4.3:3 Solubility Studies

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Sl. No.	Solvents	Solubility
1	Chloroform	Soluble
2	Methanol	Sparingly Soluble
3	Distilled water	Insoluble
4	Ethanol	Insoluble
5	IPA	Slightly soluble
6	Acetone	Slightly soluble
7.	DCM	Slightly soluble

Table 15: Solubility Studies of Drug in Different Solvent

Solvent media	Solubility in µg/ml
Solubility in distilled water	3.70
Solubility in 0.1 N HCl	10.11
Solubility in phosphate buffer pH 6.8	6.75
Solubility in phosphate buffer pH 7.4	4.23

Table 16: Saturation State Solubility Study

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Excess amount of drug was dissolved in 10 ml of water and it was shaken properly and it was kept for 48 – 72 hours for complete hydration. After 72 hours the solution was again shaken properly and filtered. The filtrate was analyzed by UV double beam Spectrophotometer by taking absorbance at wavelength 276 nm.

4.3:4 Partition Coefficients

A. In phosphate buffer pH-7.4

- 25ml n- Octanol and 25ml of phosphate buffer pH-7.4 and 25mg drug were taken in a separating funnel and shaken well for about 30 minute. Then allowed to separate both layer and aqueous layer, the absorbance was taken at 276 nm.
- Absorbance was found to be = 0.862
- Partition coefficient (log P) value found to be =1.35

B. In distilled water

- 25ml n- Octanol and 25ml of distilled water and 25mg drug were taken in a separating funnel and shaken well for about 30 minute. Then allowed to separate both layer and aqueous layer, the absorbance was taken at 274nm.
- Absorbance was found to be = 0.166
- Partition coefficient (log P) value found to be =1.25

C. In phosphate buffer pH-6.8

- 25ml n- Octanol and 25ml of phosphate buffer pH-6.8 and 25mg drug were taken in a separating funnel and shaken well for about 30 minute. Then allowed to separate both layer and aqueous layer, the absorbance was taken at 276 nm.
- Absorbance was found to be = 0.622
- Partition coefficient (log P) value found to be =1.29

D. In 0.1 N HCl

- 25ml n- Octanol and 25ml of pH-0.1 N HCl and 25mg drug were taken in a separating funnel and shaken well for about 30 minute. Then allowed to separate both layer and aqueous layer, the absorbance was taken at 278.5 nm.
- Absorbance was found to be = 0.115
- Partition coefficient (log P) value found to be=1.37

4.4 EVALUATION OF PRE-COMPRESSION PHYSICAL PARAMETERS OF SUSTAINED RELEASE MATRIX TABLET OF GLIPIZIDE

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Formulation code	Angle of Repose	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner's Ratio
F_1	23.74	0.36	0.44	18.24	1.22
F_2	25.80	0.71	0.86	17.44	1.21
F_3	26.89	0.68	0.81	16.04	1.19
F_4	28.24	0.70	0.89	21.34	1.27
F_5	24.32	0.71	0.83	14.45	1.16
F_6	24.88	0.72	0.93	22.25	1.29

Table 22: Evaluation of Physical Properties of Powder Blend of All Formulations

Mean (n=3)

Discussion: All these pre-compression parameters values (Table No 22) were within the Pharmacoepeial limits.

- Bulk density of pre-compression blends was found to be in the range of 0.36 to 0.72 gm/ml
- Tapped density was found to be in the range of 0.44 to 0.93 gm/ml.
- Carr's index values were in the range of 14.45% to 22.25%.
- Angle of repose was in the range of 23.74 to 28.24.
- Hausner's ratio was in the range of 1.16 to 1.29.

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4.5 EVALUATION OF POST-COMPRESSION PHYSICAL PARAMETERS OF SUSTAINED RELEASE MATRIX TABLETS OF GLIPIZIDE

Formulation	Hardness (kg/cm^2) ± S.D	Thickness (mm) ± S.D	Friability (%)	Average Weight (gm) ± S.D	% Drug Content
F_1	5.16 ± 0.288	2.26 ± 0.057	0.42%	197.4 ± 1.67	77.12%
F_2	5.5 ± 0.5	2.31 ± 0.105	0.34%	194.8 ± 0.83	91.27%
F_3	5.33 ± 0.288	2.27 ± 0.052	0.33%	196.6 ± 1.67	84.93%
F_4	5.16 ± 0.288	2.34 ± 0.085	0.42%	196.2 ± 1.68	76.49%
F_5	4.66 ± 0.288	2.27 ± 0.105	0.37%	195.8 ± 1.39	77.02%
F_6	5 ± 0.5	2.28 ± 0.026	0.45%	196.3 ± 1.63	89.12%

Table 23: Post – Compression Parameters of Formulations

Mean ± S.D (n=3)

Discussion:

- The measured hardness of the formulated tablets (F_1 to F_6) ranged between 4.66 ± 0.288 kg/cm^2.
- Thickness of the formulation was measured with Vernier Caliper. The measured thickness of matrix tablets of each formulation ranged between 2.26 ± 0.057 mm to 2.34 ± 0.085 mm.
- The values of friability test were tabulated in above table within the pharmacoepeial limit.
- All the formulated tablets (F_1 to F_6) passed weight variation test as the % weight variation 194.8 ± 0.83 to 197.4 ± 1.67 gm was within the Pharmacopeial limits.
- The percentage of drug content was found to be between 76.49% to 91.27%.It complies with official specifications and signifies the well entrapment efficiency of prepared formulation.

