Introduction
1. Introduction:
Over the past 30 years, as the expenses and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery (CDD), greater attention has been focused on development of controlled-release drug delivery system (CRDDS). This has been due to various factors viz. the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. Now-a-days, the technology of controlled release is also being applied to veterinary products.

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body and then maintain the desired drug concentration. That is, the drug delivery system should deliver drug at a rate dictated by the needs of the body over the period of treatment. The goal in designing controlled drug delivery system (CDDS) is to reduce the frequency of dosing and /or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery.

To deliver the therapeutic agent to a specific site for a specific period of time, the two aspects are most important to drug delivery; viz., spatial placement and temporal delivery of the drug. In other words, the system attempts to control drug concentration in the target tissue \(^1\). Spatial placement relates to targeting a drug to a specific organ or a tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. An appropriately designed CRDDS can be a major advance towards solving these two problems. It is for this reason that the science and technology responsible for development of CR pharmaceuticals have been and continue to be the focus of a great deal of attention in both industrial and academic laboratories.

1.1 Rationale of Controlled Drug Delivery \(^2\)
The basic rationale for CRDDS is to optimize the biopharmaceutical, pharmacokinetic and pharmacodynamics properties of pharmacologically active moieties in such a way that its utility is maximized through reduction in side-effects and cure or control of disease condition in the shortest possible time by using smallest quantity of drug, administered by the most suitable route.
1.2 Terminology \(^2,3\)

Controlled Drug delivery is the phasing of the drug administration to needs of a condition at hand so that an optimal amount of drug is used to cure or control the condition in minimum time. The term 'controlled release' includes not only the notion of prolonged duration as implied by the term 'sustained release' but goes further in denoting predictability and reproducibility of release kinetics.\(^4\)

1.3 Advantages of Controlled Release Dosage Forms \(^5,6,7\)

1. Improved Patient Compliance
   - Reduced 'see-saw' fluctuation

![Figure 1.1: Drug blood level versus time profile](image)

2. Economy:
   - Average cost of treatment over an extended period may be less.
   - Decrease in nursing time and hospitalization
   - Reduce amount of drug administration
   - Maximizing availability with a minimum dose
   - Safety margin of high potency drugs can be increased.

3. Improved therapy
   - Sustained blood level
   - Attenuation of adverse effects

1.4 Disadvantages of Controlled Release Dosage Forms: \(^6,7\)

- **Dose dumping** due to food, physiological or formulation variables or chewing or grinding of oral formulations by the patient and thus, increased risk of toxicity. \(^10\)
Less flexibility in accurate dose adjustment as CR property may get lost, if dosage form is fractured.

Poor in vitro – in vivo correlation

Co-administration of other drugs, presence or absence of food and residence time in GI tract is different among patients which gives rise to variation in clinical response among the patient.

Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.

Higher cost of formulations.

1.5 Factors in the Design of CRDDS:

The various factors to be considered in the design of CRDDS as mentioned in Table 1.1

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Properties of Candidate Drug</th>
<th>Desired Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Biopharmaceutic Properties</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Molecular size</td>
<td>Less than 600 Daltons</td>
</tr>
<tr>
<td>2.</td>
<td>Aqueous solubility</td>
<td>More than 0.1 mg/mL</td>
</tr>
<tr>
<td>3.</td>
<td>Partition coefficient Ko/w</td>
<td>1-2</td>
</tr>
<tr>
<td>4.</td>
<td>Dissociation constant pKa</td>
<td>Acidic drugs, pKa &gt; 2.5 Basic drugs, pKa &lt; 11.0</td>
</tr>
<tr>
<td>5.</td>
<td>Ionisation at physiological pH</td>
<td>Not more than 95%</td>
</tr>
<tr>
<td>6.</td>
<td>Stability in GI milieu</td>
<td>Stable at both gastric and intestinal pH</td>
</tr>
<tr>
<td>7.</td>
<td>Absorption mechanism</td>
<td>Passive, but not through a window</td>
</tr>
<tr>
<td>B. Pharmacokinetic Properties</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Absorption rate constant Ka</td>
<td>High</td>
</tr>
<tr>
<td>2.</td>
<td>Elimination Half life t(_{1/2})</td>
<td>2-6 hours</td>
</tr>
<tr>
<td>3.</td>
<td>Metabolism rate</td>
<td>Not too high</td>
</tr>
<tr>
<td>4.</td>
<td>Dosage form index</td>
<td>One</td>
</tr>
<tr>
<td>C. Pharmacodynamic properties</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Dose</td>
<td>Maximum 1.0 g (in CR form)</td>
</tr>
<tr>
<td>2.</td>
<td>Therapeutic range</td>
<td>Wide</td>
</tr>
<tr>
<td>3.</td>
<td>Therapeutic index</td>
<td>Wide</td>
</tr>
<tr>
<td>4.</td>
<td>PK/PD relationship</td>
<td>Good</td>
</tr>
</tbody>
</table>

