FORMULATION AND *IN-VITRO* EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF GLICLAZIDE

A Dissertation Submitted to

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MASTER OF PHARMACY

(Pharmaceutics)

Submitted by

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APRIL- 2013

CERTIFICATE

This is to certify that the dissertation entitled "**FORMULATION AND *IN-VITRO* EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF GLICLAZIDE**" submitted to The Tamil Nadu Dr. M.G.R. Medical University in partial fulfillment for the award of the Degree of the Master of Pharmacy (Pharmaceutics) was carried out by **BINGI RAGHURAM (Register No. 26116004)** in the Department of Pharmaceutics under my direct guidance and supervision during the academic year 2012-2013.

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CERTIFICATE

This is to certify that the dissertation entitled "**FORMULATION AND *IN-VITRO* EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF GLICLAZIDE**" the bonafide research work carried out by **BINGI RAGHURAM (Register No. 26116004)** in the Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, Melmaruvathur which is affiliated to The Tamil- Nadu Dr. M.G.R. Medical University under the guidance of **Dr. S. SHANMUGAM, M. Pharm., Ph.D.** Professor, Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, Melmaruvathur.

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Dedicated to

My beloved

Parents & Friends…

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BINGI RAGHURAM

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ABBREVIATION AND MEANING

%	Percentage
µ	Micron
µg/ml	Microgram per milliliter
^0C	Degree Celsius
GLI	Gliclazide
Cm^{-1}	Centimeter inverse
C_{max}	Peak plasma concentration
DSC	Differential scanning calorimetry
e.g.	Example
EC	Ethyl cellulose
Edn	Edition
F	Formulation
F/C	Film coated
FTIR	Fourier transform infrared spectroscopy
g/ml	gram per milliliter
GIT	Gastro intestinal tract
HCl	Hydrochloric acid
HPC	Hydroxy propylcellulose

HPMC	Hydroxy propyl methylcellulose
Hrs	Hours
ICH	International conference on harmonization
BP	British pharmacopoeia
IP	Indian pharmacopoeia
Kg/cm^2	kilogram per centimeter square
LBD	Loose bulk density
mg	Milligram
ml	Millilitre
ml/min	millilitre per minute
mm	Millimeter
N	Normality
NaOH	Sodium hydroxide
NF	National formulary
nm	Nanometer
º	Degree
Ph	Negative logarithm of hydrogen ion
PKa	Dissociation constant

Qs	Quantity sufficient
RH	Relative humidity
rpm	Revolution per minute
S.No.	Serial number
SD	Standard deviation
SR	Sustained release
$t_{1/2}$	Biological half life
TBD	Tapped bulk density
T_{max}	Time of peak concentration
USP	United states pharmacopoeia
UV	Ultraviolet
w/w	weight per weight
λ_{max}	Absorption maximum

INTRODUCTION

1.INTRODUCTION

1.1. Oral drug delivery system: *(Banker G.S. and Rhodes C.T., 2009; Chein Y.W., 2009; http://www.pharmainfo.net)*

Oral route has been the commonly adopted and most convenient route for the drug delivery. Oral route of administration has been received more attention in the pharmaceutical field, because of the more flexibility in the designing of dosage form than drug delivery design for other routes. The oral drug delivery depends on various factors such as type of delivery system, the disease being treated, the patient, the length of the therapy and the properties of the drug. Most of the oral controlled drug delivery systems (OCDDS) relay on diffusion, dissolution, or combination of both mechanisms, to release the drug in a controlled manner to the gastro intestinal tract (GIT). The physico-chemical properties include crystal nature, solubility, partition coefficient, intrinsic dissolution, etc. dosage form characteristics are controlled and optimized with respect to the physico-chemical properties of the drug and relevant GI environmental factors. Other factors need to be considered are diseased state, the patient compliance & length of therapy. The goal of targeted oral drug delivery systems is to achieve better therapeutic success compared to conventional dosage form of the same drug. This could be achieved by improving the pharmacokinetic profile, patient convenience and compliance in therapy.

Oral route of drug delivery has been known for decades as the most to a wide extent used route of administration among all the routes that have been travel through to learn about it the systemic delivery of drugs via various pharmaceutical manufactured products of various dosage forms.

Oral route of administration has been used as either conventional or novel drug delivery system. There are many merits are there for this, not the least of which would include willingness to accept by the patient and facility of administration. Types of sustained release system employed for oral route of administration include virtually every at the present time now the theoretical mechanism for such application. This is because the manufacturing of dosage form is more flexibility, since constraint, such as sterility problem and potential damage at the site of administration are minimized. Because of this, it is easy to development of different types of dosage forms by customary those developed for oral route of administration as initial examples.

Regarding orally administered drugs, targeting is not a primary concern, and it is usually done on purpose for active component to permeate to the blood circulation and permeation through the other body tissue (the obvious exception being medication intended for local gastrointestinal tissue treatment). For this justification, most system employed the sustained release variety.

Concentration of drug level it will increasing the rate absorption region and also, increase circulating blood levels, which in turn to raise to greater concentration of active content at the site of action.

1.2. Drawbacks of Conventional Dosage Forms: *(Brahmankar D.M. and Jaiswal S.B., 2009; Shalin A. Modi, et al., 2011)*

1. Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.

2. The unavoidable fluctuations of drug concentration may lead to under medication or over medication.

3. A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.

4. The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.

1.3. Sustained release drug delivery system: *(Banker G.S. and Rhodes C.T., 2009; http://www.pharmainfo.net)*

Over past 30 year as the expanse and complication involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. There are several reasons for the attractiveness of these dosage forms. It is generally recognized that for many disease states, a substantial number of therapeutically effective compounds already exist.

The effectiveness of these drugs, however, is often limited by side effects or the necessity to administer the compound in a clinical setting, the goal in designing sustained or controlled delivery system is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery. Sustained release constitutes any dosage form that provides medication over and extended time. Controlled release, however, denotes that the system is able to provide some actual therapeutic control, whether this is of a temporal nature, spatial nature or both.

This correctly suggests that there are sustain release system that cannot be considered controlled release system. In general, the goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of drug for an extended period this is usually accomplished by attempting to obtain zero-order release from the dosage form; zero-order release constitutes drug release from the dosage form. Sustained release systems generally do not attain this type of release and provides drug is a slow first order fashion. In recent year sustained release dosage forms continue to draw attention in the search for improved

patient compliance and decreased incidence of adverse drug reactions. Sustained release technology is relatively cow field and as a consequence, research in the field has been extremely fertile and has produced many discoveries.

Sustained release, sustained action, prolonged action controlled release, extended action, timed release, depot and repository dosage forms are terms used to identify drug delivery system that are designed to achieve or prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

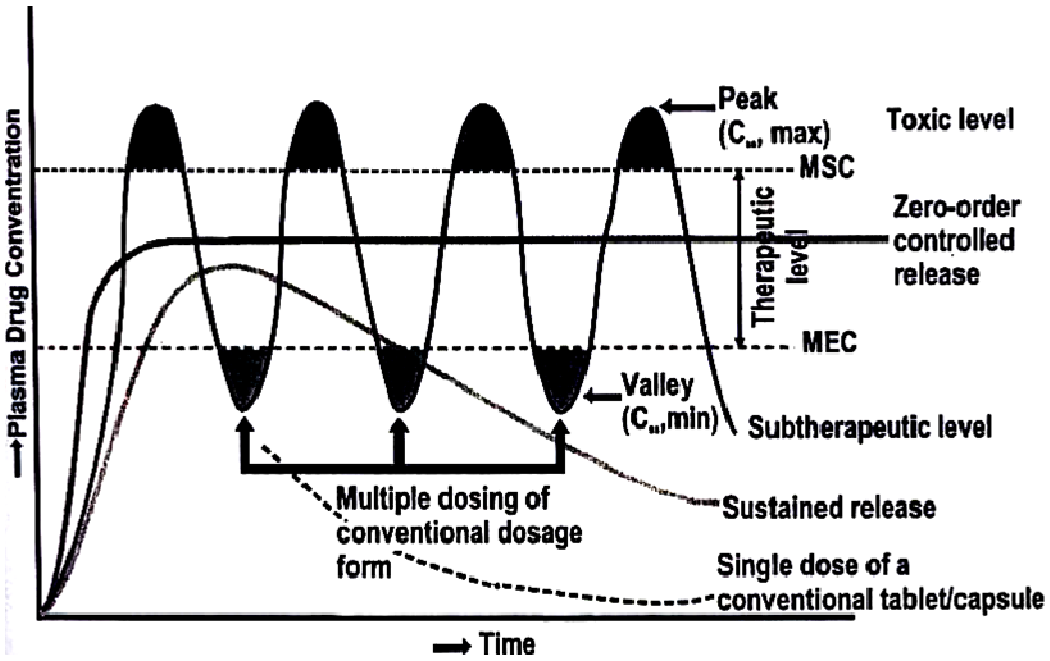


Figure 1.1: Plasma concentration versus time profile from conventional dosage and doses of sustained and controlled delivery formulation.

Systems that are designed as prolonged release can also be considered as attempts at achieving sustained-release delivery. Repeat action tablets are an alternative method of sustained release in which multiple doses of drug are contained within a dosage form, and each dosage is related to a periodic interval. Delayed release systems, in contrast may not be sustaining, science often function of these dosage forms is to maintain the drug within the

dosage form for some time before release. Commonly the release rate of drug is not altered and does not result in sustained delivery once drug release has begun.

Successful fabrication of sustained release products is usually difficult & and involves consideration of physicochemical properties of drug, pharmacokinetic behavior of drug, route of administration, disease state to be treated and, most importantly, placement of the drug in dosage form total will provide the desired temporal and spatial delivery pattern for the drug.

The slow first order release obtained by a sustained release pre parathion is generally achieved by the release of the drug from a dosage form. In some cases in some cases, this achieved by making slow the release of drug from a dosage form. In some cases, this is accomplished by a continuous release process.

1.3.1. Potential advantages of Sustained release drug delivery system:

(http://www.pharma info.net)

1. Patient compliance due to reduction in the frequency of designing.
2. Employ minimum drug.
3. Minimize or eliminates local and systemic side effects.
4. Obtain less potentiating or deduction in drug activity with chronic use.
5. Minimize drug accumulation with chromic dosing.
6. Improves efficacy in treatment.
7. Cure or control confirm more promptly.
8. Improve control of condition i.e. reduce fluctuation in drug level.
9. Improve bioavailability of same drugs.
10. Make use of special effects, e.g. sustained release aspect for morning relief of arthritis by dosing before bedtime.

1.3.2. Disadvantages of Sustained release drug delivery system: (*http: //www. pharmainfo.net)*

1. They are costly.
2. Unpredictable and often poor in-vitro in-vivo correlations, dose dumping, reduced potential for dosage adjustment and increased potential first pass clearance.
3. Poor systemic availability in general.

1. Effective drug release period is influenced and limited by GI residence time.

1.3.3. Rationale of sustained release drug delivery system: *(Ansel H.C., 2009; Vyas S.P and Khar R.K., 2002)*

To optimizing the factor such as pharmacokinetic, pharmacodynamic and biopharmaceutical these are the rationale of sustained release dosage form, these properties of active ingredient in such a type its maximum reducing the adverse effect and controlling disease growth condition in short time period by loading less quantity of drug, when we are administered in the suitable route. Many drugs are longer action because half life and only need for once day dosing so these type of drug not for sustained or controlled release tablet to give therapeutic effect in blood and this nature of drug we can be manufacturing in immediate release tablet as like conventional tablet. However, some drugs are not long action and need multiple daily dosing to obtain the therapeutic results.

Multiple daily dosing is inconvenient for the patient, chance of missed doses, made up doses and non compliance with the regimen. When the conventional tablet which may causes variation of plasma level peaks and valley associated with the using of each dose. However, when a dose should not be administering such a manner because the obtaining result like peaks and valley give the less action of therapy. For example if a dosage form is administered short time interval, minimum toxic concentration of drug may be reached, with toxic side effect can occur. If doses are missed or forgetted, the administered drug goes to

sub therapeutic levels on those below the minimum effective concentration (MEC) may result, so there is no use to the patient.

1.3.4. Designing sustained-release drug delivery system: *(Shalin A. Modi, et al., 2011)*

Most of the 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. It is assumed that increasing concentration at the absorption site will increase circulating blood levels, which in turn, promotes greater concentration of drug at the site of action. If toxicity is not an issue, therapeutic levels can thus be extended. In essence, drug delivery by these systems usually depends on release from some type of dosage form, permeation through biological milieu and absorption through an epithelial membrane to the blood. There are a variety of both physicochemical and biological factors that come into play in the design of such system.

1.3.5. Factors Affecting Sustained Release Dosage Forms: (*Chein Y.W., 2009; http://www.pharmainfo.net)*

1.3.5.1. Physicochemical properties of drug:

a) Dose Size:

If an oral product has a dose size greater that 0.5gm it is a poor candidate for sustained release system, Since addition of sustaining dose and possibly the sustaining mechanism will, in most cases generates a substantial volume product that unacceptably large.

b) Aqueous Solubility:

Most of drugs are weak acids or bases, since the unchanged form of a drug preferentially permeates across lipid membranes drugs aqueous solubility will generally be decreased by conversion to an unchanged form for drugs with low water solubility will be difficult to incorporate into sustained release mechanism. The lower limit on solubility for such product has been reported 0.1mg/ml. drugs with great water solubility are equally difficult to incorporate in to sustained release system. pH dependent solubility, particularly in the physiological pH range, would be another problem because of the variation in pH throughout the GI tract and hence variation in dissolution rate.

c) Partition Coefficient:

Partition coefficient is generally defined as the fraction of drug in an oil phase to that of an adjacent aqueous phase. Accordingly compounds with relatively high partition coefficient are predominantly lipid soluble and consequently have very law aqueous solubility. Compounds with very law partition coefficients will have difficulty in penetrating membranes resulting poor bioavailability.

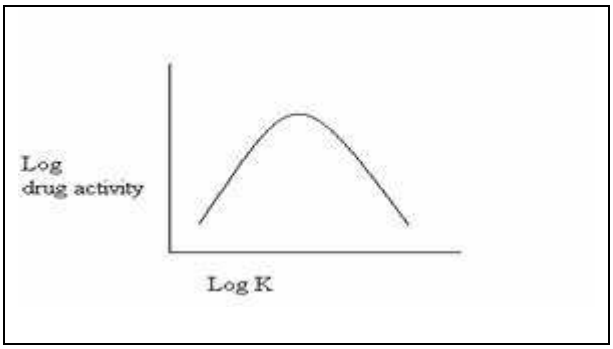


Figure 1.2: Typical relationship between drug activity and partition coefficient K.

d) Dissociation constant (pka):

The relationship between dissociation constant of compound and absorptive environment. Presenting drug in an unchanged form is adventitious for drug permeation but solubility decrease as the drug is in unchanged form.

e) Drug Stability:

Orally administered drugs can be subject to both acid base hydrolysis and enzymatic degradation. Degradation will proceed at the reduced rate for drugs in the solid state, for drugs that are unstable in stomach, systems that prolong delivery ever the entire course of transit in GI tract are beneficial. Compounds that are unstable in the small intestine may demonstrate decreased bioavailability when administered form a sustaining dosage from. This is because more drug is delivered in small intestine and hence subject to degradation.

f) Molecular size and diffusivity:

The ability of drug to diffuse through membrane it's so called diffusivity & diffusion coefficient is function of molecular size (or molecular weight). Generally, values of diffusion coefficient for intermediate molecular weight drugs, through flexible polymer range from 10-8 to 10-9 cm^2 / sec. with values on the order of 10-8 being most common for drugs with molecular weight greater than 500, the diffusion coefficient in many polymers frequently are so small that they are difficult to quantify i.e. less than 16-12 cm^2/sec. Thus high molecular weight drugs and / or polymeric drugs should be expected to display very slow release kinetics in sustained release device using diffusion through polymer membrane.

g) Protein binding:

It is well known that many drugs bind to plasma proteins with a concomitant influence on the duration of drug action. Since blood proteins are for the most part re-

circulated and not eliminated, drug Protein binding can serve as a depot for drug producing a prolonged release profile, especially if a high degree of drug binding occurs.

Extensive binding to plasma proteins will be evidenced by a long half life of elimination for drugs and such drugs generally most require a sustained release dosage form. However drugs that exhibit high degree of binding to plasma proteins also might bind to bio-polymers in GI tract which could have influence on sustained drug delivery. The presence of hydrophobic moiety on drug molecule also increases the binding potential.

1.3.5.2. Biological factors:

a) Biological Half Life:

The usual goal of an oral sustained release product is to maintain therapeutic blood levels over an extended period. To action this, drug must enter in the circulation of approximately the same rate of which it is eliminated. The elimination rate is quantitatively described by half-life ($t_{1/2}$). Therapeutic compounds with short half lives are excellent candidates for sustained release preparations. Since this can reduce dosing frequency. In general drugs with half-lives shorter than 3hrs are poor candidates of sustained release dosage forms of dose size will increase as well as compounds with long half lives, more than 8 hrs are also not used in sustained release forms because their effect is already sustained.

b) Absorption:

The rate, extent and uniformity of absorption of a drug are important factors when considered its formulation into a sustained release system. As the rate limiting step in drug delivery from a sustained-release system is its release from a dosage form, rather than absorption. Rapid rate of absorption of drug, relative to its release is essential if the system is to be successful. It we assume that transit time of drug must in the absorptive areas of the GI tract is about 8-12 hrs. The maximum half life for absorption should be approximately 3-

4 hrs. Otherwise device will pass out of potential absorption regions before drug release is complete.

c) Distribution:

The distribution of drugs into tissues can be important factor in the overall drug elimination kinetics. Since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibrium with blood and extra vascular tissue, consequently apparent volume of distribution assumes different values depending on time course of drug disposition. For design of sustained/ controlled release products, one must have information of disposition of drug.

d) Metabolism:

Drugs that are significantly metabolized before absorption, either in lumen or the tissue of the intestine, can show decreased bioavailability from slower-releasing dosage forms. Most intestinal wall enzymes systems are saturable. As drug is released at a slower rate to these regions less total drug is presented to the enzymatic. Process device a specific period, allowing more complete conversion of the drug to its metabolite.

e) Side effects:

The incidence of side effect of a drug is depends on its therapeutic concentration level in blood. It can be remedy by the drug concentration level is controlled at which timing that drug exists in blood after administration. Toxic effect of a drug is expected above the maximum effective range level and fall in the therapeutic effect if a drug below the level of minimum effective range. So the above problem we can solve by making sustained release preparation.

f) Margin of safety:

Therapeutic index of a drug is very important for either sustained or controlled release delivery system. Its value only desired the margin of safety. Therapeutic index value

it has been longer means excellent for preparation of sustained release tablet. Narrow therapeutic index of some drug precise to release the active content in therapeutic safe and effective range. Some drug like cardiac glycosides that therapeutic index value is very small, so it's not used for sustained release delivery system.

Therapeutic index = TD_{50}/ED_{50}

Where, TD_{50} - Median toxic dose

ED_{50} - Median effective dose.

1.4. Oral controlled and sustained release systems: (*Chein Y.W., 2009; http://www.pharmainfo.net; Shalin A. Modi, et al., 2011)*

The controlled release systems for oral use are mostly solids and based on dissolution, diffusion or a combination of both mechanisms in the control of release rate of drug. Depending upon the manner of drug release, these systems are classified as follows:

1.4.1. Continuous release systems:

These systems release the drug for a prolonged period of time along the entire length of gastrointestinal tract with normal transit of the dosage form. The various systems under this category are as follow,

A. Dissolution controlled release systems

B. Diffusion controlled release systems

C. Dissolution and diffusion controlled release systems

D. Ion exchange resin- drug complexes

E. pH dependent formulation

F. Osmotic pressure controlled systems

A. Dissolution controlled release systems:

These types of systems are easiest to design. The drug present in such system may be the one:

- With inherently slow dissolution rate e.g. Griseofulvin and Digoxin.
- That produces slow dissolving forms, when it comes in contact with GI fluids.
- Having high aqueous solubility and dissolution rate.

Drugs having high aqueous solubility and dissolution rate, shows challenge in controlling their dissolution rate. Dissolution-controlled release can be obtained by slowing the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer and coating drug particles or granules with polymeric materials of varying thickness. The rate limiting step for dissolution of a drug is the diffusion across the aqueous boundary layer. The solubility of the drug provides the source of energy for drug release, which is countered by the stagnant-fluid diffusional boundary layer. The rate of dissolution (dm/dt) can be approximated by below equation.

$$Dm/dt = ADS/h$$

Where, S = Aqueous solubility of the drug.

A = Surface area of the dissolving particle or tablet.

D = Diffusivity of the drug and

h = Thickness of the boundary layer.

a) Matrix (or monolithic) dissolution controlled systems:

As the drug is homogeneously dispersed throughout the rate controlling medium, this system is also called as monolith system. It is very common and employs waxes such as bees wax, carnauba wax which control the drug release rate 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. The drug release is often first order from such matrices.

b) Reservoir (Encapsulation) dissolution controlled systems:

In this type, the drug particles are coated or encapsulated by one of the several microencapsulation techniques with slowly dissolving materials like cellulose and polyethylene glycol. The dissolution rate of coat depends upon the solubility and thickness of the coating.

B. Diffusion controlled systems:

The basic mechanism of drug release from these two systems is fundamentally different besides these simple systems, combination of reservoir and monolithic systems also exist in practice.Diffusion systems are characterized by release rate of drug is dependent on its diffusion through inert water insoluble membrane barrier.

There are basically two types of diffusion devices.

a) Reservoir devices

b) Matrix devices

a) Reservoir Devices:

Reservoir Devices are those in which a core of drug is surrounded by polymeric membrane. The nature of membrane determines the rate of release of drug from system. The process of diffusion is generally described by a series of equations governed by Fick's first law of diffusion.

$$J = -D (DC/ DX)\ldots\ldots. (1)$$

Where, 'J' is the flux of drug across the membrane given in units of amount / area time.

'D' is diffusion coefficient of drug in membrane in units of area / time. This is reflecting to drug molecule's ability to diffuse through the solvent and is dependent on the factors as molecular size and charge.

'dc/dt' represents rate of change in concentration C relative to a distance X in the membrane.

The law states that amount of drug passing across a unit area, is proportional to the concentration difference across that plane.

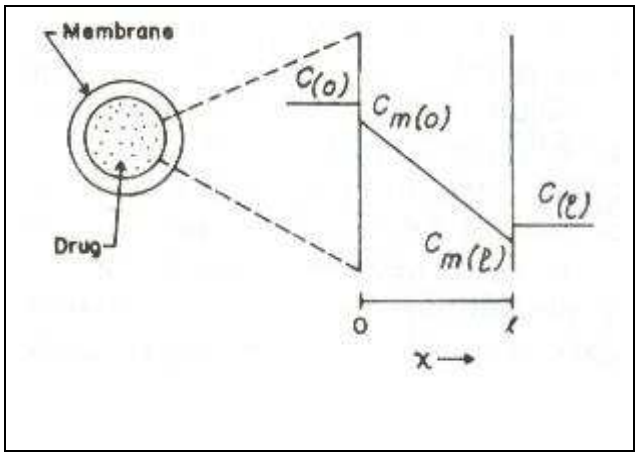


Figure 1.3: Schematic representation of reservoir diffusion device Cm (o), and Cm (d) represent concentration of drug inside surfaces of membrane and C (o) & C(d) represents concentration in adjacent regions.

If it is assumed that the drug on the both side of membrane is in equilibrium with its respective membrane surface which in equilibrium between the membrane surfaces and their bathing solutions as shown in Figure. Therefore the concentration just inside the membrane surface can be related to the concentration in the adjacent region by following expression.

$$K = Cm(o) / C(d) \quad \text{at } X = o \qquad (2)$$

$$K = Cm(d) / C(d) \quad \text{at } X = d \qquad (3)$$

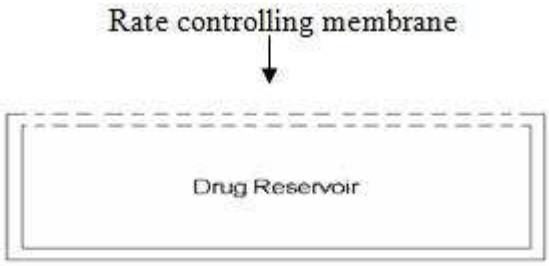
Where K = partition coefficient.

