1.1 CONTROLLED DRUG DELIVERY SYSTEM

1.1.1 Introduction

Parenteral route is the preferred route of administration for moderate to severe complication, even though patients compliance are rather low for this mode of drug delivery as it is invasive drug delivery technique, requiring frequent pricking with needle.

All conventional dosage form except intravenous infusion, follow second-order kinetics. Dosage form releases drug initially at faster rate, leading to quick rise in blood level of drug and then falls exponentially until a further dose is administered. This results in peak and valleys pattern of drug concentration in blood and tissues. Thus, for most of the time the concentration of drugs either above the required therapeutic level or below it. The time course of various modes of administration is represented in figure 1.1.1.

It is evident that the quality of the rate of absorption and the rates of metabolic elimination would result on the equilibrium distribution of the drug in tissues and blood, but however missing in the case of conventional dosage forms. This factor as well as some other factors such as repetitive dosing and unpredictable absorption, led to the concept of drug delivery system or the therapeutic system.

Drug delivery system may be a controlled release drug delivery system where there is predictive control over the release pattern, and subsequent tissue or blood levels can be achieved. From figure 1.1.1, it is observed that the equality of the rate of absorption and the rate of metabolism is only in the case of rectal drug delivery system.
Figure 1.1.1: Time course of various modes of administration

(1) Conventional single administration
(2) Multiple administrations
(3) Sustained release administration
(4) Controlled drug delivery administration

Administration of drug in conventional dosage form requires large dose, frequent administration and lacks extended duration, with chances of toxicity. While in controlled drug delivery devices there is efficient utilization of drug, desired extended duration, with very low chances of toxicity, facilitating enhanced complication of patient, leading to better management of therapeutics. The efficacious use of drug influences cost factor and economy of therapy too.
It seems that the controlled delivery should be the goal for all products and now a day’s drug firms have been allocating large resources on the reformulation of older, existing drugs, in sustained and controlled drug delivery often resulting in special economic gains.

1.1.2 Types of controlled release preparation

On the basis of technical sophistication, controlled drug delivery system can be categorized into 3 major classes.

A. Rate programmed drug delivery system

These drug delivery system are those from which the drug release has been programmed at specific rate profiles. They are further subdivided into following subclasses.

1. Dissolution drug delivery system
   - Slow dissolution rate of the drug
   - Slow dissolution rate of the reservoir membrane or matrix

2. Diffusion drug delivery system
   - Porous matrix controlled system
   - Porous membrane controlled systems

3. Erosion drug delivery system
   - Surface erosion
   - Bulk erosion

4. Dissolution, Diffusion and/or Erosion drug delivery system
   - Reservoir system (membrane Rectal drug delivery system)
   - Matrix system (monolithic drug delivery system)
   - Hybrid systems (membrane cum matrix drug delivery system)

B. Stimuli activated drug delivery system

1. Activation by physical process
2. Activation by chemical process
3. Activation by biological system
C. Site targeted drug delivery system
1. Polymeric carriers for drug targeting
2. Albumin as carrier for drug targeting
3. Lipoprotein as carrier for drug targeting
4. Liposomes as carrier for drug targeting

1.1.3 Drug release mechanisms
Most of the design of controlled release dosage form employs polymers for controlling the drug release. There are three fundamental mechanisms by which polymers release drugs.¹⁴
(1) Diffusion e.g. Reservoir type systems
□ Microcapsules
□ Matrix/laminates

(2) Chemical reaction
Water or enzyme causes degradation of a polymer which is used to encapsulate a drug.
□ Erodible
□ Degradable systems
□ Pendant chain systems

(3) Solvent activated
In this case drug is entrapped in the polymer until either external systems solvent swells the polymer or water imbibement creates osmotic pressure.

1.2 RECTAL DRUG DELIVERY SYSTEM
1.2.1 Introduction
Conventional systems of medication that require multi dose therapy are having many problems. The controlled drug delivery is a newer approach is to deliver drug in to systemic circulation at a predetermined rate. Our system should duplicate continuous intravenous infusion, which not only by passes hepatic ‘first pass’ elimination but also maintains a constant, prolonged and therapeutically effective drug level in the body. This is made possible by using intact skin as a port of drug administration to provide continuous delivery of drug in to systemic circulation. Following skin permeation, the drugs first reach the systemic circulation. The drug molecules are then transported to
the target site, which could be relatively remote from the site of administration, to produce therapeutic action.

Rectal drug delivery offers the following potential advantages $^{15,16,17}$

1. Avoid the risks and inconveniences of intravenous therapy and of varied conditions of absorption and metabolism associated with the oral therapy.
2. Continuity of drug administration in CDDS permits the use of a drug with short biological half-life.
3. Rectal drug delivery improves the bioavailability that reduces the total daily dose.
4. Avoids first-pass hepatic metabolism.
5. Less chances of over or under dosing as the result of prolonged pre-programmed delivery of drug at the required therapeutic rate.
6. Decrease gastrointestinal side effects.
8. Increased patient compliance in following manner
   - Provisions of simplified therapeutic regimen.
   - Painless delivery of drug.
   - Eliminates swallowing.
   - No chances of forgetting the dose.
   - Easy to carry a patch in wallet or ladies purse.
9. Patches offer less friability problems of wear and tear than the tablets.
10. In a multi drug regimen RDDS avoids drug interaction in GIT.
11. It is easy to terminate the medication simply by removing the drug delivery device from the skin surface.
12. RDDS system can be taken without any aid, which makes it most suitable formulation; for instance, tablet and capsule need little water. Liquid oral preparation needs teaspoon and parenteral delivery needs specialized person whereas if a patient is told to apply RDDS patch, he/she can do it any where e.g. in office, in theatre, in club, in house without any aid.
13. Chance of toxicity due to additives e.g. preservatives, stabilizing agent antioxidants etc. are less as compared to other dosage forms.
14. Problem of dose dumping is least in RDDS, because stratum corneum is more resistant than the inner membranes (i.e. mucous membrane in case of oral controlled release delivery systems) and stratum corneum itself is a rate limiting factor.

15. Need not to be sterile, obviates processing problem.

Disadvantages of rectal drug delivery system

1. The limitation of rectal drug delivery is principally associated with skin barrier function, which severely constrains the absolute amount of drug that can be absorbed across reasonable area of skin during the dosing period. Thus, the major disadvantage of the method is that it is limited to potent drug molecule typically those requiring a daily dose on the order of 20 mg or less.

2. Even if the drug is sufficiently potent, it must yet satisfy other criteria to be considered a viable candidate for rectal drug delivery. For example its physiochemical properties must allow to be absorbed percutaneously. This mean that its molecular weight should ideally be less than 500 Daltons and it should have adequate solubility in both lipophillic and aqueous environments since, to reach dermal micro circulation and gain access to systemic circulation, the molecule must cross that stratum corneum (a lipid barrier) and then transfer through the much-more-aqueous-in-nature viable epidermis and upper dermis. Absence of either oil or water solubility altogether, will preclude permeation at a useful rate.

3. The pharmacokinetic and pharmacodynamic characteristic of the drug must be such that relatively sustained and slow input provided by rectal delivery makes sense. Tolerance inducing compounds are not intelligent choice for this mode of administration unless until an appropriate “wash out” period is programmed into the dosing regimen.

4. Drugs that can be given once a day orally, with reproducible bioavailability and which are well tolerated by patient do not really need a patch formulation.
1.2.2 Factors affecting Rectal Permeation

(A) Physicochemical properties of the diffusant;

**Partition Coefficient:**

Partition coefficient plays an important role in establishing flux from a membrane and skin to receiver fluid. For drugs the passage through skin, stratum corneum is rate limiting. The stratum corneum to vehicle partition coefficient is then crucially important in establishing a high initial concentration of diffusant in first layer of tissue. Drugs possessing both water and lipid solubility is favorably absorbed through skin. Rectal permeability coefficient shows a linear dependency on partition coefficient.