1.6 MATRIX TABLETS:)

These are one of the most widely used dosage forms within CR techniques in pharmaceutical manufacturing standards, as drug release rates are controlled mainly by the type and proportion of excipients used in the preparations and no complex production procedures such as coating and pelletization are required.

Matrix devices have a major advantage over other CR devices, as they cannot undergo sudden dose dumping and relatively easy to fabricate compared to reservoir devices. This
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gives a higher initial release rate and can be made to release at a nearly constant rate. In matrix device the active agent is present as dispersion within the polymer matrix, and they are typically formed by the compression of a polymer/drug mixture or by dissolution or melting.

The drug release properties of monolithic devices (Figure 1.2) is dependent upon-

a. Initial concentration of drug in the matrix.
b. Solubility of the drug.
c. Presence of water soluble additives or surfactants that create pores and/or facilitate water permeation in the matrix and wetting of drug.
d. Porosity and tortuosity of matrix as influenced by compression force.
e. Polymer system forming the matrix.

Figure 1.2 shows the overall mechanisms involved while the matrix undergoes hydration, swelling and drug release.

![Matrix (monolithic) Drug Delivery System](image)

The drawback of conventional matrix-type delivery systems is their first order drug delivery mechanism in which the release rate of drug decreases proportionately over time caused by changing surface area and drug diffusion path length with time. The polymer when incorporated into pharmaceutical dosage forms such as tablets by manipulating tablet geometry, polymer variables and formulation aspects have been shown a tendency to linearise the drug release curves and gives zero order release.9

Some examples of such designs are multilayer matrices as bilayer or trilayer matrices. In recent times, multi-layer matrix tablets are gaining importance in the design of oral CDDS. One or two layers of release retardant polymer are applied on both sides of a matrix tablet such that the swollen hydrophilic polymer controls the drug release after oral administration. These formulations are designed to deliver the drugs at a controlled and predetermined rate, maintaining their therapeutically effective concentrations in systemic circulation for prolonged periods of time. The widely used polymers for
controlling the drug delivery are HPMC, NaCMC, Chitosan, HPC, MC, Eudragits, Natural gums etc.

Due to these unique designs of tablets coupled with polymer properties and formulation components enable to achieve desired drug release patterns such as-

- **Zero order release** – a constant rate of drug release over a defined period of time.

![Controlled release is achieved by constructing a tablet of two basic components](image)

**Figure 1.3: Trilayer Matrix Tablet Design with Drug in Central Layer**

- Binary controlled release – of two different drugs in a single tablet.
- Quick-slow release – to provide a quick burst of drug release followed by constant rate of release over a defined period of time.
- Slow-quick release – to provide an initial constant rate of release followed by a quick burst of drug release at a predetermined time.
- Positioned release – that delivers the drug to a predetermined position in the digestive system before it begins to release the active drug compounds.
- Accelerated release – that provides a constantly accelerating rate of drug release.
- Delayed release – that provides a predetermined time lag before it begins releasing drug molecules.
- Multiple pulse release – that provides an initial quick burst of drug release followed by a predetermined period of no release.