If we consider K & D are constants then equation (1) becomes,

$$J = D K \Delta C/d \qquad (4)$$

Where Δc is the concentration difference across the membrane and d is path length of diffusion. The simplest system to consider is that of slab, where drug release is from only one surface as shown Figure in this case equation (4) becomes

$$dMt/dt = ADK\Delta C/d \quad (5)$$



Non permeable polymer shell

Figure 1.4: Diagrammatic representation of slab configuration of reservoir diffusion system.

Where Mt = Mass of drug released after time t, dMt/dt. Steady state drug release rate of time‘t’; A= surface area of device.

In equation (7) if variables of right side of equation remain constant, then left side of equation represents release rate of system, a true controlled release system with a zero-order release rate.

A constant effective area of diffusion, diffusional path length, concentration difference, and diffusion coefficient are required to obtain a release rate that is constant. Reservoir diffusional systems have several advantages over conventional dosage forms. They can after zero order release of drug, kinetics of which can be controlled by changing the characteristics of the polymer to meet the particular drug and therapy conditions.

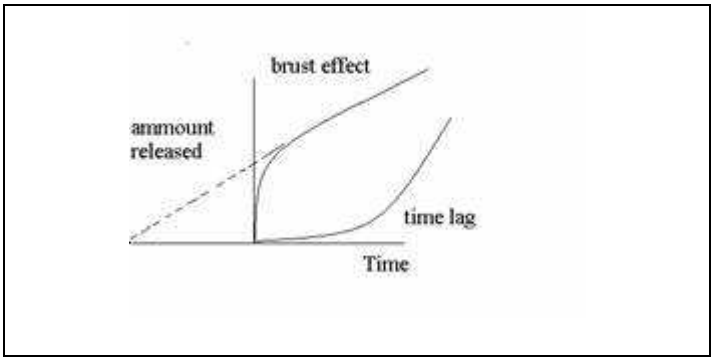


Figure 1.5: Plot showing approach to steady state for reservoir device that has been stored for an extended period (the burst effect curve) and for device that has been freshly made (the time lag curve).

Common methods used to develop reservoir type of devices include micro encapsulation of drug particles and press coating of tablets containing drug cores. In most cases particles coated by microencapsulation form a system where the drug is contained in the coating film as well as in the core of micro capsule. The drug release generally involves combination of dissolution and diffusion with dissolution being process that controls the release rate. If encapsulating material is selected properly will be the controlling process. Some materials such as membrane barrier coat alone or in combination, are hardened gelatin, methyl or methylcellulose, polyhydroxy methacrylate hydroxypropyl methylcellulose, polydroxy methacrylate, polyvinyl acetate & various waxes.

Matrix devices:

A matrix device, as the name implies, consists of drug dispersed homogenously throughout a polymer.

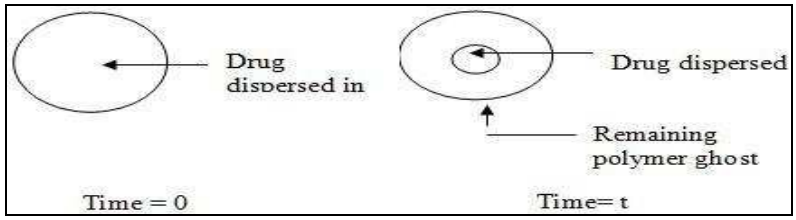


Figure 1.6: Matrix diffusion system before release (time=0) & after partial drug Release (time=t).

In this model drug in outside layer exposed to the bathing solution is dissolved first and diffused out of the matrix. This process continues with the interface between bathing solution and the solid drug moving controlled, the rate of dissolution of drug particles within the matrix must be faster that the diffusion rate of dissolved drug leaving matrix.

Following assumptions are made in retrieving the mathematical models are:

i. A pseudo steady state is maintained during drug release.
ii. The diameter of drug particles is less than the average distance of drug Diffusion through the matrix.
iii. The bathing solution provides sink conditions.
iv. The diffusion coefficient of drug in the matrix remains constant.

The next equation that describes the rate of release drugs dispersed in an inert matrix system has been derived by Higuchi.

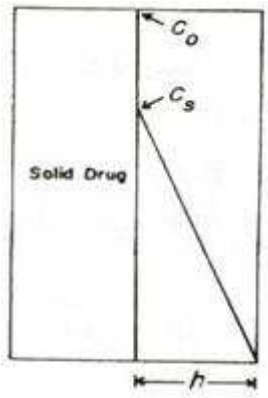


Figure 1.7: Schematic representation of the physical model used for a planer slab matrix diffusion device.

The change in amount of drug released per unit area dM and change in the thickness of the zone of the matrix that has been depleted of the drug,

$$dM/dh = Co\ dh - Cs/2 \qquad (6)$$

By Fick's first law,

$$dm = (Dm\ Cs/h)\ dt. \qquad (7)$$

where, Dm is diffusion coefficient in matrix if equation (6) & (7) are equated & solved for D that value of h sustituted back into the integrated form of equation (7) An equation for M is obtained.

$$M = [Cs\ Dm\ (2Co - Cs)\ t]\ ½ \qquad (8)$$

Similarly, a drug released from porous or granular matrix is described.

$$M = [Ds\ Ca\ (\epsilon/\tau)\ (2Co - \epsilon\ Ca)\ t]\ ½ \qquad (9)$$

Where, e = Porosity of matrix

τ = tortuosity.

Ca = Solubility of drug in release medium

Ds = diffusion coefficient of drug in release medium.

In this system drug is leached from matrix through channels or pores.

$$M = Kt½$$

$$M = K\ \sqrt{t} \qquad (10)$$

Where K is constantan so, that plot amount of drug released verses square root of time should be linear if the release of drug from the matrix is diffusion controlled. The release rate of drug from such a device is not zero order, since if decreases with time but as previously mentioned, this may be clinically equivalent to constant drugs.

1.5. Matrix tablets: (*Chein Y.W., 2009; Harnish Patel, et al., 2011)*

Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating SR dosage form. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems.

Matrix systems are widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs.

1.5.1. Advantages of matrix tablets:

- Easy to manufacture
- Versatile, effective and low cost
- Can be made to release high molecular weight compounds
- The sustained release formulations may maintain therapeutic concentrations over prolonged periods.
- The use of sustain release formulations avoids the high blood concentration.

- Sustain release formulations have the potential to improve the patient compliance.
- Reduce the toxicity by slowing drug absorption.
- Increase the stability by protecting the drug from hydrolysis or other derivative changes in gastrointestinal tract.
- Minimize the local and systemic side effects.
- Improvement in treatment efficacy.
- Minimize drug accumulation with chronic dosing.
- Usage of less total drug.
- Improvement the bioavailability of some drugs.
- Improvement of the ability to provide special effects.

  Ex: Morning relief of arthritis through bed time dosing.

1.5.2. Disadvantages of matrix tablet:

- The remaining matrix must be removed after the drug has been released.
- High cost of preparation.
- The release rates are affected by various factors such as, food and the rate transit through the gut.
- The drug release rates vary with the square root of time. Release rate continuously diminishes due to an increase in diffusional resistance and/or a decrease in effective area at the diffusion front. However, a substantial sustained effect can be produced through the use of very slow release rates, which in many applications are indistinguishable from zero-order.

1.5.3. Classification of matrix tablets:

1.5.3.1. On the Basis of Retardant Material Used:

Matrix tablets can be divided into 5 types.

1. Hydrophobic Matrices (Plastic matrices):

The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. In this method of obtaining sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in to a tablet.

Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles. Examples of materials that have been used as inert or hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers. The rate-controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid.

2. Lipid Matrices:

These matrices prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation.

3. Hydrophilic Matrices:

Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. The formulation of the drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients is of particular interest in the field of controlled release. Infect a matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swellable controlled release systems.

The polymers used in the preparation of hydrophilic matrices are divided into three broad groups,

A. Cellulose derivatives:

Methylcellulose 400 and 4000Cps, Hydroxy ethylcellulose; Hydroxypropyl methylcellulose (HPMC) 25, 100, 4000 and 15000Cps; and Sodium carboxy methyl cellulose.

B. 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:

Carbopol-934, the most used variety.

4. 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. They are biologically degraded or eroded by enzymes generated by surrounding living cells or by non-enzymatic process in to oligomers and monomers that can be metabolized or excreted. Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

5. Mineral Matrices:

These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaephyceae) by the use of dilute alkali.

1.5.3.2. On the Basis of Porosity of Matrix:

Matrix system can also be classified according to their porosity and consequently, Macro porous; Micro porous and Non-porous systems can be identified:

1. Macro porous Systems:

In such systems the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 μm. This pore size is larger than diffusant molecule size.

2. Micro porous System:

Diffusion in this type of system occurs essentially through pores. For micro porous systems, pore size ranges between 50 – 200 A°, which is slightly larger than diffusant molecules size.

3. Non-porous System:

Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.

1.5.4. Polymers used in matrix tablet:

Hydrogels:

Polyhydroxy ethyl methacrylate (PHEMA), Cross-linked polyvinyl alcohol (PVA), Cross-linked polyvinyl pyrrolidone (PVP), Polyethylene oxide (PEO), Poly acrylamide (PA).

Soluble polymers:

Polyethyleneglycol (PEG), polyvinyl alcohol (PVA), Polyvinyl pyrrolidone (PVP), Hydroxypropyl methyl cellulose (HPMC).

Biodegradable polymers:

Polylactic acid (PLA), Polyglycolic acid (PGA), Poly caprolactone (PCL), Poly anhydrides, Poly orthoesters.

Non-biodegradable polymers:

Polyethylene vinyl acetate (PVA), Poly dimethyl siloxane (PDS), Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC).

Mucoadhesive polymers:

Poly carbophil, Sodium carboxy methylcellulose, Polyacrylic acid, Tragacanth, Methyl cellulose, Pectin.

Natural gums: Xanthan gum, Guar gum, Karaya gum, Locust bean gum.

1.5.5. Mechanism of drug release from matrix tablet:

Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix. Derivation of the mathematical model to describe this system involves the following assumptions:

a) A pseudo-steady state is maintained during drug release,

b) The diameter of the drug particles is less than the average distance of drug diffusion through the matrix,

c) The bathing solution provides sink conditions at all times.

1.6. Methods used in tablet manufacturing: *(Lieberman H.A. and Lachman L., 1999; Ansel H.C., 2009; http://www.pharmainfo.net)*

Granulation:

Granulation may be defined as a size enlargement process which converts small particles into physically stronger & larger agglomerates.

The reason for granulation:

- ❖ Become the pharmaceutical ingredient are free flowing
- ❖ Increase the denseness of ingredient
- ❖ We can formulate uniform granular size that does not existing apart
- ❖ Produce better compression characteristic of drug
- ❖ Controlling the rate of drug release from the dosage form
- ❖ Reduce dust in granulation technique
- ❖ The appearance of tablet can be achieved

Methods:

1. Direct compression
2. Wet granulation
3. Dry granulation

1.6.1. Direct compression:

In early days, most of the tablets require granulation of the powdered Active Pharmaceutical Ingredient (API) and Excipients. At the availability of new excipients or modified form of old excipients and the invention of new tablet machinery or modification of old tablet machinery provides an ease in manufacturing of tablets by simple procedure of direct compression.

Amongst the techniques used to prepare tablets, direct compression is the most advanced technology. It involves only blending and compression. Thus offering advantage particularly in terms of speedy production. Because it requires fewer unit operations, less machinery, reduced number of personnel and considerably less processing time along with increased product stability.

1.6.1.1. Definition:

The term "direct compression" is defined as the process by which tablets are compressed directly from powder mixture of API and suitable excipients. No pretreatment of the powder blend by wet or dry granulation procedure is required.

1.6.1.2. The events that motivates the industry people to use direct compression technique:

I. Commercial availability of the directly compressible excipients possessing both good compressibility and good flowability. For example, Spray dried lactose, Anhydrous lactose, Starch-1500, microcrystalline cellulose, Di-Pac^{Ò}, sorbitol.

II. Major advances in tablet compression machinery:

i) Improved positive die feeding,

ii) Precompression of powder blend.

1.6.1.3 Merits:

i) Direct compression is more efficient and economical process as compared to other processes, because it involves only dry blending and compaction of API and necessary excipients.

ii) The most important advantage of direct compression is economical process. Reduced processing time, reduced labor costs, fewer manufacturing steps, and less number of equipments are required, less process validation, reduced consumption of power.

iii) Elimination of heat and moisture, thus increasing not only the stability but also the suitability of the process for thermolabile and moisture sensitive API's.

iv) Particle size uniformity.

v) Prime particle dissolution.

In case of directly compressed tablets after disintegration, each primary drug particle is liberated. While in the case of tablets prepared by compression of granules, small drug

particles with a larger surface area adhere together into larger agglomerates; thus decreasing the surface area available for dissolution.

vi) The chances of batch-to-batch variation are negligible, because the unit operations required for manufacturing processes is fewer.

vii) Chemical stability problems for API and excipient would be avoided.

viii) Provides stability against the effect of aging which affects the dissolution rates.

1.6.1.4. Merits over wet granulation process:

The variables faced in the processing of the granules can lead to significant tableting problems. Properties of granules formed can be affected by viscosity of granulating solution, the rate of addition of granulating solution, type of mixer used and duration of mixing, method and rate of dry and wet blending. The above variables can change the density and the particle size of the resulting granules and may have a major influence on fill weight and compaction qualities. Drying can lead to unblending as soluble API migrates to the surface of the drying granules.

1.6.1.5. Demerits:

Excipients Related:

i) Problems in the uniform distribution of low dose drugs.

ii) High dose drugs having high bulk volume, poor compressibility and poor flowability are not suitable for direct compression.

iii) The choice of excipients for direct compression is extremely critical. Direct compression diluents and binders must possess both good compressibility and good flow ability.

iv) Many active ingredients are not compressible either in crystalline or amorphous forms.

v) Direct compression blends may lead to unblending because of difference in particle size or density of drug and excipients. Similarly the lack of moisture may give rise to static charges, which may lead to unblending.

vi) Non-uniform distribution of colour, especially in tablets of deep colours.

Process Related:

i) Capping, lamination, splitting, or layering of tablets is sometimes related to air entrapment during direct compression. When air is trapped, the resulting tablets expand when the pressure of tablet is released, resulting in splits or layers in the tablet.

ii) In some cases require greater sophistication in blending and compression equipments.

iii) Direct compression equipments are expensive.

1.6.1.6. Manufacturing steps for direct compression:

Direct compression involves comparatively few steps:

- Milling of drug and excipients.
- Mixing of drug and excipients.
- Tablet compression.

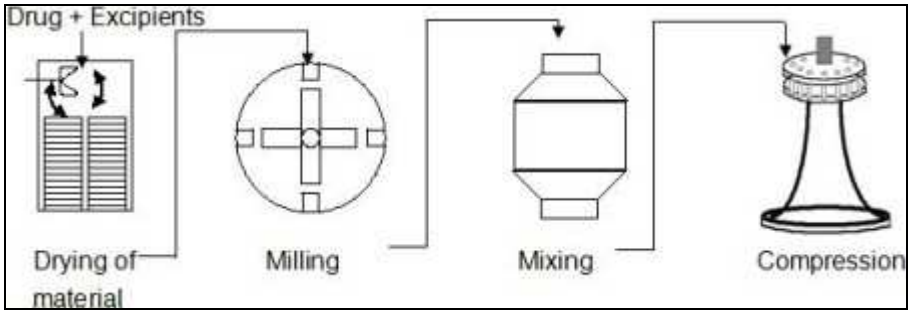


Figure 1.8: Manufacturing Steps for Direct Compression.

1.6.1.7. Direct compression Excipients:

Direct compression excipients mainly include diluents, binders and disintegrants. Generally these are common materials that have been modified during the chemical manufacturing process, in such a way to improve compressibility and flowability of the material.

The physicochemical properties of the ingredients such as particle size, flowability and moisture are critical in direct compression tableting. The success of direct compression formulation is highly dependent on functional behavior of excipients.

1.6.1.7.1. An ideal direct compression excipient should possess the following attributes:

i) It should have good compressibility.

ii) It should possess good hardness after compression, that is material should not possess any deformational properties; otherwise this may lead to capping and lamination of tablets.

iii) It should have good flowability.

iv) It should be physiologically inert.

v) It should be compatible with wide range of API.

vi) It should be stable to various environmental conditions (air, moisture, heat, etc.).

vii) It should not show any physical or chemical change in its properties on aging.

viii) It should have high dilution potential i.e. able to incorporate high amount of API.

ix) It should be colourless, odorless and tasteless.

x) It should accept colourants uniformity.

xi) It should possess suitable organoleptic properties according to formulation type, that is in case of chewable tablet diluent should have suitable taste and flavor. For example, mannitol produces cooling sensation in mouth and also sweet test.

xii) It should not interfere with bioavailability and biological activity of active ingredients.

xiii) It should be easily available and economical in cost.

Granulation method can be broadly classified into two types:

- Wet granulation and
- Dry granulation.

1.6.2. Wet granulation:

The most widely used process of agglomeration in pharmaceutical industry is wet granulation. Wet granulation process simply involves wet massing of the powder blend with a granulating liquid, wet sizing and drying.

1.6.2.1. Important steps involved in the wet granulation:

i) Mixing of the drug(s) and excipients

ii) Preparation of binder solution

iii) Mixing of binder solution with powder mixture to form wet mass.

iv) Coarse screening of wet mass using a suitable sieve (6-12 # screens).

v) Drying of moist granules.

vi) Screening of dry granules through a suitable sieve (14-20 # screen).

vii) Mixing of screened granules with disintegrant, glidant, and lubricant.

1.6.2.2. Limitations of wet granulation:

i) The greatest disadvantage of wet granulation is its cost. It is an expensive process because of labor, time, equipment, energy and space requirements.

ii) Loss of material during various stages of processing

iii) Stability may be major concern for moisture sensitive or thermo labile drugs

iv) Multiple processing steps add complexity and make validation and control difficult.

v) An inherent limitation of wet granulation is that any incompatibility between formulation components is aggravated.

1.6.3. Dry granulation:

In dry granulation process the powder mixture is compressed without the use of heat and solvent. It is the least desirable of all methods of granulation. The two basic procedures are to form a compact of material by compression and then to mill the compact to obtain a granules. Two methods are used for dry granulation. The more widely used method is slugging, where the powder is pre-compressed and the resulting tablet or slug are milled to yield the granules.

The other method is to pre-compress the powder with pressure rolls using a machine such as Chilosonator.

1.6.3.1. Advantages:

The main advantages of dry granulation or slugging are that it uses less equipments and space. It eliminates the need for binder solution, heavy mixing equipment and the costly and time consuming drying step required for wet granulation. Slugging can be used for advantages in the following situations:

i) For moisture sensitive material

ii) For heat sensitive material

iii) For improved disintegration since powder particles are not bonded together by a binder

1.6.3.2. Disadvantages:

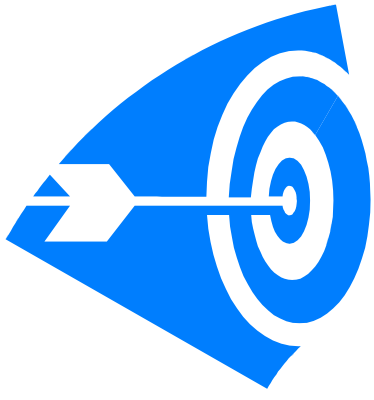
i) It requires a specialized heavy duty tablet press to form slug

ii) It does not permit uniform colour distribution

iii) Achieved with wet granulation where the dye can be incorporated into binder liquid.

iv) The process tends to create more dust than wet granulation, increasing the potential contamination.

Need and Objectives



2. NEED AND OBJECTIVE

- The basic goal of therapy is to achieve a steady state blood or tissue level that is therapeutically effective and non-toxic for an extended period of time. Sustained release drug delivery systems, with an aim of improved patient compliance, better therapeutic efficacy, less side effects and reduced dosage regimen with less toxicity for treatment for many acute and chronic diseases**.**
- Gliclazide is oral hypoglycaemic drug which lowers blood glucose level. It provokes a brisk release of insulin from pancreas and shows peculiar pharmacokinetic characteristics. It is extensively protein bound (87% to 94%) in circulation. It is first sulfonylurea for which it is possible to detail its action from the moment of oral administration through to it's on long term glycemic control. Its plasma peak concentration occurs between 4 to 6 hours. Therefore, gastric and intestinal transient times have a significant effect on the rate and extent of oral absorption of the drug.
- Matrix tablets are very useful in the field of healthcare for sustained release dosage regimen.
- Keeping this in view, the present investigation has been aimed at designing suitable sustained release matrix tablets using polymers as hydroxylpropyl methylcellulose and hydroxyl propyl cellulose.

The major objectives of the investigation are as follows:

1. To perform preformulation studies like flowing properties & bulking density for powders of drug and polymers.

2. To formulate matrix tablets of Gliclazide by wet granulation method by using different polymers like HPMC, HPC.
3. To evaluate prepared formulations for physical parameters like weight variation, friability, and hardness etc.
4. To study *in-vitro* drug release performance of different tablets formulations.
5. To study the effect of different polymers on drug release.
6. To ascertain the release mechanics and kinetics of drug release from compressed matrix tablets.
7. To perform stability studies as per ICH guidelines.

BASIS FOR DRUG SELECTION AND DOSAGE SELECTION.

- For many drugs, the optimal therapeutic response is observed only when adequate blood levels are achieved and maintained with minimum variations, (the matrix tablets will give more consistent blood levels).
- Sulfonylurea with long half-life such as gliclazide has sustained stimulation on insulin secretion compared to repaglinide which has short half-life for only about 1 h.
- Gliclazide with biological half-life is 10 to 12hr. It is oral hypoglycaemic drug which lowers blood glucose level and extensively protein bound in circulation.
- It has been recommended for use on the basis of both its metabolic and non metabolic effects.

PLAN OF WORK

3. PLAN OF WORK

The present work was carried out to design and evaluate sustained-release tablets of Gliclazide, an anti diabetic drug. The sustained-release matrix tablets were prepared by direct compression method using HPMC K100M, ethyl cellulose, PVP K30, magnesium stearate and lactose keeping in view the objectives described above the following plan of work was adopted.

THE SCHEME OF THE ENTIRE WORK IS LISTED AS FOLLOWS:

- Literature review
- Selection of drug and excipients
- Procurement of drug and excipients
- Physicochemical studies (organoleptic properties, melting point and solubility)
- Standardization of the method and construction of calibration curve for the estimation of Gliclazide, quantification of drug.
- Compatibility studies of drug and polymer by FTIR spectral and DSC studies
- Formulation of Gliclazide sustained release matrix tablets by using polymers like HPMC K100M and ethyl cellulose and by direct compression method.
- Evaluation of blend characteristics of prepared granules (pre-compression parameters)
    i. Angle of repose
    ii. Determination of bulk density

iii. Determination of tapped density

iv. Compressibility index

v. Hausner ratio

- Evaluation of physical parameters of Gliclazide sustained-release tablets (post-compression parameters)

i. Thickness and diameter

ii. Hardness

iii. Friability

iv. Weight variation

v. Drug content

- Evaluation of *in vitro* release characteristics of all formulations by using USP dissolution apparatus type I (Basket).
- To study the mechanism of drug release by applying kinetic parameters.
- To perform stability studies as per ICH guidelines.

LITERATURE REVIEW

4. LITERATURE REVIEW

Ahmed A.*, et al.* (2008) estimated the influence of EC with different viscosity grades on in vitro drug release from EC matrix tablets containing Indomethacin. Four viscosity grades were studied (7, 10, 50 and 100 cps). The drug release from the tablet is determined by dissolution testing as described in the USP. Based upon the pore characteristic studies which was determined by using helium pycnometry and mercury porosimetry the release rate constant has been found for different viscosity grades. From the result it is indicated the release rate is increased with an increase in viscosity grade.