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4.6 IN-VITRO DISSOLUTION DRUG RELEASE STUDY

TIME	% DRUG RELEASE OF DIFFERENT FORMULATIONS					
	F_1	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**
0	0	0	0	0	0	0
30	2.28 ± 0.535	2.84 ± 0.90	2.27 ± 0.473	3.41 ± 0.580	2.40 ± 0.54	2.56 ± 0.48
60	3.41 ±0.58	3.65 ± 0.90	3.45 ± 0.56	4.32 ± 0.47	3.12 ± 0.57	3.36 ± 0.34
90	5.17 ±0.67	5.76 ± 0.59	4.95 ± 0.27	5.25 ± 0.55	4.96 ± 0.33	5.29 ± 0.65
120	8.39 ±0.45	8.35 ± 0.65	7. 25 ± 0.60	8.39 ± 0.50	7.36 ± 0.47	8.38 ± 0.66
180	20.95±0.96	21.05 ± 0.46	18.67 ± 0.55	20.96 ± 0.86	18.67 ± 0.55	21.05 ± 0.51
240	35.27 ±0.39	35.56 ± 0.68	32 ± 0.29	34.62 ± 0.60	32.33 ± 0.60	35.79 ± 0.66
300	53.48 ±0.68	53.89 ± 0.40	48.73 ± 0.65	51.35± 0.65	50.03± 0.63	53.95 ± 0.26
360	73.83 ±0.41	74.76 ± 0.53	67.46 ± 0.31	69.51± 0.26	68.84 ± 0.51	74.69 ± 0.54
420	76.4 ±0.42	77.63 ± 0.61	71.45 ± 0.23	72.47± 0.78	71.31 ± 0.40	78.54± 0.83
480	81.26 ± 0.75	84.74 ± 0.22	76.12 ± 0.57	79.65 ± 0.34	78.08 ± 0.49	83.4 ± 0.75

Mean ± S.D (n=3)

Table 24: % (Percentage) Drug Release

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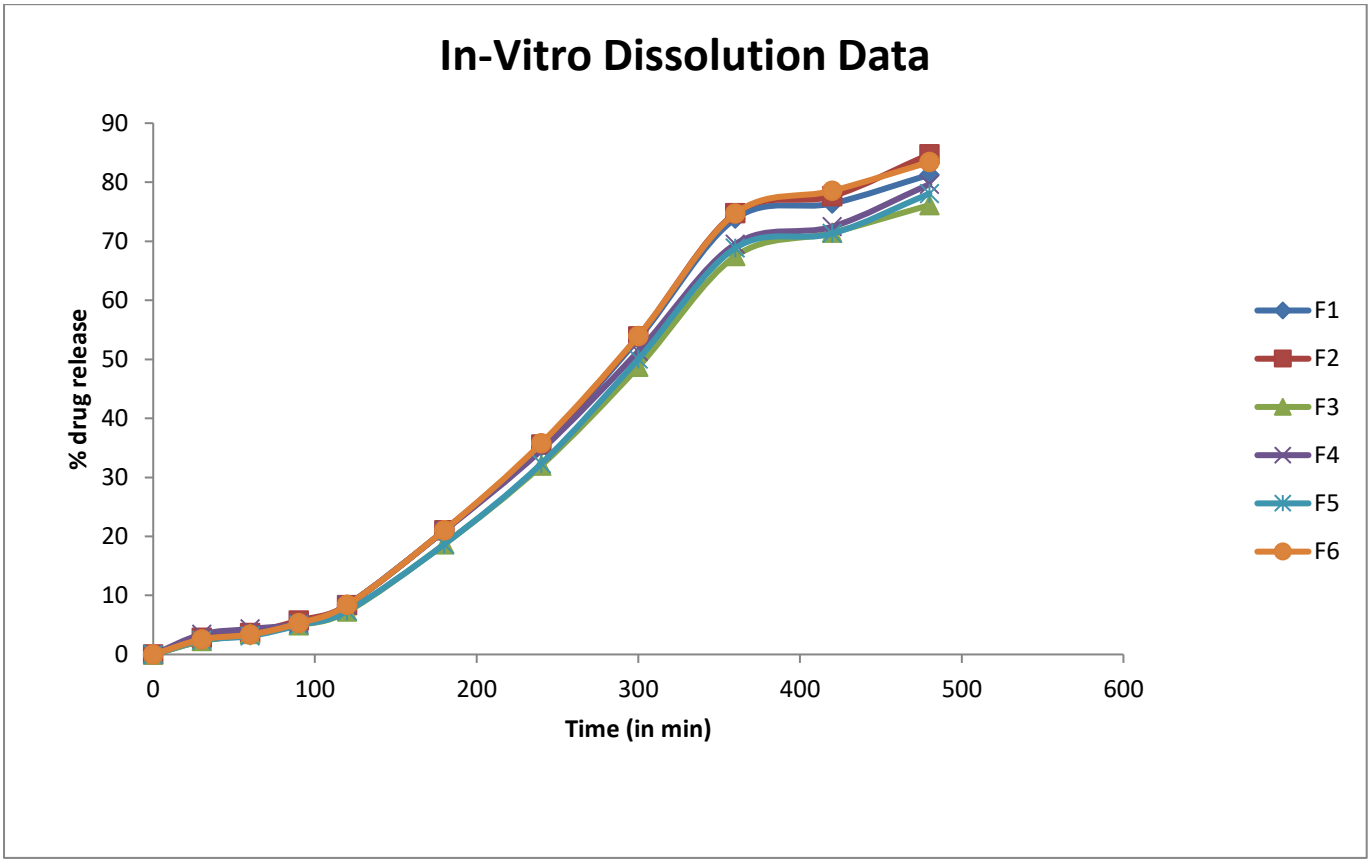

