1.1 INTRODUCTION TO DIABETES MELLITUS

Diabetes mellitus is a chronic disease that is characterized by disorders in carbohydrate, protein and lipid metabolism\(^1\). Its central disturbance appears to involve an abnormality either in the secretion of or effects produced by Insulin although other factors also may be involved. Diabetes mellitus is a metabolic disorder in which carbohydrate metabolism is reduced while that of proteins and lipids is increased\(^2\). The external secretion of the pancreas is digestive in function and the intestinal secretions play a major role in the regulation of metabolism. The hormones which regulate the level of blood sugar are mainly two; glucagon from the alpha-cells and Insulin from the β-cells of the islets of Langerhans\(^3\). Diabetes occurs in mainly two idiopathic forms, type 1 and type 2. Both type 1 and type 2 are at least partially inherited. India has the highest cases of diabetes in the world (32 million expected to increase to 78 million by 2030 according to WHO estimate) \(^4\). According to World Health Organization estimates, by 2025, over 350 million would be affected and over 75% of these diabetes cases will be in the developing world\(^5\). As India has no subsidized, coordinated diabetes care programs, reducing treatment costs through raising public awareness, regular monitoring and earlier diagnosis should be a key objective\(^6\).
Table 1.1: Complications of Diabetes Mellitus

<table>
<thead>
<tr>
<th>Body Location</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes</td>
<td>Retinopathy, cataract formation, glaucoma and periodic visual disturbances; leading cause of new blindness.</td>
</tr>
<tr>
<td>Mouth</td>
<td>Gingivitis, increased incidence of dental cavities and periodontal disease.</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Born of large babies, miscarriages, neonatal deaths and congenital defects.</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Motor, sensory and autonomic neuropathy leading to impotence, neurogenic bladder, parathesias, gangrene.</td>
</tr>
<tr>
<td>Vascular system</td>
<td>Large vessel disease and micro angiopathy.</td>
</tr>
<tr>
<td>Skin</td>
<td>Numerous infections and specific lesions due to small vessel disease, increased lipids in blood and pruritus.</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Diabetic glomerulosclerosis causing nephropathy.</td>
</tr>
<tr>
<td>Infections</td>
<td>Diabetics have a higher incidence of cystitis, tuberculosis and skin infections; moniliasis is common in diabetic women.</td>
</tr>
</tbody>
</table>

1.1.1 Types of Diabetes Mellitus

On the basis of etiology three main categories of diabetes are recognized, viz.

1. Primary diabetes
   
   (i) Type I (Insulin Dependent Diabetes Mellitus) (IDDM)
   
   (ii) Type II (Maturity onset Diabetes Mellitus)(Non-Insulin Dependent Diabetes Mellitus) (NIDDM)

2. Secondary diabetes

3. Gestationnel Diabetes Mellitus
1.1.2 Classification of Anti diabetic Drugs:  

Anti-diabetic drugs are classified as

- **Sulfonylureas:**
  - **First Generation Analogs**
    E.g., Tolbutamide, Chlorpropamide, Acetohexamide, Tolazamide
  - **Second Generation Analogs**
    E.g., Glibenclamide, Glipizide, Gliclazide

- **Biguanides:**
  E.g., Phenformin, Metformin

- **Miscellaneous:**
  E.g., Acarbose, Guargum

- **Other Hypoglycemic Agents:**
  Ciglitazone
  Pioglitazone
  Thiazolidinediones

1.2 INTRODUCTION TO CONTROLLED DRUG DELIVERY SYSTEMS

Controlled-release oral delivery systems have been an integral part of pharmaceutical technology for several decades. Within the pharmaceutical industry delivery systems and formulations have been developed which can provide a wide variety of drug release profiles, including systems designed for immediate, continuous, pulsatile and delayed administration. In recent years, much of the focus in oral controlled-release technology has been directed towards site-specific delivery in the GI tract, chronobiology as related to oral delivery systems and the development of technology to control the release and delivery of
non-traditional drug candidates, i.e. peptides and proteins. Included in these various technologies are osmotically controlled devices, matrix tablets, hydrogels, polymeric systems, multi particulates and erosion systems regulated by geometric design. In spite of the availability of numerous technologies to achieve up to 24 h controlled drug release, relatively few products that are efficacious for once-a-day dosing have reached the market. One of the problems associated with these products is poor colonic drug absorption that limits the once daily efficacy of dosage forms\textsuperscript{10}.