Amelia Avachat, *et al.* (2007) was developed and characterized an oral controlled release drug delivery system for concomitant administration of diclofenac sodium (DS) and chondroitin sulfate (CS). A hydrophilic matrix-based tablet using different concentrations of hydroxypropyl methylcellulose (HPMC) was developed using wet granulation technique to contain 100 mg of DS and 400 mg of CS. Formulations prepared were evaluated for the release of DS and CS over a period of 9 hours in pH 6.8 phosphate buffer using United States Pharmacopoeia (USP) type II dissolution apparatus. Along with usual physical properties, the dynamics of water uptake and erosion degree of tablets were also investigated. The in vitro drug release study revealed that HPMC K100 CR at a concentration of 40% of the dosage form weight was able to control the simultaneous release of both DS and CS for 9 hours. The release of DS matched with the marketed CR tablet of DS with similarity factor (f2) above 50.

Deepak S.*, et al.* (2010) had developed sustained release formulation of quetiapine fumarate using HPMC and PVP K30. The study involves fixing the drug and polymer ratio for control the drug release up to the desired time. The effect of polymer concentration and

polymer blend concentration were also studied. Dissolution studies were performed in 0.1N HCl for 2 hrs and in phosphate buffer up to 12 hours. From the release it was observed that the polymer blend of HPMC/PVP K30 were successfully sustained the release of drug up to 12 hrs.

Gohel M.C., *et al.* (2007) was developed modified release of isoniazid using hydroxypropyl methylcellulose as a rate controlling agent. The low viscosity grade hydroxypropyl methylcellulose, medium viscosity grade hydroxypropyl methylcellulose and high viscosity grade Hydroxypropyl methylcellulose were used to prepare the matrix tablets. The tablets, prepared by direct compression, were subjected to physical characterization and *in-vitro* drug release studies. The release rate was strongly influenced by the type of polymer and concentration of polymer.

Harris Shoaib M., *et al.* (2006) had formulated a once daily sustained release matrix tablet of ibuprofen using HPMC as release controlling factor and to evaluate drug release parameters as per various release kinetic models. The tablets were directly compressed using Avicel pH 101 and magnesium stearate. Different dissolution models were applied to drug release data in order to evaluate release mechanism. The drug release data fit well to the Higuchi expression.

Indranil Kumar Yadav, *et al*. (2010) was developed the oral sustained release matrix tablets of aceclofenac using hydrophilic and hydrophobic polymers. Aceclofenac is a non steroidal anti-inflammatory agent used in symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis and its biological half life is 4hrs. Controlled release formulations of aceclofenac (200 mg) were prepared by direct compression method. The tablets were subjected to physicochemical, in-vitro drug release and stability studies. The drug release from optimized formulations F1, F4 and F7 was extended for a period of 12 hrs. The optimized formulations were subjected to stability studies for three months at 45°C

temperature with RH 75±5%, and showed stability with respect to physicochemical parameters and release pattern. Results of the present study indicated the suitability of hydrophilic and hydrophobic polymers in the preparation of matrix based sustained release formulation of aceclofenac.

Kalyani C., *et al.* (2009) had designed oral sustained matrix tablets of zidovudine using HPMC K4M, guar gum and ethyl cellulose as the retardant polymers. Factors like polymer proportion, polymer type and effect of filler type on the in vitro release of the drug. The formulations were prepared by wet granulation technique. The granules were evaluated and all formulations showed compliance with pharmacopoeial standards. Formulation F2 and F8 sustained the release for 12 hrs. Formulation F5 was found to be best which contains 15% HPMC using MCC as diluent release 10 hours only.

Kumar pal T., *et al.* (2007) was designed an oral sustained release matrix tablet of metformin HCl and to optimize the drug release profile using response surface methodology. Tablets were prepared by non-aqueous wet granulation method using HPMC K15M as matrix forming polymer.

Madhusmruti K., *et al.* (2010) was developed sustain release matrix formulation of Propanolol hydrochloride and investigate the effects of both hydrophilic and hydrophobic polymer on *in-vitro* drug release. Matrix tablets were prepared by direct compression method using different concentrations of Hydroxypropyl methyl cellulose (HPMC) and Ethyl Cellulose (EC). Prepared formulations were subjected to various studies like hardness, friability, thickness, % drug content, weight variation, dynamic of water uptake and erosion etc. Tablets were subjected to *in-vitro* drug release in 0.1N HCl (pH 1.2) for first 2 hours followed by phosphate buffer (pH 6.8) remaining time.

Patil U.K., *et al.* (2008) prepared and evaluated sustained release matrix tablet using natural polymers like pectin, guar gum and xanthan gum. Furosemide is used as the model drug and the formulations were compressed by a direct compression. The tablets were evaluated for physical characteristic and all the formulations were found to be in acceptable limits. Among the polymers guar gum was found to exhibit greater swelling index than pectin and xanthan gum.

Paul J. Sheskey, *et al.* (1994) was studied the effect of roller compaction in the dry granulation of a controlled-release (CR) matrix formulation containing methylcellulose or hydroxypropyl methylcellulose (HPMC), niacinamide, and magnesium stearate. The authors investigated the use of roller compaction to enhance material flow in CR tablet formulations and evaluated the effect of roller compaction variables, such as roller pressure and product recycle, on tablet physical characteristics and drug-release profiles.

Prabu Moses, *et al.* (2010) had formulated Ciprofloxacin controlled release matrix tablets using HPMC K100M, Guar gum, Carboxy methylcellulose, starch, polyvinyl pyrrolidone k30, magnesium stearate, isopropyl alcohol. Formulated tablets were taken to evaluation studies such as hardness, weight variation, friability, drug content and thickness.

Raghuram Reddy K., *et al.* (2003) had formulated once daily sustained release matrix tablets of nicorandil, a novel potassium channel openers used in the treatment of cardiovascular disease. The tablets are prepared by wet granulation technique using ethanolic solutions of ethylcellulose (EC), Eudragit RL-100, Eudragit RS-100, and polyvinyl pyrrolidone as granulating agents with hydrophilic matrix materials such as HPMC, sodium carboxylic cellulose and sodium alginate. The granules were studied for physiochemical characteristics and for evaluation parameters. Granules showed good flow property and tablet formulations are all within official limits. From the dissolution studies the formulation F1

could extend the release for 24 hrs and thus it exhibited the most successful formulation of the study.

Raju Manda, *et al.* (2010) was developed a sustained release matrix tablet of aceclofenac using different natural polymers (Guar gum, Xanthan gum, Chitosan) in various proportions as release controlling factor by direct compression method. The *in vitro* dissolution study was carried out for 11 hours using United States Pharmacopoeia (USP) 1 Basket-type dissolution apparatus in 0.1N hydrochloric acid for first 2 hours and phosphate buffer pH 7.4 for 9 hours. The in vitro release study shows that only F9 formulation was releases the drug in a sustained manner for 11 hours. This study explored the optimum concentration and effect of polymer(s) on acelofenac release pattern from the tablet matrix for 11 hour period.

Saleh M. Saidan, *et al.* (2005) developed guar gum matrix tablets for oral controlled release of water-soluble Diltiazem hydrochloride prepared by using microcrystalline cellulose, starch, magnesium stearate and talc. In vitro drug release studies were performed using USP dissolution rate apparatus.

Sandip B. Tiwari, *et al.* (2003) had formulated Tramadol hydrochloride using hydrophilic and hydrophobic matrix system for controlled release. The effect of concentration of hydrophilic and hydrophobic polymers on the release rate of Tramadol was studied. Hydrophilic matrix tablets prepared by wet granulation technique, while hydrophobic matrix tablets prepared by melt granulation technique. In vitro dissolution studies were performed.

Saravanabhavan Shanmugam, *et al*. (2010) was developed sustained release matrix tablets of aceclofenac. The tablets were prepared with different ratios of hydroxypropyl methylcellulose K100M and ethylcellulose by wet granulation technique. The solubility study of the aceclofenac was conducted to select a suitable dissolution medium for in vitro drug release studies. In vitro dissolution study was carried out for all the formulation and the

results compared with marketed sustained release tablets**.** The drug release from matrix tablets was found to decrease with increase in polymer ratio of hydroxypropyl methylcellulose as well as ethylcellulose. Formulation F3 exhibited almost similar drug release profile in different dissolution media as that of marketed tablets.

Seema Pushkar, *et al.* (2009) was developed the extended release tableted matrix devices for once daily dosing of diclofenac sodium, and their evaluation for performance and compliance with official pharmacopoeial and allied pharmaceutical requirements. The matrix tablets were prepared by drug incorporated polymer matrix, formulated using different combinations and ratios of hydroxypropyl methylcellulose (HPMC), sodium carboxy methylcellulose (Sodium CMC), and sodium alginate (NaAlg). Several preformulation trials were conducted to study the effect and optimization of various formulation and process parameters. The drug loaded polymeric matrices so prepared were compressed to tablets and studied for drug the release behaviour and comparative kinetic characterization along with six popular marketed brands of Diclofenac SR tablets. The formulated granules and tablets compressed complied with compendial and mechanistic requirements. The *in vitro* results shown a better release profile of formulated delivery system when compared to marketed brands extended up to 24 hours. The various formulations have shown an extended release up to 11 – 23 hours in different release environments.

Sundaramoorthy K., *et al*. (2011) had formulated monolithic matrix tablets of metformin hydrochloride as extended release tablets by employing ethyl cellulose polymer and the extended release characterization of the formulated tablets was investigated. Extended release matrix tablets containing 500 mg metformin hydrochloride were developed by changing concentration of drug: polymer (EC) in the ratio of 5:1, 5:2, 5:3 and 5:4 by direct compression. Formulations were optimized based on the acceptable tablet properties *in-vitro* and *in-vivo* drug release. The result of *in-vitro* and *in-vivo* drug release studies indicated that

formulation (drug: polymer =5:3), was the most successful of the study and exhibited constant and extended release of metformin hydrochloride 99-100.5% release at the end of 10 hours compared with reference standard. A decrease in release of the drug was observed on increasing polymer ratio at certain level. The $t_{25\%}$, $t_{50\%}$ and $t_{90\%}$ drug release values were calculated from selected formulation F3 on every specified period of stability studies and comparison of both room and accelerated condition by statistical t-test, there was no difference between storage temperature. The formulation F3 was showed similar *in-vitro* and *in-vivo* drug release when compared to market sustained release tablet (F5M).

Literature review indicating work carried out on selected drug Gliclazide is given below:

Gopal Venkatesh Shavi1, *, et al.* (2010) Gliclazide is practically insoluble in water and its bioavailability is limited by dissolution rate. To enhance the dissolution rate and bioavailability the present study was aimed to formulate solid dispersions using different water soluble polymers such as polyethylene glycol 4000 (PEG 4000), polyethylene glycol 6000 (PEG 6000) using fusion method and polyvinyl pyrrolidone K- 30 (PVP K 30) by solvent evaporation method. The interaction of gliclazide with the hydrophilic polymers was studied by Differential Scanning Calorimetry (DSC), Fourier Transformation-Infrared Spectroscopy (FTIR) and X-Ray diffraction analysis. Solid dispersions were characterized for physicochemical properties like drug content, surface morphology and dissolution studies. Various factors like type of polymer and ratio of the drug to polymer on the solubility and dissolution rate of the drug were also evaluated. Pharmacokinetic studies of optimized formulation were compared with pure drug and marketed formulation in wistar rats. The dissolution of the pure drug and solid dispersion prepared with PVP K 30 (1:1) showed 38.3 $\pm$ 4.5 % and 95 $\pm$ 5.2 % release respectively within 30 min. Peak plasma concentration of pure drug, solid dispersion (PVP K 30) and marketed formulation was found to be 8.76 $\pm$ 2.5,

16.04 ± 5.5 and 9.24 ± 3.6 μg/ml respectively, from these results it was observed that there is two fold increase in peak plasma concentration compared to pure drug. Solid dispersion is an effective technique in increasing solubility, dissolution rate and bioavailability of the poorly soluble drugs.

P.N. Dhabale, ***, et al.*** **(2010)** Two simple, accurate, precise, reproducible and economical procedures for simultaneous estimation of Gliclazide(GLZ) and Metformine hydrochloride (MET) in tablet dosage form have been developed. First method based on solving of simultaneous equation using 228 nm (λmax of GLZ) and 234 nm (λmax of MET) as two analytical wavelengths for both drugs in mixture of Water and Methanol (60:40) solvent. Second method based on an equation of area calculation of curve at two wavelength resion (233 to 223nm and 239 to 229 nm).Linearity was observed in the concentration range of 2-24 μg/ml for GLZ and 2-14 μg/ml for MET. The result of analysis have been validated satistically and by recovery study.

Panchal V.N, *etal.* (2011) The objective of the present study was to develop "once daily" sustained release tablets of gliclazide by wet granulation using hydroxy propyl methyl cellulose, hydroxy propyl cellulose and their combination as polymers. The drug excipient mixtures were subjected to preformulation studies while the tablets were subjected to physicochemical studies, *in vitro* drug release, stability studies and validation studies. The physicochemical properties of tablets were found within the limits. Formulation F6 & F9 containing HPMC K4M and HPMC K4M & HPC 75-100 cps combination respectively were found to release the drug in sustained manner upto 12 hour and were stable under accelerated conditions of temperature for 6 months since there were no significant changes in drug content and physical parameters.

RajeshKaza, *etal.* (2012) The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Gliclazide

(GLZ) BCS class II drug, is an oral antihyperglycemic agent used for the treatment of non-insulin-dependent diabetes mellitus However, low aqueous solubility and poor dissolution of this molecule, delays its rate of absorption and finally the onset of action. Solid dispersion has been successfully utilized as dissolution enhancement technique using natural polymers for wide variety of poorly water-soluble drugs. The present study aims at enhancement of dissolution profile of Gliclazide using Xanthan gum, Guar gum and Hupu gum as carriers by solid dispersion technique. Solid dispersion containing GLZ was further investigated by Fourier transform infrared spectroscopy (FTIR). FTIR patterns suggest that there is no interaction between drug and excipients. From the study it concluded that the *in vitro* dissolution of Gliclazide can be enhanced by solid dispersion technique. Amongst the solid dispersions prepared. F6 formulation prepared by co-grinding method using Guar gum as carrier in 1:3 ratio shown the better release of Gliclazide (96.79 %) with in 60 min.

S. Areefulla Hussainya, *et al.* (2012) The objective of the present study is to evaluate HPMC K100M, HPMC K4M and carbopol 934P as matrix formers in this design of floating tablets of gliclazide, a poorly water soluble drug. Floating tablets of gliclazide (60 mg) were formulated employing (i) HPMC K100M (ii) HPMC K4M and (iii) Carbopol 934P as matrix formers at 30% and 50% strength, sodium bicarbonate at 7.5%, 10% & 12.5% strength as gas generating agent and bees wax (10%) as floating enhancer and the tablets were evaluated for floating and drug releases characteristics. Gliclazide floating tablets formulated employing HPMC K100M and HPMC K4M as matrix formers at 50% strength and containing sodium bicarbonate (12.5%) as gas generating agent exhibited floating over 31 to 44 h with a floating lag time of less than 1 min. These floating tablets also gave slow and controlled release of gliclazide over 24 h and were found suitable for once a day administration (24 h). HPMC K100M and HPMC K4M were better suitable as matrix formers than Carbopol 934P for floating tablets of gliclazide, a poorly water soluble drug.

Sandra Grbic,et.al, (2011) The aim of this study was to develop a drug-specific absorption model for gliclazide (GLK) using mechanistic gastrointestinal simulation technology (GIST) implemented in GastroPlusTM software package. A range of experimentally determined, in silico predicted or literature data were used as input parameters. Experimentally determined pH-solubility profile was used for all simulations. The human jejunum effective permeability (Peff) value was estimated on the basis of in vitro measured Caco-2 permeability (literature data). The required PK inputs were taken from the literature. The results of the simulations were compared with actual clinical data and revealed that the GIST-model gave accurate prediction of gliclazide oral absorption. The generated absorption model provided the target in vivo dissolution profile for in vitro–in vivo correlation and identification of biorelevant dissolution specification for GLK immediate-release (IR) tablets. A set of virtual in vitro data was used for correlation purposes. The obtained results suggest that dissolution specification of more than 85% GLK dissolved in 60 min may be considered as "biorelevant" dissolution acceptance criteria for GLK IR tablets.

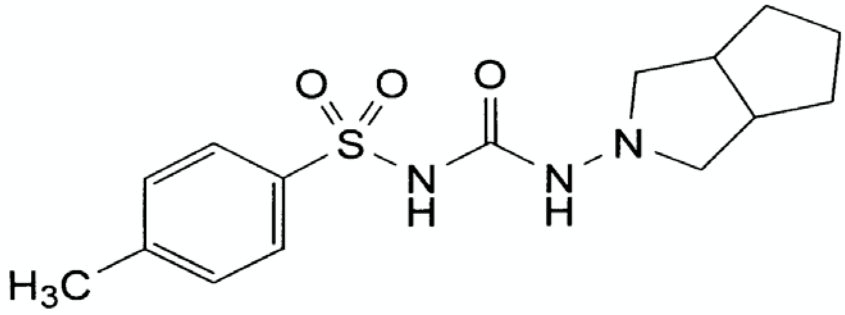
Samina A. Jamadar , et.al. (2011) The article describes a simple, sensitive, rapid, accurate and precise spectrophotometric method for the estimation of gliclazide in bulk and pharmaceutical dosage forms. The wavelength maxima for gliclazide was found to be 229.5 nm with molar absorptivity of 1.4962×104l/mol/cm. Beer's law was obeyed in the concentration range of 7-27 μg/ml. The limit of detection (LOD) and limit of quantification (LOQ) were found to be 0.31 μg/ml and 0.92 μg/ml, respectively. The percentage recovery of the drug for the proposed method ranged from 98.68-100.12% indicating no interference of the tablet excipients. The results demonstrate that proposed method is accurate, precise, and reproducible while being simple and rapid too for the determination of gliclazide in tablet dosage form.

DRUG AND EXCIPIENTS PROFILE

5. DRUG AND EXCIPIENTS PROFILE

5.1. Drug profile:

GLICLAZIDE



Gliclazide, 1-(3-azabicyclo (3.3.0) oct-3-yl)-3-*p*tolylsulphonylurea is an oral hypoglycemic agent used in the treatment of non-insulin-dependent diabetes mellitus (NIDDM). It contains not less than 99.0 % and not more than the equivalent of 101.0% of 1-(hexahydrocyclopenta[*c*]pyrrol-2(1*H*)-yl)-3-[(4-methylphenyl)sulphonyl]urea, calculated with reference to the dried substance.

Characteristics: A white or almost white powder.

Melting point: 180ºC-182ºC

Solubility:

Practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in acetone, slightly soluble in alcohol.

Pharmacological effects:

Gliclazide is oral hypoglycaemic drug which lowers blood glucose level. It provokes a brisk release of insulin from pancreas and shows peculiar pharmacokinetic characteristics.

Pharmacokinetics:

It is extensively protein bound (87% to 94%) in circulation. It is first sulfonylurea for which it is possible to detail its action from the moment of oral administration through to it's on long term glycemic control. Its plasma peak concentration occurs between 4 to 6 hours. Therefore, gastric and intestinal transient times have a significant effect on the rate and extent of oral absorption of the drug.

Therapeutic uses:

This medication is used in conjunction with diet and exercise regimens to control high blood sugar in non-insulin dependent diabetic patients. Controlling high blood sugar helps prevent heart disease, strokes, kidney disease, circulation problems, and blindness.

Preparation:

Gliclazide tablets each containing 30 mg, 40 mg and 60 mg of Gliclazide are official in USP and BP. Tablets containing 30 mg and 40 mg of Gliclazide are available commercially in the market.

Mechanism of action:

Sulfonylureas provoke a brisk release of insulin from pancreas. They act on the so called sulfonylurea receptors (SUR1) on the pancreatic β cell membrane-cause depolarization by reducing conductance of ATP sensitive K^+ channels. This enhances Ca^{2+} influx degranulation. The rate of insulin secretion at any glucose concentration is increased. In type 2 DM the kinetics of insulin release in response to glucose or meals is delayed and subdued.

Dose: 40 mg to 320 mg twice a day.

Side effects:

Hypoglycaemia: - It is the commonest problem, may occasionally be severe and rarely fatal. It is more commonly in elderly, liver and kidney disease patients and when potentiating drugs are added.

Hypersensitivity: - Rashes, photosensitivity, purpurea, transient lukopenia, rarely agranulocytosis.

Nonspecific side effects: - Nausea, vomiting, flatulence, diarrhea or constipation, headache, paresthesias and weight gain

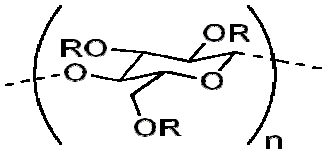
5.2. Excipients profile:

HYDROXY PROPYL METHYL CELLULOSE

Synonyms: Benecel, HPMC, Methocel, Hydroxy propyl methyl cellulose

Molecular weight: 10,000-15,000

Structure:



R = H or CH_3 or $CH_2CH(OH)CH_3$

Description **:** slightly off-white to beige powder in appearance and may be formed into granules.

Colour **:** white to yellowish white

Odour **:** odorless or nearly odorless

Taste **:** bland taste

Texture **:** powder

Acidity / Alkalinity **:** pH 5.5-8.0 for a 1%w/w aqueous solution.

V**iscosity for 2 %(w/v) aqueous solution:** 4000mpas (Viscosity measured at 200C)

Solubility:

Soluble in cold water, forming a viscous colloidal solution, practically insoluble in mixtures of ethanol and dichloromethane, mixtures of alcohol and water

Functional category:

Coating agent, film former, and rate controlling polymer for sustained release, stabilizing agent, suspending agent and viscosity builder.

Applications in pharmaceutical technology:

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.

Stability and Storage:

Stable between pH 3-11, should be stored in a well-closed container in a cool and dry place.

Incompatibilities:

Incompatible with some oxidizing agents such as hydrogen peroxide, potassium permanganate.

ETHYL CELLULOSE

Nonproprietary Names:

BP: Ethyl cellulose

PhEur: Ethyl cellulose

USP-NF: Ethyl cellulose

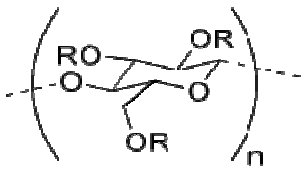
Synonyms: Aquacoat ECD; Aqualon; Ashacel; E462; Ethocel; ethylcellulosum;Surelease.

Chemical Name: Cellulose ethyl ether

CAS Registry Number: [9004-57-3]

Empirical Formula and Molecular Weight: Ethyl cellulose is partially ethoxylated. Ethyl cellulose with complete ethoxyl substitution (DS = 3) is $C_{12}H_{23}O_6$ ($C_{12}H_{22}O_5$) $nC_{12}H_{23}O_5$ where n can vary to provide a Wide variety of molecular weights. Ethyl cellulose, an ethyl ether of cellulose, is a long-chain polymer of b- anhydroglucose units joined together by acetal linkages.

Structural Formula:



R = H or CH_2CH_3

Functional Category:

Coating agent, flavouring agent, tablet binder, tablet filler, viscosity increasing agent.

Description:

Ethyl cellulose is a tasteless, free-flowing, and white to light tan-colored powder.

Color **:** white to light tan-colored powder

Odour **:** odorless.

Taste **:** tasteless

Texture **:** powder

Solubility:

Ethyl cellulose is practically insoluble in glycerin, propylene glycol, and water. Ethyl cellulose that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, methyl acetate, and tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%). Ethyl cellulose that contains not less than 46.5% of ethoxyl groups is freely soluble in chloroform, ethanol (95%), ethyl acetate, methanol, and toluene.

Stability and Storage Conditions:

Ethyl cellulose is a stable, slightly hygroscopic material. It is chemically resistant to alkalis, both dilute and concentrated, and to salt solutions, although it is more sensitive to acidic materials than are cellulose esters. Ethyl cellulose is subject to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. This may be prevented by the use of antioxidant and chemical additives that absorb light in the 230–340nm range. Ethyl cellulose should be stored at a temperature not exceeding 328C (908F) in a dry area away from all sources of heat. It should not be stored next to peroxides or other oxidizing agents.

Incompatibilities:

Incompatible with paraffin wax and microcrystalline wax.