A lipid water partition coefficient of 1 or greater is required for optimum rectal permeability.\(^{19-22}\) The partition coefficient of a drug molecule may be altered by chemical modification of its functional groups,\(^{23}\) by varying the vehicle, or by incorporating lipophillic agent with drug e.g. pentanol, which effect skin vehicle partition coefficient.
Diffusant solubility:
Flux of a solute is proportional to the concentration gradient across the entire barrier phase. Therefore for maximal flux, solute should be in saturated solution in donor phase. The solubility of a solute can be controlled by controlling solvent composition of the vehicle.

Effective Concentrations:
The concentration differential is considered as driving force for diffusion, in actual it is the chemical potential gradient or activity gradient which is the fundamental parameter. The thermodynamic activity of penetrant in either the donor phase or the membrane may be radically altered by such phenomena as (i) pH changes (ii) complex formation (iii) co-solvents, (iv) presence of surfactants, micelle etc.

pH variation:
According to pH partition hypothesis, only unionized molecules pass across lipid membranes in significant amount. Ionized species do not have favorable free energies for transfer to lipid phase. Weak acids and the weak basis dissociated to different degrees, depending on the pH and the pKa and pKb of diffusant. Thus the fraction of unionized drug in the applied phase determines the effective membrane gradients, and this fraction is function of pH. Usually flux of drug increases with increasing pH up to approximately 1 to 2 pH units higher than the pKa value or decreasing 1 to 2 pH lower than pKb values, at which point the drug molecule exist totally as the non protonated form.

Co-solvents:
Co-solvents are used to increase solubility of solute in vehicle, so as to maximize the concentration gradient across stratum corneum, membrane. In general partition coefficient of a drug between a membrane and a solvent mixture falls as the drug solubility in the solvent system rises. Hence it is important not to over solubilize a drug in a vehicle if the aim is to promote penetration through stratum corneum.
Surface Activity and Micellization:
When surface active agent forms micelle, the total apparent solubility of agent in the aqueous phase increases dramatically, with a consequent decrease, in the apparent partition coefficient Figure 1.1.2. When drug and surfactant are different, the part played by surfactant is more complicated. Sometimes surfactant decreases permeation, reflecting reduced biological activity e.g. retarded rectal absorption of triiodophenol.  

Complexation:
Complex formation influences apparent solubility and apparent partition coefficient of a drug. When complex is formed in donor solution, flux of diffusant across skin or membrane decreases, because concentration of free drug falls. It is reported that complexes have lowered partition Coefficient than respective free drugs.

Molecular Weight:
(a) Convection
Usually the lower the molecular weight the faster and more complete is the transport. Small molecules may pass through pores of the membrane by convective transport. Spherical compounds up to MW of 150 and thread like compounds up to MW 400 are considered of being permeable by convective transports.
(b) Diffusion:
Most drugs are transported across membrane by passive diffusion, since in passive diffusion the drug outside and inside the aqueous compartment is in true solution, but dissolves in the lipid material of the membrane during the transport across the barrier. The compound must possess minimal lipid solubility.\textsuperscript{30,31}

The transport stream $Q$ depends on the diffusion constant of drug in lipid material $D$, the surface area $A$, the partition coefficient $K$, the membrane thickness "$h"$ and the concentration $C_0$ and $C_i$ on both sides of the membrane.

$$Q = \frac{DAK (C_0 - C_i)}{h}$$

Under sink condition, where the drug is immediately carried away by the blood after crossing the membrane and diluted within the volume of distribution, according to Ficks first law. The flux and diffusion coefficient $D$ decreases with increasing MW.

**pKa: Ionization at Physiological pH.**

The nonionized moiety is usually lipid soluble hence may dissolve in the lipid material of a membrane and may be transported by passive diffusion, whereas the ionized moiety usually is not lipid soluble enough to permit permeation. The percent of ionization can be calculated from Henderson-Hasselbalch equation.

To cross or to reach membrane or regions by passive diffusion within the body the percentage of drug nonionized at that site should be between at least 0.1 and 0.5%.

**Isoelectric Point**

Isoelectric point is the pH at which the zwitterion concentration of protein or peptide is at a maximum and the net movement of molecule is negligible. The permeation across the membrane is at its minimum at the isoelectric point. The permeation across skin upon topical administration of vasopressin was minimum at isoelectric point.\textsuperscript{32}

**(B) Physicochemical properties of drug delivery system**

**Release characteristics:**
The affinity of the vehicle for the drug molecule can influence the release of drug molecule from the vehicle.\textsuperscript{33} The solubility in the vehicle will determine the release rate of drug. Generally more easily the drug is released from the drug delivery system; higher will be the rate of rectal permeation. A linear relationship is observed between the median effective dose of a corticosteroid against product of partition coefficient
and square-root of their solubility in vehicle;\(^{34}\) pH of the vehicle can also influence the rate of release of drug from the drug delivery system.

**Composition of drug delivery system:**
The vehicle used in drug delivery system usually assumed to be "inert" but it is not so. The composition of the vehicle and drug delivery system influences greatly on percutaneous absorption of drug particles. It may affect not only the rate of drug release but also the permeability of stratum corneum by means of hydration, mixing with skin lipids, or other sorption promoting effects.

**Enhancers / sorption promoters:**
Sorption promoters or sorption enhancers are not drugs but they are molecules which reversibly decrease the barrier nature of the stratum corneum.\(^{35,36,37,38}\) Sorption promoters allow the drugs to penetrate into skin and the permeate across more readily and thus increase systemic availability.\(^ {39,40}\)

Sorption promotes act by interaction with intracellular lipids leading to disruption of their organization and increasing their fluidity.\(^ {41}\) Some of them also interact with intercellular protein, keratin denaturation (azone and oleic acid)\(^ {32,43}\) while others act by both mechanism (DMSO and propylene glycol).\(^ {44}\) Another possible mechanism is by altering the skin hydration.\(^ {45,46}\)

The mechanism of these sorption promoters to some extent is also related to octanol/water partition co-efficient.\(^ {47}\) Recently, lipid-protein partition theory has been formulated to describe the potential mechanism of action of sorption promoters.\(^ {35,44,48}\)

**Mechanism of penetration enhancers on skin\(^ {49,50}\)**
Most of the enhancer especially chemical enhancer works on the either lipophilic part or hydrophilic part of the bilayer of SC and alter its property and ultimately increases the delivery of the drug through the skin. Chemical enhancers may either work of lipid portion of the lipid bilayer (intracellular mechanism) or they may work on the protein part of the cell (cellular mechanism).

They may act as lipid enhancer and so here total lipidic portion increases and ultimately lipophilic drug can penetrate easily, some chemical enhancer are increases the total hydrophilic portion and so they increases flux of hydrophilic drug, some drug may able to change the polarity of bilayer and as rule of thumb like dissolve like drug of nearly similar polarity may penetrate through skin easily.
Some enhancer work of cellular part of SC. Enhancers (chemical or other) may increase the distance between the two cell and so large molecule can penetrate through skin or they may change the arrangement of cellular keratin fibers and generate vacuoles in it so it become more permeable to drug.

**Figure 1.2.3: Action of chemical enhancer on Intercellular lipids**

Some enhancer causes the phase separation of bilayer and so drug can penetrate through skin. Some enhancer develop pool of increases the flux of hydrophilic drug. Solvent like ethanol have tendency to dissolve lipid and it extract out lipid of SC and so obstruction for hydrophilic molecule decreases.
Figure 1.2.4: Action of penetration enhancer on the integrity of stratum corneum adhesion.

