FORMULATION OF GLIPIZIDE TIME-CONTROLLED RELEASE TABLETS BY PRESS COATING USING HYDROPHILIC AND HYDROPHOBIC POLYMERS – ITS *IN VITRO* DISSOLUTION, TIME LAG AND KINETIC MODELS

Dissertation work submitted to

THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI

In partial fulfillment of the award of degree of

MASTER OF PHARMACY (PHARMACEUTICS)

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College of Pharmacy

SRI RAMAKRISHNA INSTITUTE OF PARAMEDICAL SCIENCES

Coimbatore – 641044

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Submitted by

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Certificate

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Dedicated to
My Beloved Parents, Brother
& Almighty

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S. Chaitanya Kumar

CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

API	-	Active pharmaceutical ingredient
BP	-	British pharmacopoeia
CR	-	Controlled release
CRDDS	-	Controlled release drug delivery systems
DISSO	-	Dissolution
EC	-	Ethyl cellulose
FT-IR	-	Fourier transform- infrared
Gli	-	Glipizide
HEC	-	Hydroxy ethyl cellulose
Hrs	-	Hours
I.V.	-	*In vitro*
ICH	-	International conference on harmonization
IP	-	Indian pharmacopoeia
JP	-	Japanese pharmacopoeia
MCC	-	Microcrystalline cellulose
MEC	-	Minimum effective concentration
Min	-	Minutes
NF	-	National formulary
NIDDM	-	Non-insulin dependent diabetes mellitus
PEG 6000	-	Polyethylene glycol 6000
Ph Eur	-	European pharmacopoeia
USP	-	United States pharmacopoeia
UV	-	Ultra Violet

Chapter 1 Purpose of Work

PURPOSE AND PLAN OF WORK

PURPOSE OF WORK

- Glipizide is a second generation of sulphonyl urea for lowering blood glucose, due to its short half-life (2 to 5 hrs) and extensive protein binding nature (98-99%) that makes Glipizide an ideal candidate for controlled release formulations.
- The general oral formulation of glipizide is usually absorbed in the gastrointestinal tract quickly and completely, which leads to an immediate action of lowering blood glucose and a probable side effect of hypoglycemia. However, an oral controlled release formulation facilitates the administration, particularly administration just once a day, to control the blood glucose concentration at a constant level, which results in better compliance by patients and fewer side effects.
- The main aim of the work is to achieve time-controlled disintegration with distinct predetermined time lag.
- To study the effect of formulation of outer shell comprising both hydrophobic polymer and hydrophilic excipients on the time lag of drug release.
- To find out the suitable weight ratios of hydrophilic excipients, to modulate the time lag of time controlled disintegrating tablets.

Chapter 1 Purpose of Work

- To investigate the influence of the type and amount of excipients mixed with micronized EC in the outer shell on the time lag and time controlled disintegration or rupturing function of press coated tablets.
- To study the drug release kinetics from data obtained through *in vitro* dissolution studies.

PLAN OF WORK

The present work was carried out in the following lines:

- Literature survey on Glipizide drug and time controlled release dosage forms.
- Analytical methods
- Formulation of time-controlled disintegrating press-coated tablets of Glipizide using hydrophilic excipients and hydrophobic polymers.
- Evaluation studies
- Dissolution kinetics

INTRODUCTION

Tablets may be defined as solid pharmaceutical dosage forms containing drug substance with (or) without suitable diluents and prepared by either compression (or) molding[1].

ADVANTAGES[2]

- They are unit dosage forms and offer the greatest capabilities of all oral dosage forms for the greatest dose precision and the least content variability.
- Their cost is lowest of all oral dosage forms.
- They are the lightest and most comfort of all oral dosage forms
- Product identification is potentially simplest and cheapest, requiring no additional processing steps when employing an embossed (or) monogrammed punch face.
- They may provide the greatest ease of swallowing with the least tendency for “hang up” above the stomach, especially when coated, provided the tablet disintegration is not excessively rapid.
- They lend themselves to certain special release profile product, such as enteric (or) delayed release products.
- They are better suited to large-scale production than other unit oral dosage forms.

- They have the best-combined properties of chemical, mechanical and microbiologically stability of all the oral dosage forms.
- Tablet is a tamper proof dosage form.

DISADVANTAGES

- Drugs with poor wetting, slow dissolution properties intermediate to large dosages (or) any combination of these features may be difficult (or) impossible to formulate and manufacture as a tablet.
- Some drugs resist compression into dense compact, owing to their amorphous nature (or) flocculent, low density character.
- Bitter tasting drugs, drugs with an objectionable odour (or) drugs that are sensitive to oxygen (or) atmospheric moisture may require encapsulation (or) the tablet may require coating. In such cases the capsule may offer the best and lowest cost approach.

Properties of tablets

The attributes of an acceptable tablet are as follows:

1. The tablet must be sufficiently strong and resistant to shock and abrasion, to withstand handling during manufacture, packaging, shipping and use. This property is measured by two tests, the hardness and friability tests.
2. Tablets must be elegant in appearance and must have the characteristic shape, color and other markings necessary to identify

the product. Markings are usually the monogram (or) logo of the manufacturer.

3. Tablets often have the National Drug Code Compendium of the Food and Drug Administration. Another marking that may appear on the tablet is a score (or) crease across the face, which is intended to permit breaking the tablet into equal parts for the administration of half a tablet. However, it has been shown that substantial variation in drug dose can occur in the manually broken tablets.
4. Tablets must be uniform in weight and in drug content of the individual tablet. This is measured by the weight variation test and the content uniformity test.
5. The drug content of tablet must be bioavailable. This property is also measured by two tests, the disintegration test and the dissolution test.
6. Bioavailability of a drug from a tablet (or) other dosage form is a very complex problem and the results of these two tests do not by themselves provide an index of bioavailability. This must be done by drug levels in blood.
7. Tablets must retain all of their functional attributes, which include drug stability and efficacy.

Ideal characteristics of tablet dosage form

- It has its own identity free of chips, cracks, discoloration and contamination.
- Should have strength to withstand vigorous mechanical shocks encountered in its production, packaging, shipping and dispensing.
- Should have chemical and physical stability.

On the other hand

a) It must be able to release the medicinal agent in the body in a predictable and reproducible manner.

b) Must have a suitable chemical stability overtime so as not to allow alterations of the medicinal agents.

c) Pre-compression of amorphous powders cause negative effect on dissolution and disintegration rates.

TYPES AND CLASSES OF TABLETS[3]

Tablets are classified by their route of administration (or) function, by the type of drug delivery system. They represent within that route, by their form and method of manufacture.

Tablets ingested orally

1) Compressed tablets (CT)
2) Multiple compressed tablets (MCT)
    (a) Layered tablets
    (b) Compression coated tablets
3) Repeat action tablets
4) Delayed action and enteric coated tablets
5) Sugar and chocolate-coated tablets
6) Film coated tablets
7) Air suspension coated tablets
8) Chewable tablets

Tablets used in oral cavity

1) Buccal tablets
2) Sublingual tablets
3) Troches, lozenges and dental cones

Tablets used to prepare solution

1) Effervescent tablets
2) Dispensing tablets (DT)
3) Hypodermic tablets (HT)
4) Tablet triturate (TT)

Chapter 2 Introduction

COMPRESSION COATED TABLETS

These are compressed tablets made by more than one compression cycle[1].

Recently a compression coated tablet has received increasing attention to deliver a drug in a pulsatile fashion rather than in a continuous way at predetermined times and/or sites following oral administration.

This novel system is not only rate controlled but time controlled to deliver the drug when it is required.

The compression coated tablet consists of an inner core and an outer coating shell. The outer coating material may be compressed on to the inner core with a special compression technique.

The manufacturing method of this tablet cannot only eliminate the time consuming and complicated operation processes but also improves the stability of drug by preventing it from moisture. To design a novel compression-coated tablet, the outer coating layer is critical in ensuring reliable tolerance to reach the predetermined site.

These are also referred to as dry-coated are prepared by feeding previously compressed tablet into a special tabletting machine and compressing another granulation layer around the preformed tablets.

An example of a press-coated tablet press is the manesty drycota. Drycota[4]: In 1937 Killion, a German inventor received a British patent for a unit which compressed tablets on one machine and held them in the upper punches. These punches had rods passing lengthwise through them. The

compression wheel was recessed so that it could compress the cores without activating the core rod. The cores were carried around the turret to the transfer mechanism. At this point the upper punches passed under a roller which pressed down the core rods, to the coating machine. It is evident that the manesty drycota adopted the idea of two machines running synchronously from this patent.

Advantages

1) They have all the advantages of compressed tablets i.e. slotting monogramming, speed of disintegration.
2) Masking the taste of the drug substance in the core tablets.
3) Used to separate incompatible drug substances.
4) Means of giving an enteric coating to the core tablets.
5) Widely used in prolonged dosage forms.

Tabletting methods[1]

The three basic methods for the preparation of compressed tablets are

1) Wet granulation method
2) Dry granulation method
3) Direct compression

Direct compression

- In spite of enormous improvements in wet granulation techniques high shear granulation, fluid bed granulation, continuous granulation and all in one granulation; tablet production by direct compression has increased steadily over the years because it offers economic advantage through its elimination of wet granulation and drying steps.
- The granulation technique that uses slugging (or) roller compaction is no longer a method of choice to produce compressed tablets.
- Direct compression consists of compressing tablets directly from powdered material without modifying the physical nature of material itself. It involves only two operations, in sequence, powder mixing and tabletting.

Advantages[4]

1) The most obvious advantage is economy. Saving can occur in a number of areas including reducing process, time and thus reduced labour cost, fewer manufacturing steps and fewer equipments.
2) Another advantage is in terms of tablet quality are that is processing without the need of moisture and heat.
3) Optimization of tablet disintegration in which each primary drug particle is liberated from and available for dissolution.

4) Fewer chemical stability problems would occur in direct compression.

5) In direct compression, the disintegrate is able to perform optimally and when properly formulated tablet made by direct compression should disintegrate rapidly to primary particles.

Requirements for directly compressible filler binder are:

- ❖ High compactability to ensure that the compacted mass will remain bonded after the release of the compaction pressure.
- ❖ Most directly compressible filler binders have undergo physical modification in order to improve tabletting properties mainly compactability, flowability and apparent density.
- ❖ Good blending properties in order to avoid segregation.
- ❖ Most directly compressible materials are prepared by crystallization. The crystal size and in part the crystal shape are selected by sieving (or) in some cases after grinding.

Excipients used in direct compression

The various forms of cellulose used in direct compression are microcrystalline cellulose which is described in the NF of a purified partially depolymerized cellulose and powdered cellulose NF which is a purified mechanically disintegrated cellulose.

MCC (Avicel)

- ❖ Most widely used as a direct compression tablet filler.
- ❖ This inert diluents can have the function of disintegrate binder.
- ❖ Compatible with other excipients and other active ingredients.

Properties

- ➢ High dilution capacity
- ➢ Low lubricant requirements
- ➢ High compressibility
- ➢ Fast disintegration
- ➢ These have low bulk density which imparts high covering power as well as broad particle size distribution which allows optimum packaging density.
- ➢ It has very low coefficient of friction and therefore has no lubricant requirement of itself.
- ➢ The reason for the fast disintegration of MCC compacts is the immediate disruption of hydroxyl bonds when tablet disintegrates in water, since the MCC allows quick penetration of the water by the tablet.
- ➢ Relatively high expensive material when used as diluents in high concentration and thus is typically combined with other materials.
- ➢ Therefore MCC be used together with dibasic calcium phosphate as the best combination to produce a versatile direct compression

vehicle with good flow that yields tablets of high tensile strength, friability and fast disintegration.

Starch

Commonly the starch source consists of two polysaccharide amylase and amylopectin that are based on a glucose monomer. In a study about tabletting properties of potato, corn, wheat and barley starch, corn starch was best in compactability where as potato starch was best with respect to flowability. Modified corn starch is also used as an excipient in direct compression is marked as sepistab ST 200 which is of particle size 300 µm and has good compactability and lubricant properties.

Inorganic salts

- Di-calcium phosphate di-hydrate is the most commonly used inorganic salt filler binder.
- Di-tab is brand of unmilled di-calcium phosphate di-hydrate where as Em-compress is a unique form of di-calcium phosphate di-hydrate in which particle size distribution is controlled to ensure flowability.
- An advantage of using di-calcium phosphate in tablets for vitamin (or) mineral supplement is the high calcium and phosphorous content.
- Brittle in nature.

- Tricalcium phosphate can be used as a filler binder in direct compression and as filler in tablets prepared by new granulation.
- Direct compression grades of sorbitol can be used for the production of lozenges, chewable tablets and disintegrating tablets. The inclusion of pregelatinized starch in sorbitol tablet can prevent recrystallization and increase in tablet crushing strength.
- Tablets compressed from lactose monohydrate without a lubricant disintegrate very quickly in water as a result of rapid liquid uptake and fast dissolution of the bonds. The presence of hydrophobic lubricant has a strong inhibiting effect on water penetration and hence on disintegration time. This effect can be easily counteracted by the addition of microcrystalline cellulose (or) high swelling disintegrate such as sodium starch glycolate (or) croscarmelose sodium.
- Sucrose is commonly used in modified form that makes it more efficient for direct compression. The modified form is known as compressible sugar NF XVII. Nutab from ingredient technology contains sucrose about 4% invert sugar and small percentages of corn starch and magnesium stearate.
- Mendes *et al.* evaluated NU-tab as a chewable filler binder for direct compression in combination with several active ingredients and 1.0% magnesium stearate. Generally good tablets could be prepared with NU-tab.

- When compared the performances of food grade of hydrous and anhydrous dextrose with spray dried lactose as an excipient in direct compression tablets, the result indicates that hydroxyl dextrose can be partly (or) completely substituted for spray dried lactose in some formulations. Dextrose was found to give less browning than spray dried lactose in formulation containing no amines, more browning was observed in the presence of amines.

Co-processed products

Excipient mixtures are generally produced to make use of the advantages of each component and to overcome specific disadvantages. The functionality of excipient mixtures is enhanced by a special process by which mixtures are combined. The excipient mixtures used in direct compression have added value compared to physical mixture of excipients. For this reason ready to use blends for direct compression were offered from different suppliers, most important are the binding and blending properties of the co-processed excipients which must be better than those of physical mixture of the starting materials. Cost is another factor to consider in the selection of combination products. Other examples of co-processed products are indipress cellactose and pharmatose DCL 40.

Chapter 2 Introduction

A SYSTEMATIC AND MODERN APPROACH TO TABLET PRODUCT DESIGN[5]

Tablet product design requires two major activities. First, formulation activities begin by identifying the excipients most suited for a prototype formulation of the drug. Second, the levels of those excipients in the prototype formula must be optimally selected to satisfy all process/product quality constraints.

Factors affecting the type of excipients used in a tablet formula

The type of excipient used may vary depending on a number of preformulation, medical, marketing, economic and process/product quality factors as discussed in the following sections. Here we mainly focus on the process/product quality.