1.2.1 Advantages & Disadvantages of Oral Controlled Release Drug Delivery Systems:

The following advantages\textsuperscript{11} are offered by oral controlled release drug delivery systems

- Avoids patient compliance problems
- Minimize or eliminate local and systemic side effects
- Reduces dose frequency
- Reduces fluctuations in blood levels
- Improve bioavailability of drugs
- A smoother therapeutic response over the dose interval

The following disadvantages\textsuperscript{12} are observed with oral controlled release drug delivery systems.

- Administration of controlled release medication does not permit the prompt termination of therapy
• The physician has less flexibility in adjusting the dosage regimens
• Controlled release forms are designed for the normal population. So, Economic factors must also be assessed
• Patients may need additional information for the proper use of controlled release products
• Complexity of controlled release dosage forms may lead to stability problems

1.2.2 Drugs Which Are Unsuitable For Oral Controlled Release Drug Delivery Systems: 13-15

1. Long biological half-life > 12 h (E.g., Diazepam, Phenytoin)
2. Not effectively absorbed in the lower intestine (E.g., Riboflavin)
3. Absorbed and excreted rapidly; short biological half-life < 1 h (E.g., Penicillin G, Furosemide)
4. Large doses required (E.g., Sulfonamides).
5. Drugs with low therapeutic index (E.g., Phenobarbital, Digoxin).
6. Precise dosage to individuals is required (E.g., Anti-coagulants, cardiac glycosides)
7. No clear advantage for sustained release formulation (E.g., Griseoflavin).
1.2.3 Approaches to Achieve Controlled Release Drug Delivery

In general, controlled release formulations can be divided into different categories based on the mechanism of drug release\textsuperscript{16}

1. Dissolution controlled release
   (a) Matrix dissolution control
   (b) Reservoir dissolution control

2. Diffusion controlled release
   (a) Matrix diffusion control
   (b) Reservoir diffusion control

3. Osmotic controlled release

4. Ion exchange resins

5. Gastroretentive systems

6. pH regulated systems

Fig 1.1: A hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations.
1.3 INTRODUCTION TO ORAL MATRIX TABLETS

A matrix system consists of active and inactive ingredients, which are homogeneously dispersed and mixed in the dosage form. It is by far the most commonly used oral controlled release technology and the popularity of the matrix systems can be attributed to several factors which will be discussed in the later section. The release from matrix type formulations governed by Fick’s first law of diffusion\(^{17}\) and shown in eq.1

\[
J = \frac{dQt}{dt} = -\frac{D}{dx} dC \quad \text{................................. (1)}
\]

Where \(J\) is flux, or rate of diffusion, while \(Q\) is the amount diffused per unit of time \(t\), and \(D\) is diffusion coefficient.

1.3.1 Hydrophobic Matrix System

The polymers used in hydrophobic matrix are water insoluble in nature. These ingredients include waxes, glycerides, fatty acids and polymeric materials such as ethyl cellulose, methyl cellulose and acrylate
copolymers\textsuperscript{18}. Soluble ingredients such as lactose incorporated into formulation to modulate drug release. The presence of insoluble ingredient in the formulations helps to maintain the physical dimension of hydrophobic matrix during drug release. Hydrophobic matrix systems generally are not suitable for insoluble drug because the concentration gradient is too low to render adequate drug release. As such, depending on actual ingredient properties or formulation design, incomplete drug release within the gastrointestinal transit time is a potential risk and need to be delineated during the development.