![Action at Desmosomes and Protein Structures](image)

![Action within Corneocytes](image)

Table 1.2.1: Different classes of sorption promoters

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Sorption Promoters</th>
<th>Example</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Sulfoxides and similar Compounds</td>
<td>Dimethyl sulfoxide</td>
<td>37,40,51,52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dimethyl acetamide</td>
<td></td>
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<td></td>
<td></td>
<td>Dimethyl formamide</td>
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<td></td>
<td></td>
<td>N- methyl formamide</td>
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<tr>
<td>2.</td>
<td>Pyrrolidone</td>
<td>2-pyrrolidone</td>
<td>37,40</td>
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<tr>
<td></td>
<td></td>
<td>1-methyl 2-pyrrolidone</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>5-methyl 2-pyrrolidone</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1,5-methyl 2-pyrrolidone</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-ethyl 2-pyrrolidone</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Fatty acids</td>
<td>Oleic acid, lauric acid, linolic acid, myristic acid</td>
<td>37,40,41,43,53</td>
</tr>
<tr>
<td>4.</td>
<td>Azone</td>
<td>Laurocapram and its derivatives</td>
<td>37,40,53,54,55,56</td>
</tr>
<tr>
<td>5.</td>
<td>Urea</td>
<td>Urea</td>
<td>37,38,40</td>
</tr>
<tr>
<td>6.</td>
<td>Surfactant</td>
<td>Sodium lauryl sulfate, Triethyl ammonium bromide</td>
<td>37,40</td>
</tr>
<tr>
<td>Chapter</td>
<td>Introduction</td>
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<td>---------</td>
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<tr>
<td>7.</td>
<td>Alcohols</td>
<td></td>
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<tr>
<td></td>
<td>Ethanol</td>
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<td></td>
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<tr>
<td></td>
<td>Lauryl alcohol</td>
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<td></td>
<td>Linolenyl alcohol</td>
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<tr>
<td></td>
<td>Octanol</td>
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<td></td>
<td>Synperonic NP series</td>
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<tr>
<td>8.</td>
<td>Glycols</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Propylene glycol</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>PEG 400</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>37,44,40,53</td>
<td></td>
<td></td>
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<tr>
<td>9.</td>
<td>Terpenes and terpenoids</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Menthol</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Camphor</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>37,48,58,59</td>
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<tr>
<td>10.</td>
<td>N-pentyl N-acetyl prolinate</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>-</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>60</td>
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<tr>
<td>11.</td>
<td>Latam N-acetic acid esters</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>61</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1.2.3 TYPES OF RECTAL PATCHES
There are mainly four types of basic rectal patches.\textsuperscript{62,63,64}

(1) Drug in adhesive type
In this type drug is loaded in adhesive itself and stratum corneum acts as rate controlling barrier. This is most old type of rectal patch design. This type of drug delivery system is best illustrated by the development and marketing of a nitroglycerin releasing system named as deponit by PharmaSchwartz/Lohmann in Europe. Basic construction includes backing membrane, adhesive loaded with drug and release liner.

(2) Multi laminate type
This is most complicated type of design for Rectal patches. Basic construction includes backing membrane, drug in adhesive, rate controlling membrane, then again adhesive (loaded with drug) on to it. This shows that there are two adhesive layers. First layer that is in contact with the release liner is actually delivering drug and second layer of adhesive (after membrane) acts as depot of drug. The example is scopolamine releasing CDDS named as Transderm-scop by Ciba and clonidine releasing CDDS named as CataPress-TTS by Boehringer Ingelheim.

(3) Reservoir type
In this type the drug is incorporated in reservoir which is lined with membrane. The adhesive is coated on to this membrane. This membrane can be rate controlling. Basic construction includes backing membrane, drug in reservoir, membrane, adhesive and release liner. Example of this type of CDDS is nitro-glycerine releasing system named as Nitrodisc by Searle.

(4) Matrix type
In this type, the drug is incorporated in the matrix of polymer which itself releases drug in zero order. The adhesive layer is just at the periphery and little inside the periphery of the patch. Basic construction includes backing membrane, adhesive, and drug in matrix and release liner. The example of matrix type rectal patch in nitroglycerine releasing CDDS named as Nitro-dur by Key.
Figure 1.2.5 Basic patch construction

Single-layer Drug-in-Adhesive

Multi-layer Drug-in-Adhesive

Drug Reservoir-in-Adhesive

Drug Matrix-in-Adhesive
1.2.4 Drugs Studied For controlled Drug Delivery System

For atenolol, guinea pig and rat skin can be used. For nitroglycerine, human studies can be done. For nicardipine, hairless guinea pig can be used for the study.

1.2.5 Evaluation of Rectal Drug Delivery Device

Table 1.2.2: Testing of Rectal drug delivery system \(^{65,66}\)

<table>
<thead>
<tr>
<th>TYPE OF TEST ON FINAL PRODUCT</th>
<th>TESTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemical test</strong></td>
<td></td>
</tr>
<tr>
<td>□ Content</td>
<td></td>
</tr>
<tr>
<td>□ Content uniformity</td>
<td></td>
</tr>
<tr>
<td>□ Purity</td>
<td></td>
</tr>
<tr>
<td>□ Residual Solvent</td>
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<tr>
<td><strong>Physical test</strong></td>
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<tr>
<td>□ USP apparatus 5 (Paddle over disk)</td>
<td>Release testing</td>
</tr>
<tr>
<td>□ USP apparatus 6 (Cylinder)</td>
<td></td>
</tr>
<tr>
<td>□ USP apparatus 7 (Reciprocating disk)</td>
<td></td>
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<tr>
<td><strong>Test for adhesion</strong></td>
<td></td>
</tr>
<tr>
<td>□ Peel property</td>
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<tr>
<td>□ Tack property</td>
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</tr>
<tr>
<td>Thumbtack test</td>
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</tr>
<tr>
<td>Rolling ball tack test</td>
<td></td>
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<tr>
<td>Quick stick test</td>
<td></td>
</tr>
<tr>
<td>Probe tack test</td>
<td></td>
</tr>
<tr>
<td>□ Shear strength</td>
<td></td>
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<tr>
<td><strong>Cutaneous toxicity</strong></td>
<td></td>
</tr>
<tr>
<td>□ Contact dermatitis</td>
<td></td>
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<tr>
<td>□ Growth of microorganisms</td>
<td></td>
</tr>
<tr>
<td>□ Cytotoxicity</td>
<td></td>
</tr>
<tr>
<td>□ Sensitization study</td>
<td></td>
</tr>
<tr>
<td><strong>Percutaneous absorption model</strong></td>
<td></td>
</tr>
<tr>
<td>□ In vitro testing</td>
<td></td>
</tr>
<tr>
<td>□ In vivo testing</td>
<td></td>
</tr>
</tbody>
</table>
Proper skin preparation and appropriate cell design gives good *in vivo* results. Skin preparation includes selection of proper skin. One can choose human skin or can also go for animal or artificial membrane like Nylon, Cellulose acetate etc. Skin separation includes the treatments needed for separation of required part of skin from other unwanted parts. Then separated skin we mount on the diffusion cell which can be one chambered (one donor compartment) or two chambered (two donor compartment).
Selection of membrane for in vitro study of Rectal drug delivery system Though there is no rule regarding the selection of the skin model, generally researchers starts with artificial membrane, then in vitro animal skin, then in vitro human skin (cadaver skin), then in vivo animal skin, then finally in vivo human skin.

Figure 1.2.7: Selection of membrane.

Franz diffusion cell

It is one chambered (vertical) type cell. Most widely used for in-vitro testing of RDDS. Many modifications have been made in the Franz diffusion cell design according to the requirement. Here skin is mounted on the plate above O ring. 20-70 ml phosphate buffer of pH 7.4 is filled in reservoir compartment. Rectal patch is applied on upper layer of skin. Diffusion medium in reservoir is stirred at particular rpm. Sampling is done at particular interval from reservoir compartment i.e. specified volume of fluid is withdrawn and is replaced by equivalent amount of the same fluid.

In vitro drug release profile modeling

In-vitro drug release has been recognized as an important tool in drug development and as an important parameter in quality control. Under certain conditions, it can be used as a surrogate for the assessment of bio-equivalence or prediction of bioequivalence.