### 1.6.1 RESERVOIR SYSTEM: laminated matrix device.

- Hollow system containing an inner core surrounded in water insoluble membrane.
- Polymer can be applied by coating or micro encapsulation.
- Rate controlling mechanism - partitioning into membrane with subsequent release into surrounding fluid by diffusion.
- Commonly used polymers - HPC, ethyl cellulose & polyvinyl acetate.
• Zero order drug delivery is possible.
• Release rate can be easily modulated by polymer type, polymer membrane thickness and membrane porosity.
• Examples: Nico-400, Nitro-Bid
• Disadvantages as possibility of dose dumping and higher cost of formulation compared to matrix formulation.

![Figure 1.4: Reservoir system](image)

1.7 MECHANISMS OF DRUG RELEASE FROM MATRIX SYSTEMS:
The release of drug from controlled devices is via dissolution or diffusion or a combination of the two mechanisms.

1.7.1: DISSOLUTION CONTROLLED SYSTEMS:
A drug with slow dissolution rate will demonstrate sustaining properties, since the release of the drug will be limited by the rate of dissolution. In principle, it would seem possible to prepare CR products by decreasing the dissolution rate of drugs that are highly water-soluble.

This can be done by:

- Preparing an appropriate salt or derivative
- Coating the drug with a slowly dissolving material – encapsulation dissolution control
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- Incorporating the drug into a tablet with a slowly dissolving carrier–matrix dissolution control (a major disadvantage is that drug release rate continuously decreases with time). 10

The dissolution process can be considered diffusion-layer-controlled, where the rate of diffusion from the solid surface to the bulk solution through an unstirred liquid film is the rate-determining step. The dissolution process at steady-state is described by the Noyes-Whitney equation:

\[
\frac{dC}{dt} = k_D \cdot A \cdot (C_s - C) = \frac{D}{h} \cdot A \cdot (C_s - C)
\]  

Where, \( \frac{dC}{dt} \) - Dissolution rate; \( k_D \) - The dissolution rate constant (equivalent to the diffusion coefficient divided by the thickness of the diffusion layer \( D/h \)); \( D \) - Diffusion coefficient; \( C_s \) - Saturation solubility of the solid; \( C \) - Concentration of solute in the bulk solution

Equation (1) predicts that the rate of release can be constant only if the following parameters are held constant as Surface area, Diffusion coefficient, Diffusion layer thickness and Concentration difference. These parameters, however, are not easily maintained constant, especially surface area, and this is the case for combination of diffusion and dissolution systems. 10

1.7.2: DIFFUSION CONTROLLED SYSTEMS:

Diffusion systems are characterized by the release rate of a drug being dependent on its diffusion through an inert membrane barrier. 11 Usually, this barrier is an insoluble polymer. In general, two types or subclasses of diffusional systems are recognized: reservoir devices and matrix devices. It is very common for the diffusion-controlled devices to exhibit a non-zero order release rate due to an increase in diffusional resistance and a decrease in effective diffusion area as the release proceeds. 12

Diffusion in matrix devices- In this model, drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows obviously that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix. 10
Derivation of the mathematical model to describe this system involves the following assumptions:

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

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

c) The diffusion coefficient of drug in the matrix remains constant (no change occurs in the characteristics of the polymer matrix)  

d) The bathing solution provides sink conditions at all times;

e) No interaction occurs between the drug and the matrix;

f) The total amount of drug present per unit volume in the matrix is substantially greater than the saturation solubility of the drug per unit volume in the matrix (excess solute is present);  

g) Only the diffusion process occurs;

For a homogenous monolithic matrix system, corresponding to the schematic in Figure 1.7, the release behavior can be described by the following equation:

\[
\frac{dM}{dh} = C_0 \cdot dh - \frac{C_s}{2}
\]

(2)

Where dM - Change in the amount of drug released per unit area
dh - Change in the thickness of the zone of matrix that has been depleted of drug