1.3.2 Hydrophilic Matrix System

The hydrophilic matrix polymers swell on contact with aqueous solution and form a gel layer on the surface of the system. When the release medium (i.e. water) is thermodynamically compatible with a polymer, the solvent penetrates into the free spaces between macromolecular chains. The polymer may undergo a relaxation process, due to the stress of the penetrated solvent, so that the polymer chains become more flexible and the matrix swells. This allows the encapsulated drug to diffuse more rapidly out of the matrix\textsuperscript{19}. On the other hand, it would take more time for drug to diffuse out of the matrix since the diffusion path is lengthened by matrix swelling. Moreover, it has been widely known that swelling and diffusion are not the only factors that determine the rate of drug release. For dissolvable polymer matrix, polymer dissolution is another important mechanism that can modulate the drug delivery rate. While either swelling or dissolution can
be the predominant factor for a specific type of polymers, in most cases drug release kinetics is a result of a combination of these two mechanisms. The penetrant concentration gradient, polymer concentration gradient and osmotic force behavior are observed as a result of polymer network. Appropriate polymer can counterbalance normal Fickian diffusion by hindering the release of embedded drug, leading to an extended period of drug delivery, and possibly zero-order release. Regarding the mechanism of release, the results showed that in most cases the drug release was controlled by both diffusion and erosion depending on the polymer type and concentration. On the other hand, incorporation of water soluble fillers like polyethylene glycol, lactose and surfactant into gel forming matrices can improve phenomenon of insufficient drug release, because these excipients can enhance the penetration of the solvent or water into the inner part of matrices, resulting in drug release from the matrices.20

1.3.3 Advantages of Oral Matrix Tablets

- Matrix design can be manufactured using conventional processes and equipments
- The development cost and time associated with the matrix systems generally less and no additional capital investment is required.
- A matrix system is capable of accommodating both low and high drug loading and active ingredients with a wide range of physical and chemical properties.
1.3.4 Limitations of The Matrix tablets

- Lack flexibility in adjusting to constantly changing dosage levels as required by clinical studies.
- For some products that require unique release profiles (dual release or delayed plus extended release), more complex matrix-based technologies such as layered tablets are required.
- Dose dumping (problem only in case of membrane controlled tablet systems)
- Increased potential for hepatic first-pass metabolism (problems only in case of drugs that degrade by first pass metabolism).

1.4 INTRODUCTION TO TRANSDERMAL DRUG DELIVERY SYSTEM:

These are topically applied medicated patches which delivers the drug(s) in to systemic circulation at a predetermined and controlled rate. A drug is kept in a relatively high dosage inside of a patch, which is allowed to stick to skin surface for a specified period. The drugs enter in to systemic circulation by diffusion mechanism. The high concentration of drug in the patch and low in the blood makes the drug to diffuse into the blood for an extended period of time and maintains constant drug concentration in the blood. This technique has many advantages than traditional methods. Compared to the oral route, transdermal drug delivery is devoid of GI absorption, enzymatic/pH associated deactivation and reduced pharmacological dosing due to the shortened metabolisation pathway compared to oral route. Transdermal
therapy is multi-day therapy with a single application and the therapy can be terminated simply by removing the patch\textsuperscript{24}.

1.4.1 Advantages & Disadvantages of Transdermal Drug Delivery Systems:

The following advantages\textsuperscript{25} are offered by transdermal patches.

- Convenient to apply
- Continuous delivery
- Increasing patient compliance
- Improving tolerability and dosing
- The steady permeation of drug across the skin allows for more consistent serum drug levels, often a goal of therapy
- The lack of peaks in plasma concentration can reduce the risk of side effects
- Drugs that require relatively consistent plasma levels are very good candidates for transdermal drug delivery
- If toxicity develops from a drug administered by transdermal route, the effects could be terminated by removing the patch
- Transdermal drug delivery can be used as an alternative route of administration to accommodate patients who cannot tolerate oral dosage forms
- It is of great advantage in patients who are nauseated or unconscious
- Drugs that cause gastrointestinal upset can be good candidates for transdermal delivery because this method avoids direct effects on the stomach and intestine
- Drugs that are degraded by the enzymes and acids in the gastrointestinal system may also be good targets
• First pass metabolism, an additional limitation to oral drug delivery, can be avoided with transdermal administration

The following disadvantages\textsuperscript{26} of transdermal patches.

• Erythema, edema or local irritation can be caused by the drug/adhesive/excipients used in the patch formulation

• Many drugs with a hydrophilic structure permeate the skin too slowly to be of therapeutic benefit. Drugs with a lipophilic character, however, are better suited for transdermal delivery

• A stable concentration gradient to be maintained in the mechanism of dosage form to get constant drug levels in blood

• Some transdermal patches contain more amounts of drug that will be slowly absorbed during its use. Thus, after removal, these patches contain sufficient quantity (>90\%) of the total amount of drug initially in the patch. So, chances of drug wastage

• Any damage to a transdermal patch (membrane/reservoir) can result in poor control over the drug release. So, patients should be directed to remove the patch if any damage to the outer packaging/patch.