Typical tests performed on tablets are as follows:

- Weight variation
- Hardness
- Friability
- Disintegration time
- Dissolution
- Water content
- Potency
- Content uniformity

Chapter 2 Introduction

Product quality is most often assessed at the tablet development stage. However, it is also important to monitor the processing quality of a formulation during development. They are

a. To optimize the process as well as the product.

b. To establish in-process quality control tests for routine production.

It is more difficult to quantify the processing quality of a formulation than it is to measure the product quality. Some measurements that could be performed on the process include:

- Ejection force
- Capping
- Sticking
- Take-off force
- Flow of lubricated mixture
- Press speed (maximum)
- Frequency of weight control adjustments
- Sensitivity of formula to different presses
- Tooling wear
- Effect of consolidation load (batch size)
- Hopper angle for acceptable flow
- Hopper orifice diameter for acceptable flow
- Compression forces
- Environment conditions (temperature, humidity, and dust)

Each of the above processing parameters can become a source of trouble in scale-up (or) routine production. By monitoring these parameters in development, it may be possible to adjust the formula (or) process early enough to alleviate the source of trouble. The expected production output (number of tablets) per unit time will determine what speed tablet press will be required for a particular tablet product. If the anticipated unit output for a tablet product is expected to be large, a high-speed press will be required.

Attempts should be made in formulation development to design a tablet formula that will perform well on a high-speed press. A formula to run on a high-speed press should have excellent flow to maintain uniform die fill during compression. It should have good bonding characteristics so that it can compress with a minimal dwell time.

1. Environmental conditions ambient (or) humidity control
2. Stability of the final product
3. Bioavailability of the active drug content of the tablet.

The selection of excipients is critical in the formulation of tablets, once the formulator has become familiar with the physical and chemical properties of drug. The process of selecting excipients has begun. The stability of the drug should be determined with each proposed excipient.

This can be accomplished as follows:

In the laboratory, prepare an intimate mixture of the drug with an excess of each individual excipient and hold at 60°C for 72 hr in a glass

container. At the end of this period analyze for the drug using a stability indicating assay.

DIFFERENT ADJUVANTS USED IN TABLET FORMULATION

In addition to the active or therapeutic ingredient, tablets contain a number of inert materials called as additives or excipients. They may be classified according to the part they play in the finished product. The first group contains those that help to impart satisfactory processing and compression characteristics to the formulation which includes diluents, binders, glidants and lubricants. The second group of added substances helps to give additional desirable physical characteristics to the product. They include disintegrants, colors, flavors, sweetening agents.

Diluents or fillers[4]

These are inert substances which will increase the bulk of the tablet. Selecting the diluents is an important character while tabletting. These agents may not be necessary if the dose of the drug per tablet is high. Generally a tablet should weigh at least 50mg and therefore very low dose drugs will invariably require diluents to bring the overall tablet weight to at least 50mg.

Diluents or fillers fall into two general categories

1. Carbohydrate and modified carbohydrate excipients.
2. Inorganic materials

In wet granulation process, such carbohydrate substances as sugars, starches and cellulose may also function as binder, whereas in direct compression systems, they serve as diluents carrier. The inorganic excipients, when used in either system, are not a binder, which is a cohesive agent in directly compressible system. Hence they function more as a carrier.

Microcrystalline cellulose (MCC) (AVICEL) is most widely used as direct compression tablet filler. It has a function of disintegrant besides that of a dry binder and is compatible with most excipients and active ingredients.

Lactose is inexpensive, soluble and easily granulated diluents, because it lacks flowability and compressibility in its common form. Lactose in modified form can only be used in direct compression.

The other commonly used diluents are mannitol, Kaolin, dry starch, calcium sulfate, dicalcium phosphate.

Binders or Adhesives[6]

Binders are solid materials in the manufacture of solid dosage forms because of their adhesive and cohesive properties. Their role is to assist size enlargement by adding cohesiveness to powders, thereby

providing granules and tablets with necessary bond strength, they improve the appearance, hardness and friability of preparations, but are not intended to influence the dissolution or disintegration of active substances.

Binders are starch, gelatin, sugars or polymeric substances. The later fall into two classes:

a) Natural polymers such as starches or gum including acacia, tragacanth, gelatin.

b) Synthetic polymers such as polyvinyl pyrrolidone, methyl and ethyl cellulose and hydroxypropyl cellulose.

c) The quantity of binder used has a considerable effect on the characteristic of the compressed tablets. The use of too much binder or too strong binder will make a hard tablet that will not disintegrate easily. Binders are used both as solution and in dry form, depending on other ingredients in the formulation and method of preparation. However pregelatinised starches available are intended to be added in dry form so that water alone can be used for granulating solution.

The direct compression method for preparing tablets requires a material that is not only free flowing but also sufficiently cohesive to act as a binder. For this microcrystalline cellulose, amylase and polyvinyl pyrrolidone is used.

MCC is a non fibrous form of cellulose. It is water insoluble but has the ability to draw fluid into tablet by capillary action. It swells on contact

and thus acts as disintegrating agent. The material flows well and has a degree of self lubricating qualities.

Starch paste is a common binder. Starch extracted from maize, potato, rice, wheat is widely used as tablet binder. It has a concentration between 5 and 25%. It produces relatively soft and friable granules and tablets disintegrate readily. High viscosity is its drawback. Pregelatinized starch can be used instead of starch paste.

Disintegrants

Disintegrants is the term applied to various agents added to tablet granulation for the purpose of causing the compressed tablet to break apart (disintegrate) when placed in aqueous environment. Basically the disintegrants' major function is to oppose the efficiency of tablet binder and the physical forces that act under compression to form tablet. The stronger the binder, the more effective must be the disintegrating agent in order for the tablet to release its medication. Ideally it should cause the tablet to disrupt, not only into the granules from which it was compressed, but also into the powder particle from which the granulation was prepared.

There are two methods used for incorporating disintegrating agents into the tablet:

1) External addition

2) Internal addition

In this, the disintegrant is added to the sized granulation with mixing just prior to compression. In the internal addition method, the disintegrant is mixed with some other powders before wetting the powder mixture with granulating solution. Thus, the disintegrant is incorporated within the granule. When this method is used, part of the disintegrant can be added internally, and part externally. This provides immediate disruption of tablet.

Disintegrants act by different mechanisms

1. They enhance action of capillaries in producing a rapid uptake of aqueous fluids: E.g. starch, microcrystalline cellulose.
2. Those that swell on contact with water E.g. Sodium starch glycolate, carboxy methylcellulose.
3. That release has to disrupt the tablet structure. E.g. certain peroxides.
4. That destroys the binder by enzymatic action. E.g. starch amylase. The other mechanisms like heat of wetting also exist.

Disintegrants constitute a group of material that on contact with water, swell, hydrate, change in volume or form, or react chemically to produce a disruptive change in tablet. These groups include various forms of starch, cellulose, bentonite, aligns, vegetable gums, clays, ion exchange resins and acid base combinations. Carboxy methyl cellulose, corn and potato starch are popular disintegrants. They have great affinity for water

and swell when moistened, then facilitating, the rupture of tablet matrix. Starch usually 5 to 15% is used.

A group of materials known as superdisintegrants have gained popularity. Croscarmelose, crospovidone and sodium starch glycolate represent examples of a cross linked cellulose, a cross linked polymer and cross linked starch respectively.

Sodiumlauryl sulphate in combination with starch is an effective disintegrant. In some cases the effectiveness of surfactants in improving tablet disintegration is postulated as due to an increase in the rate of swelling.

The binder, tablet hardness, lubricants can also affect disintegration time.

Glidants[1]

Glidants improve the flow characteristics of the powder mixture. These materials are added in the dry state just prior to compression. Colloidal silicon dioxide is the most commonly used glidant and generally used in low concentration of 1% or less. Talc is also used and may serve the dual purpose of glidant/lubricant.

It is important to optimize the order of addition and mixing process of these materials to maximize their effect and to make sure that their influence on lubricants is minimized.

Lubricants

They have a number of functions in tablet manufacture.

1. They prevent adhesion of the tablet material to the surface of the dies and punches.
2. Reduce interparticle friction.
3. Facilitate the ejection of tablets from the die cavity.
4. Improves the rate of flow of tablet granulation.

Commonly used lubricants include talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils. Most lubricants are used in concentration below 1% when used alone. Talc is used in concentration as high as 5%. Lubricants are mostly hydrophobic materials. Poor selection or excessive amounts can result in waterproofing the tablets, resulting in poor tablet disintegration and/or delayed dissolution of drug substance.

Antiadherents

These are useful in formulation, which have a tendency to pick easily. Multivitamin products containing high vitamin E levels often display extensive picking which can be minimized through the use of colloidal silica such as syloid (0.1 to 0.5).

Adsorbents

Adsorbents are substances included in a formulation that are capable of holding quantities of fluids in an apparently dry state. Oil soluble drug fluid extractors (or) oils can be mixed with adsorbents and then granulated and compressed into tablet. E.g. fumed silica, microcrystalline cellulose, magnesium carbonate, Kaolin, bentonite, etc.

Coloring agents

Color helps the manufacturer to control the product during its preparation, as well as serving as means of identification to the users.

All colorants used in pharmaceuticals must be approved by FDA. Lake is the combination of a water soluble dye to a hydrous oxide of a heavy metal resulting in an insoluble form of the dye. The most common method of adding color to a tablet formulation is to dissolve the dye in the binding solution prior to the granulating process. Migration of colors may be reduced by drying the granules slowly at lower temperature and stirring the granules while it is drying.

Different colorants used are D and C Red 33, iron oxide, red-caramel, titanium oxide, cochineal extract.

Sweetening agents

In addition to the sweetness which may be afforded by the diluents of the chewable tablet. E.g. Mannitol (or) Lactose. Sweeteners other than sugar that have an advantage of reducing the bulk volume are cyclamates, saccharin, aspartame (Searle).

Surfactants

Molecules (or) ions that are adsorbed at interfaces are termed as surfactants. Depending on the number and nature of the polar and non-polar groups present, the amphiphile may be predominantly hydrophilic suggesting that the molecules (or) ion have a certain affinity for both polar and non-polar solvents.

The hydrophilic portion of the surfactant is soluble in the polar solvent and the lipophilic portion is soluble in the non-polar solvent. The surfactant occupies the interface to decrease interfacial tension and thereby increases the solubility. Release of poorly soluble drugs from tablet and hard gelatin capsules may be increased by the inclusion of surfactants in the formulations.

PRODUCTION OF TABLETS[3]

Tablets are made by compressing the formulation containing a drug or drugs with excipients on stamping machines called presses. Tablet

compression machine or tablet presses are designed with the following basic components:

1) Hoppers for holding and feeding granulation to be compressed.
2) Dies that define the size and shape of the tablet.
3) Punches for compressing the granulation within the dies.
4) Cam tracks for guiding the movement of the punches.
5) A feeding mechanism for moving granulation from the hopper into the dies.

Punches and Dies

They are usually fabricated from special steels, the working surface being accurately machined and highly polished to ensure proper mechanical operation and well finished tablets.

Punches and dies (tooling) must be stored, lightly oiled, in containers which prevent accidental contact. The ease of manufacture and the final appearance of the tablet depend on unblemished, highly polished working surfaces. Punch edges must be sharp and free from burrs.

Operation

Once the machine has been assembled, trial tablets may be made with the press. The optimum tablet hardness depends on the material to be compacted and the ultimate use of the tablets.

As the head of the press rotates, the punches are guided up and down by fixed cam tracks, which control the sequence of filling, compression and ejection. The portions of the head that hold the upper and lower punches are called the upper and lower turrets respectively and the portion holding the dies is called the die table. At the start of a compression cycle, granulation stored in a hopper empties into the feed frame which has several interconnected compartments. These compartments spread the granulation over a wide area to provide time for the dies. The pull down cam guides the lower punches to the bottom of their vertical travel, allowing the dies to overfill. The punches then pass over a weight control cam which reduces the fill in the dies to the desired amount. A wipe off blade at the end of the feed frame removes the excess granules and directs it around the turret and back into the front of the feed frame. Next the lower punches travel over the lower compression roll, while simultaneously the upper punches ride beneath the upper compression roll. The upper punches enter a fixed distance into the dies, while the lower punches are raised to squeeze and compact the granulation within the dies. After the movement of compression, the upper punches are withdrawn. The lower punches ride up the cam which brings the tablets flush with or slightly above the surface of the dies. The tablet strike a sweep-off blade affixed to the front of the feed frame and slide down a chute into a receptacle. At the same time the lower punches reenter the pull down cam and the cycle is repeated.

SITE SPECIFIC DELIVERY

Most drugs - whether taken orally (or) via injection are delivered to the body system-wide (systemically). The medication circulates throughout the body affecting organs and cells that are dysfunctional as well as those that are healthy. Because systemic drug delivery floods the body with medication, it can sometimes cause serious side effects.

Advantages in medical device technology such as the development of fully implantable infusion systems now allow for site-specific drug delivery. Site specific drug delivery is preferred when higher regional drug levels can be obtained as compared to those of other routes of administration. A resultant benefit is reduced (or) eliminated side effects related to high systemic drug levels.

Direct infusion of medication into the largest organ (or) blood vessels supplying those organs goes directly to the site in the body that needs it most site specific drug delivery allows for higher drug concentrations, increase quality of life for patients and in some cases extend lives.

⇒ Site specific drug delivery has several distinct advantages over other means of delivering drugs. For example direct infusion into the target organ (or) vasculature surrounding and supplying blood to the organ ensures that the majority of drug goes to the site it is intended to act on. This allows for the use of more toxic drug

against (e.g. Chemotherapeutic) in high concentrations because the exposure of other organs to the compound is limited.

⇒ Site specific drug delivery[7] requires completion of several sequential but independent events. These include localization of drug and carrier within the desired target organ, recognition and interaction of the carrier with specific target cell(s) and delivery therapeutic concentration of drug to the target cell(s) with little (or) no uptake by non-target (normal) cells.

Site specific drug delivery can be classified according to the level of specificity achieved in the delivery process:

1. Delivery to individual organs (or) tissues (organ targeting)
2. Targeting to a specific cell type(s) with a tissue (cellulose targeting).
3. Delivery to different intracellular compartments in target cells by engineering the internalization of drug and drug carrier construct via specific transport pathways (intracellular targeting)

However the role of carrier systems in providing site specificity can be evident from the terms like “Passive and Active” targeting approaches.

Passive targeting involves therapeutic exploitation of the natural (intrinsic / inherent) distribution pattern of a drug-carrier construct *in vivo*. For example the role of the reticulo endothelial system (RES) in cleaning foreign particulate materials from the blood permits drug encapsulated in particulate materials from the blood permits drug encapsulated in

particulate carriers like liposome and microspheres to be passively targeted to macrophages.

In contrary “active targeting” is aimed at altering the natural distribution pattern of drug-carrier construct either away from RES (long circulatory) or to the specific cells, tissues (or) organs (liquid intervention).

Optimized drug delivery[8]

- This can be achieved by targeted prodrug design.
- Site selective targeting with prodrugs to a specific enzyme (or) specific membrane transporter, or both, has potential as a selective drug delivery system in cancer chemotherapy (or) as an efficient oral drug delivery system.
- On the other hand targeted prodrug design represents a new strategy for directed and efficient drug delivery.
- Site specific drug delivery can be achieved by the enzyme-targeted prodrug.
- In prodrug design enzymes can be recognized as systemic metabolic sites (or) prodrug-drug *in vivo* reconversion sites.