A good understanding of the release mechanism of the dosage form as well as the physical chemical properties of the drug will enable development of accurate dissolution tests.
1.3 SKIN IRRITATION AND SKIN SENSITIZATION STUDIES

1.3.1 Skin Irritation and Sensitization

The concept of skin irritation or inflammation has a very long history. Egyptian scrolls, dated perhaps as early as 2650 BC, have several references to a word indicating inflammation that is associated with wounds. In 1889, Julius Cohnheim described inflammation as a series of changes to the affected area including redness, swelling, pain, warmth. Earlier to 1985 it was thought that chemical irritation to the skin occurs in phases like increased permeability and blood flow, infiltration of cells, leucocytosis etc. After 1985 Patrick et al., Agner and serup 1987 reported that irritation of chemical and resulting effects on the skin appeared to be related to the specific irritant applied. Further more, skin irritation appears to be produced by multiple mechanisms resulting invariable patterns of response.\(^{71,72}\)

We can broadly classify skin sensitization irritation and inflammation in to following categories.\(^{73,74}\)

1. Allergic Contact Dermatitis (Skin Sensitization)

**Definition and Description**\(^{75,76}\)

Allergic contact dermatitis or dermatitis venenta, is the result of an interaction between the complicated pathophysiological mechanisms of type-IV cell mediated immunity and environmental sensitizer (allergens). Acute contact dermatitis is characterized by papules and sharply demarcated erythema. Blisters are also produced following the release of cytotoxic compounds by white cells attracted to the affected site. The key element in the formation of sub chronic and chronic allergic dermatitis is due to recurrent exposure to the causative agent.

2. Light induced cutaneous toxicity\(^{74,77}\)

The wavelength of light found in UV-B spectrum is generally considered the primary source of toxic changes in the skin. The specific wavelength responsible for a particular biological response is termed as “action spectrum” for that effect. In some cases, xenobiotics play a role in these effects while in others, the interaction of light...
with the normal compound of the skin is responsible in either case; adverse reaction of the skin to light (UV or Visible) is termed as photo sensitization.

2.1 Photo sensitization not related to xenobiotics
The exposure of the unprotected skin to UV light (from sunlight or artificial sources) can result toxic responses. These includes short term, generally reversible effects such as sunburn (erythema) and tanning (enhanced pigment darkening) as well to as long term, generally irreversible effects such as premature skin ageing (actinic elastosis) and development of the skin cancer.

2.2 Photo sensitisation related to xenobiotic exposure
Xenobiotics localized within the skin can interact with light and produces adverse reaction in the skin in many ways. These include phototoxicity, photo allergy depigmentation, induction of endogenous photosensitizes and induction of photosensitive disease states.\(^78\)

3. Cutaneous Carcinogenesis\(^79\)
The skin is the most common site of cancer in humans. Both benign and malignant tumors may be derived from viable keratinocytes and melanocytes of the epidermis, and rarely from skin appendages, blood vessels, peripheral nerves and lymphoid tissue of the dermis. Histologically, basal cell and squamous cell carcinomas that develop from keratinocytes account for 60% and 30% for all the skin cancers respectively.

4 Acne-like eruptions\(^74\)
These reactions are initiated by the proliferation of the epithelium of sebaceous glands and formation of keratin cyst resulting in the development of a pustule filled with fatty compounds and other product of sebaceous origin.
Chapter - 1

Introduction

Evaluating chemicals for the adverse effect on the skin

1. Sensitization testing in animals

Sensitizations test is done to evaluate the allergic potential of chemicals, to assess potential sensitization properties. Animals is treated with an intial or several doses of chemical (the induction phase) by intradermal or cutaneous application. Following an incubation or sensitization phases for approximately two weeks the animal is treated with second dose or series of doses of the same test chemical (the challenge phase). Sensitization is evaluated by examining the skin reaction following the challenge phase compared with any skin reaction immediately following the induction phase.

Intradermal Techniques

Draize et, al.\textsuperscript{80} were the first to describe standardized irritation and sensitization tests. The Draize test is the simplest and most predictive tests to perform. However the test have several draw backs including high incidence of negatives with weak sensitizers\textsuperscript{81} further more, the test; recommends a consistent induction concentration of 0.1% injected intradermally without regard to use pattern or exposure potential of the chemicals.\textsuperscript{82}

Freud’s complete adjuvant test\textsuperscript{83} is the test in which test substances is mixed with Freud’s complete adjuvant (FCA a mixture of heat killed Mycobacterium tuberculosis, paraffin oil and mannide monooleate) prior to intradermal injection for induction. The use of FCA increases the immunological response and aids in the detection of weak sensitizers. This test utilizes three injections of this mixture at different sites during induction phase. In the challenge phase the test substance is generally applied on epidermally (non-occluded) in range of non-irritating concentrations. This test is considered as sensitive as the optimization test and is of low cost to perform. The primary drawback of this test is the use of intradermal induction doses which actually bypasses the effect of stratum corneum and stratum corneum is highly important to limit the absorption of potential sensitzers. Further more the use of FCA may cause the sensitizing potential of the test chemical to be over-estimated.\textsuperscript{84}
Chapter 1

Introduction

Epicutaneous Techniques

The open epicutaneous test utilizes an induction phase of repeated applications of an undiluted test substance (which may be a formulation of a final product for consumer exposure) over several weeks. The challenge phase separated in to initial and rechallenge phases. Klecak et al (1977) found this test to be sensitive, highly predictive test.\textsuperscript{85}

The buckler test was designed to reproduce a human patch test in animals and therefore allows variation of conditions to optimize detection of moderate strong sensitizers prior to testing in humans. This test utilizes induction and challenge phases of occluded epidermal doses of the test substances that may be allergic chemicals or final product formulations.\textsuperscript{86}

2. Irritation testing in animals

The evaluation of compound for irritability in animals correlates well with the degree of skin response in humans.

Single Application Irritation Testing

The test described by Draize et al.\textsuperscript{80} or slight modification of this test is the most widely used for predicting the potential skin irritation of chemicals and chemical mixtures. In this test hair are clipped from the back of a rabbit and four distinct areas for the application of test substances are identified. Two of four areas were abraded by making four epidermal incisions in the appropriate areas. All four areas were covered by gauze that is held in place with adhesive tape and the test substance is applied to the appropriate area under the gauze.

The entire trunk of the rabbit is wrapped in impervious cloth or plastic to hold the patches in place and decrease the evaporation of volatile test substances. The rabbits were generally remain wrapped for 24 hr after treatment and are evaluated for irritation at the time of unwrapping and 24 and 48 hr after being unwrapped. Generally four test substances are evaluated in a series of six rabbits.
Table-1.2.3: Division of various elements of irritation in to distinct categories of grading according to Draiz et al.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Skin reaction</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><strong>Erythema Formation</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Very slight erythema (barely perceptible)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Well defined erythema</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Moderate to severe erythema</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Severe erythema (beet redness) to slight Escher formation</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Total possible erythema score</td>
<td>4</td>
</tr>
<tr>
<td>2.</td>
<td><strong>Edema Formation</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Very slight Edema (Barely perceptible)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Slight Edema edges of area well defined by definite raising)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Moderate edema (area raised approximately 1mm)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Severe edema (raised 1mm and extending beyond the area of exposure)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Total possible edema score</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Total possible score for primary irritation</td>
<td>8</td>
</tr>
</tbody>
</table>

**Repetitive Application Irritation Testing**

The repetitive application over at least 7-14 days appears to be better able to predict the irritability of test substances than the single application. Additionally, the repetitive application test to assess irritability can be combined with an assessment for systemic toxicity by cutaneous route. This is highly relevant especially in the case of Rectal drug delivery. In repetitive irritant testing usually, three or more groups of five to ten animals per sex are used with each group receiving a different dose of test substance daily for 2,3,4 or 13 weeks. An additional group of animals is handled similarly but treated with the vehicle or when no vehicle is used with water to serve as control group is removed from the back of the animal. The animal is then wrapped with an occlusive dressing and returned to its home cage for the period of 6 hr. The wrapping is removed and the back is gently wiped. The animals are observed daily for the signs of cutaneous irritation.
1.4 CARDIOVASCULAR DISEASE
Cardiovascular diseases are the class of diseases that involve the heart or blood vessels (arteries and veins).

- Heart diseases which affect the heart in several different ways but they all cause the ultimate problem of disrupting the vital pumping action of the heart. e.g. Cardiac arrhythmias, Heart attack, Myocardial infarction, Valvular disorders, Coronary artery disease, Congenital heart disease; Heart muscle disease or Cardiomyopathy; Pericardial diseases.

- Vascular disease or Blood vessel disease which affects the blood vessels and ultimately causes heart dysfunctioning. e.g. Hypertension, Hypotension, Atherosclerosis, Embolism etc.