Applications in Pharmaceutical Formulation or Technology

- Ethyl cellulose is widely used in oral and topical pharmaceutical formulations.
- The main use of ethyl cellulose in oral formulations is as a hydrophobic coating agent for tablets and granules. Ethyl cellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulation. For example where granules are coated with ethyl cellulose to inhibit oxidation.
- Modified-release tablet formulations may also be Produced using ethyl cellulose as a matrix former. Ethyl cellulose, dissolved in an organic solvent or solvent mixture, can be used on its own to produce water-insoluble films.
- Drug release through ethyl cellulose-coated dosage forms can be controlled by diffusion through the film coating. This can be a slow process unless a large surface area (e.g. pellets or granules compared with tablets) is utilized. In those instances, aqueous ethyl cellulose dispersions are generally used to coat granules or pellets.
- Ethyl cellulose-coated beads and granules have also demonstrated the ability to absorb pressure and hence protect the coating from Fracture during compression.
- High-viscosity grades of ethyl cellulose are used in drug microencapsulation.
- Release of a drug from an ethyl cellulose microcapsule is a function of the microcapsule wall thickness and surface area.
- In tablet formulations, ethyl cellulose may additionally be employed as a binder, the ethyl cellulose being blended dry or wet granulated with a solvent such as ethanol (95%).
- Ethyl cellulose produces hard tablets with low friability, although they may demonstrate poor dissolution. Ethyl cellulose has also been used as an agent for delivering therapeutic agents from oral (e.g. dental) appliances.

- In topical formulations, ethyl cellulose is used as a thickening agent in creams, lotions, or gels, provided an appropriate solvent is used. Ethyl cellulose has been studied as a stabilizer for emulsions. Ethyl cellulose is additionally used in cosmetics and food products.

Table 5.2.: Uses of ethyl cellulose.

Use	**Concentration(%)**
Microencapsulation	10.0–20.0
Sustained-release tablet coating	3.0–20.0
Tablet coating	1.0–3.0
Tablet granulation	1.0–3.0

MAGNESIUM STEARATE *(Raymond C.R., et al., 2009)*

Nonproprietary names:

BP **:** Magnesium stearate

JP **:** Magnesium stearate

PhEur **:** Magnesii stearas

USPNF **:** Magnesium stearate

Synonyms:

Magnesium octa decanoate, Magnesium salt.

Chemical name and CAS registry number

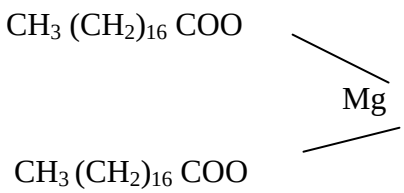
Octa decanoic acid magnesium salt [557-04-0]

Functional category : Tablet and capsule lubricant

Empirical formula : $C_{36}H_{70}MgO_4$

Molecular weight : 591.3

Structure:



Description:

It is a fine, white, precipitated or milled, impalpable powder of low bulk density and having a faint odor of stearic acid, characteristic taste.

Solubility:

It is insoluble in water, ethanol and ether. It can slightly soluble in warm ethanol and benzene.

Stability and storage conditions:

Stable, Store in a well closed container in a cool, dry place.

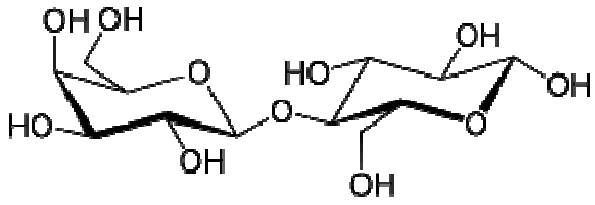
LACTOSE MONOHYDRATE

Synonyms : Milk sugar; Pharmatose; Lactochem; Lactohale; Prismalac; Saccharum lactis

Category : Diluent for dry powder, tablet and capsule diluents

Chemical Name : o-ß-D-Galactopyranosyl- (1→4) –α-D-glucopyranose monohydrate

Structure:



Empirical Formula : $C_{12}H_{22}O_{11}. H_2O$

Molecular Weight : 360.31

Description : It is a crystalline powder which is white to off white in color, odorless, weet tasting.

Density : 1.54 g/cm^3

Melting Point : 201-202ºC

Moisture Content : It contains up to 1 % w/w water

Stability : Lactose may develop a brown coloration on storage

Storage : It is stored in well closed container in a cool and dry place

Incompatibilities : Incompatible with amino acid, aminophyllines.

POLYVINYL PYRROLIDINE

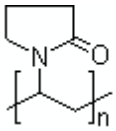
Synonym:

Plasdone K-30, Luviskol K30, Plasdone, Povidone, PVP P, PVP-K 30; PVP; Polyvinylpyrrolidone; Poly [1-(2-oxo-1-pyrrolidinyl) ethylene); Povidone K-30; Poly(n-vinlybutyrolactam);Poly(1-vinylpyrrolidinone);

Chemical Name: Poly (1-vinyl-2-pyrrolidinone)

Chemical Formula: (C6H9NO)n

Chemical structure:



Physical state and appearance: Solid. (Powdered solid.)

Odor: Odorless.

Molecular Weight: (111.14) n g/mole

Color: Creamy White.

Boiling Point: 90°C (194°F) - 93 C

Melting Point: 13.9°C (57°F)

Specific Gravity: Density: 1.23 - 1.29(Water = 1)

Incompatibility with various substances: Reactive with oxidizing agents

Solubility:

- Soluble in cold water.
- Soluble in water giving a colloidal solution.
- Soluble in chloroform, alcohol, chlorinated hydrocarbons, amines, nitro paraffin's, lower weight fatty acids.

Specification:

1. **Application**: PVP K series can be used as film forming agent, viscosity-enhancement agent, lubricator and adhesive. They are the key component of hair sprays, mousse, gels and lotions & solution. They are also convenience assistant in skin care product, hair-drying reagent, shampoo, eye makeup, lipstick, deodorant, sunscreen and dentifrice.

2.**Pharmaceutical**: Povidone K 30 and K 25 is a new and excellent pharmaceutical excipient. It is mainly used as binder for tablet, dissolving assistant for injection, flow assistant for capsule, dispersant for liquid medicine and pigment, stabilizer for enzyme and heat sensitive drug, co precipitant for poorly soluble drugs, lubricator and antitoxic assistant of eye drug. PVP has been used as excipients in more than one hundred drugs.

COLLOIDAL SILICON DIOXIDE

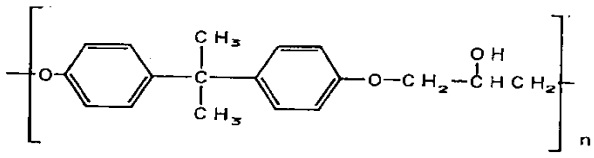
Synonyms: Aerosil; Cab-O-Sil; Cab-O-Sil M-5P; colloidal silica

Chemical name: Silica

Empirical formula: SiO_2

Molecular Weight: 60.08

Structure:



Description: It is a light, loose, bluish-white-colored, odorless, tasteless, amorphous powder

Melting point: 1600^0C

Solubility: Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide.

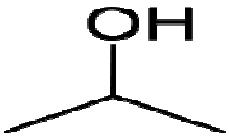
Incompatibilites: Incompatible with diethylstilbestrol preparations.

Stabilities and Storage condition: Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. When used in aqueous systems at a pH 0–7.5, colloidal silicon dioxide is effective in increasing the viscosity of a system. Colloidal silicon dioxide powder should be stored in a well-closed container

Application: Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products. Colloidal silicon dioxide is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations. In aerosols, other than those for inhalation, colloidal silicon dioxide is used to promote particulate suspension, eliminate hard settling, and minimize the clogging of spray nozzles. Colloidal silicon dioxide is also used as a tablet disintegrant and as an adsorbent dispersing agent for liquids in powders.

ISOPROPYL ALCOHOL

Structure:



Synonyms	Di methyl carbinol, isopropanol , 2-propanol.
Empirical formula	C_3H_8O
Molecular wt	60.1
Description	Clear , colorless, mobile, volatile, flammable liquid with characteristic, spirituous odor& slightly bitter taste
Functional category	Disinfectant, solvent
Solubility	Miscible with benzene, chloroform, ethanol. Soluble in acetone Insoluble in salt solutions.
Storage conditions	Store in a airtight container in a cool & dry place
Incompatibility	Incompatible with H_2O_2& Nitric acid. Salting out from aqueous preparations by adding sodium salts
Applications	Tablets - Film forming agent & Granulating agent 70%v/v used as disinfectant Not recommended for oral use

MATERIALS AND EQUIPMENTS

6. MATERIALS AND EQUIPMENTS

6.1. Materials used:

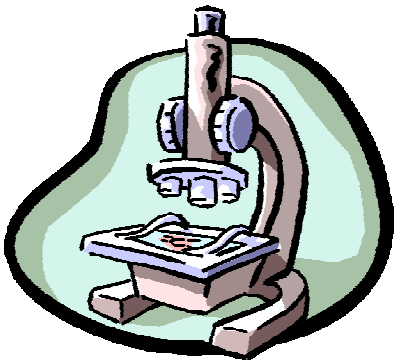
Table 6.1: List of materials with source

S.No.	Name of Ingredients	Name of supplier
1	Gliclazide	Sunglow pharmaceuticals, Puducherry.
2	HPMC K100M	Tristar formulations Pvt. Ltd., Puducherry.
3	Ethyl cellulose	Tristar formulations Pvt. Ltd., Puducherry.
4	Polyvinyl pyrrolidone K30	Nickon laboratories Pvt. Ltd., Puducherry.
5	Magnesium stearate	Loba chemie Pvt.Ltd., Mumbai.
6	Lactose	Loba chemie Pvt.Ltd., Mumbai.
7	Aerosil	S d fine-chem limited, Mumbai.
8	Isopropylalcohol	Qualigens fine chemicals, Mumbai.

6.2. Equipments used:

Table 6.2: List of equipments with model/make

S.No.	Equipment	Model/ Make
1	Electronic balance	Shimadzu BL-220H, Japan.
2	Bulk density apparatus	Indolabs VTAP/MATIC-II, Chennai.
3	Standard sieves	Jayant scientific, India.
4	Hot air oven	Precision scientific Co., Chennai.
5	Sixteen punch tablet compression machine	Cadmach, Ahmadabad, India.
6	Friability apparatus	Veego scientific VFT-DV, Mumbai.
7	Hardness tester	Monsanto
8	Vernier caliper	Indolabs, Mitutoyo.
9	Humidity chamber	Labtech, Ambala.
10	USP dissolution test apparatus Type I	Veego scientific VDA-8DR, Mumbai.
11	UV-Visible spectrophotometer	Elico-SL 159 UV-Visible spectrophotometer, Japan.
12	FTIR spectrophotometer	Shimadzu, Japan.
13	Differential scanning calorimeter	Shimadzu, Japan.



Experimental Work

7. EXPERIMENTAL WORK

7.1. Preformulation study:

Preformulation testing is an investigation of physical and chemical properties of a drug substance alone. It is the first step in rational development of dosage form.

7.1.1. Identification of drug:

7.1.1.1. Identification by FTIR spectroscopy: *(IP, 2007; Skoog D.A., et al., 2004)*

Gliclazide discs were prepared by pressing the Gliclazide with potassium bromide and the spectra ranges between 4000 to 600 cm^{-1} was obtained under the operational conditions. The absorption maximums in spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum.

7.1.1.2. Identification by melting point: *(IP, 2007)*

Melting point of the drug was determined by capillary tube method.

7.1.2. Physicochemical parameters:

7.1.2.1. Organoleptic properties: *(Lachman L., et al., 1991; Banker G.S., et al., 2009)*

The color, odor and taste of the drug were recorded using descriptive terminology.

7.1.2.2. Solubility study: *(IP, 2007)*

It is important to know about solubility characteristic of a drug in aqueous system, since they must possess some limited aqueous solubility to elicit a therapeutic response. The solubility of drug was recorded by using various descriptive terminology specified in Indian Pharmacopoeia, 2007.

7.1.3. Analytical methods:

7.1.3.1. Determination of absorption maximum in 0.1 N HCl:

A stock solution of Gliclazide was prepared by dissolving 100 mg of drug in 0.1 N HCl and final volume was made to 100 ml. From the stock solution, 1 ml was pipettted out into 100 ml volumetric flask to obtain concentration of 10µg/ml. The solution was scanned in the range of wavelength of 200 to 400 nm region on shimadzu- 1700 pharmaspec UV- Visible spectrophotometer.

7.1.3.2. Preparation of standard graph of Gliclazide using phosphate buffer pH 7.4:

Beer's law is obeyed in the concentration range of 5 – 25 mcg/ml.

Method:-

50 mg of Gliclazide was accurately weighed into 100ml volumetric flask and dissolved in phosphate buffer pH 7.4. The volume was made up to 100ml to get a concentration of (0.5 mg/ml.) stock solution- I. From this, 1 ml was withdrawn and diluted to 10 ml to get a concentration of (25 µg/ml) stock solution -II.

Scanning of Drug:-

From stock solution-II (SS-II), 4 ml was withdrawn and the volume was made up to 10 ml with phosphate buffer pH 7.4 to get a concentration of 10 µg/ml. UV scan range was taken between the wavelengths 200-400 nm. It gave a peak at 226.5 nm and 225.5 nm and the same was selected as λ_{max} for Gliclazide.

7.1.3.3. Preparation of standard curve of Gliclazide in 0.1N HCl:

A stock solution of gliclazide was prepared by dissolving 100 mg of drug in 0.1 N HCl and final volume was made to 100 ml to give a solution concentration 1000 µg/ml. From the stock solution, 10 ml was pipettted out into 100 ml volumetric flask to obtain concentration of 100µg/ml. From the standard stock solution of gliclazide, appropriate aliquots of 2.5, 5.0, 7.5, 10.0, 12.5 and 15.0 ml were pipetted out into 50 ml volumetric flask and final volume was made with 0.1 N HCl. To obtained concentration of 5, 10, 15, 20, 25 and 30 µg/ml. Absorbance spectra of each solution against 0.1 N HCl as blank were measured at 281 nm using Elico-SL 159 UV-Visible spectrophotometer.

7.1.3.5. Determination of Percentage purity of Drug:

An accurately weighed 100 mg of Gliclazide was dissolved in 100 ml of methanol followed by mixing for 10 minutes. From the stock solution, 10 ml was pipettted out into 100 ml volumetric flask to obtain concentration of 100µg/ml. The solution was filtered through a 0.45µ membrane filter. From the above solution, aliquots of 0.6 ml were transferred to 10 ml volumetric flasks and final volume was made to 10 ml with methanol and the absorbance of resultant solution was measured by using Elico-SL 159 UV-Visible spectrophotometer at 271.5 nm using methanol as blank.

7.1.4. Determination of drug-polymer compatibility: ***(****Aulton M.E., 2007)*

Differential scanning calorimetry, Fourier transforms infrared spectroscopy studies were used for the evaluation of physicochemical compatibility and interaction, which helps in the prediction of interaction of the drug and polymers. Each polymer used in the formulations was blended with the drug levels that are realistic with

respect to the final dosage form. Each polymer was thoroughly blended with drug to increase drug- polymer molecular contacts to accelerate the reactions if possible.

7.1.4.1. Fourier transform infrared spectroscopy: *(Althaf A.S., et al., 2010; Raju M.,et al., 2010; Silverstein R.M., 2003)*

FTIR studies are very helpful in the evaluation of drug polymer interaction studies. If there is any incompatibility between the drug and polymer, these can be predicted by changes in the functional peaks. Infrared spectrum of gliclazide was determined on Fourier transform infrared spectrophotometer using potassium bromide dispersion method. The base line correction was done using dried potassium bromide. Then the spectrum of dried mixture of drug and various polymers were thoroughly mixed with potassium bromide. The crushed powders were compressed using a hydraulic compactor at approximately 20,000 pounds under vacuum for 3 minutes. FTIR instrument were performed under nitrogen atmosphere at a flow rate of 50 standard cubic feet per hour. Spectral scanning was conducted from 4000 to 400 cm^{-1} at a resolution of 4 cm^{-1} by using Shimadzu (Japan) FTIR spectrophotometer.

7.1.4.2. Differential scanning calorimetry: ***(****Raju M.,et al., 2010; Willard H.H., et al., 2008)*

Any possible drug polymer interaction can be studied by thermal analysis. The DSC analyses of pure drug, drug + HPMC K100M and drug + ethyl cellulose were carried out using Shimadzu to evaluate any possible drug-polymer interaction. The 2 mg sample were heated in a hermetically sealed aluminum pans in the temperature range of 25-300ºC at heating rate of 10ºC /min under nitrogen flow of 30 ml/min.

7.1.5. Formulation of Gliclazide sustained release matrix tablets: *(panchal v.n, et al., 2011)*

All the ingredients mentioned in Table 7.1 were pre-weighed and passed through mesh #60 separately. The drug and polymer were blended first in mortar and pestle then the remaining ingredients are added in that and blended for 15 minutes and the blend is finally passed through mesh #20 and used for evaluation of flow characteristic.

Table 7.1: Composition of gliclazide SR matrix tablets

Ingredients(mg)	LF1	LF2	LF3	LF4	LF5	LF6	LF7	LF8	LF9
Gliclazide	60	60	60	60	60	60	60	60	60
HPMC K100M	35	70	105	-	-	-	17.5	35	52.5
Ethyl cellulose	-	-	-	35	70	105	17.5	35	52.5
Lactose	240	205	170	240	205	170	240	205	170
Polyvinyl pyrrolidone-k30	10	10	10	10	10	10	10	10	10
Magnesium stearate	4	4	4	4	4	4	4	4	4
Aerosol	1	1	1	1	1	1	1	1	1
Isopropyl alcohol	**Q.S**	**Q.S**	**Q.S**	**Q.S**	**Q.S**	**Q.S**	**Q.S**	**Q.S**	**Q.S**
Total weight	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**

All the quantities are expressed as mg per tablet.

7.1.6. Evaluation of pre-compression blend:

7.1.6.1. Angle of repose: *(Lachman L., et al., 1991)*

The angle of repose was determined by the funnel method. An accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured. The angle of repose was calculated using the following equation.

$$\tan(\theta) = \frac{h}{r}$$

Where '**h**' and '**r**' are the height and radius respectively of the powder cone.

Table 7.2: Standard values of angle of repose (°)

S. No.	Flowability	Angle of repose
1	Excellent	<25
2	Good	25-30
3	Passable*	30-40
4	Poor	37-45
5	Very poor	>45

* Adding glidant for improving flow

7.1.6.2. Loose bulk density: *(Lachman L., et al., 1991)*

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced in to a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. The loose bulk density of powder blends was determined using the following formula.

Loose bulk density = Total weight of powder / Total volume of powder

7.1.6.3. Tapped bulk density: *(Lachman L., et al., 1991)*

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The tapped bulk densities of powder blends were determined using the following formula.

Tapped bulk density= Total weight of powder / Total volume of tapped powder

7.1.6.4. Hausner's ratio: *(Aulton M.E., 2007)*

It is related to interparticulate friction and could be used to predict powder flow properties. Hausner's ratio was determined by following equation,

Hausner's Ratio = Tapped bulk density / Loose bulk density

A Hausner ratio less than 1.25 indicates good flow while greater than 1.5 indicates poor flow.

7.1.6.5. Carr's compressibility index: *(Aulton M.E., 2007)*

It is a simple index that can be determined on small quantities of powder. The compressibility indices of the powder blends was determined using following formula,

Carr's compressibility index (%) = [(TBD-LBD)/ TBD] x100

Relationship between % compressibility and flowability is shown in the table 7.3.

Table 7.3: Standard values of Carr's index

S. No.	Carr's index	Type of flow
1	5-15	Excellent
2	12-16	Good
3	18-21	Fair to passable
4	23-35	Poor*
5	33-38	Very poor*
6	>40	Extremely poor*

* May be improved by glidant

7.2. Preparation of SR Matrix Tablets:

Direct compression method:

All the ingredients metioned in Table 7.1 were passed through Sieve no. 60 mesh separately and collected. Ingredients were mixed in geometrical order and thoroughly mixed for 15 minutes to get a uniform mixture and the blend is finally passed through mesh #20. LACTOSE and magnesium stearate were added to the powder mixture and compressed on a 16- station rotary tablet compression machine using 11mm round, biconcave punches.

The drug polymer ratio was developed to adjust drug release as per theoretical release profile and to keep total weight of tablet constant for all the fabricated batches under experimental conditions of preparations. The total weight of the matrix tablets was 350 mg with different drug polymer ratios.

In the formulations prepared, the release retardants included were hydroxypropyl methylcellulose (HPMC K100M), and ethylcellulose.lactose is used as diluent. Magnesium stearate 1% and aerosil were used as lubricant and glidant.

7.3. Evaluation of gliclazide sustained release matrix tablets:

7.3.1. Appearance: *(Lachman L., et al., 1991)*

The tablets were visually observed for capping, chipping and lamination.

7.3.2. Dimension (Thickness and Diameter): *(Lachman L., et al., 1991)*

The thickness and diameter of tablets were important for uniformity of tablet size. The thickness and diameter of the tablets was determined by using Vernier caliper. Ten tablets from each type of formulation were used and average values were calculated.

7.3.3. Tablet hardness: *(Lachman L., et al., 1991)*

For each formulation, the hardness of 10 tablets was determined using the Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm^2. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg/cm^2.

7.3.4. Percent friability: *(Lachman L., et al., 1991)*

Friability is the measure of tablet strength. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of pre weighed tablets was placed in Roche friabilator which was then operated for 100 revolutions. The tablets were then dedusted and reweighed. A loss of less than 1 % in weight is generally considered acceptable. Percent friability (% F) was calculated as follows.

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

7.3.5. Weight variation: *(IP, 2007; Lachman L., et al., 1991)*

To find out weight variation 20 tablets of each formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight. The test was performed according to the official method.

Weight variation importance during tablets compression section, each and every time intervals we must check the weight of tablet. If we are not maintaining the weight variation means it will give the deviation of drug content as well as yield of tablets.

Table 7.4: Specifications of % weight variation allowed in tablets as per Indian Pharmacopoeia

S. No.	Average weight of tablets (mg)	Maximum percent deviation allowed (%)
1	80 or less	10
2	More than 80 but less than 250	7.5
3	More than 250	5

7.3.6. Drug content:

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to 100 mg of gliclazide was transferred into a 100 ml standard volumetric flask. Then added 50ml of pH 7.4 phosphate buffer solution. It was gently shaken for 15 minutes. Then made upto the mark with pH 7.4 phosphate buffer solution. The solution was filtered through a whatmann filter paper, diluted suitably and the absorbance of resultant solution was measured by using Elico-SL 159 UV-Visible spectrophotometer at 225.5 nm using pH 7.4 phosphate buffer as blank.

7.3.7. *In vitro* release studies:

The release rate of gliclazide from matrix tablets was determined using United States Pharmacopoeia dissolution testing apparatus I (Basket method; Veego Scientific VDA-8DR, Mumbai, India). The dissolution test was performed at 100 rpm using 900 ml of pH 1.2 for the first 2 hrs and phosphate buffer pH 7.4 from 2-10 hrs at 37 ± 0.5°C. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted suitably. Absorbance of these solutions was measured at 225.5 nm using Elico-SL 159 UV-Visible spectrophotometer. For each formulation, the experiments were carried out in triplicate. The release data were analyzed to study the release kinetics using zero order, first order and matrix, korsmeyer-peppas equations by using PCP disso V3 software.

7.3.8. Kinetics of *in vitro* drug release: *(Brahmankar D.M. and Jaiswal S.B., 2009; Harris S.M., et al., 2006)*

To study the release kinetics of *in vitro* drug release, the data was applied to kinetic models such as zero order, first order, higuchi and korsmeyer- Peppas.

- **Zero order**

$$C = K_0 t$$

Where K_0 - Zero-order rate constant expressed in units of concentration/time

t - Time in hrs.

- **First order**

$$LogC = LogC_0 - Kt / 2.303$$

Where C_0 - Initial concentration of drug,

K - First order constant and t - Time in hrs.

- **Higuchi**

$$Q_t = Kt^{1/2}$$

Where Q_t - Amount of the release drug in time t,

K- Kinetic constant and t- is time in hrs

- **Korsmeyer Peppas**

$$M_t / M_\infty = Kt\ n$$

Where, Mt - represents amount of the released drug at time t,

M_∞- Overall amount of the drug (whole dose) released after 12 hrs

K- Diffusion characteristic of drug/ polymer system constant

n- Diffusion exponent that characterizes the mechanism of release of drug.