Strategy for site-specific drug delivery

- The use of prodrugs has been actively pursued to achieve very precise and direct effects at the “site of action” with minimal effect on the rest of the bodies.

- ❖ Stella and Himmelstein suggested that at least 3 factors should be optimized for site specific delivery of drugs by using prodrug approach.

1. The prodrug must be readily transported to the site of action, and uptake to the site must be rapid and essential perfusion rate limited.
2. Once at the site, the prodrug must be selectively cleaved to the active drug relative to its conversion at other sites.
3. Once selectively generated at the site of action, the active drug must be somewhat retained by the tissue.

In the prodrug approach, site-specific drug delivery can be obtained from tissue-specific activation of a prodrug, which is the result of metabolism by an enzyme. That is either unique for the tissue (or) present at a higher concentration (compared with other tissues), thus it activates the prodrug more efficiently.

For example, glycosidase activity of colonic micro flora offers opportunities to design colon-specific drug derivatives are hydrophilic and poorly absorbed from the small intestine, but once they reach the colon, they can be effectively cleaved by bacterial glycosidase to release the free drug or be absorbed by the colonic mucosa.

Site-specific (or) targeted delivery involves drug delivery to a specific organ (or) class of cells (or) physiological compartment. Site-specific drug delivery can be aimed at systemic absorption (or) for local effects.

Various site-specific oral controlled release systems have been developed, depending upon the target site which can be classified as

I. Systems targeted to duodenum/stomach

II. Systems targeted to small intestine

III. Systems targeted to lymphatic

IV. Systems targeted to colon

1. Systems targeted to stomach/duodenum

These types of system not only prolong the stomach residence time, but also in the area of the GI tract such that the active ingredients reach their optimum absorption site in solution and are ready for absorption. These type of systems are used with

⇒ Drugs insoluble in intestinal fluid.

⇒ Drugs exerting its therapeutic action in stomach / duodenum E.g. antacids such as oxides, hydroxides and carbonates of magnesium, aluminum hydroxides and magnesium trisilicate.

⇒ Drugs exhibiting site specific absorption from duodenum E.g. chlorphenaramine maleate.

⇒ Drugs absorbed significantly from stomach e.g. certain vitamins (Vit. B and Vit C) and minerals.

⇒ Highly acidic drugs e.g. aspirin produce irritation on contact with stomach wall, which can be prevented by these types of systems.

Different systems used for stomach/duodenum targeting are

a) Hydrodynamically balanced systems (low density formulations)

b) Air entrapped systems

c) Size-based systems

d) Bioadhesive systems

2. Systems targeted to small intestine

These systems are made such that they permit the safe passage of a system through the acid environment of the stomach to more suitable juices of the intestines.

These type of systems used with

⇒ Drugs destroyed by gastric acid e.g. enzymes and some antibiotics e.g. Erythromycin

⇒ Drugs irritating to gastric mucosa, e.g. sodium salicylate.

⇒ Drugs which are required at intestine for local action, e.g. intestinal antiseptics

Systems for intestinal targeting are

(a) Enteric coated tablets

(b) Bioadhesive systems

3. Systems targeted to lymphatic

The intestinal lymphatic system consists of a network of vessels throughout the small and large intestine which are involved in the potential

uptake of particulates administered orally of nanometer and micrometer size range. These lymphatic play a major role in the absorption of a variety of nutrients, lipids, fluids and drugs.

These systems are used for the following purposes:

1. Avoidance of hepatic first pass metabolism.
2. Selective treatment of diseases and infections of mesenteric lymphatic.
3. Enhanced absorption of large molecules of higher weight, such as peptides and particulates.
4. Inhibition of cancer cell metastasis.
5. Drugs susceptible to chemicals and/or enzymes in luminal fluids.
6. Drugs which are highly hydrophilic and ionizable at all pH values as streptomycin, gentamycin and vanomycin.
7. Drugs which are highly hydrophobic.
8. Drugs exhibiting poor and unpredictable bioavailability.
9. Oral administration of antigens.

Different systems used for lymphatic targeting

(1) Lipidic systems

(2) Polymeric systems

4. Systems targeted to colon

Drug delivery selectively to the colon through the oral route has been the subject of new research initiatives. Drug release is delayed until it enters the colon. This approach utilizes colonic micro flora and colonic pH as in-house mechanism for selective drug release and its absorption at the colon.

Although the system needs wider study before its regular implementation in drug delivery.

These types of system are used for

- ✓ Drugs used for local effects in colon for inflammatory bowel diseases (E.g. ulcerative colitis and Crohn's disease), irritable colon syndrome, infectious diseases and colon cancer for effective and safe therapy. E.g. 5-amino salicylic acid, mebeverine hydrochloride, sulphasalazine, hydrocortisone acetate, 5-flourouracil, dozorubicin, nimustine.
- ✓ Drugs which are poorly absorbed orally, as colon has longer residence time and is highly responsive to agents that enhance the absorption of poorly absorbable drugs.
- ✓ For the avoidance of hepatic first pass metabolism of drugs.
- ✓ Where the delay in system absorption is therapeutically desirable, especially in diseases susceptible to diurnal variation.
- ✓ Some orally administered drugs which exhibit poor uptake in upper GI tract (or) show enzymatic degradation, can be investigated for

better bioavailability through colon. E.g. metoprolol, nifedipine, isosorbide, brompheniramine, diclofenac, ibuprofen.

Drug delivery systems targeted to colon can be broadly classified as:

- pH based drug delivery systems
- Enzyme based systems
- Prodrugs based drug delivery system
- pH independent biodegradable polymer based drug delivery systems.

Advances

⇒ Two advances in medical technology have allowed the development of new strategies for site-specific delivery of medication.

1. First, the ability to place and manage indwelling catheters in the vascular space (e.g. hepatic artery for liver tumors, (or) metastases) and in the spinal space (for the management of intractable pain and other central nervous system disorders).
2. Second, the development of reliable, totally implantable drug pumps.

⇒ Site-specific drug delivery can offer significant advantages for some patients in the later stages of the disease, for example in the case of hepatic arterial infusion (HAI) therapy for treatment of metastatic

colon cancer, it is known that these tumors receive an estimated 80% of their blood supply from the hepatic artery.

⇒ Site-specific delivery of chemotherapy is not new, but early experiments required patients to be hospitalized for the procedure. External catheters were placed through the skin, increasing the risk for infection. The development of fully implantable, continuous infusion pumps allow patients to be mobile and reduces the need for inpatient clinic visits for drug infusion. These pumps also have the advantage of requiring little (or) no home care. Patients often can participate in activities of daily living, as their illness permits, with little hindrance from side effects (or) administration of drugs.

⇒ Site specific delivery is cost effective when compared with medical management (e.g. oral medications, physic or psychotherapy, use of resources, site-specific drug delivery for the treatment of chronic pain pays itself in about two years of treatment. Medical condition, stage of illness, and other disease related criteria determine candidates for site-specific drug delivery. As with any medical treatment, patients should talk with their doctors about the risks involved. For example, because the pump and catheter are surgically placed, infections are possible. The catheter could become dislodged or blocked. These events, while rare, could cause a reduction in (or) loss of therapeutic effect.

Drug related side effects also can occur.

Site specific drug delivery is an exciting disease management alternative for appropriately selected patients, offering potentially and life-enhancing benefits.

CONTROLLED RELEASE TECHNOLOGY[7]

Conventional drug therapy typically involves the periodic dosing of a therapeutic agent that has been formulated in a manner to ensure its stability, activity and bioavailability. For most of the drugs, conventional methods of formulation are quite effective. However some drugs are unstable and toxic and have a narrow therapeutic range, exhibit extreme solubility problems, require localization to a particular site in the body or require strict compliance or long term use. In such cases a method of continuous administration of drug is desirable to maintain fixed plasma drug levels. The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required to providing uniform drug delivery. So, controlled release dosage form is a dosage form that release one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ. Controlled release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery.

Terminology[9]

Modified release delivery systems may be divided conveniently into four categories.

A) Delayed release

B) Controlled release

1 Sustained release

2 Extended release

C) Site specific targeting

D) Receptor targeting

A) Delayed Release

These systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form.

Examples of delayed release systems include repeat action tablets and capsules and enteric-coated tablets where timed release is achieved by a barrier coating.

B) Controlled release

These systems also provide a slow release of drug over an extended period of time and also can provide some control, whether this be of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells.

1) Sustained release

Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rates and necessarily reduce the dosage frequency by two folds.

2) Extended release

These systems include any drug delivery system that achieves slow release of drug over an extended period of time.

C) Site specific targeting

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.

D) Receptor targeting

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue.

Site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be controlled drug delivery systems.

Potential advantages of controlled drug therapy[10]

- All controlled release products share the common goal of improving drug therapy over that achieved with their non-controlled counterparts. This improvement in drug therapy is represented by

several potential advantages of the use of controlled release systems as mentioned below.

A) Avoid patient compliance problems.

B) Employ less total drug

- Minimize or eliminate local side effects.
- Minimize or eliminate systemic side effects.
- Obtain less potentiation or reduction in drug activity with chronic use.
- Minimize drug accumulation with chronic dosing.

C) Improves efficiency in treatment

- Cure or control condition more promptly
- Improves control of condition i.e. reduce fluctuation in drug level.
- Improves bioavailability of some drugs.
- Make use of special effects e.g. sustained release aspirin for morning relief of arthritis by dosing before bedtime.

D) Economy

Limitations of Oral CRDDS

On the other hand oral CRDDS suffer from a number of potential disadvantages:

- Relatively poor *in vitro* - *in vivo* correlation
- Possible dose dumping

- Reduced potential for dose change or withdrawal in event of toxicity
- Loss of effect due to diarrohea (too fast transit time)

Reasons for Oral CRDDS

There is a clinical need to develop the CR formulations to improve drug therapy over that achieved with their conventional counterparts, especially in the following cases:

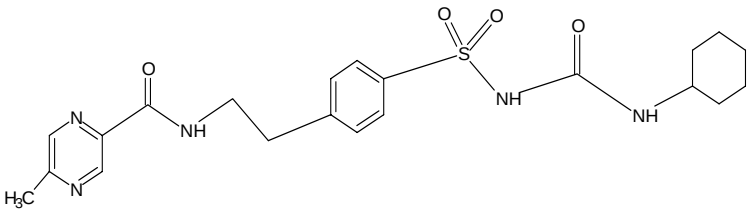
1. Short elimination half-life (t½) and minimum effective concentration (MEC) required for the therapy. Shorter the half life of a drug, larger will be the fluctuations between the maximum steady state concentration (C^{ss}_{max}) and the minimum steady state concentration (C^{ss}_{min}) upon multiple dosing. If MEC is therapeutically required, either frequent dosing of a conventional drug product or development of a CR product is necessary.
2. Similarly the drugs having reasonably long elimination half life and either wide or narrow therapeutic range may also need to be formulated as CR products mainly for:

- Two to three day extension and
- Minimize the fluctuations between C^{ss}_{max} and C^{ss}_{min} with narrow therapeutic range drugs.

DRUG PROFILE

DRUG PROFILE[11, 12, 13]

Product Name : Glipizide.



Molecular Formula : $C_{21}H_{27}N_5O_4S$

Formula Weight : 445.53518

Composition : C (56.61%), H (6.11%), N (15.72%), O (14.36%), S (7.20%)

Synonym : 1-cyclohexyl-3-[[4-[2-[[(5-methylpyrazin-2-yl) carbonyl]amino]ethyl]-phenyl]sulphonyl] urea.

It contains not less than 98.0% and not more than 102.0% of $C_{21}H_{27}N_5O_4S$ calculated with reference to the dried.

1. PHYSICAL AND CHEMICAL PROPERTIES

Physical state and appearance : Solid. (Solid powder), a white (or) almost white, crystalline powder

Odor : Odorless

Molecular weight	:	445.55 g/mole
Melting point	:	208.5° C (407.3° F)
Dispersion properties	:	Is not dispersed in cold and hot water
Solubility	:	Insoluble in cold and hot water

2. STABILITY AND REACTIVITY

Stability	:	The product is stable
Polymerization	:	No

3. TOXICOLOGICAL INFORMATION

Routes of Entry	:	Absorbed through skin. Eye contact. Inhalation. Ingestion.
Carcinogenic effects	:	Classified None by NTP, None by OSHA, None by NIOSH.
Teratogenic effects	:	Classified none for human.
Development toxin	:	The substance is toxic to blood, liver, cardiovascular system, central nervous system (CNS).

4. CLINICAL PHARMACOLOGY

4.1. Mechanism of action

The primary mode of action of glipizide in experimental animals appears to be the stimulation of insulin secretion from the beta cells of pancreatic islet tissue and is thus dependent on functioning beta cells in the pancreatic islets. In humans, glipizide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets.

4.2. Other Effects

It has been shown that glipizide therapy was effective in controlling blood sugar without deleterious changes in the plasma lipoprotein profiles of patients treated for NIDDM. In a placebo-controlled, crossover study in normal volunteers, glipizide had no antidiuretic activity, and, in fact, led to a slight increase in free water clearance.

5. PHARMACOKINETIC DATA

Bioavailability	:	100% (regular formulation), 90% (extended release)
Protein binding	:	98 to 99%
Metabolism	:	Hepatic hydroxylation
Half life	:	2 to 5 hrs
Excretion	:	Renal and fecal

6. CONTRAINDICATIONS / CAUTIONS

Contraindicated in patients with

: Known hypersensitivity to the drug.

: Diabetic ketoacidosis, with or without coma.

This condition should be treated with insulin.

Warnings!!! : Special warning on increased risk of cardiovascular mortality.

7. ADVERSE REACTIONS

7.1. Gastrointestinal

Diarrohea, one in seventy; constipation and gastralgia, one in one hundred. They appear to be dose-related and may disappear on division or reduction of dosage. Cholestatic jaundice may occur rarely with sulfonylureas, glipizide should be discontinued if this occurs.

7.2. Dermatologic

Allergic skin reactions including erythema, morbilliform or maculopapular eruptions, urticaria, pruritus, and eczema have been reported in about one in seventy patients.

7.3. Hematologic

Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas.

7.4. Metabolic

Glipizide pretreatment did not cause an accumulation of acetaldehyde after ethanol administration. Clinical experience to date has shown that glipizide has an extremely low incidence of disulfiram-like alcohol reactions.

7.5. Endocrine Reactions

Cases of hyponatremia and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion have been reported with this and other sulfonylureas.

7.6. Miscellaneous

Dizziness, drowsiness, and headache have each been reported in about one in fifty patients treated with glipizide. They are usually transient and seldom require discontinuance of therapy.

7.7. Laboratory Tests

The pattern of laboratory test abnormalities observed with glipizide was similar to that for other sulfonylureas. Occasional mild to moderate elevations of SGOT, LDH, alkaline phosphatase, BUN and creatinine were noted. One case of jaundice was reported. The relationship of these abnormalities to glipizide is uncertain, and they have rarely been associated with clinical symptoms.