1.4.1 Cardiac arrhythmias
The rhythm of the heart is normally generated and regulated by pacemaker cells within the sinoatrial (SA) node, which is located within the wall of the right atrium. SA nodal pacemaker activity normally governs the rhythm of the atria and ventricles.

Causes of Cardiac arrhythmias
A frequent cause of arrhythmia is coronary artery disease because this condition results in myocardial ischemia or infarction. When cardiac cells lack oxygen, they become depolarized, which lead to altered impulse formation and/or altered impulse conduction. The former concerns changes in rhythm that are caused by changes in the automaticity of pacemaker cells or by abnormal generation of action potentials at sites other than the SA node (termed ectopic foci). Altered impulse conduction is usually associated with complete or partial block of electrical conduction within the heart. Altered impulse conduction commonly results in reentry, which can lead to tachyarrhythmia. Finally, many different types of drugs (including antiarrhythmic drugs) as well as electrolyte disturbances (primarily K⁺ and Ca²⁺) can precipitate arrhythmias.

Classification of Cardiac Arrhythmias
Bradycardia denotes a decrease in heart rate.
Tachycardia is the term denoting an increase in heart rate.
Extrasystoles: these are premature beats that occurs before the next expected beats. This may be atrial, ventricular or nodal, depending on its site of origin.
Paroxymals Supraventricular Tachycardia: It is the condition in which the heart rate suddenly increases to 150-200 beats/min and 1:1 AV conduction is maintained.

Atrial-flutter: It is a very rapid but regular beating of atria with a rate between 240-400 per min.

Atrial Fibrillation: It is a rapid, continuous chaotic and irregular beating of atria. It is of great danger.

Ventricular Fibrillation: It is an irregular and chaotic ventricular arrhythmia with rapid rate and disorganized spread of impulses throughout the ventricular myocardium. It is Very Dangerous.

Heart block: It is the term applied to a condition in which the nerve impulses are delayed or fail to get through from their source in the right atrium to the ventricles. It is obstruction of the impulse, in the heart thus suddenly, decreasing the heart rate and the pulse rate.

Cardiac arrhythmias treatment

When arrhythmias require treatment, they are treated with drugs that suppress the arrhythmia. These drugs are called antiarrhythmic drugs. There are many different types of antiarrhythmic drugs and many different mechanisms of action. Most of the drugs affect ion channels that are involved in the movement of sodium, calcium and potassium ions in and out of the cell. These drugs include mechanistic classes such as sodium-channel blockers, calcium-channel blockers and potassium-channel blockers. By altering the movement of these important ions, the electrical activity of the cardiac cells (both pacemaker and non-pacemaker cells) is altered, hopefully in a manner that suppresses arrhythmias.

Classification of Antiarrhythmic drugs

Class I: Na channel blockers (membrane-stabilizing drugs) block fast Na channels, slowing conduction in fast-channel tissues Class I drugs are subdivided based on the kinetics of the Na channel effects. e.g. Quinidine, Procainamide

Class Ia drugs have a intermediate kinetic

Class Ib drugs have fast kinetics

Class Ic drugs have slow kinetics.

Class II: Class II drugs are β-blockers, which affect predominantly slow-channel tissues (SA and AV nodes), where they decrease rate of automaticity, slow conduction velocity, and prolong refractoriness. Thus, heart rate is slowed. e.g. Propranolol
Class III: Class III drugs are primarily K channel blockers, which prolong action potential duration and refractoriness in slow- and fast-channel tissues. e.g. Amioderone, Sotalol

Class IV: Class IV drugs are the nondihydropyridine Ca channel blockers, which depress Ca-dependent action potentials in slow channel tissues and thus decrease rate of automaticity, slow conduction velocity, and prolong refractoriness. Heart rate is slowed. e.g. Verapamil, Diltiazem.

1.4.2 Hypertension

Hypertension or high blood pressure is a condition in which the blood pressure in the arteries is chronically elevated. With every heart beat, the heart pumps blood through the arteries to the rest of the body. Blood pressure is the force of blood that is pushing up against the walls of the blood vessels. If the pressure is too high, the heart has to work harder to pump, and this could lead to organ damage and several illnesses such as heart attack, stroke, heart failure, aneurysm, or renal failure.

Classification of hypertension

Hypertension may be classified as essential or secondary. Essential hypertension is the term for high blood pressure with unknown cause. It accounts for about 95% of cases. Secondary hypertension is the term for high blood pressure with a known direct cause, such as kidney disease, tumors, or other diseases.

Causes of Hypertension

Though the exact causes of hypertension are usually unknown, there are several factors that have been highly associated with the condition. These include Smoking, Obesity or being overweight, Diabetes, Sedentary lifestyle, Lack of physical activity, High levels of salt intake (sodium sensitivity), Insufficient calcium, potassium, and magnesium consumption, High levels of alcohol consumption, Stress, Aging, Medicines such as birth control pills, Genetics and a family history of hypertension, Chronic kidney disease, Adrenal and thyroid problems or tumors.

Symptoms of Hypertension

There is no guarantee that a person with hypertension will present any symptoms of the condition. Extremely high blood pressure may lead to some symptoms, however, and these include severe headaches, Fatigue or confusion, Dizziness, Nausea,
Problems with vision, Chest pains, Breathing problems, Irregular heartbeat, Blood in the urine.

**Treatment of Hypertension**

Medications most often prescribed for high blood pressure include the following:

**Water pills (diuretics)**

Diuretics are used very widely to control mildly high blood pressure, and are often used in combination with other medications. They increase sodium excretion and urine output and decrease blood volume. The sensitivity to the effect of other hormones in your body is decreased. e.g. Hydrochlorothiazide.

**Beta-blockers**

Beta-blockers reduce heart rate and decrease the force of heart contraction, thereby reducing the pressure generated by the heart. They are preferred for people who have associated coronary heart disease, angina, or history of a heart attack, since they also prevent recurrent heart attacks and sudden death. e.g. Carvedilol, metoprolol, atenolol.

Side effects - Fatigue, depression, impotence, nightmares

**Calcium channel blockers**

Calcium channel blocking agents work by relaxing the muscle in the walls of the arteries.

They also reduce the force of contraction of the heart. e.g. Nifedipine, diltiazem, verapamil, nicardipine, amlodipine, felodipine.

Side effects - Ankle swelling, fatigue, headache, constipation, flushing

**Angiotensin-converting enzyme (ACE) inhibitors**

ACE inhibitors stop the production of a chemical called angiotensin II, a very potent chemical that causes blood vessels to contract, a cause of high blood pressure. Blockage of this chemical causes the blood vessels to relax. e.g. Captopril, enalapril, lisinopril.

**Angiotensin receptor blockers**

Angiotensin receptor blockers work on receptors in tissues all over the body to prevent uptake of angiotensin II, and therefore inhibit the vasoconstrictor effect of angiotensin II. e.g. Losartan, valsartan.

**Alpha-blockers**

Alpha-blockers relax blood vessels by blocking messages from the nervous system that cause muscular contraction. Examples – Terazosin, doxazosin.
Chapter - 1

**Introduction**

**Blockers of central sympathetic (autonomic nervous) system**

These agents block messages out of the brain from the autonomic nervous system that contract blood vessels. The autonomic nervous system is the part of the nervous system that is automatic and controls heart rate, breathing rate, and other basic functions. The effect of these drugs is to relax blood vessels, thus lowering blood pressure. e.g. Clonidine.

**Direct vasodilators**

Direct vasodilators relax (dilate) the blood vessels to allow blood to flow under lower pressure. These medications are often given through an IV line in an emergency (that is, in malignant hypertension). e.g. Nitroprusside/diazoxide. Oral medications are hydralazine and minoxidil.

**1.5 INTRODUCTION TO DRUG**

**1.5.1 Diltiazem HCl**

Diltiazem is a benzothiazepine calcium channel-blocking agent most similar to verapamil in its clinical effects. Diltiazem increases exercise capacity and improves multiple markers of myocardial ischemia, reduces heart rate, may improve cardiac output, improve myocardial perfusion, educes left ventricular work load and may prevent calcium induced perfusions injury that occurs after procedures such as angioplasty.