Table 7.5: Diffusion exponent and solute release mechanism

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45<n <0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n>0.89	Super case-II transport

7.4. Stability study: *(Carstensen J.T., et al., 2008; Manavalan R., et al., 2008)*

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. Generally, the observation of the rate at which the product degrades under normal room temperature

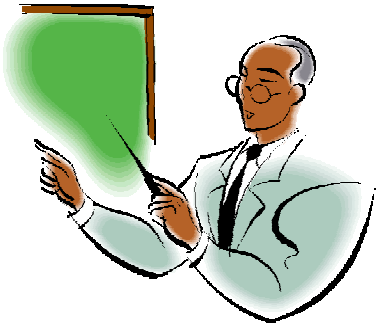
requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted.

ICH specifies the length of study and storage conditions

- **Long-Term Testing**: 25°C ± 2°C at 60% RH ± 5% for 12 Months
- **Accelerated Testing:** 40°C ± 2°C at 75% RH ± 5% for 6 Months

In present study the selected formulation LF3 exposure up to 3 months stability studies at accelerated condition (40°C ± 2°C at 75% RH ± 5% RH) to find out the effect of aging on hardness, drug content and *in vitro* drug release.

Stability studies were carried out at accelerated condition (40°C ± 2°C at 75% RH ± 5% RH) for the optimized formulation LF3. The matrix tablets were stored at 40°C ± 2°C at 75% RH ± 5% RH for accelerated temperature in closely packed with aluminium foil for 3 months. The samples were withdrawn after periods of 1st month, 2nd month and 3rd month. The samples were analyzed for its hardness, drug content and *in vitro* drug release.



RESULTS AND DISCUSSION

8. RESULTS AND DISCUSSION

8.1. Preformulation parameters:

8.1.1. Identification of drug:

8.1.1.1. Identification by FTIR spectroscopy:

The FTIR spectrum of gliclazide was shown in Figure 8.1 and the interpretations of FTIR frequencies were showed in Table 8.1.

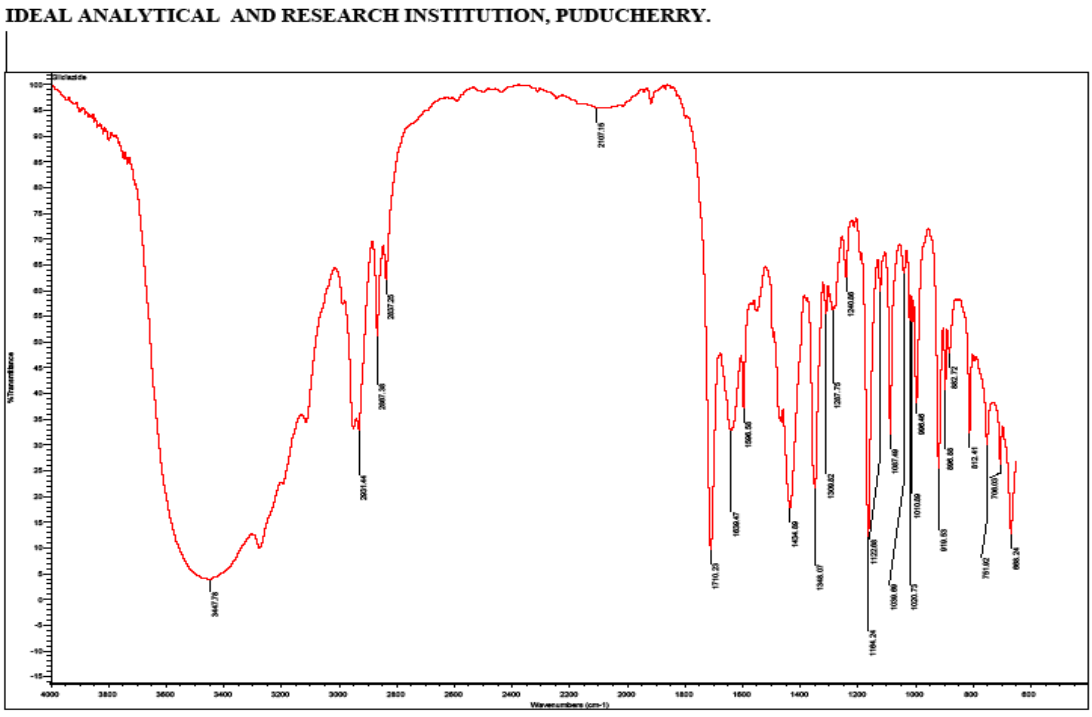


Figure 8.1: FTIR spectrum of gliclazide

- **Interpretation of FTIR Spectrum:**

Major functional groups present in gliclazide shows characteristic peaks in FTIR spectrum. Table 8.1 shows peaks observed at different wave numbers and the functional group associated with these peaks. The major peaks are identical to functional group of gliclazide. Hence, the sample was confirmed as gliclazide.

Table 8.1: Characteristic frequencies in FTIR spectrum of gliclazide

Wave No.(cm^{-1})	Functional group
3447.78	N-H stretching
2931.44	CH3 asymmetric stretching
2867.38	CH3 absorption
1710.23	C-O stretching
1639.47	NH2 deformation
1596.58	C=C stretching
1348.07	C-C stretching
1164.24	C-N stretching

8.1.1.2. Melting point:

Melting point of gliclazide sample was found to be 180.4^0C. The reported melting point for gliclazide was in range of 180 to 182^0C. Hence, experimental values are in good agreement with official values.

8.1.2. Physicochemical parameters of drug:

8.1.2.1. Organoleptic properties:

Odour : Odorless

Colour : A White (or) almost white powder

Taste : Bitter taste

8.1.2.2. Solubility study:

Table 8.2: Solubility of gliclazide in different solvents

Name of solvents	Solubility
Distilled water	InSoluble
Methanol	Sparingly soluble
0.1N HCl	Freely Soluble
Dichloro methane (or) methylene chloride	Freely Soluble
Phosphate buffer (pH 7.4)	Freely Soluble
Acetone	Soluble

8.1.3. Analytical methods:

8.1.3.1. Determination of absorption maximum in 0.1 N HCl:

The absorption maximum for gliclazide was found to be 281 nm.

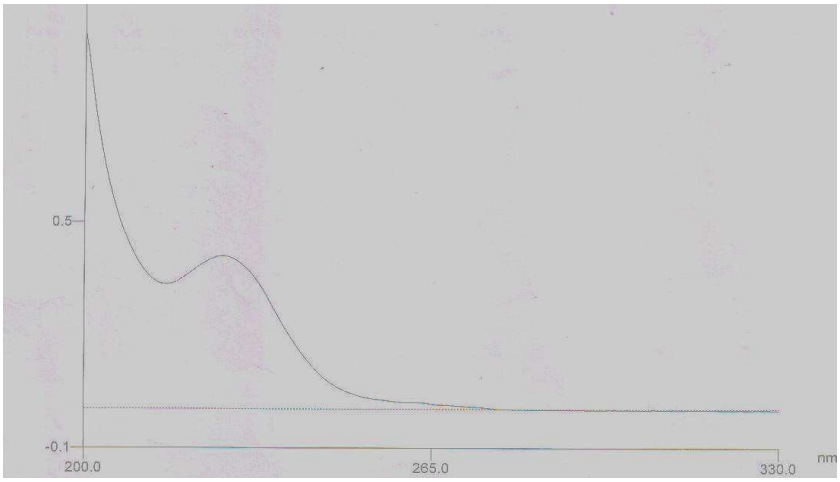


Figure 8.2: λ_{max} observed for gliclazide in 0.1N HCl

8.1.3.2. Determination of absorption maximum in pH 7.4 phosphate buffer:

The absorption maximum of gliclazide was found to be 225.5 nm.

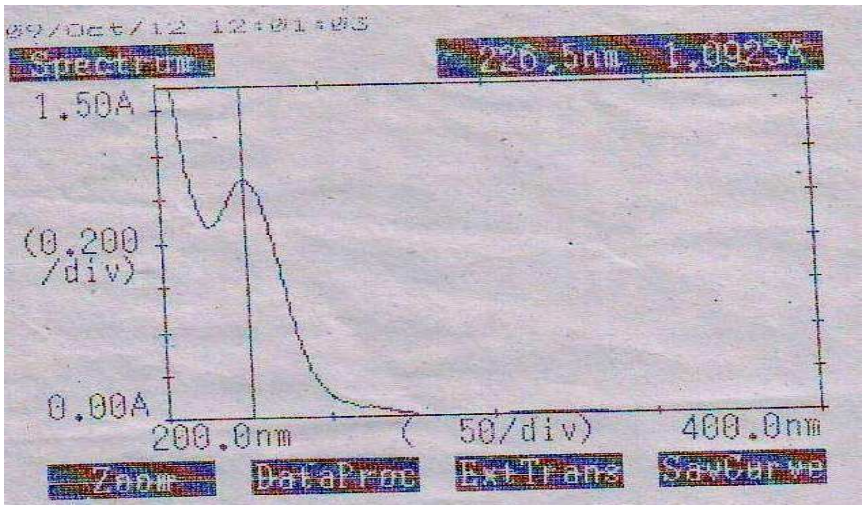


Figure 8.3: λ_{max} observed for gliclazide in pH 7.4 phosphate buffer.

8.1.3.3. Preparation of standard curve of gliclazide in 0.1 N HCl:

UV absorption spectrum of gliclazide in 0.1N HCl showed λ_{max} at 281 nm. Absorbance obtained for various concentrations of gliclazide in 0.1N HCl are given in Table 8.3. The curve of absorbance versus concentration for gliclazide was found to be linear in the concentration range of 0–30 µg/ ml. The drug obeys Beer- Lambert's law in the range of 0–30 µg/ ml.

Table 8.3: Concentration and absorbance of gliclazide in 0.1N HCl

S. No.	Concentration (µg/ml)	Absorbance
1	0	0.000
2	5	0.304
3	10	0.597
4	15	0.901
5	20	1.173
6	25	1.472
7	30	1.760

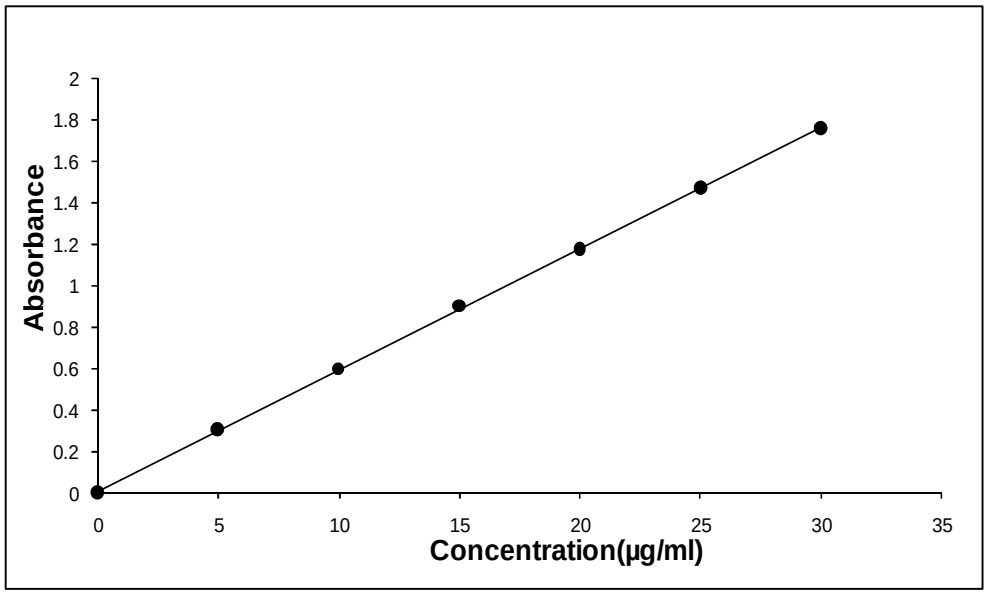


Figure 8.4: Calibration curve of gliclazide in 0.1N HCl

Table 8.4: Calibration parameter values in 0.1 N HCl

S. No.	Parameters	Values
1	Correlation coefficient (r)	0.9999
2	Slope (m)	0.0585
3	Intercept (c)	0.0090

8.1.3.4. Preparation of standard curve of gliclazide in pH 7.4 phosphate buffer:

UV absorption spectrum of gliclazide in pH 7.4 showed λ_{max} at 225.5 nm. Absorbance obtained for various concentrations of gliclazide in pH 7.4 are given in Table 8.5. The curve of absorbance versus concentration for gliclazide was found to be linear in the concentration range of 0–30 µg/ ml. The drug obeys Beer- Lambert's law in the range of 0–30 µg/ ml.

Table 8.5: Concentration and absorbance of gliclazide in pH 7.4 phosphate buffer

S. No.	Concentration (µg/ml)	Absorbance
1	0	0.000
2	5	0.210
3	10	0.409
4	15	0.592
5	20	0.788
6	25	0.981
7	30	1.183

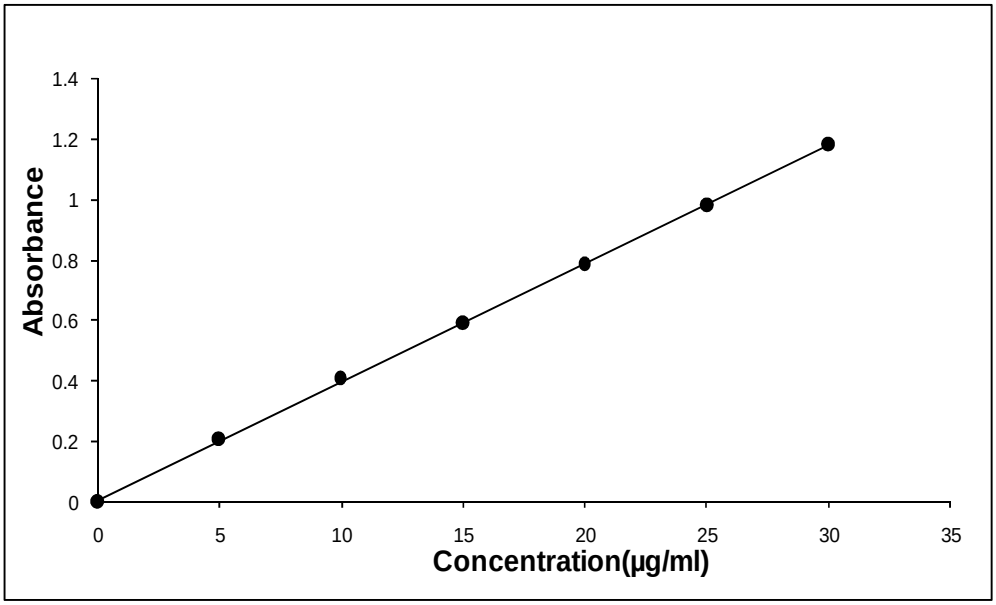


Figure 8.5: Calibration curve of gliclazide in pH 7.4 phosphate buffer

Table 8.6: Calibration parameter values in pH 7.4 phosphate buffer

S. No.	Parameters	Values
1	Correlation coefficient (r)	0.9999
2	Slope (m)	0.0391
3	Intercept (c)	0.0086

8.1.3.5. Percentage purity of drug:

The percentage purity of drug was calculated by using calibration curve method. The percentage purity of drug was found in official limits.

Table 8.7: Percentage purity of gliclazide in pure drug

S. No.	Percentage purity (%)	Average percentage purity (%)
1	99.79	100.13 ± 0.30
2	100.29	
3	100.33	

The reported percentage purity for gliclazide in IP 2007 is 97 to 102%.

8.1.4. Compatibility testing of drug with polymer:

Compatibility of drug and polymers was found to be as following methods such as Fourier transform infrared spectroscopy and differential scanning calorimetry.

8.1.4.1. Fourier transform infrared spectroscopy:

The FTIR spectrums of gliclazide with different polymers used in formulation are shown in Figures 8.6, 8.7 and Table 8.8.

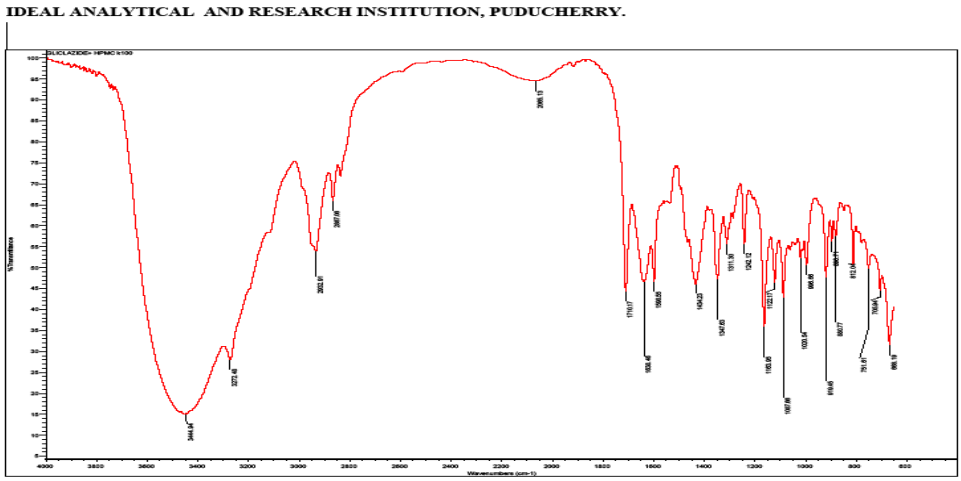


Figure 8.6: FTIR spectrum of gliclazide with HPMC K100M

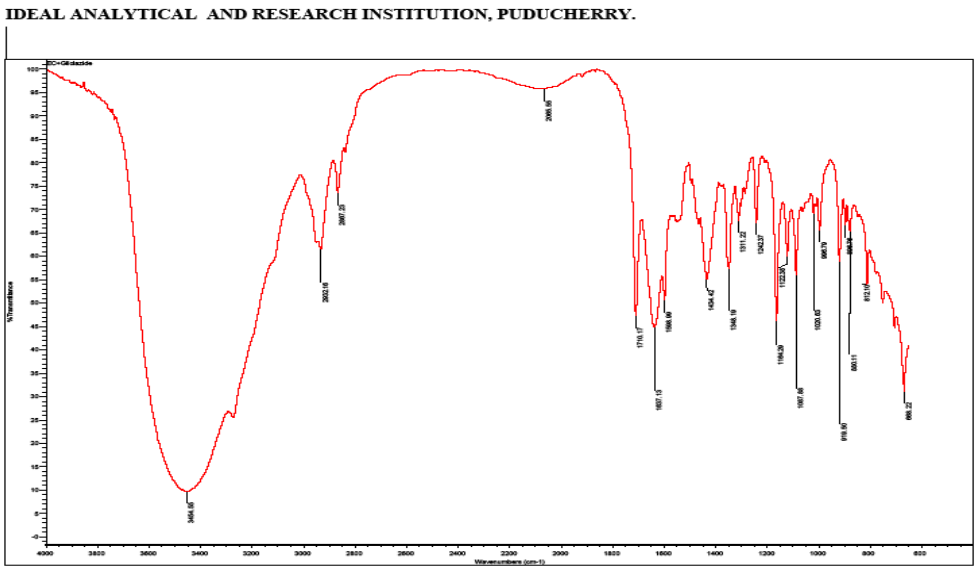


Figure 8.7: FTIR spectrum of gliclazide with ethyl cellulose

Table 8.8: FTIR peak observed for gliclazide with different polymers used in formulations.

Functional groups	Peaks observed [Wave No. (cm^{-1})]		
	GLI + HPMC K100M	**GLICLAZIDE**	**GLI + Ethyl cellulose**
N-H stretching	3444.94	3447.78	3454.55
CH3 asymmetric stretching	2932.91	2931.44	2932.16
CH2 absorption	2867.06	2867.38	2867.23
C-O stretching	1710.17	1710.23	1710.17
NH2 deformation	1638.46	1639.47	1637.13
C=C stretching	1598.55	1596.58	1598.99
C-C stretching	1347.63	1348.07	1348.19
C-N stretching	1163.95	1164.24	1164.29

According to Table 8.8 and Figures 8.1, 8.6, and 8.7, FTIR spectrum showed that there was no major difference in peak when compared between pure drug of gliclazide and gliclazide with different polymers. Therefore it could indicate that there was no incompatibility between drug and different polymers.

8.1.4.2. Differential scanning calorimetry:

The compatibility and interactions between drug and polymers were checked using differential scanning calorimetry and the results were shown in Figures 8.8, 8.9 and 8.10.

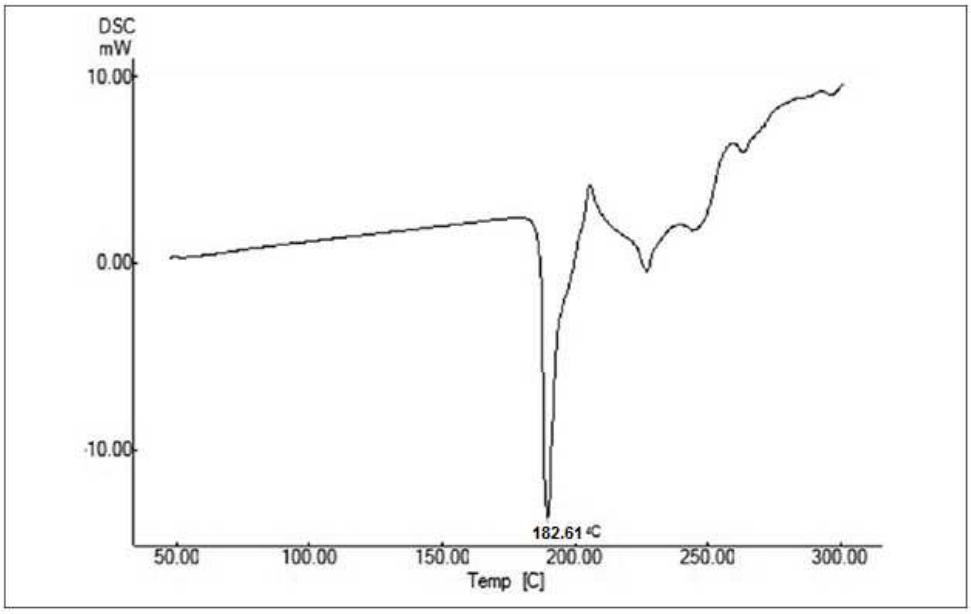


Figure 8.8: DSC thermal analysis of gliclazide

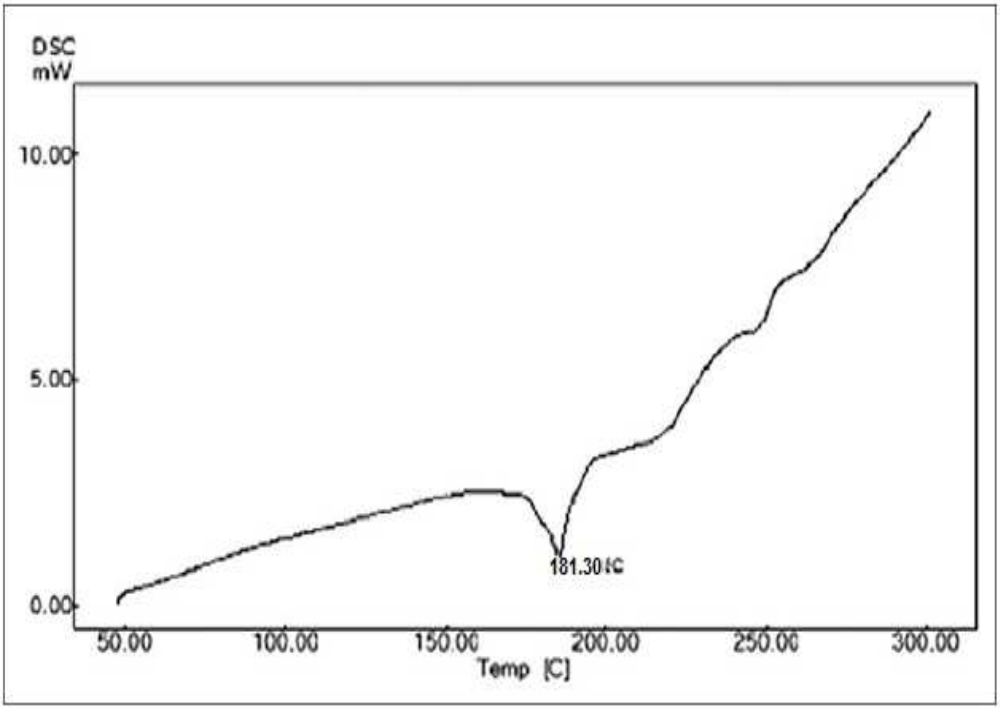


Figure 8.9: DSC thermal analysis of gliclazide + HPMC K100M

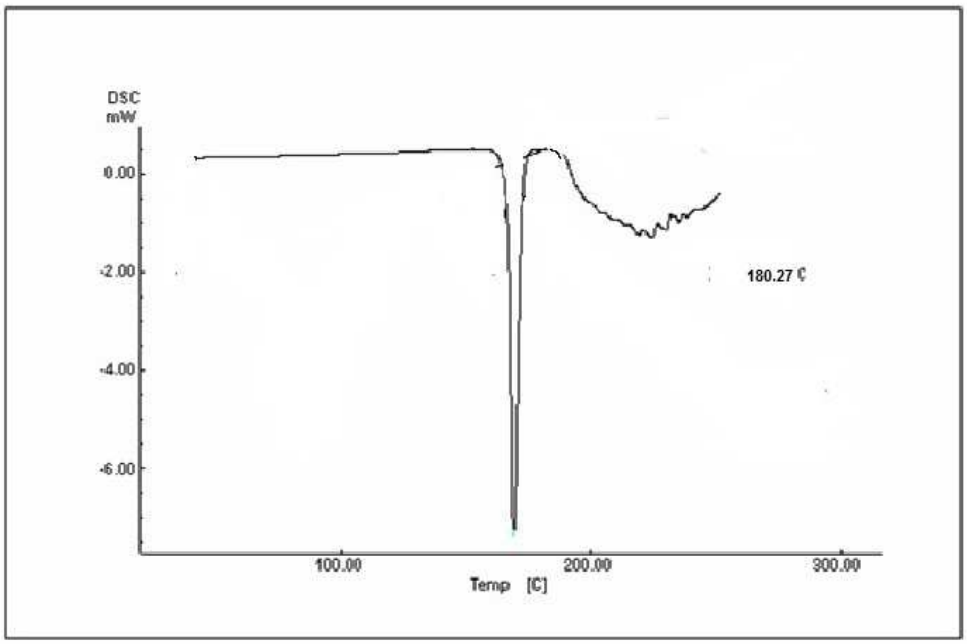


Figure 8.10: DSC thermal analysis of gliclazide + ethyl cellulose

According to Figures 8.9 to 8.12 and Table 8.9, DSC thermogram showed that there was no major difference in onset temperature, end set temperature and peak temperature when compared with pure drug thermogram. Therefore it could indicate that there was no incompatibility between drug and different polymers.