8. DRUG INTERACTIONS

The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents, some azoles, and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta adrenergic blocking agents.

8.1. Carcinogenesis, mutagenesis, impairment of fertility

A twenty month study in rats and an eighteen month study in mice at doses up to 75 times the maximum human dose revealed no evidence of drug-related carcinogenicity. Bacterial and *in vivo* mutagenicity tests were uniformly negative. Studies in rats of both sexes at doses up to 75 times the human dose showed no effects on fertility.

8.2. Pregnancy

Pregnancy Category C: Glipizide was found to be mildly fetotoxic in rat reproductive studies at all dose levels (5 – 50 mg/kg).

8.3. Nonteratogenic effects

Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery.

8.4. Geriatric use

Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

9. DOSAGE AND ADMINISTRATION

9.1. Initial dose

The recommended starting dose is 5 mg, given before breakfast. Geriatric patients or those with liver disease may be started on 2.5 mg. Dosage adjustments should ordinarily be in increments of 2.5 to 5 mg, as determined by blood glucose response. The maximum recommended once daily dose is 15 mg. Doses above 15 mg should ordinarily be divided and given before meals of adequate caloric content. The maximum recommended total daily dose is 40 mg.

9.2. Patients receiving insulin

As with other sulfonylurea-class hypoglycemics, many stable non-insulin-dependent diabetic patients receiving insulin may be safely placed on glipizide when transferring patients from insulin to glipizide.

POLYMER PROFILE[14]

ETHYLCELLULOSE

Nonproprietary Names

BP	:	Ethylcellulose
PhEur	:	Ethylcellulosum
USPNF	:	Ethylcellulose

Synonyms

Aquacoat ECD; Aqualon; E462; Ethocel; Surelease.

Chemical Name and CAS registry number

Cellulose ethyl ether [9004-57-3]

Functional category

Coating agent; suspending agent; tablet binder; thickening agent; viscosity – increasing agent.

Applications in pharmaceutical formulation or technology

Ethylcellulose is widely used in oral and topical pharmaceutical formulations; see table 1.

The main use of ethylcellulose in oral formulations is as a hydrophobic coating agent for tablets and granules. Ethylcellulose coatings are used to modify the release to a drug to mask an unpleasant taste, or to improve the stability of a formulation; for example, where

granules are coated with ethylcellulose to inhibit oxidation. Modified – release tablet formulations may also be produced using ethylcellulose as a matrix former.

Ethylcellulose, dissolved in an organic solvent or solvent mixture, can be used on its own to produce water-insoluble films. Higher-viscosity ethylcellulose grades tend to produce stronger and more durable films. Ethylcellulose films may be modified to alter their solubility by the addition of hypromellose or a plasticizer. An aqueous polymer dispersion (or latex) of ethylcellulose such as Aquacoat ECD (FMC Biopolymer) or Surelease (Colorcon) may also be used to produce ethylcellulose films without the need for organic solvents.

Drug release through ethylcellulose-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 ethylcellulose dispersions are generally used to coat granules or pellets. Ethylcellulose-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 ethylcellulose are used in drug microencapsulation.

Release of a drug from an ethylcellulose microcapsule is a function of the microcapsule wall thickness and surface area.

In tablet formulations, ethylcellulose may additionally be employed as a binder; the ethylcellulose may additionally be wet-granulated with a solvent such as ethanol (95%). Ethylcellulose produces hard tablets with low friability, although they may demonstrate poor dissolution.

Ethylcellulose has also been used as an agent for delivering therapeutic agents from oral (e.g. dental) appliances.

In topical formulations, ethylcellulose is used as a thickening agent in creams, lotions, or gels, provided an appropriate solvent is used.

Ethylcellulose is additionally used in cosmetics and food products.

Table 1: Uses of ethylcellulose

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 - 30.0

Description

Ethylcellulose is a tasteless, free-flowing, white or light tan-colored powder.

Typical properties

Density (bulk) : 0.4 g/cm^3

Glass transition temperature : 129-133°C

Moisture content

Ethylcellulose absorbs very little water from humid air or during immersion, and that small amount evaporates readily.

Solubility

Ethylcellulose is practically insoluble in glycerin, propylene glycol, and water. Ethylcellulose 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%). Ethylcellulose that contains not less than 46.5% of ethoxyl acetate, methanol, and toluene.

Specific gravity : 1.12 - 1.15 g/cm^3

Viscosity

The viscosity of ethylcellulose is measured typically at 25° C using 5% w/v ethylcellulose dissolved in a solvent blend of 80% toluene : 20% ethanol (w/w). Grades of ethylcellulose with various viscosities are commercially available. They may be used to produce 5% w/v solutions in organic solvent blends with viscosities nominally ranging from 7 to 100 mPas (7-100 cp). Specific ethylcellulose grades, or blends of different grades, may be used to obtain solutions of a desired viscosity. Solutions of

higher viscosity tend to be composed of longer polymer chains and produce strong and durable films.

The viscosity of an ethylcellulose solution increase with an increase in ethylcellulose concentration; e.g., the viscosity of a 5% w/v solution of Ethocel Standard 4 Premium is 4 mPas (4 cP) and of a 25% w/v solution of the same ethylcellulose grade is 850 mPas (850 cP). Solutions with a lower viscosity may be obtained by incorporating a higher percentage (30 - 40%) of a low molecular-weight aliphatic alcohol such as ethanol, butanol, propan-2-ol, or n-butanol with toluene. The viscosity of such solutions depends almost entirely on the alcohol content and is independent of toluene.

In addition, non-pharmaceutical grades of ethylcellulose that differ in their ethoxyl content and degree of polymerization are available.

Stability and storage conditions

Ethylcellulose is a stable, slightly hygroscopic material. It is chemically resistant to alkalies, both dilute and concentrated, and to salt solutions, although it is more sensitive to acidic materials than are cellulose esters.

Ethylcellulose 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 230-340 nm range.

Ethylcellulose should be stored at a temperature not exceeding 32°C (90°F) 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.

Safety

Ethylcellulose is widely used in oral and topical pharmaceutical formulations. It is also used in food products. Ethylcellulose is not metabolized following oral consumption and is therefore a noncalorific substance. Because ethycellulose is not metabolized it is not recommended for parenteral products; parenteral use may be harmful to the kidneys.

Ethylcellulose is generally regarded to be a health hazard; the WHO has not specified an acceptable daily intake.

LD_{50} (rabbit, skin): >5 g/kg

LD_{50} (rat, oral): >5 g/kg

Handling precautions

It is important to prevent fine dust clouds of ethylcellulose from reaching potentially explosive levels in the air. Ethylcellulose is combustible. Ethylcellulose powder may be an irritant to the eyes and eye protection should be worn

MICROCRYSTALLINE CELLULOSE

Nonproprietary Names

BP	:	Microcrystalline cellulose
JP	:	Microcrystalline cellulose
PhEur	:	Cellulosum microcristallinum
USPNF	:	Microcrystalline cellulose

Synonyms

Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; *Fibrocel*; Pharmacel; Tabulose; Vivapur.

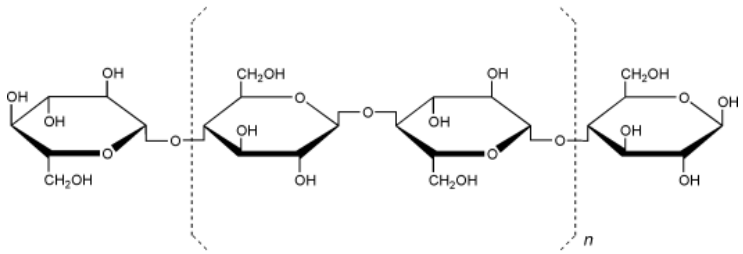
Chemical Name and Cas Registry Number

Cellulose [9004-34-6]

Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n$ ≈36 000. where n ≈ 220.

Structural Formula



Functional Category

Adsorbent; Suspending agent; Tablet and Capsule Diluent; Tablet Disintegrant.

Applications in Pharmaceutical Formulation

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting. Microcrystalline cellulose is also used in cosmetics and food products.

Table 2: Uses of microcrystalline cellulose

Use	Concentration (%)
Adsorbent	20–90
Antiadherent	5–20
Capsule binder/diluent	20–90
Tablet disintegrant	5–15
Tablet binder/diluent	20–90

Description

Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Typical Properties

Solubility

Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

Stability and storage conditions

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Microcrystalline cellulose is incompatible with strong oxidizing agents.

Safety

Microcrystalline cellulose is not absorbed systemically following oral administration and thus has little toxic potential. Consumption of large quantities of cellulose may have a laxative effect, although this is unlikely to be a problem when cellulose is used as an excipient in pharmaceutical formulations. Deliberate abuse of formulations containing cellulose, either by inhalation or by injection, has resulted in the formation of cellulose granulomas.

HYDROXYETHYL CELLULOSE

Nonproprietary Names

BP	:	Hydroxyethylcellulose
PhEur	:	Hydroxyethylcellulosum
USPNF	:	Hydroxyethyl cellulose

Synonyms

Alcoramnosan; Cellosize; cellulose hydroxyethyl ether; cellulose hydroxyethylate; ethylhydroxy cellulose; ethylose; HEC; HE cellulose; 2-hydroxyethyl cellulose ether: hydroxyethyl ether cellulose; hydroxyethyl starch; hyetellose; Idroramnosan; Liporamnosan; Natrosal; oxycellulose; Tylose PHA.

Chemical Name and CAS registry number

Cellulose, 2-hydroxyethyl ether [9004-62-0]

Empirical formula & molecular weight

Ethylcellulose with complete substitution (DS=3) is $C_{12}H_{23}O_6$ $(C_{12}H_{22}O_5)_n$ $C_{12}H_{23}O_5$ where n can vary to provide a wide variety of molecular weights. Ethylcellulose, and ethyl ether of cellulose, is a long-chain polymer of β-anhydroglucose units jointed together by acetal linkages.

Functional category

Coating agent; flavoring fixative; tablet binder; tablet filler; viscosity – increasing agent.

Applications in pharmaceutical formulation or technology

Hydroxyethyl cellulose is a nonionic, water-soluble polymer widely used in pharmaceutical formulations. It is primarily used as a thickening agent in ophthalmic and topical formulations, although it is used as a binder and film-coating agent for tablets. It is present in lubricant preparations for dry eye, contact lens care, and dry mouth. The concentration of hydroxyethyl cellulose used in a formulation is dependent upon the solvent and the molecular weight of the grade. Hydroxyethyl cellulose is also widely used in cosmetics.

Description

Hydroxyethyl cellulose occurs as a light tan or cream to white-colored, odorless and tasteless, hygroscopic powder.

Typical properties

Density (bulk)

0.35 to 0.61 g/cm ^{3} for Cellosize, 0.60g/cm^3 for Natrosol

Moisture content

Hydroxyethyl cellulose is hygroscopic, the amount of water absorbed depends upon the initial moisture content and the relative humidity of surrounding air. Commercial grades of hydroxyethyl cellulose contains less than 5% w/w of water.

Solubility

Hydroxyethyl cellulose is soluble in either hot or cold water, forming clear, smooth, uniform solutions, practically insoluble in acetone, ethanol, ether, toluene, and most other organic solvents. In some polar organic solvents, such as the glycols hydroxyethyl cellulose either swells or is partially soluble.

Specific gravity

1.38 - 1.40 g/cm^3 for Cellosize.

Stability and storage conditions

Hydroxyethyl cellulose powder is a stable, though hygroscopic, material. Aqueous solutions of hydroxyethyl cellulose are relative stable at pH 2 to 12 with the viscosity of solutions being largely unaffected. However, solutions are less stable below pH 5 owing to hydrolysis. At high pH, oxidation may occur. Increasing the temperature reduces the viscosity of aqueous hydroxyethyl cellulose solutions. However on cooling, the original viscosity is restored. Solutions may be subjected to freeze-thawing, high-temperature storage, or boiling without precipitation or gelation occurring aqueous solutions of hydroxyethyl cellulose may also be sterilized by autoclaving.

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

Incompatibilities

Incompatible with Zein and with certain fluorescent dyes, optical brighteners and certain quaternary disinfectants.

Handling precautions

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

POLYETHYLENE GLYCOL

Nonproprietary Names

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

Synonyms

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

Chemical Name

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

FUNCTIONAL CATEGORY

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

APPLICATIONS IN PHARMACEUTICAL TECHNOLOGY

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

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

Liquid polyethylene glycols are used as water-miscible solvents for the contents of soft gelatin capsules. In concentrations up to approximately 30% v/v, PEG 300 and PEG 400 have been used as the vehicle for parenteral dosage forms. Polyethylene glycols can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions with an appropriate polyethylene glycol.

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

Pharmacopeial Specifications

Typical Properties

Density	:	1.11 to 1.14 g/cm^3 at 25°C for liquid PEGs; 15 to 1.21 g/cm^3 at 25°C for solid PEGs.
Flash point	:	250°C for PEG 6000
Freezing point	:	15 to 25°C for PEG 6000
Melting point	:	55 to 63°C for PEG 6000
Moisture content	:	Liquid polyethylene glycols are very hygroscopic, hygroscopicity decreases with increasing molecular weight. Solid grades.

Solubility

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

Surface tension

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

Stability and storage conditions

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

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

Incompatibilities

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

Handling precautions

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

Regulatory status

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

LITERATURE REVIEW

1. Aruna, A. and Nancy, K (2000)[15] developed a UV spectrophotometric method based on the measurement of absorbance at 276 nm in pH 7.4 phosphate buffer for glipizide, the method obeyed Beer's law in the concentration range 5 - 30 µg/ml.
2. Kung-Hsu Lin *et al.*, (2001)[16] studied the influence of compression force to inner core tablet (or) to outer coating layer of the compression-coated tablet on the function of the time controlled disintegration.
3. Anjali M. Agarwal, Steven H. Neau (2003)[17] evaluated the wet granulated fine particle ethylcellulose matrix tablets.
4. Shan-Yang Lin and Mei-janeli (2004)[18] formulated an oral press-coated tablet by direct compression to achieve the time controlled disintegration (or) rupturing function with a distinct predetermined lag time.
5. P. Venkatesh *et al.*, (2005)[19] developed a method for the separation and simultaneous estimation of six anti-diabetic drugs - glibenclamide, gliclazide, glipizide, pioglitazone, repaglinide and rosiglitazone in pharmaceutical formulations. The assay developed for formulation analysis was found to be precise and accurate. The

calibration curves ranged from 0.1 to 100 µg/ml. The drugs were monitored at a wavelength of 260 nm.