**A. Physiochemical profile**

**Structure:**

\[
\text{Empirical formula: } C_{22}H_{26}N_{2}O_{4}S \text{ HCl}
\]

**Molecular weight:** 450.98
Chemical name: 1, 5-Benzothiazepin-4 (5H)-one, 3-(acetyloxy)-
-5- [2- (dimethylamino) ethyl]-2, 3-dihydro-2-
(4-methoxyphenyl)-, monohydrochloride

Category: Antianginal, Calcium Channel Blocker,
Antihypertensive.

Description: White crystalline powder or small crystals,
odorless and bitter taste.

Melting point: 207.5-212°C

Solubility:

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>Freely soluble</td>
</tr>
<tr>
<td>Formic acid</td>
<td>Freely soluble</td>
</tr>
<tr>
<td>Methanol</td>
<td>Freely soluble</td>
</tr>
<tr>
<td>Chloroform</td>
<td>Freely soluble</td>
</tr>
<tr>
<td>Absolute alcohol</td>
<td>Sparingly soluble</td>
</tr>
<tr>
<td>Ether</td>
<td>Insoluble</td>
</tr>
</tbody>
</table>

B. Pharmacology

Mechanism of action

**Hypertension.** Diltiazem produces its antihypertensive effect primarily by relaxation of vascular smooth muscle and the resultant decrease in peripheral vascular resistance. The magnitude of blood pressure reduction is related to the degree of hypertension; thus hypertensive individuals experience an antihypertensive effect, whereas there is only a modest fall in blood pressure in normotensives.

**Angina.** Diltiazem has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal workloads. Diltiazem has been shown to be a potent dilator of coronary arteries, both
epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasms are inhibited by diltiazem.

**Dosage:** Adult: 30-60 mg 3 times in day.

### C. Pharmacokinetics

Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous administration) of about 40%. Diltiazem undergoes extensive metabolism in which only 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show Diltiazem is 70% to 80% bound to plasma proteins. The plasma elimination half-life following single or multiple drug administration is approximately 3.0 to 4.5 hr. Desacetyl Diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as Diltiazem. Minimum therapeutic plasma Diltiazem concentrations appear to be in the range of 50 to 200ng/ml.

<table>
<thead>
<tr>
<th>Table 1.5.2: Pharmacokinetic data of Diltiazem hydrochloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extend of absorption</td>
</tr>
<tr>
<td>Bioavailability</td>
</tr>
<tr>
<td>Onset of action</td>
</tr>
<tr>
<td>Peak plasma level</td>
</tr>
<tr>
<td>Protein binding</td>
</tr>
<tr>
<td>Therapeutic serum level</td>
</tr>
<tr>
<td>Metabolite</td>
</tr>
<tr>
<td>Excreted unchanged in urine</td>
</tr>
<tr>
<td>Half life elimination</td>
</tr>
</tbody>
</table>

### D. Indication

Angina, Atrial fibrillation, Hypertension, Cardiomyopathy, Diabetic neuropathy

### E. Contraindications

Diltiazem is contraindicated in patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, second- or third-degree AV block.
except in the presence of a functioning ventricular pacemaker, hypotension (less than 90 mm Hg systolic), hypersensitivity to the drug, acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

F. Adverse effects
AV block, Confusion, Constipation, Depression, Heat failure, Hypotension, Stevens-Johnson syndrome
G. Market products of Diltiazem hydrochloride

<table>
<thead>
<tr>
<th>Table.1.5.3 Different formulations of Diltiazem hydrochlorides</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conventional Dosage form</strong></td>
</tr>
<tr>
<td><strong>Brand Name</strong></td>
</tr>
<tr>
<td>Angizem</td>
</tr>
<tr>
<td>Dicard</td>
</tr>
<tr>
<td>Dilt ime</td>
</tr>
<tr>
<td>Dilzem</td>
</tr>
<tr>
<td><strong>Modified Release Dosage forms</strong></td>
</tr>
<tr>
<td><strong>Brand Name</strong></td>
</tr>
<tr>
<td>Angizem cd</td>
</tr>
<tr>
<td>Dilter CD</td>
</tr>
<tr>
<td>Dilt ime</td>
</tr>
<tr>
<td>Dilzem</td>
</tr>
<tr>
<td><strong>Injectable dosage form</strong></td>
</tr>
<tr>
<td><strong>Brand Name</strong></td>
</tr>
<tr>
<td>Dilzem</td>
</tr>
</tbody>
</table>
1.5.2 Atenolol 97-101
Atenolol is a β-adrenolytic, cardioselective drug, having no intrinsic sympathomimetic activity.

A. Physicochemical profile

![Chemical Structure of Atenolol](image)

Empirical formula $\text{C}_{14}\text{H}_{22}\text{N}_{2}\text{O}_{3}$

**Molecular weight** 266.3

**Chemical Name** (RS)-4-(2-hydroxy-3-isopropylaminopropoxy)phenylacetamide

**Category** Antihypertensive

**Description** Atenolol is a white and odorless powder.

**Melting Point** 152-155°C

**Dissociation Constant (pKa)** 9.6 @ 24°C

**Partition Co-efficient** 0.23

<table>
<thead>
<tr>
<th>Table 1.5.4: Solubility of atenolol in different solvents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Solvent</strong></td>
</tr>
<tr>
<td>Water</td>
</tr>
<tr>
<td>Ethanol</td>
</tr>
<tr>
<td>Methanol</td>
</tr>
<tr>
<td>Ether</td>
</tr>
</tbody>
</table>
B. Pharmacology

Mechanism of action
Atenolol is a beta-adrenaoreceptor antagonist, or a more commonly known as a beta blocker. Atenolol slows down the strength of the heart’s contractions and reduces its oxygen requirements and the volume of blood it has to pump. Hypertension (high blood pressure) may be treated with these drugs because of their ability to increase the diameter of the blood vessels thus allowing blood to flow under less pressure. Some of these medicines include a diuretic to help reduce blood pressure by increasing the body’s excretion of excess fluid. Beta blockers are also used to treat Myocardial infarction (heart attack) and Arrhythmias (rhythm disorders), angina (chest pains), and disorders arising from decreased circulation and vascular constriction, including migraine.

Dosage
Adult 50-100mg daily

C. Pharmacokinetic
Bioavailability following oral administration is about 45%, but with individual variation this can triple or quadruple. Peak plasma concentrations occur 2-4 hours after oral administration and the duration of therapeutic effect is up to 24 hours. Plasma concentration increases comparatively with the patient’s age. If taken with food, the absorption is reduced by approximately 20%. Protein binding is approximately 3% and the volume of distribution is 0,7 l/kg. Atenolol has low lipid solubility. Hepatic metabolism is negligible and the drug is eliminated, almost always unchanged, through the kidneys. Only 10% of Atenolol is eliminated as metabolite, none of which have any pharmaceutical activity in man. Plasma half-life is 6-9 hours. In case of impaired renal function half-life is prolonged, but impaired hepatic function has no effect on half-life.

D. Indication
Antihypertensive, Anti-Angina, Anti-Arrhythmic, Myocardial Infarctions, Alcohol Withdrawal, Anxiety States, Migraine Prophylaxis, Hyperthyroidism, Tremor.
E. Contraindications
Atenolol is contraindicated in patient with Asthma, Congestive cardiac failure and Phaeochromocytoma.

F. Adverse effect
The most serious adverse effects are heart failure, heart block, and bronchospasm. Other more minor side-effects include fatigue and coldness of extremities. It causes CNS effect of depression, hallucination, confusion. It causes nausea, vomiting, constipation and abdominal pain. It causes skin rash, pruritis, decreased tear production, blurred vision and soreness.

G. Marketed product
Aloten (Core), Altol (Indoco), Angitol (Ind-Swift), Antipress (Saga Labs), Atcardil (Sun Pharma), AteCard (Dabur), Atecor (Win-Medicare), Atelol (Themis Pharma), Aten (Kopran), Atenex (Recon), Atenova (Lupin), Atormin (PCI), Atpark (Parke Davis), Beta (Stadmed), Betacard (Torrent), Betanol (Unisearch), beten (Sigma Labs), Biduten (Croydon), BP-NOL (Elder), Catenol (Alidac), Eucard (Malladi Drugs), Hipres (Cipla), Lakten-50 (Shalaks), Lonol (Khandelwal), Normolol (Pace, SOL), Pertenol (Karnataka Antibiotics), Telol (Max), Tenase (Jenburkt), Tenolol (IPCA), Tensicard (Troikaa), Tensimin (Unique).