Table 8.9: DSC thermogram parameters of gliclazide with various polymers

S. No.	DSC thermogram	Onset temperature (°C)	Peak temperature (°C)	End set temperature (°C)
1	Gliclazide	180.42	182.61	184.62
2	Gliclazide + HPMC K100M	178.70	181.30	183.81
3	Gliclazide + Ethylcellulose	177.75	180.27	184.59

8.2. Evaluation of powder blends:

The blended powders of different formulations were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and Hausner ratio. The results of these evaluations were as follows: -

8.2.1. Angle of repose:

Angle of repose ranged from 23.20°± 0.61 to 24.49°± 0.36. The results were found to be below 25° and hence the blend was found to have excellent flowability. (Table No. 8.10).

Table 8.10: Flow characteristics of powder blends

Formulation Code	Angle of repose (°)*	Loose bulk density (g/ml)*	Tapped bulk density (g/ml)*	Hausner ratio*	Carr's index (%)*
GF1	24.19±0.98	0.638±0.00	0.730±0.00	1.13±0.00	12.147±0.30
GF2	24.48±0.17	0.538±0.00	0.616±0.06	1.09±0.02	10.333±0.33
GF3	23.36±0.98	0.481±0.01	0.547±0.04	1.10±0.00	9.736±1.14
GF4	23.44±0.73	0.547±0.00	0.721±0.02	1.24±0.10	14.505±2.20
GF5	24.05±0.19	0.572±0.00	0.682±0.00	1.22±0.03	16.256±0.61
GF6	23.30±0.17	0.616±0.00	0.778±0.00	1.21±0.00	16.582±0.09
GF7	23.93±0.77	0.561±0.01	0.691±0.00	1.20±0.06	13.586±2.66
GF8	23.20±0.61	0.590±0.01	0.646±0.00	1.11±0.00	12.038±1.50
GF9	24.49±0.36	0.602±0.01	0.636±0.00	1.16±0.17	15.236±0.47

*All the values were expressed as mean± SD, n=3

8.2.2. Loose bulk density and tapped bulk density:

Bulk and tapped densities are used for the measurement of Compressibility index. The LBD and TBD ranged from 0.481 ± 0.01 to 0.638 ± 0.00 g/ml; and 0.547 ± 0.04 to 0.778 ± 0.00 g/ml respectively. (Table No. 8.10).

8.2.3. Compressibility index (Carr's index):

The compressibility index (%) ranged from 9.736 ± 1.14 to 16.582 ± 0.09 (Table No.8.10). The blend was found to have excellent flowing property as the result were found to be below 15%.

8.2.4. Hausner ratio:

The Hausner ratio ranged from 1.09 ± 0.02 to 1.24 ± 0.10, (Table No.8.10). The result indicates the free flowing properties of the powders.

8.3. Evaluation of sustained release matrix tablets:

8.3.1. Appearance:

Surface nature of tablets was observed visually and it was concluded they did not show any defects such as capping, chipping and lamination.

8.3.2. Physico-chemical characteristics:

The physical characteristics of gliclazide matrix tablets (GF1 toGF9) such as thickness, diameter, hardness, friability, weight variation and drug content were determined and the results were shown in table 8.11.

8.3.2.1. Dimension (Thickness and Diameter):

The size (diameter) of the tablets was found to be in the range from 11.17±0.01 mm to 11.20 ± 0.01 and thickness between 4.32 ± 0.06 to 4.58 ± 0.04 mm.

8.3.2.2. Tablet hardness:

The hardness of tablets was found to be in the range from 5.1 ± 0.10 kg/cm^2 to 6.3 ± 0.10 kg/cm^2. This indicates good mechanical strength of tablet.

8.3.2.3. Percent friability:

Percentage friability of all the formulations was found to be in the range from 0.418±0.04 to 0.846±0.09 %. This indicates good handling property of the prepared matrix tablet

Table 8.11: Physico-chemical parameters of gliclazide matrix tablets

F. Code	Dimension		Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)	Drug content (%w/w)
	Diameter (mm)	Thickness (mm)				
GF1	11.20±0.01	4.44±0.02	5.2±0.10	0.704±0.07	348.15±1.47	99.00±1.55
GF2	11.19±0.02	4.37±0.06	5.5±0.30	0.774±0.07	348.70±2.42	101.00±2.20
GF3	11.20±0.01	4.57±0.06	5.1±0.10	0.846±0.09	348.70±2.42	99.55±1.10
GF4	11.19±0.01	4.32±0.06	5.8±0.10	0.634±0.05	347.05±3.25	101.00±2.20
GF5	11.17±0.01	4.34±0.07	6.1±0.26	0.677±0.06	347.10±3.88	99.75±0.55
GF6	11.17±0.04	4.40±0.09	5.2±0.20	0.418±0.04	347.05±3.25	102±2.20
GF7	11.19±0.01	4.58±0.04	5.9±0.43	0.705±0.10	347.30±3.10	99.50±3.00
GF8	11.19±0.01	4.54±0.02	5.2±0.17	0.805±0.07	347.70±2.31	99.23±1.13
GF9	11.18±0.01	4.46±0.06	6.3±0.10	0.631±0.06	348.45±2.06	98.56±1.12

All the values were expressed as mean ± SD, n=3

8.3.2.4. Weight variation:

A tablet is designed to contain a specific amount of drug. When the average weight of the tablet is 400 mg, the pharmacopoeial limit for percentage deviation is ± 5%. The percentage deviation from average tablet weight for all the tablet was found

to be within the specified limits and hence all formulations complied with the test for weight variation according to the pharmacopoeial specifications IP 2007.

8.3.2.5. Drug content:

The drug content of all the formulation was found to be in the range from 98.56 ± 1.55 to 102 ± 2.20 % w/w, which was within the specified limit as per IP 2007.

8.3.3. *In vitro* dissolution studies:

Table.8.12: Results of *in vitro* release studies of gliclazide sustained release matrix tablets

S. No	Time in hours	Formulation code								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	1	09.21 ±0.11	12.4 ±1.54	14.5 ±1.04	16.7± 1.54	14.4± 1.56	15.6± 0.45	9.4 ±2.78	6.81± 0.45	8.8± 1.54
2	2	19.89 ±1.23	36.8 ±1.89	29.3 ±2.66	34.8± 0.61	38.7 ±1.05	30..4± 0.15	17.8 ±1.96	13.73 ±0.55	15.7 ±1.45
3	3	49.30 ±2.54	48.5 ±2.54	37.7 ±0.20	58.6± 0.02	52.9± 3.51	38.9± 1.63	29.6 ±0.12	38.6 ±0.56	26.4 ±1.52
4	4	75.00 ±1.56	68.4 ±1.65	49.7 ±1.53	79.5± 0.91	63.3 ±1.55	51.1± 3.55	47.7 ±0.56	49.2 ±0.22	33.8 ±0.01
5	5	93.10 ±2.57	79.3 ±0.22	64.2 ±2.01	92.1± 0.78	71.5 ±0.45	65.3± 2.23	68.9 ±1.56	56.9± 1.51	48.1 ±0.12
6	6	93.30 ±0.23	81.5 ±2.55	76.5 ±2.50	92.6± 0.51	84.6 ±0.61	77.5± 1.25	79.3 ±3.45	69.8 ±1.02	57.9 ±0.65
7	7	93.60 ±1.54	94.0 ±0.23	87.6 ±1.21	93.1± 0.05	93.8 ±0.49	88.9± 061	84.6± 1.56	76.4 ±2.55	66.6 ±0.54
8	8	93.90 ±2.45	94.8 ±2.55	95.6 ±0.54	93.9± 0.07	94.9 ±0.61	96.0± 0.74	95.0 ±1.26	85.1 ±2.16	78.6 ±1.55
9	9	94.10 ±2.77	95.4 ±2.54	95.8 ±0.26	94.3 ±048	95.2 ±1.54	96.2± 0.07	95.2 ±0.16	97.3 ±2.55	83.5 ±0.65
10	10	94.30 ±2.54	95.6 ±2.54	96.1 ±0.50	94.6± 0.52	95.8 ±0.91	96.5± 0.21	95.5 ±1.51	97.5 ±2.16	98.2 ±0.55