6. N. Vishal Gupta *et al.*, (2007)[20] prepared and characterized gelatin-poly (methacrylic acid) interpenetrating polymeric network hydrogels as a pH-sensitive delivery system for glipizide, drug release from the IPN hydrogels was studied in 900 ml of dissolution medium (2 h in 0.1 N hydrochloric acid solution and 10 h in pH 7.4 phosphate buffer) at 276 nm.
7. Sundaramoorthy K., Kavimani S (2008)[21] formulated and evaluated an extended release dosage form of metformin hydrochloride using combined hydrophobic and hydrophilic matrix. Extended release matrix tablets of metformin hydrochloride were formulated using ethylcellulose and hydroxypropylmethylcellulose in varying ratios by direct compression method.
8. Linsy, Lin K.H. *et al.*,[22] investigated the influence of release of drug from different weight ratios of coarse / fine particles of EC powder in outer shell of formulation.
9. Linsy, Lin K.H., Li M.J.,[23] designed a directly compressed time-controlled disintegration tablet using different grades of micronized ethylcellulose.
10. Watanable Y., Mukai B., Utoguchi N. *et al.*,[24] prepared and evaluated the press coated aminophylline tablet using crystalline

cellulose and polyethylene glycol in the outer shell for timed-release dosage forms.

11. Shan-Yang Ling *et al.*,[25] studied the influence of excipients and osmotic agents in the inner core on the time-controlled disintegration of compression-coated ethyl cellulose tablets.
12. Jomjai Peerpattana *et al.*,[26] formulated a colon drug delivery system using dry coated time controlled disintegration wax matrix tablets. The effect of pH of the dissolution medium on drug release was also investigated.
13. Ian R. Wilding[27] studied the site specific drug delivery in gastrointestinal tract to maximize therapeutic response and to reduce side effects.
14. Vyas S.P., Shihorkar V.,[28] used endogenous carriers and ligands in non-immunogenic site-specific drug delivery. To explore potential and possibilities of cell biologically related bioevents in the development of specific preprogrammed and target oriented systems.
15. Hyo-Kyung Han *et al.,*[8] developed targeted prodrug design representing a new strategy for directed and efficient drug delivery.
16. Clausen A.E. *et al.,*[29] used direct compressible polymethacrylic acid-starch compositions for site-specific drug delivery.

17. Biswanthsa, Jayantha Chowdhury, *et al.,*[30] studied the rate of release of sodium benzoate, salbutamol sulphate and caffeine from ethylcellulose microparticles.
18. S.K. Gupta, Jai Prakash, *et al.*,[31] studied about role of non-steroidal anti-inflammatory drugs in the management of cancer.
19. K.S. Aithal, *et al.,*[32] used ethylcellulose and hydroxylpropyl methylcellulose as polymer in controlled fluoride release tablets.
20. Nagesh Badwe, *et al.,*[33] gave a practical aspect of direct compression.
21. G.W. Skinner, *et al.,*[34] evaluate a new grade of ethyl cellulose, Aqualon T_{10} Pharma ethyl cellulose (T_{10} EC), for compression coating of time-controlled dosage forms. This new grade has high ethoxy content and low viscosity, yielding optimized compatibility and good powder flow.
22. Madhusudan Hariharan *et al.,* [35] developed a novel compression coated tablet dosage form which describes the dosage form not requires the separate formation of the core tablet because the core material and outer compression coating material are formed into a tablet in the same tablet press and on a single turret.
23. Wardrop J., Jaber A.B., *et al.,*[36] formulated the novel multiple layer compression coated chewable tablets and studied the effect of

humidity, stability compared to marketed chewable tablets as a reference.

24. T. Durig, W.W. Harcum, *et al.,*[37] characterized the unique physical-chemical and compaction properties of high ethoxyl, low viscosity ethylcellulose in relation to other grades of ethyl cellulose with varying ethoxyl content and molecular weight.

25. Fukui *et al.,*[38] studied on applicability of press-coated tablets, containing diltiazem hydrochloride (DIL) in the core tablet and coated with hydroxylpropylcellulose (HPC) as the outer shell, were examined for applicability as timed-release tablets with a predetermined lag time and subsequent rapid drug release phase.

26. Fukui, *et al.,*[39] formulated enteric coated timed-release press coated tablets and evaluation of their function by *in vitro* and *in vivo* tests for colon targeting.

27. Martti Marvola, *et al.,*[40] studied the development and biopharmaceutical evaluation of press-coated tablets with the intention of administering formulation in the evening at 22:00, which provides treatment for diseases in which symptoms are experienced in the early morning hours i.e. chronopharmacotherapy.

28. Melendez M., Ghaly E.S.,[41] studied the mechanism of release of drug from hydrophilic polymer and to quantify the amount of drug released.
29. Rahmounium, Lenaerts *et al.,*[42] studied the characterization of hydroxylpropylmethylcellulose in controlled release tablets.
30. Hamid A. Merchant, Harris M. Shoaib, Jaweria Tazeen[43], once-daily tablet formulation and *in vitro* release evaluation of cefpodoxime using hydroxypropyl methylcellulose: a technical note.

MATERIALS AND EQUIPMENTS

Table 3: Materials used

Material	Source
Glipizide	Franco-Indian Pharmaceuticals, Chennai.
Microcrystalline cellulose	SD Fine Chemicals, Mumbai.
Ethylcellulose	SD Fine Chemicals, Mumbai.
Hydroxyethyl cellulose	Himedia Laboratories, Mumbai.
Polyethylene glycol 6000	Himedia Laboratories, Mumbai.
Methanol	SD Fine Chemicals, Mumbai.

Table 4: Equipments used

Equipment	Model / Company
Tablet punching machine	Rimek mini press
UV-visible spectrophotometer	Jasco V-530
FT-IR spectrophotometer	Jasco-FT-IR 8201 PC
Digital balance	Denver instruments
Dissolution test apparatus	Lab India disso 2000
Pfizer Hardness tester	Scientific Engineering Corporation
Friability tester	Remi equipments

ANALYTICAL METHODS

METHODS FOR ESTIMATION OF GLIPIZIDE

1) HPLC determination of glipizide in human plasma and urine has been reported. The response was linear (0-1000 ng/ml) and the detection limit was 5-10 ng/ml in plasma or urine. A Spherisorb ODS reversed-phase column was used. Quantitation was achieved by monitoring the ultraviolet absorbance at 275 nm[44].

2) Simultaneous determination of glipizide with other antidiabetic drugs in plasma and urine were reported by liquid chromatography-tandem mass spectrometry[45].

1. THE METHODOLOGY USED IN THE PRESENT STUDY IS UV SPECTROPHOTOMETRY[46,47]

1.1. Potassium dihydrogen phosphate, 0.2 M solution

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

1.2. Sodium hydroxide 0.2 N solution

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

1.3. Preparation of pH 7.4 phosphate buffer

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

1.4 Preparation of 0.2 M potassium chloride

Dissolve 14.911 gm of potassium chloride in 1000 ml of distilled water. This will give 0.2 M potassium chloride.

1.5 Preparation of 0.2 M hydrochloric acid

Place 7.292 gm (17.8 ml) of hydrochloric acid in 1000 ml of distilled water, this will give 0.2 M HCl acid

1.6 Preparation of pH 1.2 HCl acid buffer

Place 50 ml of the 0.2 M potassium chloride in a 200 ml volumetric flask, then add 85 ml of 0.2 M hydrochloric acid and then add distilled water to make up the volume.

2. PROCEDURE FOR STANDARD GRAPHS PREPARATION

2.1. Standard graphs preparation in phosphate buffer pH 7.4[20]

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

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

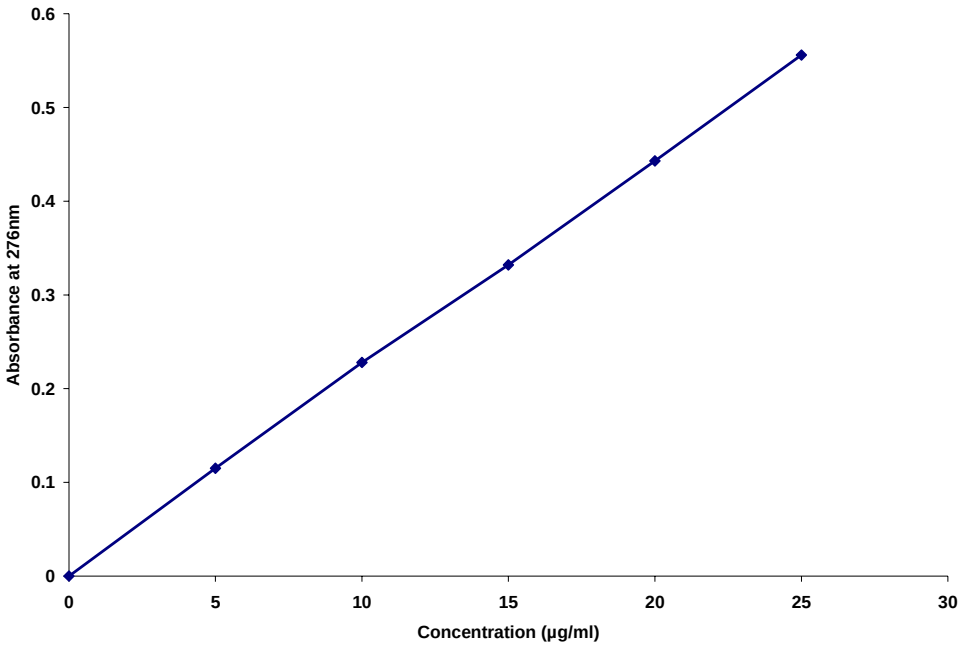
From the stock solution II, pipette out 0.5, 1.0, 1.5, 2.0, and 2.5 ml into 5 separate 10 ml volumetric flasks respectively, then make up the volume up to the mark to give 5, 10, 15, 20 and 25 µg/ml concentration solutions and the phosphate buffer pH 7.4 was taken as blank.

The absorbance was measured at 276 nm and the graph was plotted against concentration (µg/ml) vs. absorbance.

Table 5: Standard graph of glipizide in phosphate buffer pH 7.4

Sl. No.	Concentration (µg/ml)	Absorbance at 276 nm
1	0	0.000
2	5	0.115
3	10	0.228
4	15	0.332
5	20	0.443
6	25	0.556

Fig. 1: Standard graph of glipizide with phosphate buffer pH 7.4



2.2. Standard graphs preparation in hydrochloric acid buffer pH 1.2

Accurately weigh 100 mg of glipizide and transfer to a 100 ml volumetric flask and add minimum quantity of methanol to solubilise the drug, and then add phosphate buffer pH 1.2 to make up the volume up to 100 ml, this gives the stock solution I (1000 µg/ml).

From stock solution I, pipette out 10 ml and make up the volume to 100 ml with phosphate buffer pH 1.2, this gives the stock solution II (100 µg/ml).

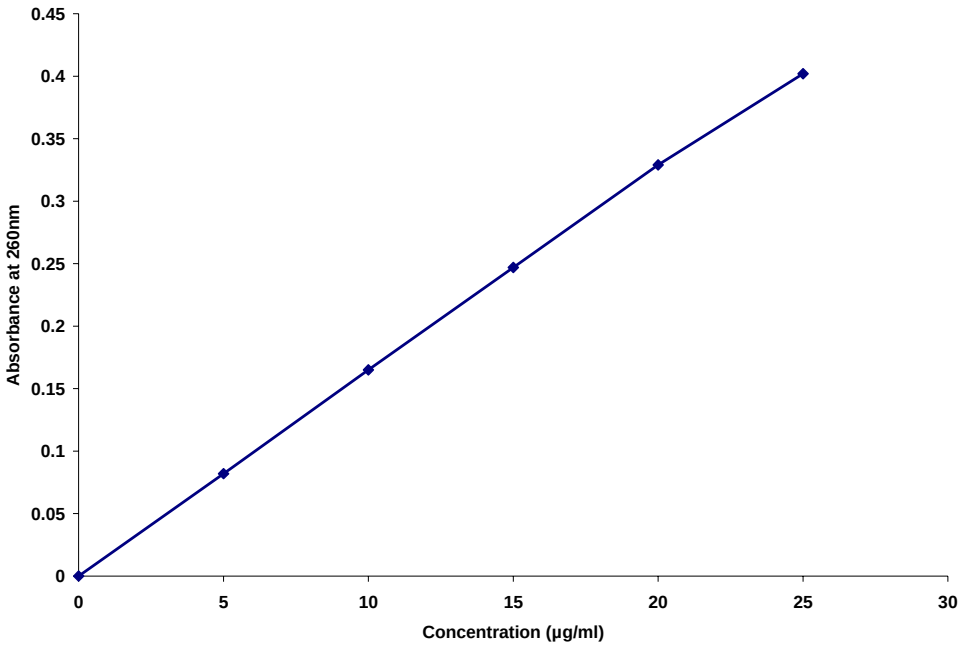
From the stock solution II, pipette out 0.5, 1.0, 1.5, 2.0, and 2.5 ml into 5 separate 10 ml volumetric flasks respectively, then make up the volume up to the mark to give 5, 10, 15, 20 and 25 µg/ml concentration solutions and the phosphate buffer pH 1.2 was taken as blank.

The absorbance was measured at 260 nm and the graph was plotted against concentration (µg/ml) vs. absorbance.

Table 6: Standard graph of glipizide in phosphate buffer pH 1.2

Sl. No.	Concentration (µg/ml)	Absorbance at 260 nm
1	0	0.000
2	5	0.082
3	10	0.165
4	15	0.247
5	20	0.329
6	25	0.402

Fig. 2: Standard graph of glipizide in phosphate buffer pH 1.2



Standard graphs preparation in methanol

Accurately weigh 100 mg of glipizide and transfer to a 100 ml volumetric flask and add methanol to solubilise the drug, and make up the volume up to 100ml, this gives the stock solution (1000 µg/ml).

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

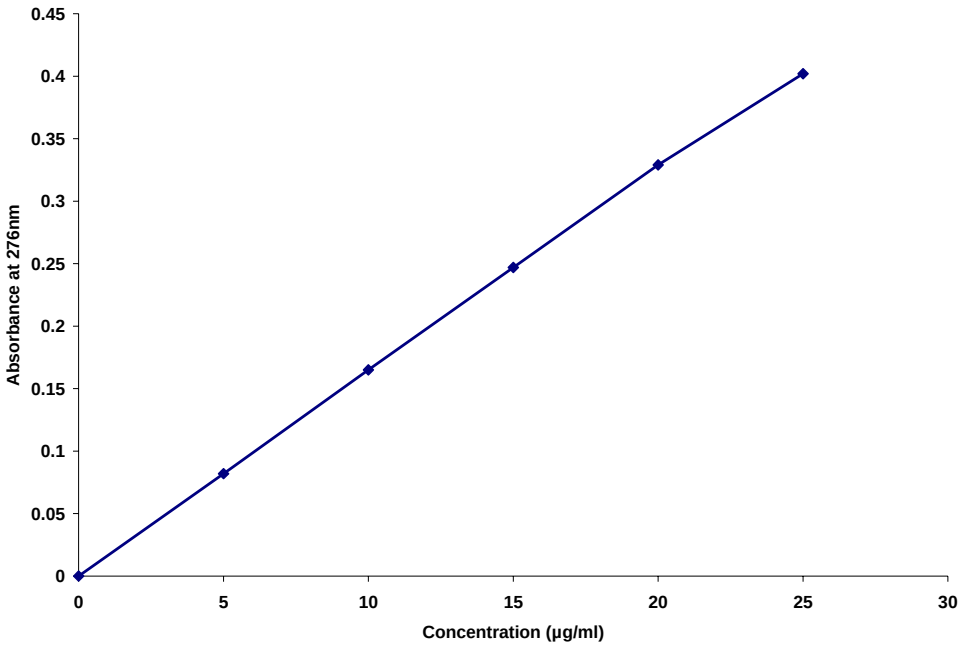
From the stock solution II, pipette out 0.5, 1.0, 1.5, 2.0, and 2.5 ml into 5 separate 10 ml volumetric flasks respectively, then make up the volume up to the mark to give 5, 10, 15, 20 and 25 µg/ml concentration solutions and the methanol was taken as blank.