1.6 INTRODUCTION TO POLYMERS
1.6.1 Ethyl Vinyl Acetate Copolymer

1. Synonyms
Acetic acid, ethylene ester polymer with ethane, CoTran; ethylene vinyl acetate copolymer; EVA; EVA copolymer, EVM; poly(ethylene co-vinyl-acetate); VA/ethylene copolymer; vinyl acetate/ethylene copolymer

2. Chemical properties
Chemical name Ethylene vinyl acetate copolymer
CAS Registry Number (24937-78-8)
Empirical formula and molecular weight \((\text{CH}_2\text{CH}_2) \times (\text{CH}_2\text{CH(\text{CO}_2\text{CH}_3)})^y\)
**Structural formula** Ethylene vinyl acetate copolymer is a random copolymer of ethylene and Vinyl copolymer of ethylene and vinyl acetate

**Functional category** Membrane, Rectal backing

3. Physical properties

**Description**

Ethylene vinyl acetate is available as white waxy solid in pellet or powder form. Films are translucent.

**Density** 0.92-0.94 gm/cm³

**Flash point** 260°C

**Melting point** 75-102°C depending on polymer ratios

<table>
<thead>
<tr>
<th>Grade</th>
<th>Vinyl acetate (%)</th>
<th>Thickness (µm)</th>
<th>Moisture vapour transmission rate (g/m²/24h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoTran 9706</td>
<td>9</td>
<td>101.6</td>
<td>26.4</td>
</tr>
<tr>
<td>CoTran 9715</td>
<td>19</td>
<td>76.2</td>
<td>64.8</td>
</tr>
<tr>
<td>CoTran 9716</td>
<td>19</td>
<td>101.6</td>
<td>48.6</td>
</tr>
</tbody>
</table>

**Stability and storage condition**

Ethylene vinyl acetate copolymers are stable under normal conditions and should be stored in a cool, dry place. Films of ethylene vinyl acetate copolymers should be stored at 0-30°C and less than 75% relative humidity.

**Incompatibilities**

Ethylene vinyl acetate is incompatible with strong oxidizing agents and bases.

4. Application in Pharmaceutical Formulation or Technology

Ethylene vinyl acetate copolymers are used as membranes and backings in laminated Rectal drug delivery system. They can also be incorporated as components in backings in Rectal systems. Ethylene vinyl acetate copolymers have been shown to be an effective matrix and membrane for the controlled delivery of atenolol1,2.
triprolidine\textsuperscript{3,4} and furosemide.\textsuperscript{5} The system for the controlled release of atenolol can be further developed using ethylene vinyl acetate copolmers and plasticizers.\textsuperscript{1}

1.6.2 Polymethacrylates\textsuperscript{107-110}

1. Synonyms

Acryl-EZE; Acryl-EZE MP; Eastacryl 30D; Eudragit; Kollicoat MAE 30 D; Kollicoat MAE 30 DP; polymeric methacrylates.

2. Chemical properties

Structural Formula

For Eudragit RL and Eudragit RS:

\[ R^1 = H, CH_3 \]
\[ R^2 = CH_3, C_2H_5 \]
\[ R_3 = CH_3 \]
\[ R_4 = CH_2CH_2N(CH_3)_3 \]\textsuperscript{+Cl}\textsuperscript{−}

Functional Category

Film former; tablet binder; tablet diluent.

Chemical Name and CAS Registry Number

Table 1.6.2: Chemical name, Trade name, Company name and CAS registry number of Polymethacrylate

<table>
<thead>
<tr>
<th>CHEMICAL NAME</th>
<th>TRADE NAME</th>
<th>COMPANY NAME</th>
<th>CAS NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) : 2 : 0.2</td>
<td>ERL 100</td>
<td>Röhm GmbH</td>
<td>[33434-24-1]</td>
</tr>
</tbody>
</table>
3. Physical properties

**Alkali Value:** 23.9–32.3 for Eudragit RL 100

**Density (Bulk):** 0.390 g/cm$^3$

**Density (Tapped):** 0.424 g/cm$^3$

**Density (True):** 0.816–0.836 g/cm$^3$ for Eudragit RL and RS PO

**Refractive Index:** $n_{20D} = 1.38–1.385$ for Eudragit RL and RS

**Viscosity (Dynamic):** $\leq$15 mPa for Eudragit RL and RS

**Stability and Storage Conditions**

Dry powder polymer forms are stable at temperatures less than 30°C. Above this temperature, powders tend to form clumps, although this does not affect the quality of the substance and the clumps can readily be broken up. Dry powders are stable for at least 3 years if stored in a tightly closed container at less than 30°C.

**Incompatibilities**

Incompatibilities occur with certain polymethacrylate dispersions depending upon the ionic and physical properties of the polymer and solvent. For example, coagulation may be caused by soluble electrolytes, pH changes, some organic solvents, and extremes of temperature.

4. Application in pharmaceutical formulation or technology

Polymethacrylates are primarily used in oral capsule and tablet formulations as film-coating agents. Depending on the type of polymer used, films of different solubility characteristics can be produced.
Eudragit RL, RS are used to form water-insoluble film coats for sustained-release products. Eudragit RL films are more permeable than those of Eudragit RS, and films of varying permeability can be obtained by mixing the two types together.

1.6.3 Ethyl cellulose: 111-114

1. Synonyms
Aquacoat EDC; Aqualon; Ethocel; Surelease

2. Chemical properties
Non proprietary name:
- BP : Ethylcellulose
- PhEur : Ethylcellulosum
- USPNF : Ethylcellulose

Chemical name: Cellulose ethyl ether.

Empirical formula: C12H23O6(C12H22O5)nC12H23O5

Functional category:
Coating agent, flavoring fixative, tablet binder, tablet filler, viscosity increasing agent.

<table>
<thead>
<tr>
<th>Table 1.6.3: Concentration of ethyl cellulose used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use</td>
</tr>
<tr>
<td>Microencapsulation</td>
</tr>
<tr>
<td>Sustained release tablet coating</td>
</tr>
<tr>
<td>Tablet coating</td>
</tr>
<tr>
<td>Tablet granulation</td>
</tr>
</tbody>
</table>

3. Physical properties

Description:
Ethyl cellulose is a tasteless, free flowing, white to light tan-coloured powder.

Density 0.4 g/cm³

Specific gravity 1.12-1.15g/cm³

Glass transition temperature 129-133°C

Solubility
It is practically insoluble in glycerin, propylene glycol and water. EC that contains less than 46.5% ethoxyl groups if freely soluble in chloroform, methyl acetate,
tetrahydrofuran. EC that contains not less than 46.5% ethoxyl groups if freely soluble in ethanol, ethyl acetate, methanol, and toluene.

**Moisture content**

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

**Stability and storage conditions**

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

**Table 1.6.4: Different grades of ethyl cellulose**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Viscosity (mPa s)</th>
<th>Mean particle size (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethocel Std 4 Premium</td>
<td>3-5.5</td>
<td>204</td>
</tr>
<tr>
<td>N-7</td>
<td>5.6-8</td>
<td>160</td>
</tr>
<tr>
<td>Ethocel Std 7FP Premium</td>
<td>6-8</td>
<td>9</td>
</tr>
<tr>
<td>Ethocel Std 7 Premium</td>
<td>6-8</td>
<td>210</td>
</tr>
<tr>
<td>N-10</td>
<td>8-11</td>
<td>225</td>
</tr>
<tr>
<td>Ethocel Std 10F Premium</td>
<td>9-11</td>
<td>5</td>
</tr>
<tr>
<td>Ethocel Std 10P Premium</td>
<td>9-11</td>
<td>5</td>
</tr>
<tr>
<td>N-14</td>
<td>12-16</td>
<td>212</td>
</tr>
<tr>
<td>Ethocel Std 20P Premium</td>
<td>18-22</td>
<td>-</td>
</tr>
<tr>
<td>N-22</td>
<td>18-24</td>
<td>243</td>
</tr>
<tr>
<td>Ethocel Std 45P Premium</td>
<td>41-49</td>
<td>-</td>
</tr>
<tr>
<td>N-50</td>
<td>40-50</td>
<td>305</td>
</tr>
<tr>
<td>N-100</td>
<td>80-105</td>
<td>-</td>
</tr>
<tr>
<td>Ethocel Std 100FP Premium</td>
<td>90-110</td>
<td>194</td>
</tr>
<tr>
<td>Ethocel Std 100P Premium</td>
<td>90-110</td>
<td>40</td>
</tr>
</tbody>
</table>

**1.6.4 Carbopol 934**

Carbopol 934P is specially tailored for pharmaceutical industries. It can be useful for internal pharmaceutical dosage forms. Carbopol 934P is high purity grade and used
for thickening, suspending and emulsifying. It is also useful in tablets for binding and sustained release formulations.