\textbf{Areas where transdermal patches should be applied:}

• Transdermal patches to be applied to appropriate skin areas, such as the upper arm or chest and behind the ear.

• It should be applied to shaved skin (if hairs present at the site of application)
- It should not be applied areas, such as skin folds, scars and calluses, or any irritated or damaged skin areas because it may cause uneven absorption.

- It should not be applied below the elbow or knee.

1.4.2 The Components of Transdermal Drug Delivery Systems

The basic components in transdermal devices are: 27

1. The Polymer
2. Active Pharmaceutical Ingredient (The drug)
3. Permeation enhancers
4. Excipients

1. The Polymer 28, 29

Table 1.2: Polymers used in Transdermal Drug Delivery Systems

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Type of System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl Cellulose T-50</td>
<td>Matrix</td>
</tr>
<tr>
<td>HPMC</td>
<td>Gel</td>
</tr>
<tr>
<td>Eudragit</td>
<td>Matrix</td>
</tr>
<tr>
<td>MDX-4-421 (a silicone)</td>
<td>Matrix</td>
</tr>
<tr>
<td>Carboxyl Vinyl polymer</td>
<td>Gel</td>
</tr>
<tr>
<td>Acrylic PSA emulsion</td>
<td>Drug-in-adhesive</td>
</tr>
<tr>
<td>CoTran9722</td>
<td>Drug-in-adhesive</td>
</tr>
<tr>
<td>Soybean lecithin (Epikuron 200)</td>
<td>Gel matrices</td>
</tr>
<tr>
<td>Cariflex TR-1107</td>
<td>Drug-in-adhesive</td>
</tr>
<tr>
<td>Acrylic adhesives</td>
<td>Drug-in-adhesive</td>
</tr>
<tr>
<td>Silicone PSA</td>
<td>Drug-in-adhesive</td>
</tr>
<tr>
<td>Silicone Oil</td>
<td>Reservoir</td>
</tr>
<tr>
<td>EVA</td>
<td>membrane</td>
</tr>
<tr>
<td>2-Ethylhexyl acrylate</td>
<td>Drug-in-adhesive</td>
</tr>
<tr>
<td>Acrylic acid copolymer</td>
<td>Drug-in-adhesive</td>
</tr>
<tr>
<td>HEMA, Styrene and N-vinyl pyrrolidone copolymer for membrane</td>
<td>Drug-in-adhesive</td>
</tr>
<tr>
<td>HPMC (Methocel K4M)</td>
<td>Matrix</td>
</tr>
<tr>
<td>Urecryl MC 808</td>
<td>Matrix</td>
</tr>
<tr>
<td>MDX4-4210 silicone elastomer</td>
<td>Matrix</td>
</tr>
<tr>
<td>Acrylate copolymer (Gelva-737)</td>
<td>Matrix</td>
</tr>
<tr>
<td>Silicon-2920 and 2675</td>
<td>Matrix</td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------</td>
</tr>
<tr>
<td>2-Ethylhexyl acrylate and acrylic acid copolymer</td>
<td>Drug-in-adhesive</td>
</tr>
<tr>
<td>2-Ethylhexyl acrylate and acrylamide copolymer</td>
<td>Drug-in-adhesive</td>
</tr>
<tr>
<td>Polyvinyl alcohol (backing), HPMC (matrix), Ethylene vinyl acetate (rate-controlling membrane)</td>
<td>Membrane controlled reservoir system</td>
</tr>
</tbody>
</table>

**2. Active Pharmaceutical Ingredient:**

The selection of drug in transdermal drug delivery system is very important for successful development of transdermal patch. The drugs which are used in transdermal delivery should have the following properties 30.

- The molecular weight of the drug should be less than 1000 daltons.
- The drug should be amphiphilic. But, high degree of partitioning behavior doesn’t help for the drug delivery through the skin.
- The drug should melt at lesser temperatures.
- Along with these properties the drug should be non-irritant, potent, and have short half-life.

**3. Permeation Enhancers:**

These promote drug permeability through skin by altering the skin surface.