The absorbance was measured at 276 nm and the graph was plotted against concentration (µg/ml) vs. absorbance.

Table 7: Standard graph of glipizide in methanol

Sl. No.	Concentration (µg/ml)	Absorbance at 276 nm
1	0	0.0000
2	5	0.1190
3	10	0.2420
4	15	0.3610
5	20	0.4810
6	25	0.6040

Fig. 3: Standard graph of glipizide in methanol



FORMULATION OF TIME CONTROLLED RELEASE TABLETS CONTAINING GLIPIZIDE

Glipizide is a second generation of sulphonyl urea, used for lowering blood glucose. The different formulations of glipizide time controlled tablets were formulated by direct compression method using a combination of hydrophobic polymer ethylcellulose and hydrophilic polymers polyethylene glycol 6000 and hydroxyethylcellulose in outer coating layer.

The formulation of time controlled release tablet by using press-coating technique with ethylcellulose as hydrophobic polymer and hydrophilic polymers polyethylene glycol (PEG) and hydroxyethylcellulose (HEC).

METHOD

The press-coated tablets were formulated by using a tablet press under constant pressure. An inner core of the drug tablet (glipizide 10 mg) was previously direct compacted with 40 mg of MCC. Different weight ratios of (w/w) of EC/excipient mixture were formulated and each EC/excipient mixture (50 mg) was first filled into a die and the inner core tablet was then manually placed in the center of the EC/excipient powder bed. The remaining EC/ excipient powder (50 mg) was then poured on to the inner core tablet and compressed to prepare the compression-coated tablet.

Table 8: Formula for glipizide time controlled release tablets

S. No.	Ingredients mg/tab	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
1.	Glipizide	10	10	10	10	10	10	10	10	10	10	10	10	10	10
2.	Microcrystalline cellulose	40	40	40	40	40	40	40	40	40	40	40	40	40	40
3.	Ethyl cellulose	100	80	60	50	40	20	0	100	80	60	50	40	20	0
4.	Polyethylene glycol 6000	0	20	40	50	60	80	100	-	-	-	-	-	-	-
5.	Hydroxy ethylcellulose	-	-	-	-	-	-	-	0	20	40	50	60	80	100

Table 9: Tablet formulation containing hydrophobic polymer ethylcellulose and hydrophilic polymer PEG as excipient in outer coating layer

S. NO.	TYPE	EC	PEG	IN PERCENTAGE
1	F1	100mg	0 mg	(100, 0)
2	F2	80 mg	20 mg	(80, 20)
3	F3	60 mg	40 mg	(60, 40)
4	F4	50 mg	50 mg	(50, 50)
5	F5	40 mg	60 mg	(40, 60)
6	F6	20 mg	80 mg	(20, 80)
7	F7	0 mg	100 mg	(0, 100)

Table 10: Tablet formulation containing hydrophobic polymer ethylcellulose and hydrophilic polymer HEC as excipient in outer coating layer

S. NO	TYPE	EC	HEC	IN PERCENTAGE
1	F8	100mg	0 mg	(100, 0)
2	F9	80 mg	20 mg	(80, 20)
3	F10	60 mg	40 mg	(60, 40)
4	F11	50 mg	50 mg	(50, 50)
5	F12	40 mg	60 mg	(40, 60)
6	F13	20 mg	80 mg	(20, 80)
7	F14	0 mg	100 mg	(0, 100)

Chapter 9 Evaluation of Tablets

EVALUATION OF TABLETS

The formulated tablets were subjected for the following quality control tests:

- Weight variation
- Friability
- Hardness
- Drug content uniformity
- Compatibility studies
- *In vitro* dissolution studies

Weight variation test

Twenty tablets were taken weighed individually as per BP. They were evaluated for the weight variations. The weight variation allowed as per BP limit is 7.5%. The weights of tablet were within the BP limits. The results were shown in table no. 12, 13.

Table 11: Percentage deviation of tablets as per weight range

Pharmaceutical form	Average mass	% Deviation
Tablets	≤ 80 mg	± 10
	> 80 mg - 250 mg	± 7.5
	≥ 250 mg	± 5

Table 12: Weight variation of glipizide tablets containing EC/PEG formulation in outer layer

S. No.	Formulation code	Weight range of 20 Tablets	Average weight	Limit range (±7.5%)
1	F1	144-156	152	140.6-163.4
2	F2	147-158	148	136.9-159.1
3	F3	145-157	146	135.1-156.9
4	F4	141-153	155	143.4-166.6
5	F5	146-154	151	139.7-162.3
6	F6	139-156	149	137.9-160.1
7	F7	143-159	154	142.5-165.5

Table 13: Weight variation of glipizide tablets containing EC/ HEC formulation in outer layer

S. No.	Formulation code	Weight range of 20 Tablets	Average weight	Limit range (±7.5%)
1	F8	142-159	153	141.6-164.4
2	F9	146-153	149	137.9-160.1
3	F10	143-159	155	143.4-166.6
4	F11	140-154	147	136.0-158.0
5	F12	144-158	151	139.7-162.3
6	F13	141-155	145	134.2-155.8
7	F14	147-159	154	142.5-165.5

Chapter 9 Evaluation of Tablets

Friability test

Friability test was performed on the formulated tablets. The weight of the tablets after undergoing 100 revolutions was found to be within the limits 0.5 to 1.0%. The results were shown in table 14, 15.

Hardness

Pfizer hardness tester was used for measuring the hardness of formulated glipizide CR tablets. Five tablets were taken randomly and subjected to test. The hardness was found to be 4-6 kg/cm^2. The results were shown in table 14, 15

Table 14: Hardness, friability of glipizide press coated tablets for EC/PEG formulation

S. No.	Formulation code	Hardness (kg/cm^2)	Friability (%)
1	F1	4.8	0.56
2	F2	5.2	0.51
3	F3	5.4	0.54
4	F4	5.0	0.61
5	F5	4.9	0.55
6	F6	4.7	0.52
7	F7	4.7	0.54

Table 15: Hardness, friability of glipizide press coated tablets for EC/HEC formulation

S No.	Formulation code	Hardness (kg/cm^2)	Friability (%)
1	F8	5.6	0.48
2	F9	5.3	0.63
3	F10	5.4	0.57
4	F11	5.1	0.52
5	F12	4.9	0.51
6	F13	5.1	0.49
7	F14	4.6	0.46

Drug content uniformity

The prepared tablets containing glipizide was tested for drug content uniformity. Tablets were dissolved in 100 ml of methanol in 100 ml volumetric flask which was previously clean and dry. This solution after suitable dilution was measured for absorbance at 276 nm in a Jasco V530 UV visible spectrophotometer. The results were shown in table 16, 17.

Table 16: Drug content uniformity for glipizide tablets containing EC/PEG formulation in outer layer

S. No.	Formulation code	Amount of Glipizide Tablet	
		Amount in milligram	Amount in %
1	F1	9.98	99.8
2	F2	10.34	103.4
3	F3	10.26	102.6
4	F4	9.93	99.39
5	F5	10.16	101.6
6	F6	10.41	104.1
7	F7	10.07	100.7

Table 17: Drug content uniformity for glipizide tablets containing EC/HEC formulation in outer layer

S. No.	Formulation code	Amount of Glipizide per Tablet	
		Amount in milligram	Amount in %
1	F8	10.38	103.8
2	F9	10.14	101.4
3	F10	10.41	104.1
4	F11	9.93	99.3
5	F12	10.16	101.6
6	F13	10.28	102.8
7	F14	10.21	102.1

Chapter 9 Evaluation of Tablets

COMPATIBILITY STUDIES

Before formulation of a drug substance into a dosage form, it is essential that it should be chemically and physically characterized. Compatibility studies give the information needed to define the nature of the drug substances and provide a frame work for the drug combination with pharmaceutical excipients in the fabrication of a dosage form.

One of the requirements for the selection of suitable excipients or carrier for pharmaceutical formulation is its compatibility. Therefore in the present work, a study was carried out by using infrared spectrophotometer to find out if there is any possible chemical interaction between glipizide and the excipients.

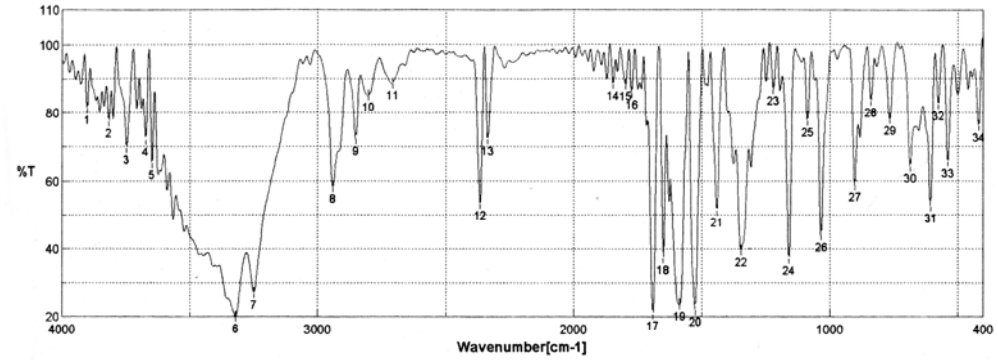
Weighed amount of drug (3 mg) was mixed with 100 mg of potassium bromide (dried at 40-50°C). The mixture was taken and compressed under 10-ton pressure in a hydraulic press to form a transparent pellet. The pellet was scanned from 4000-400cm^{-1} in IR spectrophotometer.

IR spectral analysis

Using Jasco-FT-IR 8201 PC spectrometer the compatibility studies between drug and excipients were carried out. The principal peaks were observed in the range of 1600-1000 cm^{-1}.

There was no appearance or disappearance of any characteristic peak, which confirms the absence of chemical interaction between drug and carrier. The IR spectra of glipizide time controlled release tablets were shown in fig. 4 - 10.

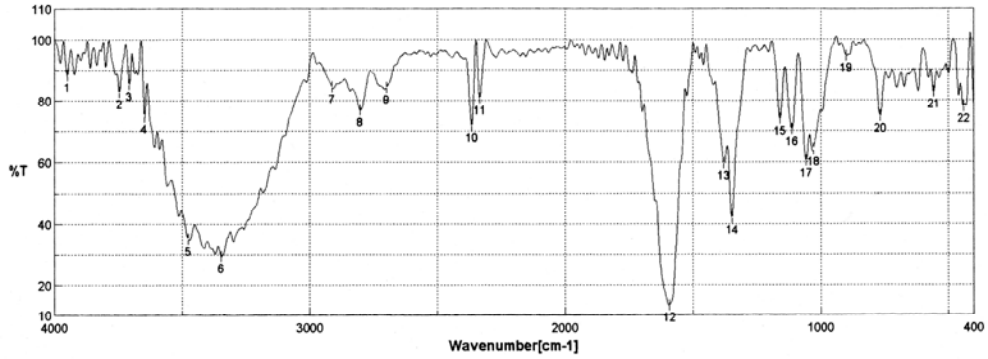
Fig. 4: IR spectra of glipizide



Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	4	Scanning Speed	2 mm/sec
Date/Time	11/5/2008 2:42PM	Update	12/18/2008 11:48AM
Operator	C.Geetha		
File Name	Glipizide(drug)		
Sample Name	Glipizide(drug)		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3901.29	81.4413	2	3818.36	77.5852	3	3747.01	69.8098	4	3672.77	72.0849	5	3648.66	65.2051
6	3321.78	20.1368	7	3250.43	27.1913	8	2940.91	58.2287	9	2853.17	72.2184	10	2803.03	85.2277
11	2709.5	88.7673	12	2366.23	53.1978	13	2336.34	72.2085	14	1846.51	88.4635	15	1797.33	88.3937
16	1774.19	85.9406	17	1690.3	21.011	18	1650.77	37.2879	19	1587.13	23.7881	20	1526.38	22.2245
21	1441.53	51.2098	22	1346.07	39.6791	23	1219.76	87.0149	24	1158.04	37.1835	25	1085.73	77.71
26	1032.69	43.8747	27	902.523	58.6972	28	839.847	83.6265	29	764.637	78.1547	30	685.57	64.2746
31	606.503	52.3812	32	576.612	82.5581	33	539.007	65.7254	34	418.477	76.154			

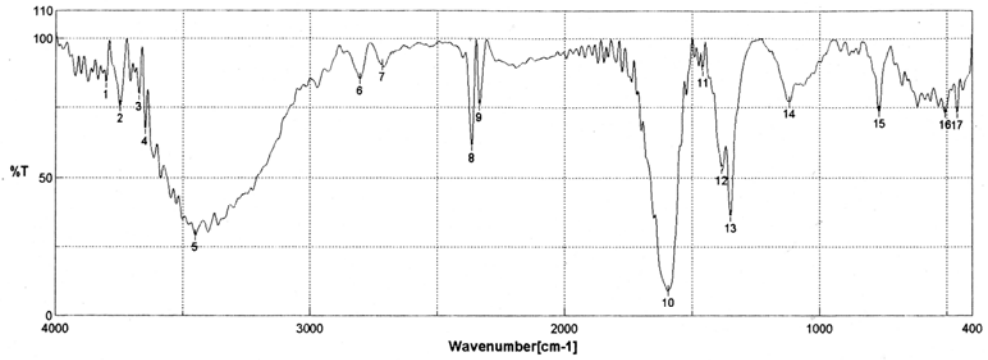
Fig. 5: IR spectra of microcrystalline cellulose



Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	11/5/2008 2:36PM	Update	12/18/2008 11:52AM
Operator	C.Geetha		
File Name	MCC		
Sample Name	MCC		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3949.5	88.3237	2	3745.08	82.8802	3	3707.48	85.4799	4	3647.7	74.728	5	3475.1	34.9964
6	3346.85	29.463	7	2913.91	84.5507	8	2803.03	76.9604	9	2700.82	84.2723	10	2366.23	71.9672
11	2335.37	80.8312	12	1592.91	13.3441	13	1378.85	59.7671	14	1347.03	42.0593	15	1159.01	73.8929
16	1111.76	70.6717	17	1056.8	60.3934	18	1027.87	64.1505	19	898.666	94.6486	20	764.637	74.9427
21	557.327	82.7622	22	440.655	77.9765									