\( C_0 \) - Total amount of drug in a unit volume of matrix

\( C_s \) - Saturated concentration of the drug within the matrix

If the release of drug from matrix is diffusion-controlled, one may control the release of drug from a homogeneous matrix system by varying the following parameters as initial concentration of drug in the matrix, porosity, tortuosity, polymer system forming the matrix and solubility of the drug

In a hydrophilic matrix, there are two competing mechanisms involved in the drug release: Fickian diffusional release and relaxation release. Diffusion is not the only pathway by which a drug is released from the matrix; the erosion of the matrix following polymer relaxation contributes to the overall release. The relative contribution of each component to the total release is primarily dependent on the properties of a given drug. For example, the release of a sparingly soluble drug from hydrophilic matrices involves the simultaneous absorption of water and desorption of drug via a swelling-controlled diffusion mechanism. As water penetrates into a glassy polymeric matrix, the polymer swells and its glass transition temperature is lowered. At the same time, the dissolved drug diffuses through this swollen rubbery region into the external releasing medium. This type of diffusion and swelling does not generally follow a Fickian diffusion mechanism. \( ^{14, 15} \) introduced a semi-empirical equation to describe drug release behaviour from hydrophilic matrix systems:

\[
Q = k \cdot t^n
\]  

(3)

Where, \( Q \) is the fraction of drug released in time \( t \), \( k \) is the rate constant incorporating characteristics of the macromolecular network system and the drug and \( n \) is the diffusional exponent.

It has been shown that the value of \( n \) is indicative of the drug release mechanism.

For \( n=0.5 \), drug release follows a Fickian diffusion mechanism that is driven by a chemical potential gradient.

For \( n=1 \); drug release occurs via the relaxation transport that is associated with stresses and phase transition in hydrated polymers.

For \( 0.5 < n < 1 \); non-Fickian diffusion is often observed as a result of the contributions from diffusion and polymer erosion. \( ^{14} \)

In order to describe relaxation transport, \( ^{16} \) introduced a second equation (13) term in
Comparative Study of Formulation and Evaluation of Controlled Release drug with different Polymeric Substances

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\[
Q = k_1 \cdot t^n + k_2 \cdot t^{2n}
\]  

(4)

Where, \( k_1 \) and \( k_2 \) - Constants reflecting the relative contributions of Fickian and relaxation mechanisms.

In the case the surface area is fixed, the value of \( n \) should be 0.5 and equation (14) becomes:

\[
Q = k_1 \cdot t^{0.5} + k_2 \cdot t
\]  

(5)

Where, the 1\textsuperscript{st} & 2\textsuperscript{nd} term represent drug release due to diffusion and polymer erosion, respectively. \(^{14}\)

1.7.3: BIOERODIBLE DIFFUSION AND DISSOLUTION SYSTEMS:

Strictly speaking, therapeutic systems will never be dependent on dissolution or diffusion only. In practice, the dominant mechanism for release will overshadow other processes enough to allow classification as either dissolution rate-limited or diffusion-CR. \(^{10}\)

As a further complication these systems can combine diffusion and dissolution of both the drug and the matrix material. Drugs not only can diffuse out of the dosage form, as with some previously described matrix systems, but also the matrix itself undergoes a dissolution process. The complexity of the system arises from the fact that as the polymer dissolves the diffusional path length for the drug may change. This usually results in moving boundary diffusion system. Zero-order release is possible only if surface erosion occurs and surface area does not change with time.

Swelling-controlled matrices exhibit a combination of both diffusion and dissolution mechanisms. Here the drug is dispersed in the polymer of which swelling occurs. This allows for the entrance of water, which causes dissolution of the drug and diffusion out of the swollen matrix. In these systems the release rate is highly dependent on the polymer-swelling rate and drug solubility. This system usually minimizes burst effects, as rapid polymer swelling occurs before drug release. \(^{10}\)

Figure 1.8: Dissolution & Diffusion Controlled Release system
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With regards to swellable matrix systems, different models have been proposed to describe the diffusion, swelling and dissolution processes involved in the drug release mechanism. However, the key element of the drug release mechanism is the forming of a gel layer around the matrix, capable of preventing matrix disintegration and further rapid water penetration.