These can be classified as follows: 31-33

**i) Solvents**

Solvents increase penetration perhaps by engulfing the polar pathway or by fluidizing lipids. E.g., Water, Methanol, Ethanol, Glycerol, propylene
glycol, Dimethyl sulfoxide, Dimethyl formamide, Pyrrolidones, silicone fluids and isopropyl palmitate etc.

ii) Surfactants

They enhance the polar pathway transport for hydrophilic drugs.

*Anionic Surfactants:* e.g., Sodium lauryl sulphate, Decodecylmethyl sulphoxide and Dioctyl sulphosuccinate, etc.

*Nonionic Surfactants:* e.g., Sodium taurocholate, Sodium deoxycholate, Sodium tauroglycocholate (bile salts), Pluronic F68 and Pluronic F127 etc.

iii) Miscellaneous

E.g., N, N-dimethyl-m-toluamide, di-o-methyl-ß-cyclodextrin, Calcium thioglycolate, Eucalyptol, soyabean casein and Urea

4. Excipients

i) Adhesives:

The pressure sensitive adhesive is required for positioning of the device on skin. The adhesive systems should fulfill the following requirements/parameters.

- Should adhere forcefully to the skin
- Can be removed easily
- Should not forbid any residue on the skin surface
- Should not stimulate the discomfort
• Should not affect the drug permeation

**ii) Backing membrane:**

They are flexible and firmly bind to the back of patch to prevent drug leaving from the patch and ease of printing on the surface of the path. E.g., metal, plastic and aluminium foil etc.

### 1.4.3 Types of Transdermal Patches

Four Major Transdermal Systems \(^{34-36}\)

**Single-layer Drug-in-Adhesive**

**Fig 1.3 Single-layer Drug-in-Adhesive transdermal patch**

This kind of patches contains the drug and skin adhesive together. In transdermal system, the adhesive serves to affix the patch to the skin and formulating foundation, containing the drug and excipients. The release rate of drug from this system is by diffusion mechanism across the skin. Single-layer Drug-in-Adhesive transdermal patch was shown in Fig 1.3.

The rate of drug release from single-layer Drug-in-Adhesive transdermal patch can be defined by eq.2.

\[
\frac{Cr}{dQ/dT} = \frac{1}{P_m + 1/P_a}
\]

Where,

\(Cr\) = drug concentration in the reservoir compartment

\(Pa\) = Permeability coefficient of the adhesive layer
**Pm** = Permeability coefficient of the rate controlling membrane

\[ Pm = \text{the sum of permeability coefficients across the pores and the polymeric material, which can be defined by eq.3 and 4.} \]

\[
Pm = \frac{Km/r \cdot Dm}{hm}..........................(3)
\]

\[
Pa = \frac{Ka/m \cdot Da}{ha}..........................(4)
\]

Where,

- \(Km/r\) = Partition coefficients of the drug in the reservoir and the membrane
- \(Ka/m\) = Partition coefficients of the drug from the membrane to adhesive
- \(Dm\) = Diffusion coefficients in the rate controlling membrane
- \(Da\) = Diffusion coefficients in the adhesive layer
- \(hm\) = Thicknesses of the rate controlling membrane
- \(ha\) = Thicknesses of the adhesive layer.

**Multi-layer Drug-in-Adhesive**

**Fig 1.4 Multi-layer Drug-in-Adhesive transdermal patch**

In this the multi-layer consists of a membrane between two layers of drug-in-adhesive layers with a single backing film. Multi-layer Drug-in-Adhesive transdermal patch was shown in Fig 1.4.
The rate of drug release from these patches can be defined by eq.5.

\[
\frac{dQ}{dt} = \frac{\frac{K_a}{r} \cdot D_a \cdot Cr}{ha} \quad \ldots \quad (5)
\]

Where,

\( K_{a/r} \) = Partition coefficient of the drug in the reservoir layer and the adhesive layer

**Liquid Reservoir**

**Fig 1.5 Liquid Reservoir type transdermal patch**

These patches were characterized by the inclusion of a drug solution/suspension and separated by a membrane and adhesive. The Liquid Reservoir type transdermal patch was shown in Fig 1.5.