1. Synonyms
Carboxy polymethylene, carboxyvinyl polymer

2. Chemical property
**Chemical name:** carboxy polymethylene

**Chemical structure:**

![Chemical structure](image)

**Nonproprietary name:**
carbopol 940 L R, carbomer, carbomera

**Functional category:**
Bioadhesive, suspending agent, viscosity increasing agent, release modifying agent, tablet binder.

3. Physical properties

**Description:**
A white, fluffy, acidic, hygroscopic powder with a slight characteristic odour.

**Typical properties:**
Carbopol is soluble in water, alcohol, and glycerin. Agents that can neutralize carbopol include sodium hydroxide, potassium hydroxide, sodium bicarbonate, borax, amino acids, polar organic amines.

**Specific gravity:** 1.41

**Density (bulk):** 5 g/cm³

**Density (tapped):** 1.4 g/cm³

**Viscosity (0.5% w/v):** 40-60 poise

**Acidity/ alkalinity:** pH = 2.7-3.5 for a 0.5 % w/v aqueous dispersion,
pH = 2.5-3.0 for a 1 %w/v aqueous dispersion.

4. Applications of carbopol in pharmaceutical formulation or technology

Carbopol are mainly used in liquid or semisolid pharmaceutical formulations as suspending or viscosity-increasing agents. Formulations include creams; gels, and ointments for use in ophthalmic, rectal, and topical preparations. Carbomer grades, even with low residual benzene content, such as Carbopol 934P, are no longer included in the PhEur 2002. Carbopol having low residuals only of ethyl acetate, such as Carbopol 971P or 974P, may be used in oral preparations, in suspensions, tablets, or sustained release tablet formulations. In tablet formulations, Carbopols are used as dry or wet binders and as a rate controlling Excipients. In wet granulation processes, water or an alcohol-water blend is used as the granulating fluid. Anhydrous organic solvents have also been used, with the inclusion of a polymeric binder. The tackiness of the wet mass can be reduced with the addition of certain cationic species to the granulating fluid or, in the case of water, with talc in the formulation.

Carbopol resins have also been investigated in the preparation of sustained release matrix beads, as enzyme inhibitors of intestinal proteases in peptide-containing dosage forms, as a bioadhesive for a cervical patch and for intranasally administered microspheres, and in magnetic granules for site-specific drug delivery to the esophagus.

Carbopols are also employed as emulsifying agents in the preparation of oil-in-water emulsions for external use. For this purpose, the Carbopol is neutralized partly with sodium hydroxide and partly have been investigated as a viscosity increasing aid in the preparation of multiple emulsions.

1.6.5 Hydroxypropyl methyl cellulose\textsuperscript{119-122}

Hydroxypropyl methyl cellulose is mixed hydroxyl alkyl cellulose ether and may be regaded as the propylene glycol ether of methyl cellulose. It is available in many grades of different viscosity range from 5 to 100000 cps.

1. Chemical properties

Chemical name and CAS registry number: cellulose, 2-hydroxypropyl methyl ether (9004-65-3)
Chapter 1

Introduction

Nonproprietary name: BP: Hypromellose, JP: Hydroxypropyl methyl cellulose, PhEurr: Hypromellosum, USP: Hypromellose

Chemical structure:

Where,

n is number of glucose units in cellulose molecule.

R is CH₃ or CH₂CH(OH)CH₃.

Viscosity (2% aqueous solution)

<table>
<thead>
<tr>
<th>HPMC</th>
<th>Viscosity (cps)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K100 LV</td>
<td>100</td>
</tr>
<tr>
<td>A15 C 2,000</td>
<td>2,000</td>
</tr>
<tr>
<td>K4M</td>
<td>4,000</td>
</tr>
<tr>
<td>K15M</td>
<td>15,000</td>
</tr>
<tr>
<td>K100M</td>
<td>1,000,000</td>
</tr>
</tbody>
</table>

Functional category

Oating agent, film former, rate-controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity increasing agent.

2. Physical properties

Description: Appearance: white or off-white powder, odorless, tasteless

Particle size: about 98.5% through 100 mesh; 100% through 80 meshes.

Carbonation temperature: 280-300°C

Specific gravity: 1.26-1.31

Temperature to change color: 190-200°C

Surface tension: 42-56 dyne/cm (2% solution).

Acidity/alkalinity: pH 5.5-8.0 for a 1% w/w aqueous solution

Ash: 1.5-3% depending upon the grade

Density (bulk): 0.341 g/cm³

Density (tapped): 0.557 g/cm³

Density (true): 1.326 g/cm³
**Glass transition temperature:** 170-180°C

**Moisture content**
Hypromellose absorbs moisture from the atmosphere, the amount of water absorbed depending upon the initial moisture content and the temperature and relative humidity of the surrounding air.

**Solubility**
It is soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solution, mixtures of dichloromethane and propan-2-ol and other organic solvents.

**Stability and storage condition**
Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3-11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol-gel transformation upon heating and cooling, respectively. The gel point is 50-90°C.

**Incompatibilities**
Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.
Applications of hydroxypropyl methyl cellulose in pharmaceutical formulation or technology

It is suspending, viscosity enhancing and film forming agent. HPMC is most widely used in hydrophilic matrix sustaining release tables and other type of controlled release pharmaceutical dosage forms, because of its characteristic namely non-toxic nature, its capacity to incorporate active pharmaceutical, manufacture of tablet by direct compression without previous granulation as well as pH independent nature.

1.6.6 Polyvinyl pyrrolidone

PVP (polyvinyl pyrrolidone, povidone, polyvidone) is a water-soluble polymer made from the monomer N-vinyl pyrrolidone:

1. Synonyms
   Polvinylpolypyrrolidone; N-Vinylbutyrolactam polymer; poly[1-(2-oxo-1-pyrrolidinyl)ethylene];

2. Chemical properties
   Chemical name
   1-Ethenyl-2-pyrrolidoinone homopolymer (IUPAC); Poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer
   CAS Registry Number 9003-39-8
   Empirical formula (C6H9NO)n
   Structural formula

   ![Structural formula of Polyvinyl pyrrolidone](image)

   Molar mass 2.500 - 2.5000.000 g·mol⁻¹
   Functional category Stabilizing agent, binding agent

4. Physical properties
   Description White to light yellow, hygroscopic, amorphous powder
   Density 1.2 g/cm³
   Melting point 110 - 180 °C (glass temperature)
Stability and storage condition
Keep in a tightly closed container, stored in a cool, dry, ventilated area. Protect against physical damage. Isolate from incompatible substances. Containers of this material may be hazardous when empty since they retain product residues (dust, solids); observe all warnings and precautions listed for the product.

Incompatibilities:
It is incompatible with strong oxidizing agent and strong reducing agents.

4. Application in Pharmaceutical Formulation or Technology
It is used as a binder in tablet formulations. PVP added to Iodine forms a complex in solution which is known under the trade name Betadine. PVP also used as coating agent for photo-quality ink-jet papers and transparencies, as well as in inks for inkjet printers. PVP is used in shampoos and toothpastes, in paints, and adhesives. It is also used in contact lens solutions and in steel-quenching solutions. PVP is used in hair sprays, hair gels, as a food additive, as a stabilizer, as a blocking agent during Western blot analysis.