When a matrix that contains a swellable glassy polymer comes in contact with a solvent or swelling agent, there is an abrupt change from the glassy to the rubbery state, which is associated with the swelling process. The individual polymer chains, originally in the unperturbed state absorb water so that their end to-end distance and radius of gyration expand to a new solvated state. This is due to the lowering of the transition temperature of the polymer (Tg), which is controlled by the characteristic concentration of the swelling agent and depends on both temperature and thermodynamic interactions of the polymer–water system. A sharp distinction between the glassy and rubbery regions is observed and the matrix increases in volume because of swelling. On a molecular basis, this phenomenon can activate a convective drug transport, thus increasing the reproducibility of the drug release. The result is an anomalous non-Fickian transport of the drug, owing to the polymer-chain relaxation behind the swelling position. This, in turn, creates osmotic stresses and convective transport effects.

The gel strength is important in the matrix performance and is controlled by the concentration, viscosity and chemical structure of the rubbery polymer. This restricts the suitability of the hydrophilic polymers for preparation of swellable matrices. Polymers such as carboxymethyl cellulose, hydroxypropyl cellulose or tragacanth gum, do not form the gel layer quickly. Consequently, they are not recommended as excipients to be used alone in swellable matrices.

The swelling behaviour of heterogeneous swellable matrices is described by front positions, where ‘front’ indicates the position in the matrix where the physical conditions sharply change. Three fronts are present as shown in Figure 1.9:

- The ‘swelling front’ clearly separates the rubbery region (with enough water to lower the Tg below the experimental temperature) from the glassy region (where the polymer exhibits a Tg that is above the experimental temperature).
- The ‘erosion front’ separates the matrix from the solvent. The gel-layer thickness as a function of time is determined by the relative position of the swelling and erosion moving fronts.
The ‘diffusion front’ located between the swelling and erosion fronts, and constituting the boundary that separates solid from dissolved drug, has been identified. During drug release, the diffusion front position in the gel phase is dependent on drug solubility and loading and is also related to drug dissolution rate in the gel.

Drug release is controlled by the interaction between water, polymer and drug. The delivery kinetics depends on the drug gradient in the gel layer. Therefore, **drug concentration** and **thickness of the gel layer** governs the drug flux. **Drug concentration** in the gel depends on drug loading and solubility. **Gel-layer thickness** depends on the relative contributions of solvent penetration, chain disentanglement and mass (polymer and drug) transfer in the solvent. Initially solvent penetration is more rapid than chain disentanglement, and a rapid build-up of gel-layer thickness occurs. However, when the solvent penetrates slowly, owing to an increase in the diffusional distance, little change in gel thickness is observed since penetration and disentanglement rates are similar. Thus, gel-layer thickness dynamics in swellable matrix tablets exhibit three distinct patterns. The thickness increases when solvent penetration is the fastest mechanism, and it remains constant when the disentanglement and water penetration occur at a similar rate. Finally, the gel-layer thickness decreases when the entire polymer has undergone the glassy–rubbery transition. In conclusion, the central element of the release mechanism is a gel-layer forming around the matrix in response to water penetration. Phenomena that govern gel-layer formation, and consequently drug-release rate, are water penetration, polymer swelling, drug dissolution and diffusion, and matrix erosion.

![Diagram of fronts in a swellable HPMC matrix](image)

**Figure 1.9: The fronts in a swellable HPMC matrix**

**1.8: MATRIX TABLET TYPES:**

Compression embedding technique has received increasing attention to prepare CR matrix tablets, and intensive research in this area is being conducted by pharmaceutical scientists.
1.8.1: HYDROPHILIC MATRICES
In hydrophilic matrices, the matrix may be tableted by direct compression of the blend of active ingredients and certain hydrophilic carriers, where hydrophilic matrix requires water to activate the release mechanism and enjoys several advantages, including ease of manufacture and excellent uniformity of matrix tablets. Drug release is controlled by a gel diffusion barrier that is formed and tablet erosion.