Figure 32: % Drug Release of Different Formulation

4.7 IN-VITRO RELEASE STUDIES:

Dissolution data of the various matrix tablets is indicated in table 24. The formulated matrix tablets released the drug for 8 hours and follow near zero order release (formulations: F_1 to F_6). All the formulations (F_1 to F_6) showed marked variation in the drug release at the end of 6 hours. Formulation F_2 showed the highest release rate (74.76%) and formulation F_3 least release rate (67.46%) at the end of 6 hours. Among all 6 formulations (F_1 to F_6), the 3 formulations (F_1, F_2 and F_6) gives good release as compared to other formulations. As per the drug content and dissolution studies are concerned, it indicated that F_2 formulation gives best drug content and shows best dissolution release.

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4.8 KINETIC PARAMETER:

Formulation	Regression value (r)				
	Zero order	**First order**	**Higuchi matrix**	**Peppas equation**	**Hix.Crow**
F_1	0.9651	0.9303	0.9514	0.9295	0.9468
F_2	0.9666	0.9231	0.9504	0.9133	0.9444
F_3	0.9653	0.9349	0.9510	0.9237	0.9488
F_4	0.9684	0.9395	0.9500	0.8971	0.9535
F_5	0.9648	0.9327	0.9514	0.9140	0.9477
F_6	0.9657	0.9265	0.9512	0.9178	0.9453

Table 25: % Cumulative Drug Release of Glipizide Matrix Tablet

Discussion: The values of correlation coefficient (r) are indicated in the above table respectively. Upon comparison of correlation coefficient values (r) of all the formulations, it was indicated that the release rates follows zero order, in all case of formulations (F_1 to F_6). Drug release rate tend to increase in the content of formulation having polymers HPMC K15 M, Ethyl cellulose and HPMC K4 M. the viscosity of the gel layer around the tablet increases with the increase in the hydrogel concentration, thus limiting the release of active ingredient.

Model Fitting	R^2	Parameters for	
		Korsmeyer-Peppas Equation	
Zero order	0.9666	n	1.2271
1st order	0.9231	k	2.1914
Higuchi matrix	0.9504	Best fit model	Zero order
Peppas	0.9133		
Hix.crow	0.9444	Super case II Transport	
Mechanism of release			

Table 26: % Cumulative Drug Release from F_2 Matrix Tablet

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5. CONCLUSION

Formulation F_1 to F_6 were designed and evaluated for Glipizide release and other parameters. The drug release from F_2 formulation revealed 74.76 ± 0.53 drug releases in 6 hrs and 84.74 ± 0.22 drug releases in 8 hrs. This followed the desired drug release profile as per specification. Further the release pattern studied for different kinetic models and it revealed that drug release was zero order as regression value was first order near to one.

The F_2 formulation was finally selected as optimized formulation as it showed desired drug release profile and all other parameters were within pharmacopeial limits. So in this work we optimized the formulation composition and other processing parameters for sustained release of Glipizide from matrix tablet.

The tablet containing composition of HPMC K 15 M, Ethyl cellulose was found to be superior as compared to other compositions for highly lipophilic drug Glipizide.

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