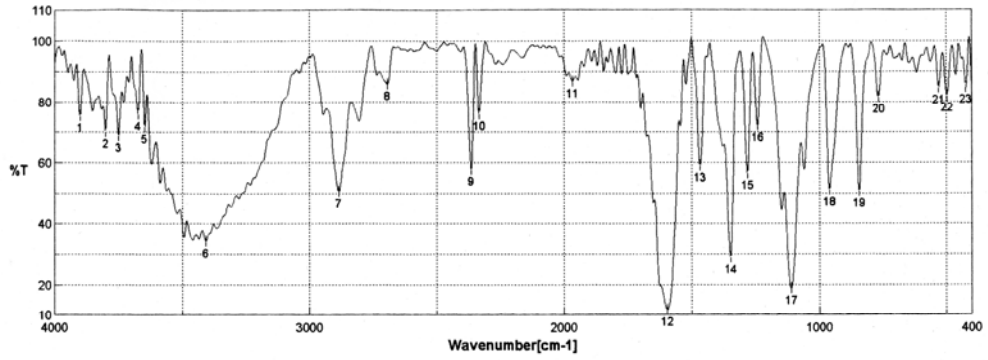
Fig. 6: IR spectra of ethylcellulose



Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	11/5/2008 2:38PM	Update	12/18/2008 11:13AM
Operator	C.Geetha		
File Name	EC		
Sample Name	EC		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3801.01	84.0996	2	3746.05	75.3767	3	3672.77	79.6059	4	3647.7	67.3247	5	3450.99	29.2568
6	2805.92	85.5915	7	2718.17	90.6021	8	2366.23	61.3505	9	2336.34	75.7811	10	1594.84	9.27843
11	1457.92	88.5063	12	1383.68	53.4102	13	1348	36.241	14	1119.48	77.0114	15	764.637	73.5986
16	506.223	73.1738	17	459.939	73.079									

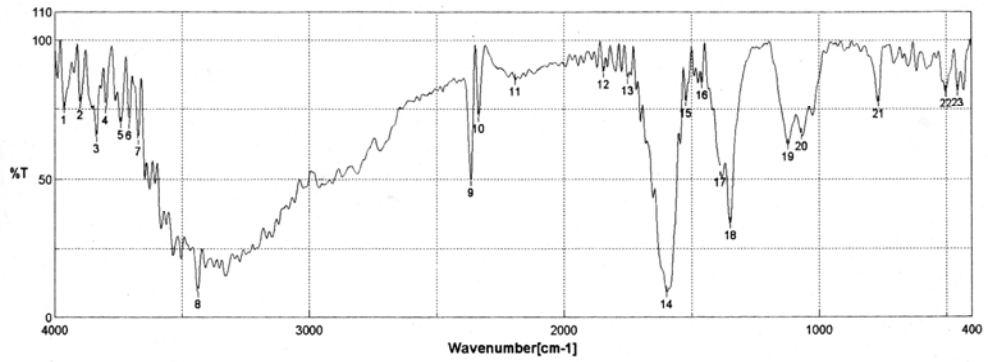
Fig. 7: IR spectra of polyethylene glycol 6000



Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	11/5/2008 2:40PM	Update	12/18/2008 11:54AM
Operator	C.Geetha		
File Name	PEG 6000		
Sample Name	PEG 6000		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3901.29	75.3594	2	3801.01	70.2839	3	3749.9	68.8808	4	3673.73	76.0006	5	3647.7	71.7602
6	3407.6	34.2875	7	2884.99	50.6628	8	2695.03	85.9572	9	2366.23	57.8074	10	2335.37	76.0544
11	1968	86.9293	12	1595.81	11.8505	13	1467.56	59.2211	14	1347.03	29.1008	15	1280.5	56.5246
16	1240	72.2355	17	1109.83	18.7923	18	959.412	51.1605	19	842.74	50.7943	20	765.601	81.7562
21	529.364	84.7059	22	497.544	82.153	23	423.298	84.7819						

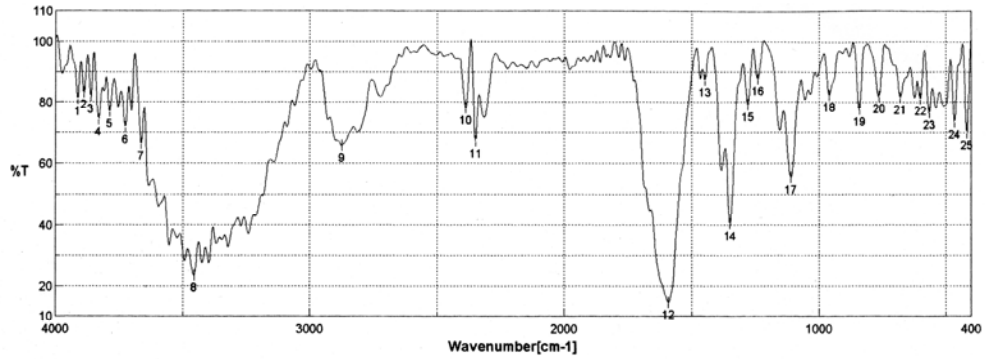
Fig. 8: IR spectra of hydroxyethyl cellulose



Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	16	Scanning Speed	2 mm/sec
Date/Time	11/5/2008 2:44PM	Update	12/18/2008 11:50AM
Operator	C.Geetha		
File Name	HEC		
Sample Name	HEC		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3963.96	75.3881	2	3900.32	77.2589	3	3836.68	65.2374	4	3800.04	75.3543	5	3742.19	70.2008
6	3709.41	69.9696	7	3672.77	64.2604	8	3439.42	9.31591	9	2366.23	49.5186	10	2336.34	72.4683
11	2192.67	85.8506	12	1846.51	88.4888	13	1750.08	86.1654	14	1597.73	9.38888	15	1522.52	77.9057
16	1459.85	84.4853	17	1387.53	53.2127	18	1348.96	34.0953	19	1120.44	62.4442	20	1067.41	65.9877
21	765.601	77.6483	22	502.366	81.4386	23	455.118	81.6973						

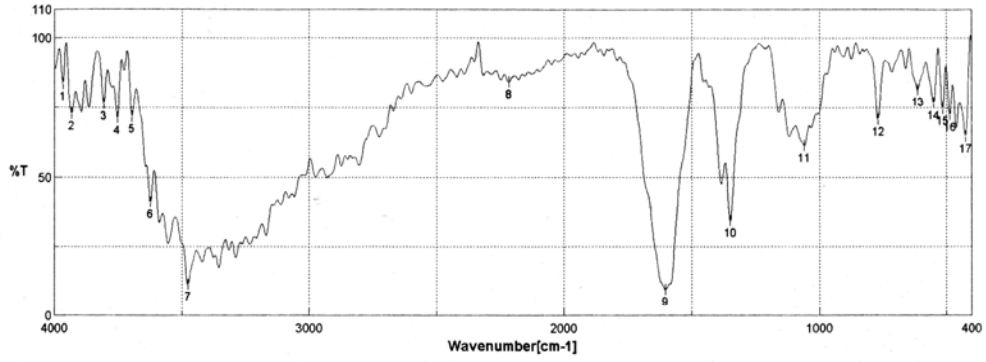
Fig. 9: IR spectra of formulation F4 (EC/PEG)



Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	16	Scanning Speed	2 mm/sec
Date/Time	11/6/2008 2:49PM	Update	12/18/2008 11:30AM
Operator	C.Geetha		
File Name	F4(EC,PEG)		
Sample Name	F4(EC,PEG)		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3913.82	81.0208	2	3888.75	83.1588	3	3862.72	81.6975	4	3830.9	74.3174	5	3787.51	76.9352
6	3725.8	71.7157	7	3663.12	66.356	8	3456.78	23.4518	9	2874.38	65.8497	10	2387.44	78.0169
11	2348.87	67.1962	12	1590.99	14.5351	13	1448.28	87.2805	14	1348	40.3581	15	1277.61	79.1089
16	1238.08	87.6023	17	1108.87	55.4753	18	959.412	82.1897	19	840.812	77.5688	20	763.673	81.8475
21	679.785	81.5982	22	600.717	81.2522	23	566.005	76.4789	24	466.689	73.3835	25	417.513	69.8718

Fig. 10: IR spectra of formulation F4 (EC/HEC)



Accumulation	40	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	16	Scanning Speed	2 mm/sec
Date/Time	11/6/2008 2:36PM	Update	12/18/2008 11:28AM
Operator	C.Geetha		
File Name	F4(EC,HEC)		
Sample Name	F4(EC,HEC)		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3966.86	83.5583	2	3933.11	72.8693	3	3807.76	78.3705	4	3754.73	71.3997	5	3696.87	71.8572
6	3623.59	41.1362	7	3477.03	11.3358	8	2218.7	84.3295	9	1602.56	9.56964	10	1348	34.3099
11	1058.73	61.4144	12	767.53	70.8169	13	613.252	81.5116	14	550.577	76.6895	15	515.865	74.559
16	486.938	72.4161	17	425.227	64.6399									

Chapter 9 Evaluation of Tablets

IN VITRO DISSOLUTION STUDIES[18,20,21]

The release of glipizide from the press-coated tablets was studied in 900 ml of dissolution medium using a USP dissolution paddle assembly (Lab India Disso 2000) instrument at 50 rpm and 37±0.5°C. The dissolution medium used were

I. Hydrochloric acid buffer (1.2 pH)

II. Phosphate buffer (pH 7.4)

Samples of dissolution medium were withdrawn at suitable time interval and was then determined spectrophotometrically at 276 nm for pH 7.4 and at 260 nm for pH 1.2. Cumulative percentage drug release was calculated using an equation obtained from the standard curve.

Percentage release of glipizide from press-coated tablets formulated by using different weight ratios of ethylcellulose with polyethylene glycol 6000 (PEG 6000) in the formulation of outer shell. The weight ratios of EC/PEG mixtures are 100%/0%; 80%/20%; 60%/40%; 50%/50%; 40%/60%; 20%/80%; 0%/100%.

Table 18: Dissolution profile of glipizide from formulation (F1)

Hours	Percentage Released	
	pH 1.2	pH 7.4
0 - 16	-	0
17	-	13
18	-	28.2
19	-	37.6
20	-	42.1
21	-	49.9
22	-	59.7

Table 19: Dissolution profile of glipizide from formulation (F2)

Hours	Percentage Released	
	pH 1.2	pH 7.4
0 - 14	-	0
15	-	13.9
16	-	29.86
17	-	40.4
18	-	45.8
19	-	54.8
20	-	62.5

Table 20: Dissolution profile of glipizide from formulation (F3)

Hours	Percentage Released	
	pH 1.2	pH 7.4
0 - 12	-	0
13	-	15.1
14	-	32.3
15	-	40.4
16	-	50.31
17	-	59.7
18	-	69.1

Table 21: Dissolution profile of glipizide from formulation (F4)

Hours	Percentage Released	
	pH 1.2	pH 7.4
0 - 10	-	0
11	-	16.3
12	-	35.5
13	-	44.1
14	-	57.6
15	-	70.3
16	-	78.1

Table 22: Dissolution profile of glipizide from formulation (F5)

Hours	Percentage Released	
	pH 1.2	pH 7.4
0 - 8	-	0
9	-	29.4
10	-	40.3
11	-	52.7
12	-	63.8
13	-	76.9
14	-	80.9

Table 23: Dissolution profile of glipizide from formulation (F6)

Hours	Percentage Released	
	pH 1.2	pH 7.4
0 - 6	-	0
7	-	34.3
8	-	44.5
9	-	59.3
10	-	72.8
11	-	80.1
12	-	86.7

Table 24: Dissolution profile of glipizide from formulation (F7)

Hours	Percentage Released	
	pH 1.2	pH 7.4
0 - 3	0	0
4	16.2	24.1
5	-	38.0
6	-	52.3
7	-	71.5
8	-	84.2
9	-	89.9
10	-	95.3

Fig. 11: Percentage of drug release of glipizide (pH 1.2) which contain EC/PEG in outer coating layer

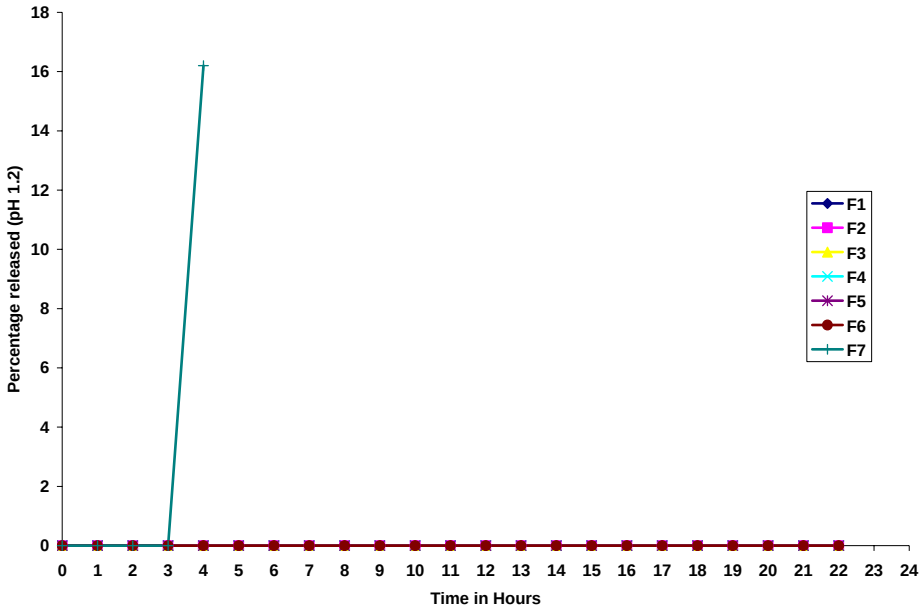
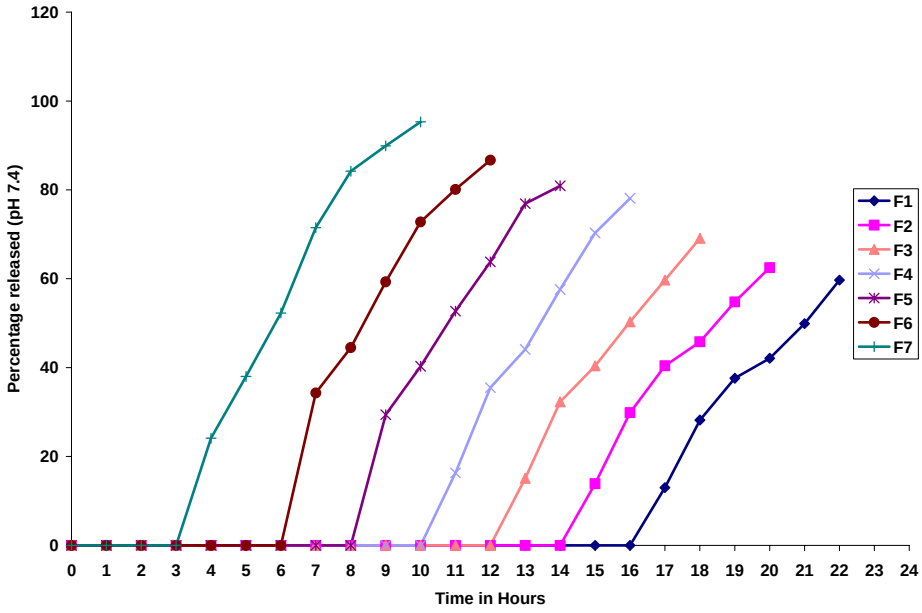


Fig. 12: Percentage of drug release of glipizide (pH 7.4) which contain EC/PEG in outer coating layer



Chapter 9 Evaluation of Tablets

Percentage release of Glipizide from press-coated tablets formulated by using different weight ratios of ethylcellulose with hydroxyethyl cellulose (HEC) in the formulation of outer shell. The weight ratios of EC/HEC mixtures are 100%/0%; 80%/20%; 60%/40%; 50%/50%; 40%/60%; 20%/80%; 0%/100%.