The rate of drug release from drug reservoir type controlled system can be expressed as eq.6.

\[
\frac{dQ}{dt} = \frac{\frac{K_a}{r} \cdot D_a \cdot A(\text{ha})}{ha(t)} \quad \ldots \quad (6)
\]

**Matrix**

**Fig 1.6 Matrix type transdermal patch**

These patches consist of a semi solid matrix with a drug solution/suspension which is in contact with the release liner. On top of
the drug reservoir it consists of adhesive and backing layer respectively. The Matrix type transdermal patch was shown in Fig 1.6.

The rate of drug release from these patches can be defined as eq.7.

\[
\frac{dQ}{dt} = \frac{ACp \cdot Dp}{2t} \quad \frac{1}{2}
\]

Where,

\( A = \) Initial drug loading dose

\( C_p = \) Solubility of the drug in the polymer

\( D_p = \) Diffusivity of the drug in the polymer

1.4.4 Transdermal Permeation

The drug permeation through skin is majorly by Fick’s First Law of Diffusion\(^{37}\) given as eq.8. (Skin can be considered a membrane)

\[
m = D \cdot k \cdot A \cdot (C_s - C_b) \cdot t \cdot d
\]

Where,

\( m = \) Mass of drug diffusing in time ‘t’

\( D = \) Drug’s diffusion coefficient

\( K = \) Partition coefficient (SC and Sebum)

\( A = \) Area for absorption through skin thickness ‘d’

\( C_s = \) Concentration of drug in sebum

\( C_b = \) Concentration of drug in systemic circulation

### Table 1.3: Marketed transdermal patches\(^{38-40}\)

<table>
<thead>
<tr>
<th>Product name</th>
<th>Drug</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alora</td>
<td>Estradiol</td>
<td>TheraTech/Proctol and Gamble</td>
</tr>
<tr>
<td>Product</td>
<td>Active Ingredient</td>
<td>Manufacturer/Partner</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------------</td>
<td>-----------------------------------------------------------</td>
</tr>
<tr>
<td>Androderm</td>
<td>Testosterone</td>
<td>TheraTech/GlaxoSmithKline</td>
</tr>
<tr>
<td>Catapres-TTS</td>
<td>Clonidine</td>
<td>Alza/Boehinger Ingelheim</td>
</tr>
<tr>
<td>Climaderm</td>
<td>Estradiol</td>
<td>Ethical Holdings/Wyeth-Ayerest</td>
</tr>
<tr>
<td>Climara</td>
<td>Estradiol</td>
<td>3M Pharmaceuticals/Berlex Labs</td>
</tr>
<tr>
<td>CombiPatch</td>
<td>Estradiol/Norethindrone</td>
<td>Noven, Inc./Aventis</td>
</tr>
<tr>
<td>Deponit</td>
<td>Nitroglycerin</td>
<td>Schwarz-Pharma</td>
</tr>
<tr>
<td>Duragesic</td>
<td>Fentanyl</td>
<td>Alza/Janssen Pharmaceutica</td>
</tr>
<tr>
<td>Estraderm</td>
<td>Estradiol</td>
<td>Alza/Norvatis</td>
</tr>
<tr>
<td>Fematrix</td>
<td>Estrogen</td>
<td>Ethical Holdings/Solvay Healthcare Ltd.</td>
</tr>
<tr>
<td>FemPatch</td>
<td>Estradiol</td>
<td>Parke-Davis</td>
</tr>
<tr>
<td>Habitraol</td>
<td>Nicotine</td>
<td>Novartis</td>
</tr>
<tr>
<td>Minitrans</td>
<td>Nitroglycerin</td>
<td>3M Pharmaceuticals</td>
</tr>
<tr>
<td>Nicoderm</td>
<td>Nicotine</td>
<td>Alza/GlaxoSmithKline</td>
</tr>
<tr>
<td>Nicotrol</td>
<td>Nicotine</td>
<td>Cygnus Inc, Ltd.</td>
</tr>
<tr>
<td>Nitrodisc</td>
<td>Nitroglycerin</td>
<td>Roberts Pharmaceuticals</td>
</tr>
<tr>
<td>Nitro-dur</td>
<td>Nitroglycerin</td>
<td>Key Pharmaceuticals</td>
</tr>
<tr>
<td>Nuvelle TS</td>
<td>Estrogen/Progesterone</td>
<td>Ethical Holdings/Schering</td>
</tr>
<tr>
<td>Ortho-Evra</td>
<td>Norelgestromin/estradiol</td>
<td>Ortho-McNeil Pharmaceuticals</td>
</tr>
<tr>
<td>Prostep</td>
<td>Nicotine</td>
<td>Elan Corp./Lederle Labs</td>
</tr>
<tr>
<td>Testoderm TTS</td>
<td>Testosterone</td>
<td>Alza</td>
</tr>
<tr>
<td>Transderm Scop</td>
<td>Scopolamine</td>
<td>Alza/Norvatis</td>
</tr>
<tr>
<td>Transderm Nitro</td>
<td>Nitroglycerin</td>
<td>Alza/Norvatis</td>
</tr>
<tr>
<td>Vivelle</td>
<td>Estradiol</td>
<td>Noven Pharmaceuticals/Norvatis</td>
</tr>
</tbody>
</table>