*All values are expressed as mean ± S.D. n=3

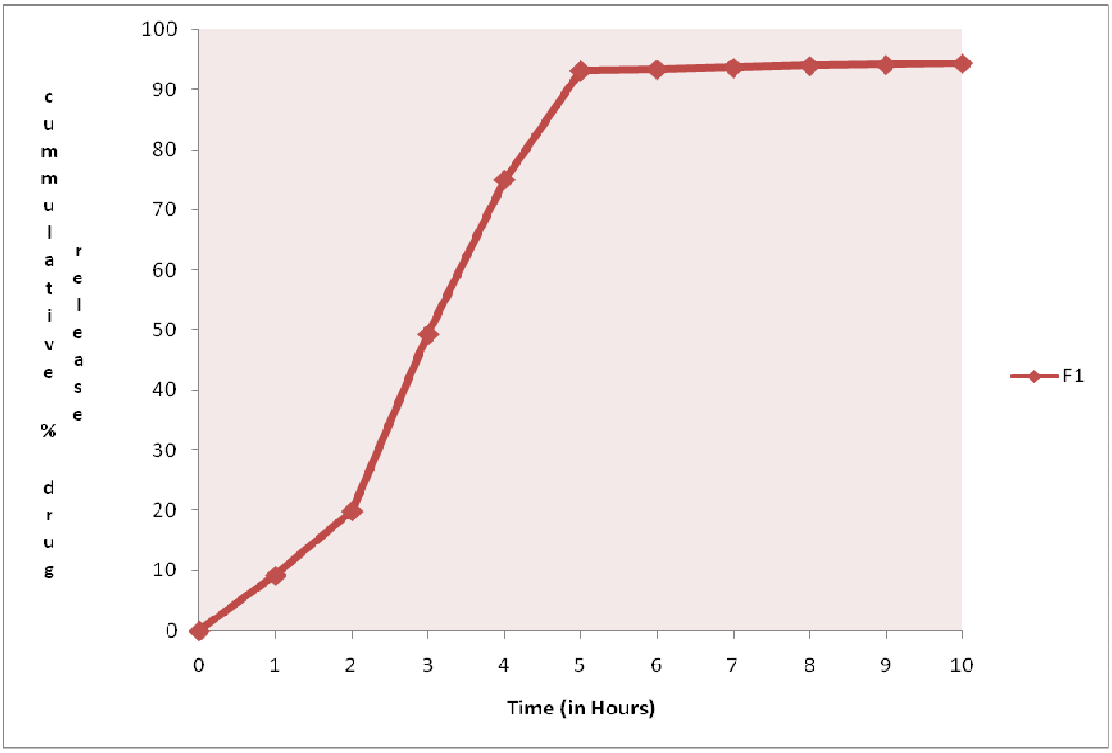


Figure 8.11: *In vitro* drug release profile of formulation GF1

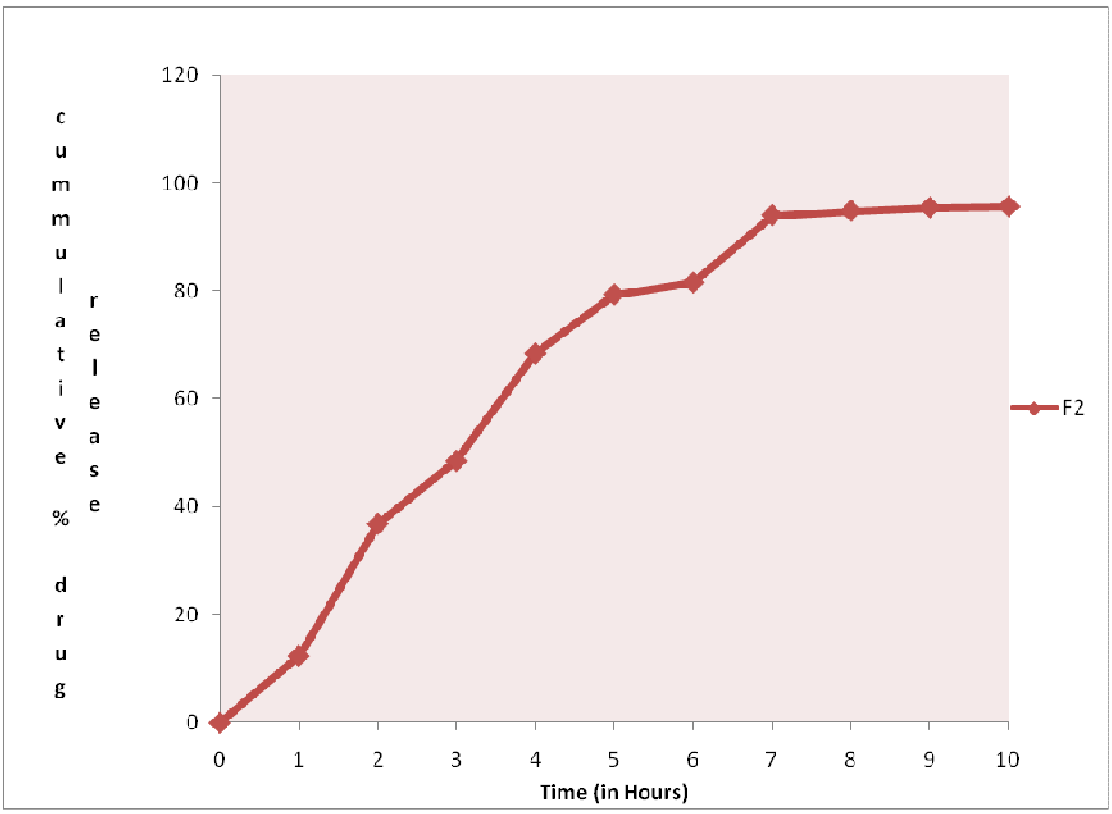


Figure 8.12: *In vitro* drug release profile of formulation GF2

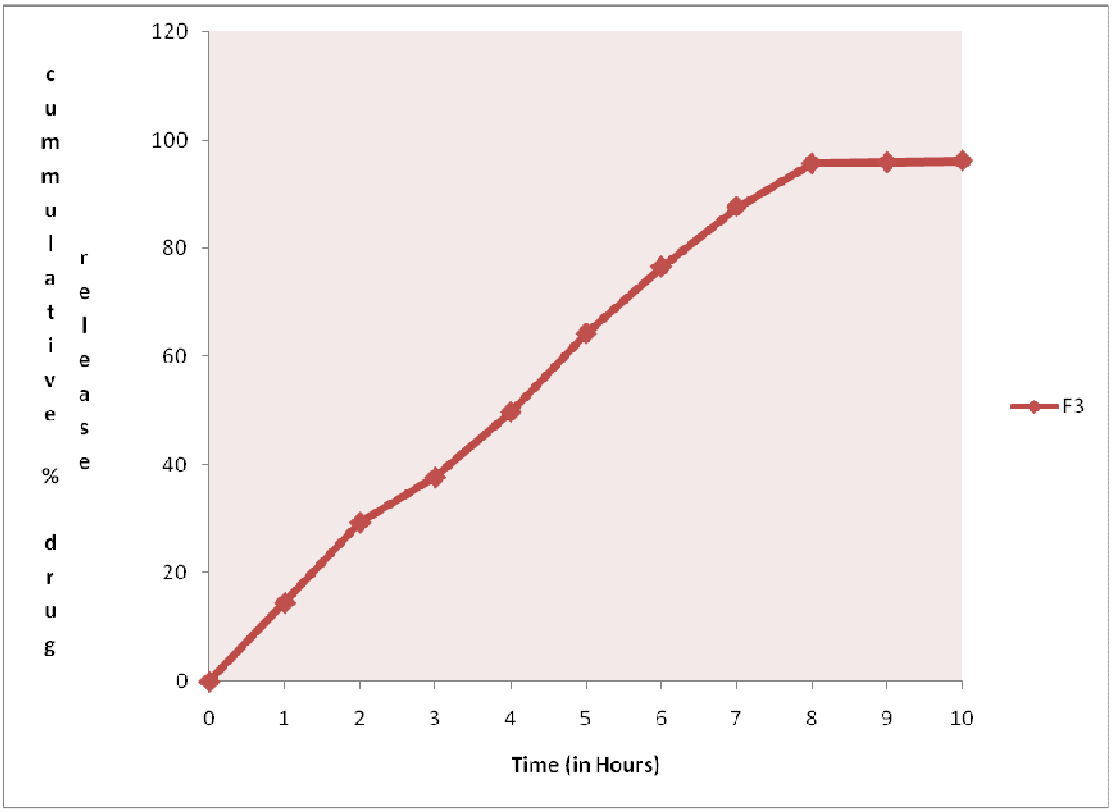


Figure 8.13: *In vitro* drug release profile of formulation GF3

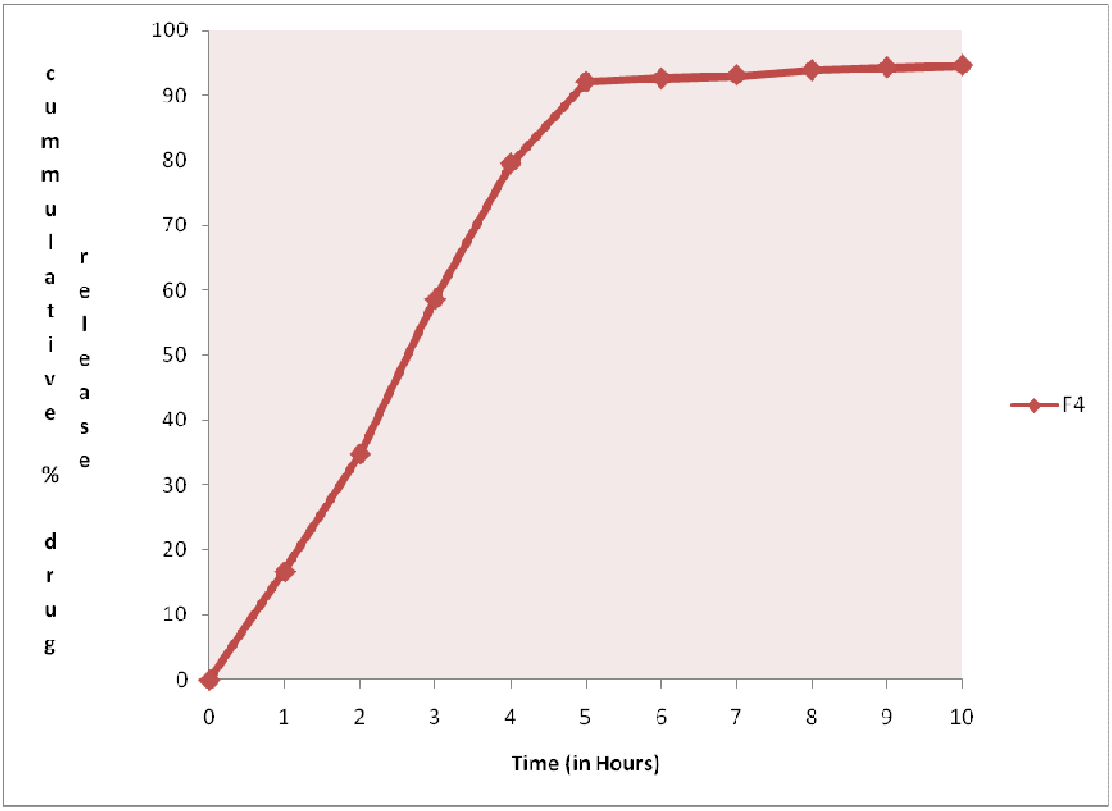


Figure 8.14: *In vitro* drug release profile of formulation GF4

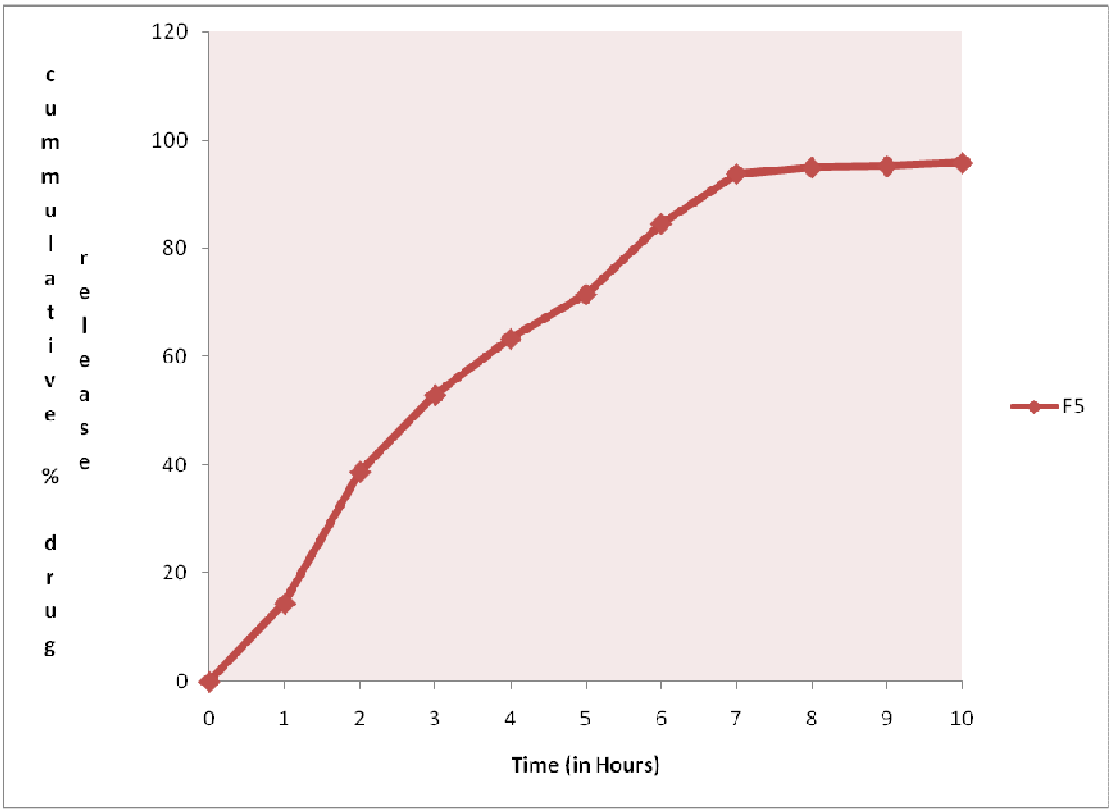


Figure 8.15: *In vitro* drug release profile of formulation GF5

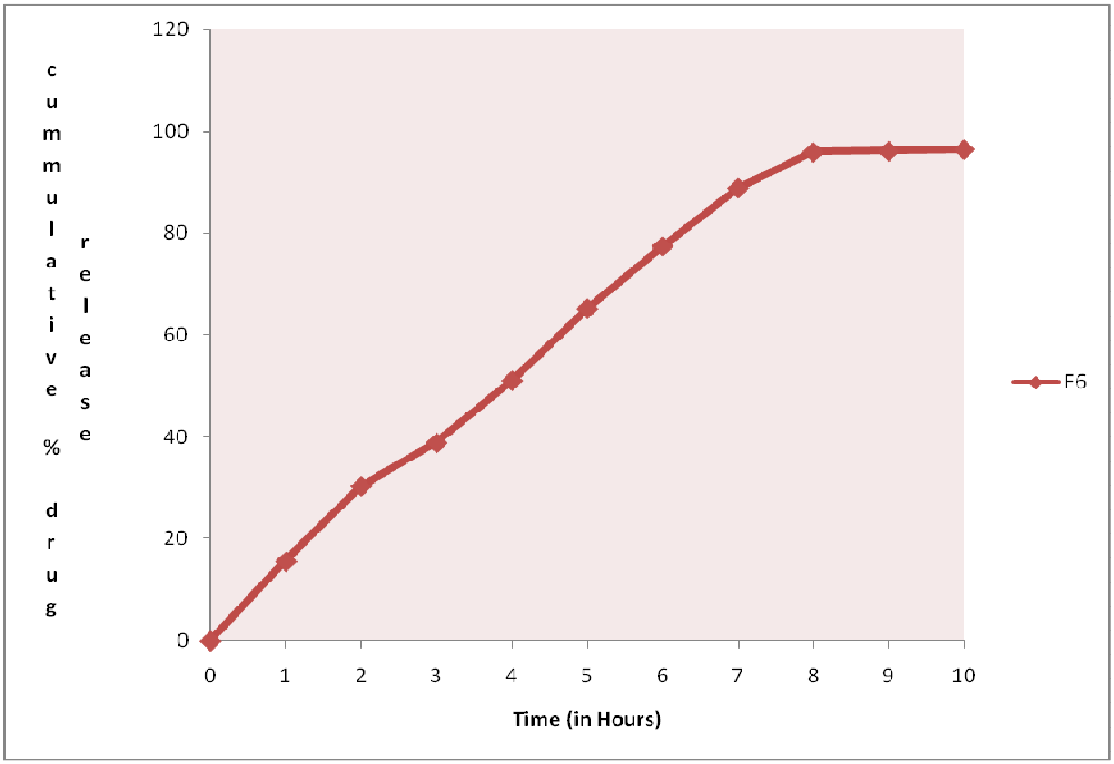


Figure 8.16: *In vitro* drug release profile of formulation GF6

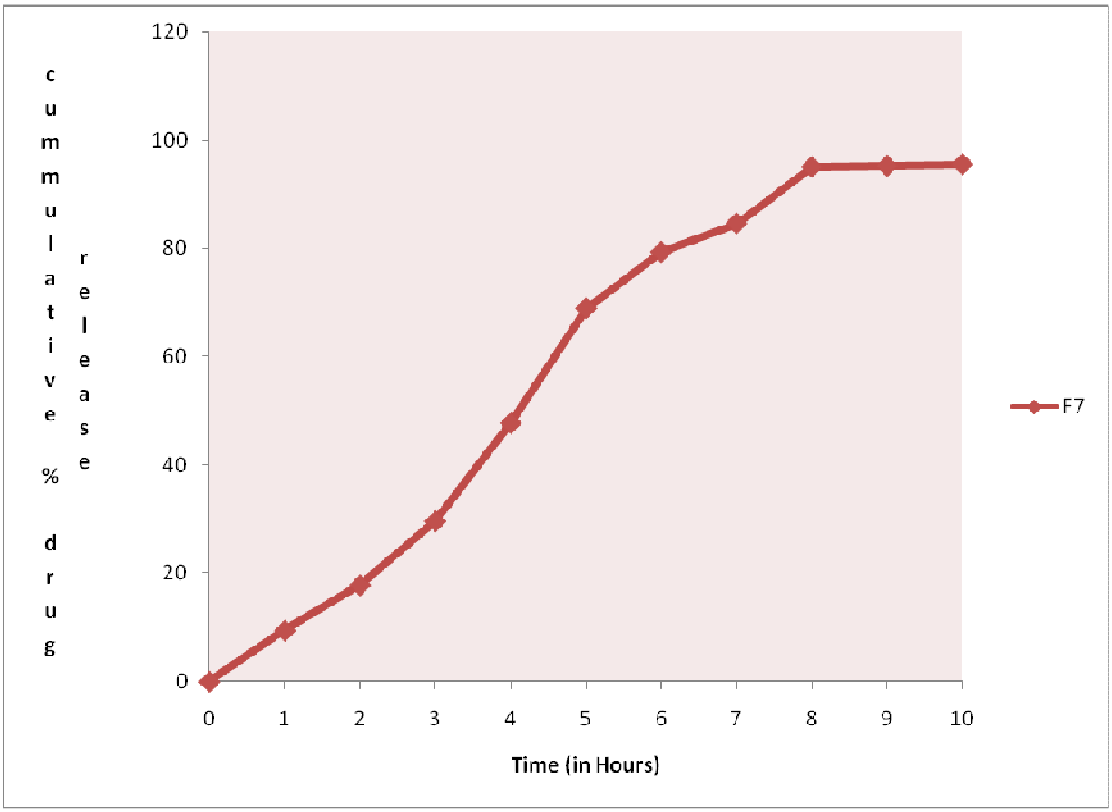


Figure 8.17: *In vitro* drug release profile of formulation GF7

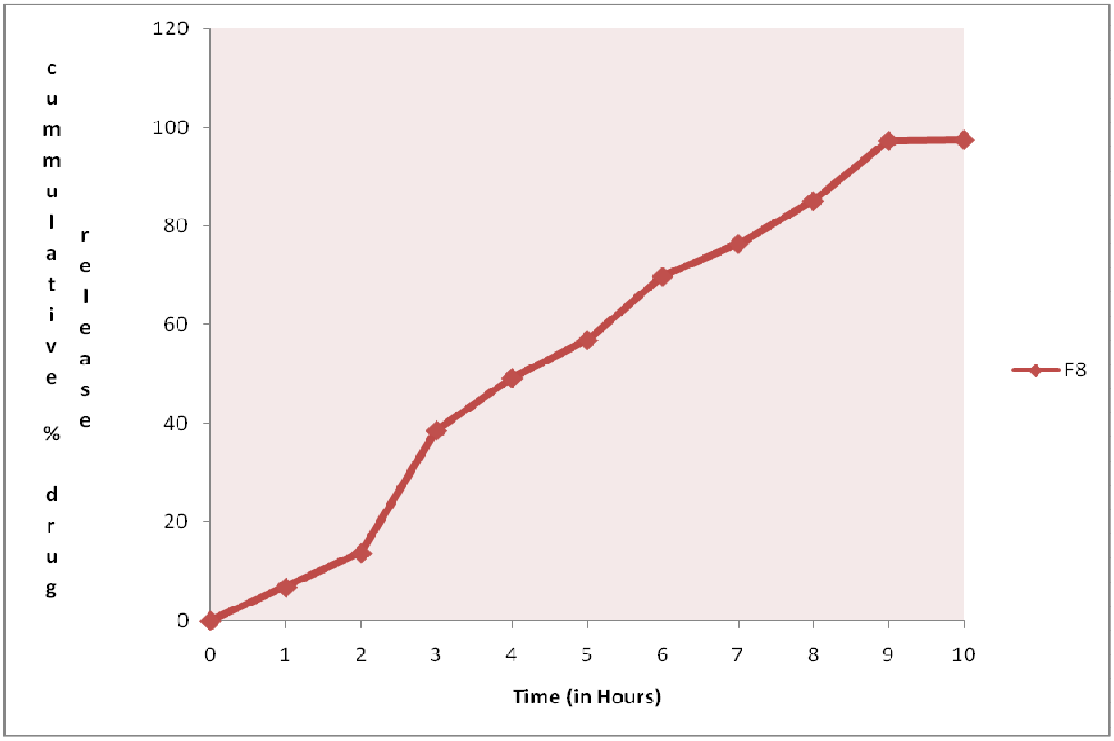


Figure 8.18: *In vitro* drug release profile of formulation GF8

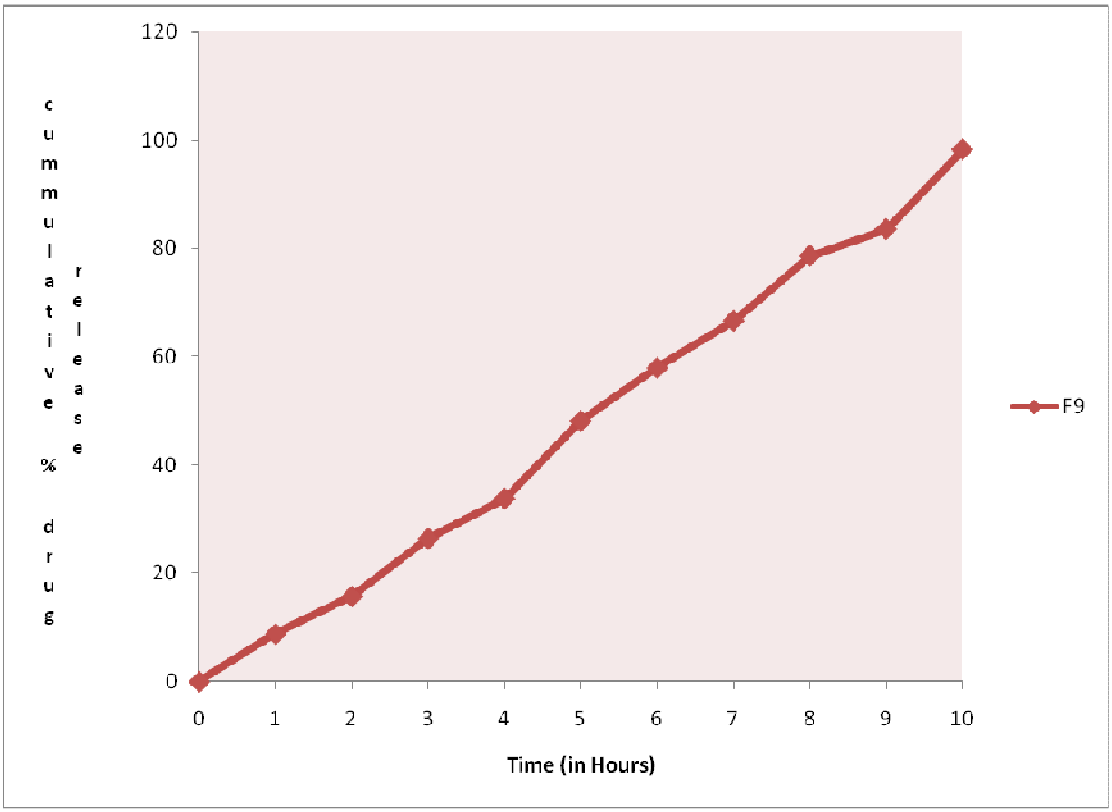


Figure 8.19: *In vitro* drug release profile of formulation GF9

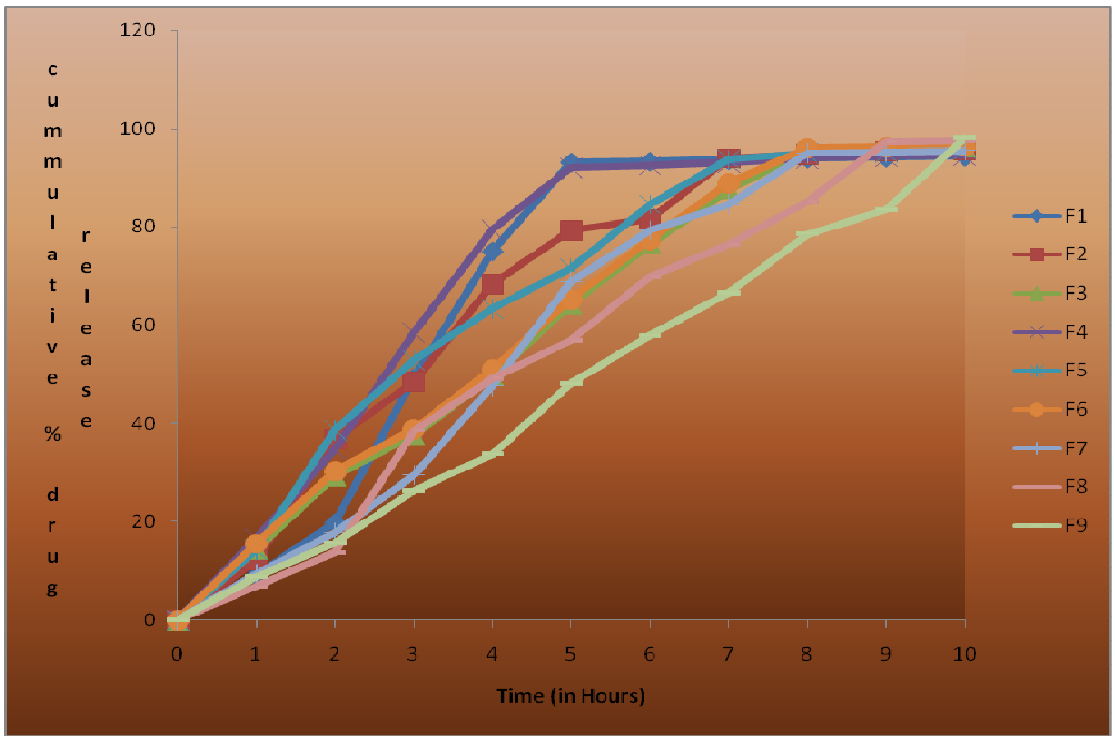


Figure 8.20: *In vitro* drug release profile of formulations GF1 to GF9.

Gliclazide drug was soluble in phosphate buffers and its release from the matrix was largely dependent on the polymer swelling, drug diffusion and matrix erosion. The concentration of polymer in the matrix tablet was a key factor in sustaining the drug release.

Various sustained release formulations were formulated with HPMC K100M, and ethyl cellulose polymer alone; polyvinyl pyrrolidone as binder and lactose was used as diluents.

The variation in drug release was due to different types of polymers and different concentrations of polymer in all the nine formulations. It is expected that the developed formulations should have the following theoretical drug release profile.

The drug released from formulation GF1 to GF3 containing HPMC K100M at three concentration levels of 10%, 20%, 30% were found to be 94.30 ± 2.54, 95.60 ± 2.54, and 96.1 ± 0.50 % for gliclazide respectively at the end of 10 hours. It was shown in Figures (8.8, 8.9 and 8.10).

The drug released from formulation GF4 to GF6 containing ethyl cellulose at three concentration levels of 10%, 20%, 30% were found to be 94.6 ± 0.50, 95.8 ± 0.91 and 96.5. ± 0.21% for gliclazide respectively at the end of 10 hours . It was shown in Figures (8.11, 8.12 and 8.13).

The drug released from formulation GF7 to GF9 containing both HPMCK100M and ethyl cellulose at three concentration levels of 10%, 20%, 30% were found to be 95.5 ± 1.51, 97.5 ± 2.16 and 98.2 ± 0.55% for gliclazide respectively at the end of 10 hours. It was shown in Figures (8.14, 8.15 and 8.16).

The drug release rate from HPMC K100M matrix was found to be less as compared to and ethyl cellulose. This might be due to slow hydration of matrix and its

property to form a thick gel layer, it's due to slow erosion of matrix and its property which retard the drug release from the tablet for long duration.

The overall release rate of gliclazide from ethylcellulose matrices are significantly higher than that from HPMC K100M matrices were shown in Figure 8.17. These results are indicating that HPMC K100M has higher drug retarding ability for long duration than ethylcellulose .

In addition to concentration of polymer, the type and viscosity of polymer also influences drug release. When drug release data obtained from dissolution study of different polymers at 10%, 20% and 30% concentration is plotted against time respectively, it was observed that low concentration of polymer induces more drug release. High concentration of polymer should be retarding the drug release for longer period of time.

From the above study, the formulation GF9 was concluded as the best formulation among all the nine formulation of this series. Hence the formulation GF9 was selected for further stability study.

8.3.4. Kinetics of *in vitro* drug release:

In order to investigate the release mechanism, the data were fitted to models representing first order, zero order, higuchi and korsmeyer- Peppas. The linear regression analysis shown as 'r' values in Table 8.22, demonstrated that all the formulated tablets follows korsmeyer- Peppas release kinetics. The result obtained was shown in Figures 8.21 to 8.29.

Table 8.13: Different kinetic models for gliclazide matrix tablets (GF1 to GF9)

F. Code	Zero order	First order	Higuchi	Korsemeyer- Peppas		Best fit model
	R^2	R^2	R^2	R^2	n	
GF1	0.978	0.918	0.970	0.987	0.720	Peppas
GF2	0.988	0.895	0.950	0.989	0.749	Peppas
GF3	0.988	0.927	0.945	0.992	0.759	Peppas
GF4	0.981	0.849	0.967	0.986	0.698	Peppas
GF5	0.986	0.890	0.962	0.989	0.731	Peppas
GF6	0.989	0.899	0.955	0.990	0.743	Peppas
GF7	0.983	0.888	0.967	0.987	0.726	Peppas
GF8	0.988	0.892	0.957	0.989	0.736	Peppas
GF9	0.989	0.922	0.955	0.990	0.759	Peppas