Table 25: Dissolution profile of glipizide from formulation (F8)

Hours	Percentage Released	
	pH 1.2	pH 7.4
0 - 17	-	0
18	-	15.9
19	-	31.0
20	-	39.2
21	-	47.7
22	-	56.4
23	-	62.1

Table 26: Dissolution profile of glipizide from formulation (F9)

Hours	Percentage Released	
	pH 1.2	pH 7.4
0 - 15	-	0
16	-	16.2
17	-	35.9
18	-	44.9
19	-	51.9
20	-	61.7
21	-	67.8

Table 27: Dissolution profile of glipizide from formulation (F10)

Hours	Percentage Released	
	pH 1.2	pH 7.4
0 - 12	-	0
13	-	28.1
14	-	38.7
15	-	52.2
16	-	61.7
17	-	72.3
18	-	81.8

Table 28: Dissolution profile of glipizide from formulation (F11)

Hours	Percentage Released	
	pH 1.2	pH 7.4
0 - 10	-	0
11	-	31.8
12	-	40.4
13	-	58.0
14	-	61.7
15	-	73.6
16	-	86.2

Table 29: Dissolution profile of glipizide from formulation (F12)

Hours	Percentage Released	
	pH 1.2	pH 7.4
0 - 7	-	0
8	-	37.6
9	-	48.2
10	-	61.2
11	-	67.0
12	-	82.9
13	-	90.3

Table 30: Dissolution profile of glipizide from formulation (F13)

Hours	Percentage Released	
	pH 1.2	pH 7.4
0 - 5	-	0
6	-	38.4
7	-	51.1
8	-	61.7
9	-	73.9
10	-	86.6
11	-	94.4

Table 31: Dissolution profile of glipizide from formulation (F14)

Hours	Percentage Released	
	pH 1.2	pH 7.4
0 - 3	0	0
4	16.0	40.0
5	-	54.3
6	-	76.0
7	-	88.7
8	-	89.9
9	-	98.1

Fig. 13: Percentage of drug release of glipizide (pH 1.2) which contain EC/HEC in outer coating layer

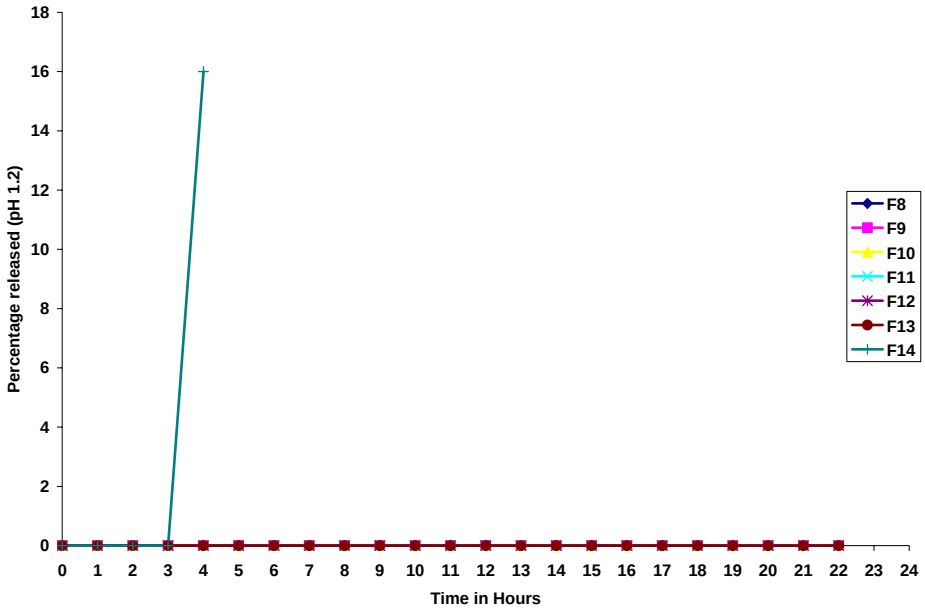
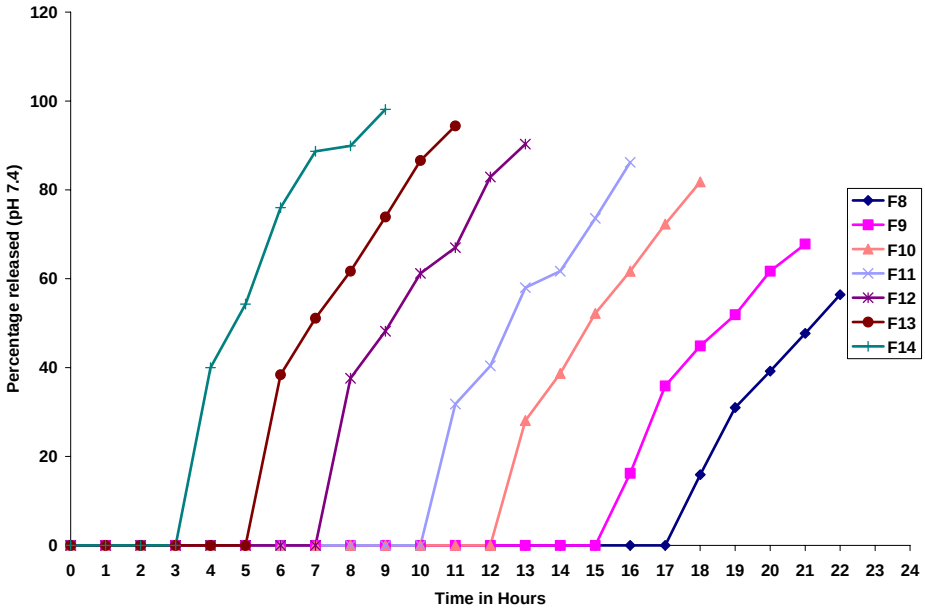


Fig. 14: Percentage of drug release of glipizide (pH 7.4) which contain EC/HEC in outer coating layer



Chapter 10 Dissolution Kinetics

DISSOLUTION KINETICS

Three categories of dissolution test specifications for drug products are described in the guidance. Single point specifications are recommended as a routine quality control test for highly soluble and rapidly dissolving drug products. This comparison method can be employed in evaluating scale-up and post-approval changes such as manufacturing site changes, component and composition changes, equipment changes and process changes. Two-point specifications are suggested for characterizing the quality of drug product and for accepting product sameness under SUPAC-related changes. In the presence of certain minor changes the single point dissolution test may be adequate to ensure unchanged product quality and performance. For more major changes a dissolution profile comparison performed under identical conditions for the product before and after the changes is recommended. Dissolution profiles may be considered similar by virtue of overall profile similarity and similarity at every dissolution sample time point.

Method used to compare dissolution data is:

- Model Dependent Methods (zero order, first order, Higuchi's, Korsmeyer's)

Chapter 10 Dissolution Kinetics

Drug Release Kinetics[43]

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted in various kinetic models: zero order (Equation 1) as cumulative amount of drug released vs. time, first order (Equation 2) as log cumulative percentage of drug remaining vs. time, and Higuchi's model (Equation 3) as cumulative percentage of drug released vs. square root of time.

$$C = K_0 t \qquad \text{(Equation 1)}$$

where K_0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours.

A graph of concentration vs. time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.

$$log_c = log\, C_0 - kt / 2.303 \qquad \text{(Equation 2)}$$

where C_0 is the initial concentration of drug,

k is the first order constant, and t is the time.

$$Q = Kt^{1/2} \qquad \text{(Equation 3)}$$

where K is the constant reflecting the design variables of the system

t is the time in hours.

Hence, drug release rate is proportional to the reciprocal of the square root of time.

Chapter 10 Dissolution Kinetics

Drug release were plotted in Korsmeyer et al., equation (Equation 4) as log cumulative percentage of drug released vs. log time, and the exponent n was calculated through the slope of the straight line.

$$M_t / M_\infty = Kt^n \qquad \text{(Equation 4)}$$

where M_t/M_∞ is the fractional solute release, t is the release time,

K is a kinetic constant

Table 32: Drug Release Kinetics for glipizide time controlled release tablets

Formulation	Zero Order R^2	First Order R^2	Higuchi's Plot R^2	Korsmeyer's Plot R^2
F1	0.774	0.774	0.683	0.578
F2	0.740	0.756	0.662	0.540
F3	0.699	0.725	0.626	0.507
F4	0.634	0.639	0.564	0.468
F5	0.782	0.774	0.736	0.652
F6	0.846	0.897	0.838	0.745
F7	0.962	0.936	0.985	0.923
F8	0.652	0.635	0.561	0.559
F9	0.779	0.718	0.708	0.769
F10	0.726	0.674	0.647	0.599
F11	0.745	0.705	0.675	0.617
F12	0.810	0.828	0.781	0.673
F13	0.845	0.897	0.860	0.722
F14	0.906	0.921	0.952	0.825

Chapter 11 Results & Discussion

RESULTS AND DISCUSSION

Based on the concept of chronotherapy (or) chronopharmacology, recent pharmaceutical investigations have focused on developing a site-or time controlled drug delivery system for the treatment of various diseases.

Site and/or time controlled release preparation is preferred when higher regional drug levels can be obtained as compared to those of other routes of administration. A resultant benefit is observed (or) eliminated side effects related to high systemic drug levels. These preparations enable us to predict and reproduce the drug absorption at the predetermined time and/or site. The press coating technique is one of the novel methods and has been applied for many drugs to develop the site – and /or time-controlled release preparation.

COMPATIBILITY STUDIES

The compatibility studies between the drugs and polymer were evaluated by using IR matching approach.

FT-IR SPECTRAL ANALYSIS

In IR studies, there was no appearance or disappearance of characteristics peaks in pure drug and drug excipient mixture. In glipizide IR spectrum, principal peaks were noticed at following wave numbers

1587, 1526, 1346, 1158, 1032 cm^{-1} (KBr pellet). The IR spectra obtained were given in fig. 4 to 10. This method confirms the absence of any chemical interaction between drug and polymer.

EVALUATION OF GLIPIZIDE TIME CONTROLLED RELEASE TABLETS

All the formulated glipizide time controlled release tablets (F1-F14) have fulfilled official requirements for weight variation and drug content uniformity (table 12, 13 and 16, 17), hardness of the tablets in all the batches were found to be in the range of 4.3 to 5.6 kg/cm^2 (table 14, 15) and was satisfactory. The percentage weight loss in the friability test was found to be less than 1% in all formulations (table 14, 15) were found to be good quality fulfilling the tablets.

DISSOLUTION STUDIES

Effect of hydrophilic excipients to modulate the time lag of drug release behavior

The dissolution profile of all the formulated glipizide time controlled release tablets were reported in table 18 - 31.

The press-coating technique is one of the novel methods and has been applied to design a time-controlled disintegrating press-coated tablet by using ethylcellulose as an outer coating shell. In this study we try to

modulate the time lag of drug released from this time-controlled disintegrating press-coated tablet by adding the hydrophilic polymer as excipient in the outer coated layer. It is well known that the additions of MCC in the inner core can improve the flow and bond prosperities of the excipients during direct compression. MCC acts as an disintegrating agent. PEG 6000 was mixed with EC to alter the time lag and time controlled disintegration of tablet and figure 11,12 shows the dissolution profiles of press–coated tablets prepared by using different weight ratios of EC and PEG 6000 in the outer shell. The profiles clearly indicate that the glipizide released from the press-coated tablet exhibited a unique release profile depending on the amount of PEG 6000 and EC used. The profile exhibited an induction period (time lag) followed by a rapid drug release phase. The drug was rapidly and completely released from the press-coated tablet after a lag period of several hours, depending upon the weight ratios of EC and PEG 6000. The formulation of tablet prepared by press-coating technique using EC as hydrophobic polymer without hydrophilic polymer exhibited a longer lag period of hours followed by faster drug release.

The sudden splitting of the outer shell of press-coated tablets into two halves after the lag period is a key factor to achieve the time-controlled delivery. The drug was immediately released from the core

tablet after rupturing, caused by the pressure build up with in the core system. Once PEG 6000 was added into the formulation of the outer shell. The time lag was shortened with the increase of the amount of PEG used. The order of the time lag changed according to weight ratios of the EC/PEG 6000 as follows:

F1 > F2 > F3 > F4 > F5 > F6 > F7

The dissolution profile of EC/HEC was also similar to that of the dissolution profile of EC/PEG 6000, showing a distinctive inducting lag followed by drug release. The time lag of the press coated tablet containing 0%, 20%, 40%, 50%, 60%, 80%, 100% of HEC was F8 > F9 > F10 > F11 > F12 > F13 > F14 respectively. It is evident that the time lag of press-coated tablet changes by varying the amount of EC and PEG 6000 or HEC in the outer shell.

DISSOLUTION KINETICS

In vitro data obtained for glipizide time controlled release tablets were used to determine the dissolution kinetics. The drug release data of glipizide were fitted to models representing zero order (cumulative amount of drug released vs. time), first order (log cumulative percentage of drug remaining vs. time), Higuchi's (cumulative percentage of drug released vs. square root of time), and Korsmeyer's equation (log cumulative percentage of drug released vs. log time) kinetics to know the release

mechanisms. The data were processed for regression analysis using MS-EXCEL statistical functions (table 32). In our study *in vitro* release profiles of drug from all the formulations could be best expressed by Higuchi's equation as the formulations showed highest linearity (R^2 0.985). This explains why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred to as square root kinetics (or Higuchi's Kinetics).

Chapter 12 Summary & Conclusion

SUMMARY AND CONCLUSION

Studies were under taken on the formulation of glipizide time controlled release tablets by press coating using hydrophilic polymers polyethylene glycol (PEG 6000) and hydroxyl ethyl cellulose (HEC) and hydrophobic polymer ethylcellulose. Here EC/PEG was used in the outer coating layer for E1 formulation and EC/HEC in outer coating layer for E2 formulation.

The order of dissolution of glipizide from E1 and E2 formulations

E1 (F1 > F2 > F3 > F4 > F5 > F6 > F7)

E2 (F8 > F9 > F10 > F11 > F12 > F13 > F14)

Chemical incompatibilities study confirmed that there is no interaction between drug and excipients in the formulation. The weight variations, drug content uniformity, hardness, friability of all the formulated tablets were within the specified requirements. Drug release kinetics confirmed that the glipizide time controlled release formulations were best expressed by Higuchi's equation.

In conclusion, the time lag of press-coated tablet could be modulated by choosing the type and amount of excipient used in the outer shell to achieve the time-controlled disintegration according to the time required The present study indicated that the time lag of the press-coated tablet can be suitably modulated by formulating the outer shell with ethyl cellulose and polyethylene glycol 6000 or hydroxyl ethyl cellulose.

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