1.5 Objectives of the Study

1.5.1 Objective of Matrix Tablets
Increased complications and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release (SR), or controlled release (CR) drug delivery systems. Matrix system is the most widely used method in the development of controlled release formulations. This technique prolongs and controls the release of drug that is dissolved or dispersed. The objectives of matrix tablets are as follows

- Pre formulation studies for Drug – Excipients Compatibility.
- Preparation of standard curve for Glipizide and Glimepiride.
- Preparation of various matrix tablets using *Aloe barbadensis miller* leaves mucilage, Guar gum and Povidone- K-30 as polymers in different concentrations.
- Evaluation of matrix tablets by following parameters:
  - General appearance
  - Thickness and diameter
  - Weight variation test
  - Hardness test
  - Friability test
  - Drug Content uniformity test
  - Swelling index of the tablets
  - *In-vitro* Tablet Dissolution studies
  - Comparison of Dissolution Characteristics of optimized formulated matrix tablet with Market tablets
  - *In-vivo* drug absorption studies
  - Accelerated Stability studies of optimized matrix tablets
The results are presented in tables and graphically by using various equations governing release kinetics. The objectives of matrix transdermal patches are as follows

**1.5.2 Objective of Transdermal Patches**

Transdermal route has advantage because of they have increasing patient compliance and free from first pass metabolism. The transdermal route furnishes both controlled and sustained delivery. Technological discoveries, over the past years, have proved the feasibility of using several methods for enhancing transdermal absorption, with this the future of transdermal drug delivery looks glossy. These discoveries are useful in the discovery of newer excipients and technologies. The objectives of matrix transdermal patches are as follows

- Pre formulation studies for Drug – Excipients Compatibility
- Preparation of standard curve for Glipizide and Glimepiride
- Preparation of various Trans dermal patches using *Ficus bengalensis*, *Ficus carica*, *Ficus glomerata* fruit mucilage and Povidone K-30 as polymers in different concentrations
- Evaluation of transdermal patches by following parameters:
  - Thickness determination
  - Uniformity of weight
  - Moisture content
  - Flatness and elongation brake
  - Moisture uptake
  - Determination of tensile strength
Drug content determination of film
- Skin irritation tests.
- *In-vitro* Skin permeation test
- *In-vivo* evaluation
- Accelerated stability studies

The results are presented in tables and graphically by using various equations governing release kinetics.

### 2.1 DRUG PROFILE

#### 2.1.1 Drug Profile of Glipizide 41-42

Glipizide contains not less than 98.0 per cent and not more than the equivalent of 102.0 per cent of 1-cyclohexyl-3-[4-][2-(5-methylpyrazine-2-carboxamido) ethyl] benzene sulphonyl] urea, calculated with reference to the dried substance.

**Name:** Glipizide

**Synonym:** Glydiazinamide

**Nomenclature:**

\[1\text{-cyclohexyl}-3\text{-}[4\text{-}[2\text{-}(5\text{-methylpyrazine-2-carboxamido)} \text{ethyl}] \text{benzene sulphonyl}] \text{urea}\]

**Standards:**

Glipizide contains not less than 98.0 per cent and not more than the equivalent of 102.0 % on dry basis.

**Molecular Weight:**

445.5 g/mol

**Molecular Formula:**

\(C_{21}H_{27}N_{5}O_{4}S\)

**Structural Formula:**