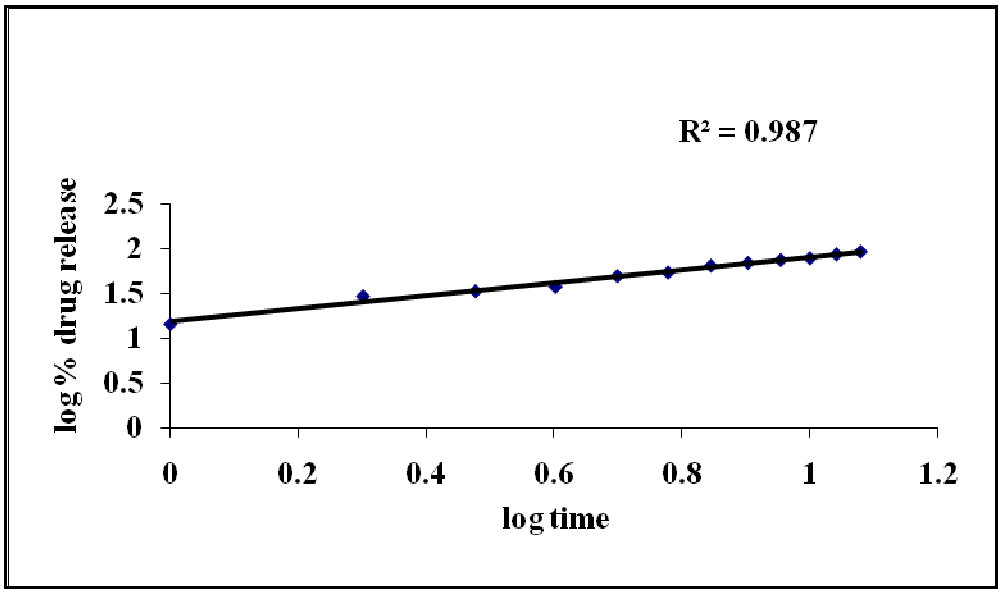


Figure 8.21: Best fit model (Peppas) of formulation GF1

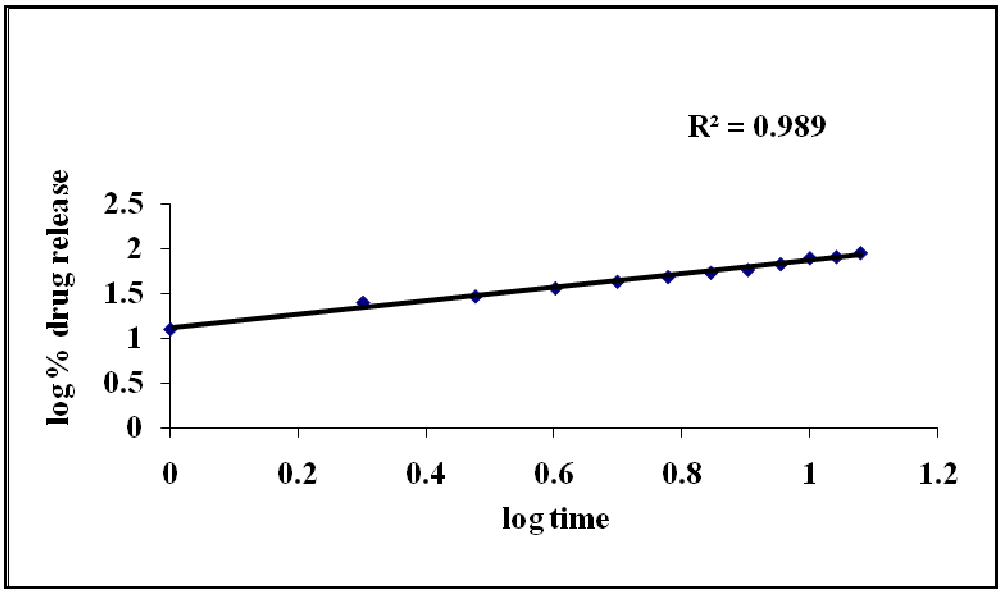


Figure 8.22: Best fit model (Peppas) of formulation GF2

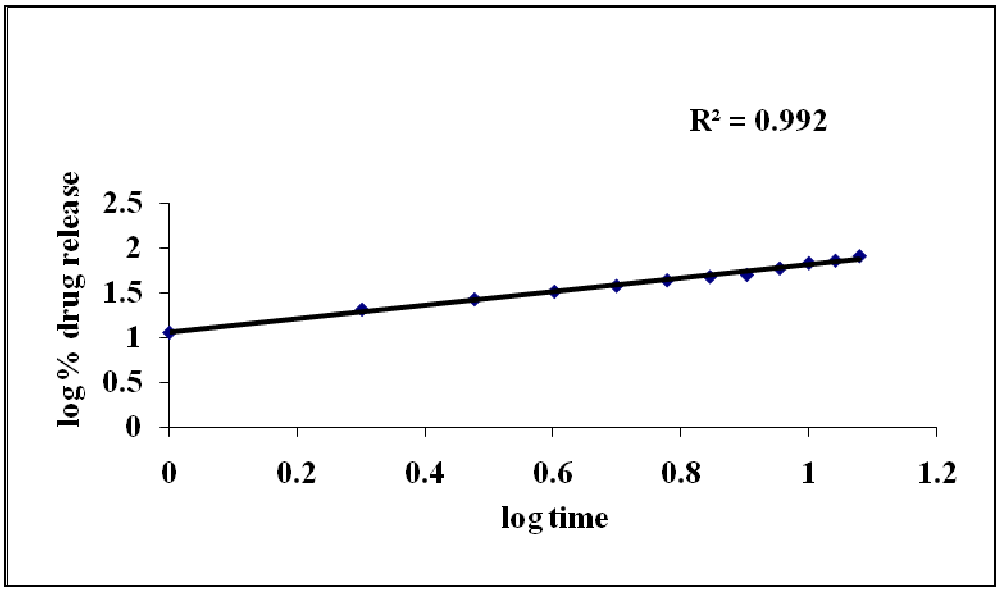


Figure 8.23: Best fit model (Peppas) of formulation GF3

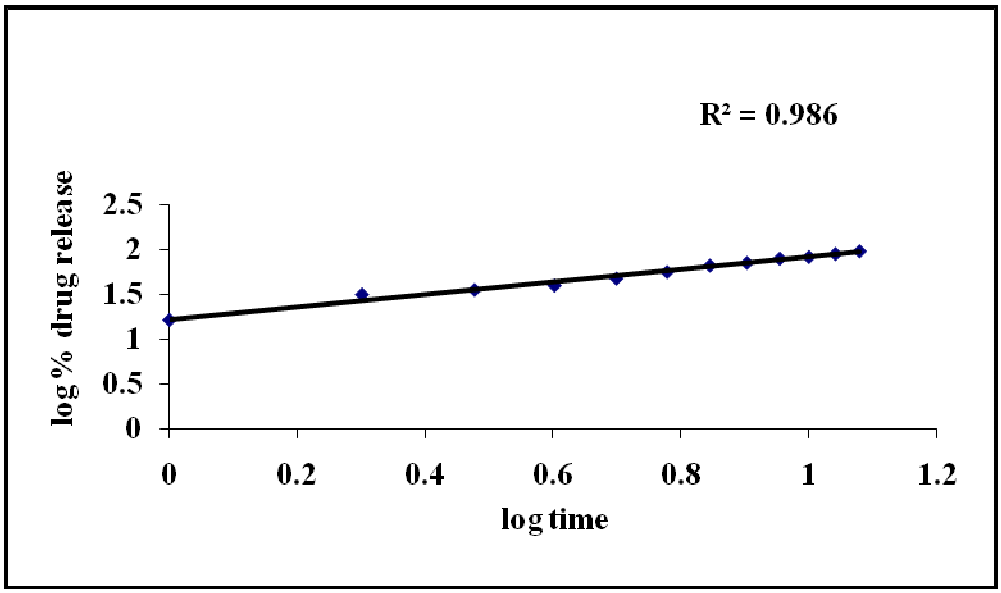


Figure 8.24: Best fit model (Peppas) of formulation GF4

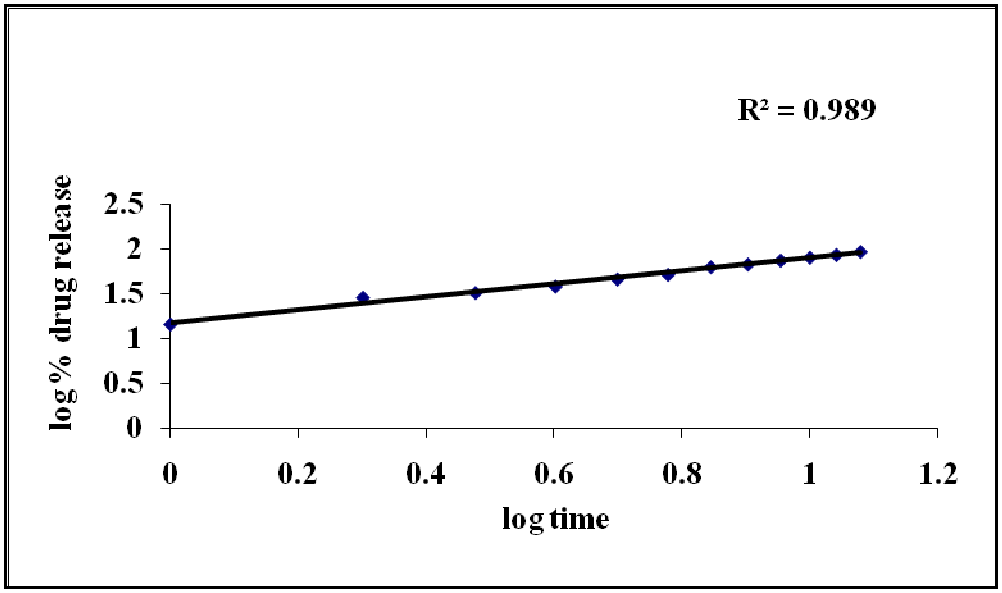


Figure 8.25: Best fit model (Peppas) of formulation GF5

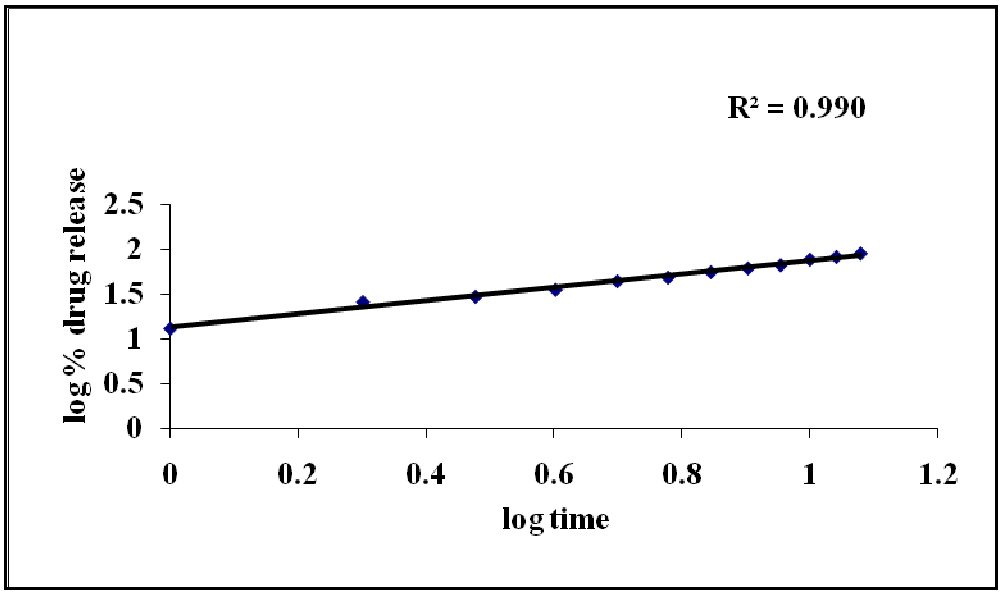


Figure 8.26: Best fit model (Peppas) of formulation GF6

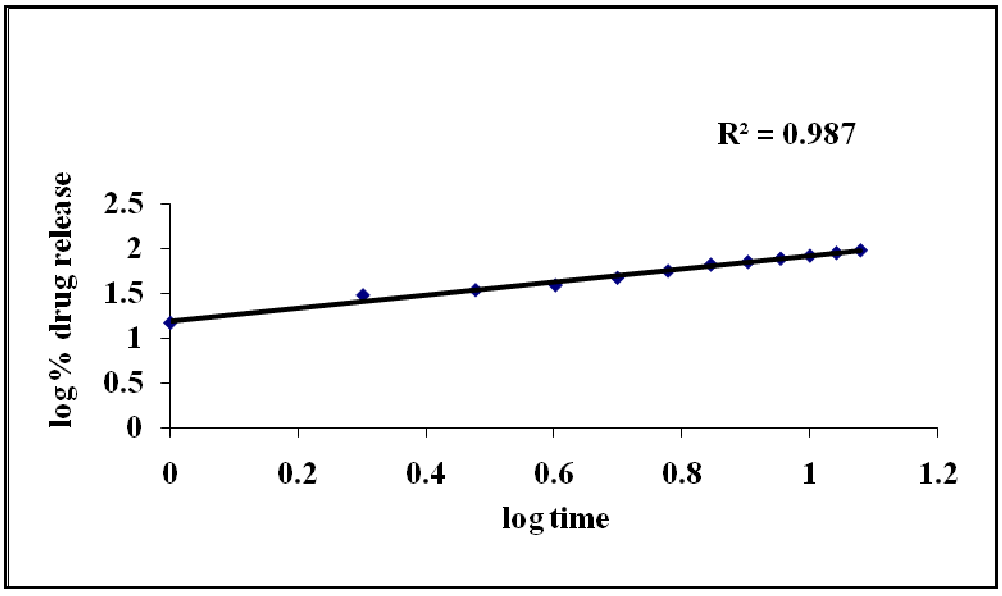


Figure 8.27: Best fit model (Peppas) of formulation GF7

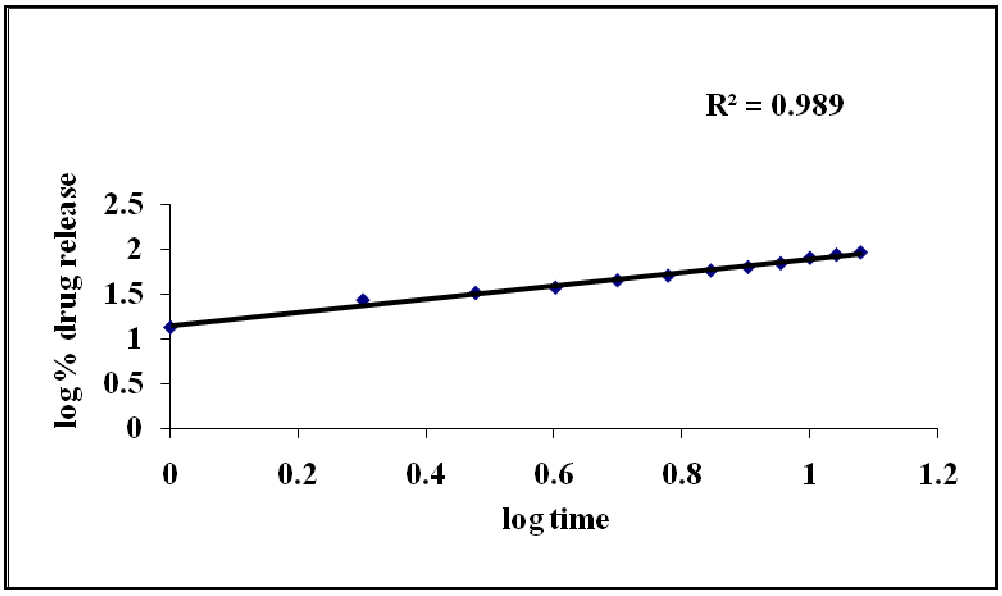


Figure 8.28: Best fit model (Peppas) of formulation GF8

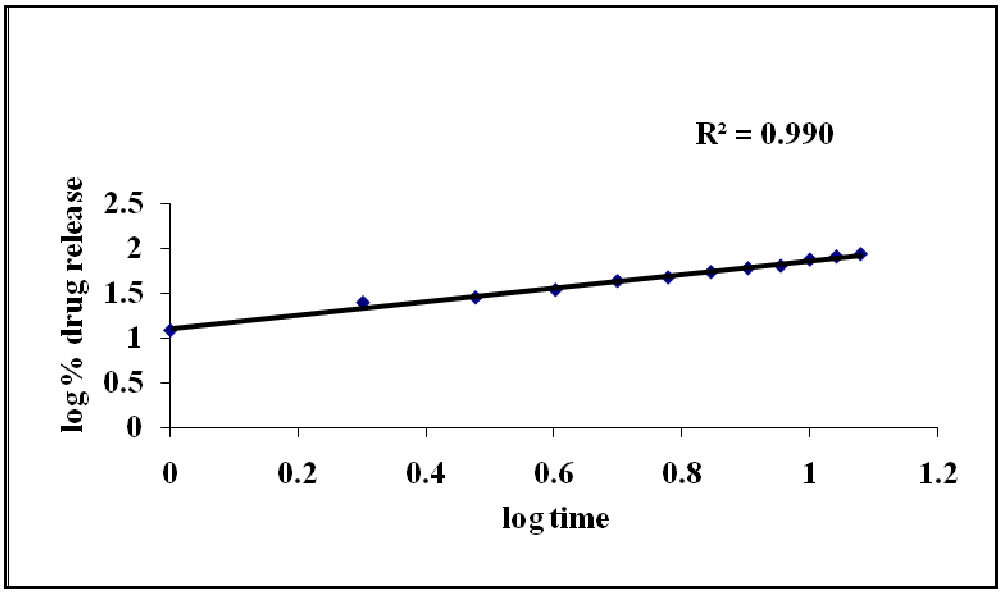


Figure 8.29: Best fit model (Peppas) of formulation GF9

Further, to understand the drug release mechanism, the data were fitted to korsmeyer- Peppas exponent equation, when n < 0.45 indicates fickian drug release. For 0.45 < n < 0.89 as anomalous diffusion (non-fickian). In the present study also it was observed that almost all the formulated tablets followed anomalous diffusion mechanism, which indicates the drug release through diffusion coupled with erosion.

8.4. Stability study:

After exposure to accelerated stability conditions the formulation was analyzed for various evaluation parameters; results were shown in Table 8.23 and Figures 8.39, 8.40 and 8.41.

Table 8.14: Stability studies of best formulation (GF9)

Stability chamber	Time	Appearance	Hardness (kg/cm^2)	Friability(%)	Drug content (%)	%drug release
	Initial	White	6.30±0.10	0.631±0.06	98.56±1.12	98.2±0.55
40±2°C with	1st month	No change	6.25±0.32	0.627±0.09	98.39±0.55	97.8±0.23
75±5°%RH	2nd month	No change	6.23±0.09	0.622±0.05	97.94±0.20	97.3±0.02
	3rd month	No change	6.18±0.06	0.614±0.10	97.63±0.08	96.9±0.30

*All the values were expressed as mean± S.D., n=3.

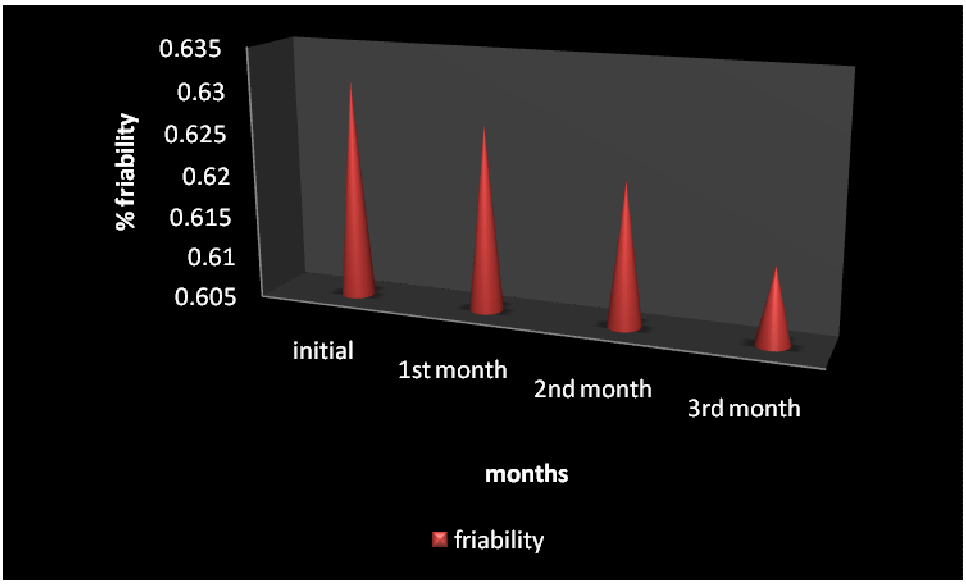


Figure 8.30: Comparison for friability before and after stability studies of best formulation GF9.

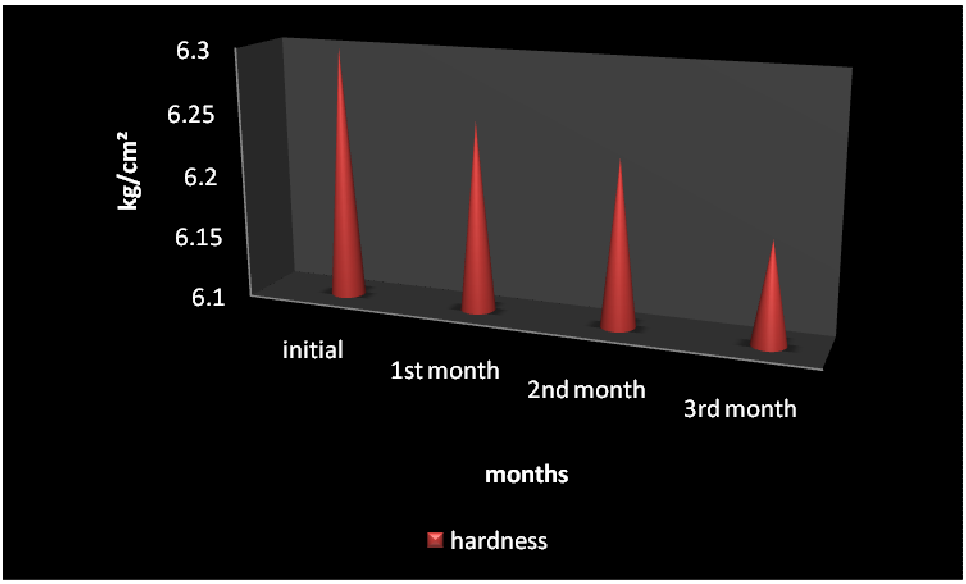


Figure 8.31: Comparison for hardness before and after stability studies of best formulation GF9.

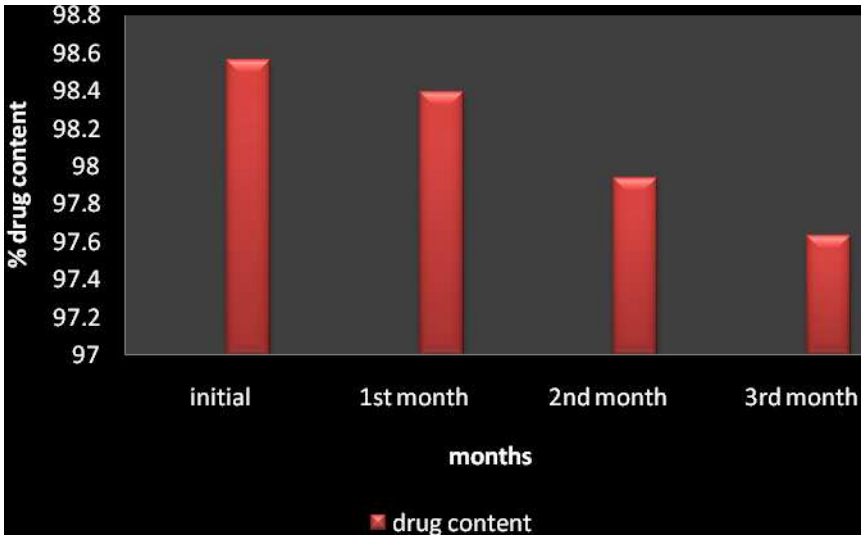


Figure 8.32: Comparison for drug content before and after stability studies of best formulation GF9.

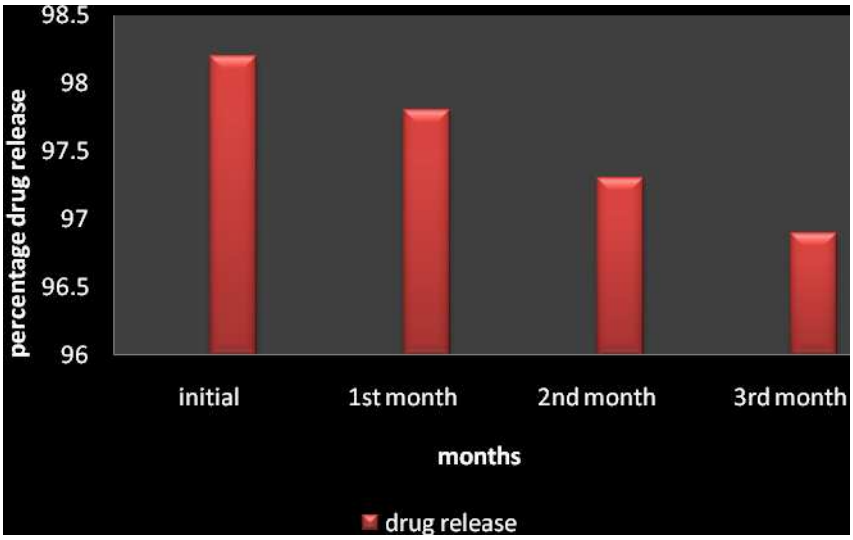


Figure 8.33 Comparisons for *in vitro* drug release profile of before and after stability studies of best formulation GF9.

From the above studies there was no significance differences was initiate between the evaluated data from initial and after stability studies and all the values were found to be accepting limits. The best formulation was showed adequate physical stability at 40^{o}C ± 2^{o}C at 75% ± 5% relative humidity.

SUMMARY AND CONCLUSION

9. SUMMARY AND CONCLUSION

Oral route has been the commonly adopted and most convenient route for the drug delivery. Oral route of administration has been received more attention in the pharmaceutical field because of the more flexibility in the designing of dosage form than drug delivery design for other routes. The oral route of delivery is perhaps the least invasive method of delivering drugs, it's a route that the patient understand and accepts, patient are able to administer the medicine to themselves. For the manufacturer, solid oral dosage form offer many advantages; are generally the most stable forms of drugs, are compact and their appearance can be modified to create brand identification.

Gliclazide was chosen as a drug having soluble in intestinal pH. Gliclazide plays a major role in treatment of Diabetic mellitus type2. The drug half-life in plasma is 10.4 hours. It is bound to plasma proteins 85 to 95%. Gliclazide is rapidly absorbed with a bioavailability of over 97% following oral ingestion, hence it was considered as an good candidate for the design of oral sustained release dosage form.

In the present study, an attempt was made to formulate the oral sustained release matrix tablets of gliclazide to provide a dosage form for prolonged period of time, in order to improve efficacy, reduce the frequency of total dose and better patient compliance. Infrared spectroscopy and differential scanning calorimetric analysis confirmed the absence of any drug polymer interaction.

The sustained release matrix tablets were prepared by the direct compression method using different polymers like hydroxypropyl methylcellulose, and

ethylcellulose as release retardant polymers. The powders were evaluated for angle of repose, bulk density, compressibility index and hausner's ratio. All the tests revealed that powders showed excellent flow properties.

The resulting monolithic tablets were evaluated for thickness, diameter, weight variation test, hardness, friability and drug content. All the tablet formulations showed acceptable pharmacotechnical properties and complied with pharmacopoeial standards. The *in vitro* release profiles from tablets of drug and different polymer ratio were applied on various kinetic models. *In vitro* release studies revealed that the release rate was decreased with increase in polymer proportion.

In the present studies, matrix formulation GF9 containing HPMC K100M and ethyl cellulose were probably showing maximum retardation of drug release and it shows anomalous diffusion mechanism, for these reasons, it was considered that the formulation GF9 as best formulation among all the nine formulations. Based on release exponent (n) values, it was concluded that mechanism of drug release was found to be diffusion coupled with erosion (anomalous transport mechanism).

From the stability studies, there was no significance difference in hardness, friability, drug content and *in vitro* release profile for the best formulation.

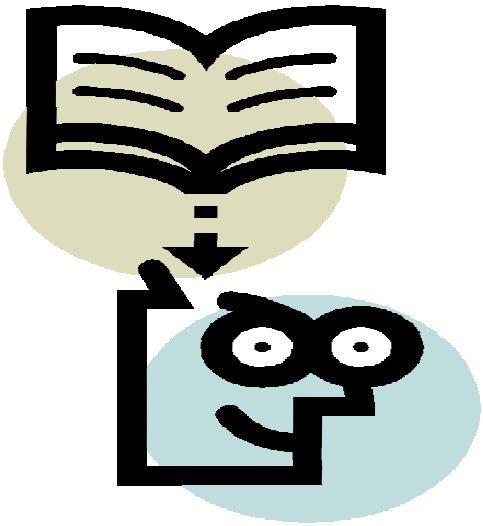
FUTURE PROSPECTS

10. FUTURE PROSPECTS

In the present work, the sustained release matrix tablets of gliclazide were prepared by direct compression technique using synthetic polymers like hydroxypropyl methylcellulose, and ethylcellulose as release retardant polymers.

In this work, only physiochemical characterization such as angle of repose, Carr's index, hausner ratio, weight variation, hardness, thickness, friability, drug content and *in vitro* evaluation of matrix tablet of gliclazide was performed. Along with *in vitro* studies, *in vivo* studies of drug is most important.

In future *in vivo* studies are required to set the *in vitro* - *in vivo* correlation (IVIVC) which is necessary for development of successful formulation and also long term stability studies are necessary.



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