1.8.1.1: Components of Hydrophilic Matrix Delivery Systems:
There are various components of hydrophilic matrices as active drug, hydrophilic colloid(s)/polymers, Fillers, Matrix modifier, Compression aid, Lubricant, Glidant etc.

1. Drug properties:
From formulation perspective, drug solubility and dose are the most important factors to consider in the design of CR matrices. In general, CR formulations at the extremes of solubility profiles along with high dose are challenging. Drugs with low aqueous solubility (e.g. < 0.01 mg/mL) may dissolve slowly and have slow diffusion through gel layer of hydrophilic matrix. Therefore the main mechanism would be through erosion of the surface of the hydrated matrix. For drugs with very high solubility, the drug dissolves quickly when exposed to dissolution medium even before complete hydration and gel formation on the tablet surfaces. Hence for such drugs, burst release is often seen.

Figure 1.10 gives a simple dose-solubility map of API's and inherent formulation considerations involved in formulating CR hydrophilic matrix tablet.

- Content uniformity is an inherent concern for low dose drugs and in some cases they may reach a plateau of drug release profile at the end of the dissolution. In these cases, special attentions will need to be given to blending and granulation processes.

On the other hand, matrix formulations of high dose drugs (> 500 mg) require careful polymer and excipients selection to provide optimized overall dosage size acceptable for oral administration. With high dose drugs, whether highly soluble or insoluble, the quantity of polymer is critical to reasonable sized-tablets, but maintains formulation robustness.

The content uniformity of the polymer inter - and intra - matrix tablet must be guaranteed to ensure robustness. In general, API's with medium dose and solubility are hence very attractive to formulate in CR hydrophilic matrix tablet and there are many successful formulation examples in the market place.
➤ **Effect of drug polymer ratio on release profile:** Drug to polymer ratio is another important parameter to consider during hydrophilic matrix formulation development. An increase in polymer concentration will lead to an increase in the viscosity of the gel layer (gel strength), slower erosion and thus longer diffusional path for drug release. This could cause a decrease in the effective diffusion of the drug and therefore a reduction in the drug release rate.

➤ **Effect of drug particle size:** It has been reported that, for highly soluble drugs, as the loading is increased, the release rate increases due to greater channel formation in the swollen matrix. The channel size is dependent on drug particle size and leads to promotion of complete release.

For poorly soluble drugs, as described above, the particle size affects rate of dissolution of the drug and thus it will affect diffusion and erosion mechanisms. There is a potential for dose dumping with poorly soluble drugs with large particle size distribution, when the formulation contains low polymer concentrations.

![Figure 1.10: Dose-solubility map and hydrophilic matrix formulation consideration](image)

2. **Matrix forming agents for hydrophilic matrices:**

Hydrogel polymers occupy 20 – 80% of the mass and amount will depend on the drug and the desired release characteristics. Hydration and swelling are the key factors of them. They include hydrophilic polymers which are listed in following Table 1.2.
Table 1.2: List of Commonly Hydrophilic Matrix Polymers in CR Tablets:

<table>
<thead>
<tr>
<th>Type</th>
<th>Swelling characteristics</th>
<th>Source</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CELLULOSICS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypromellose (HPMC)</td>
<td>pH independent</td>
<td>Semi-synthetic</td>
<td>Different chemistries such as 2208 (METHOCEL™ K) and 2910 (METHOCEL™ E) and different viscosity grades (such as K100 LV, K4M, K15M, K100M, K200M) are available. Polymer of choice for CR tablets. The hydroxypropoxyl substitution and methoxyl substitution gives particular hydration and erosion characteristics to it.</td>
</tr>
<tr>
<td>Hydroxypropyl cellulose (HPC)</td>
<td>pH independent</td>
<td>Semi-synthetic</td>
<td>Available in different viscosities. Polymer hydration and erosion only controlled via hydroxypropoxyl substitution. Higher viscosity grades have shown to work synergistically with HPMC.</td>
</tr>
<tr>
<td>Hydroxyethyl cellulose (HEC)</td>
<td>pH independent</td>
<td>Semi-synthetic</td>
<td>Available in different viscosities. Polymer hydration and erosion only controlled via hydroxyethoxyl substitution</td>
</tr>
<tr>
<td>Na Carboxymethyl cellulose (NaCMC)</td>
<td>pH independent</td>
<td>Semi-synthetic</td>
<td>It is ionic in nature and pH dependent swellable polymer. A Na-CMC matrix does not fully hydrate to form a gel when placed in SGF/0.1N HCl and it may disintegrate to cause dose dumping. It may be used in combination with HPMC.</td>
</tr>
<tr>
<td><strong>NON-CELLULOSICS, GUMS/POLYSACCHARIDES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium alginate</td>
<td>pH dependent</td>
<td>Natural</td>
<td>Sodium alginate is a pH dependent polymer and natural in origin. It forms insoluble complex with calcium salt. It may be used in combination with HPMC.</td>
</tr>
<tr>
<td>Xanthan gum (XG)</td>
<td>pH dependent</td>
<td>Natural</td>
<td>Available in different viscosity grades. Acts synergistically with other hydrophilic matrix polymers.</td>
</tr>
<tr>
<td>Carrageenan</td>
<td>pH dependent</td>
<td>Natural</td>
<td>Available in different forms such as alpha, gamma and lambda. Acts synergistically with other hydrophilic matrix polymers.</td>
</tr>
<tr>
<td>Locust bean gum (Ceratonia)</td>
<td>pH dependent</td>
<td>Natural</td>
<td>Since natural origin it is prone to variability. It has been used synergistically along with other hydrophilic polymers in matrix tablets.</td>
</tr>
<tr>
<td>Guar gum (GG)</td>
<td>pH independent</td>
<td>Natural</td>
<td>This is natural in origin and may be prone to higher microbial content and also variability. It has been used synergistically along with other hydrophilic polymer in matrix tablets.</td>
</tr>
<tr>
<td><strong>NON-CELLULOSICS OTHERS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyethylene oxide (PEO)</td>
<td>pH independent</td>
<td>Synthetic</td>
<td>Available in different viscosity grades as POLYOX™. It is a linear polymer, non-ionic, pH independent, highly swellable and fastest hydrating polymer. It is successfully used in osmotic tablets and hydrophilic matrix tablets.</td>
</tr>
<tr>
<td>Carbopol</td>
<td>pH dependent</td>
<td>Synthetic</td>
<td>Available in different viscosity grades as Carbopol 934P, 974P, 971P, 71G and Polycarbophil. It is high molecular weight, crosslinked polymer. The release tend to be more diffusion controlled in the lower pH region (stomach), while at higher pH (intestine), the drug release mechanism is more polymer relaxation controlled. It is readily hydrates, absorbs water and swell. It’s hydrophilic and highly crosslinked nature makes it a potential candidate for CR drug delivery systems.</td>
</tr>
</tbody>
</table>
3. Fillers:
Fillers or diluents comprise another most important part of hydrophilic matrix composition. Different types of fillers are given in Table 1.3.

Fillers can be classified as:

i. Highly water soluble fillers, either non-ionic such as mono or di-saccharides or ionic such as salts.

ii. Water insoluble fillers, swellable, non-ionic such as cellulose class, or ionic, such as calcium salts and

iii. Partially soluble and partially swellable.

The way fillers would work is that, if they are highly water soluble, then they would dissolve in the water entrapped by the swollen gel layer of hydrophilic matrix. This would result in either formation of water filled pores within the gel layer or dilution of the gel structure resulting in faster erosion. As a result, the drug release rate would be positively affected, i.e. increased. If the filler is insoluble in nature, then it would not result in water filled pores or dilution of gel layer and hence as a result, the drug release would not be increased. If the diluent is highly ionic then the gel strength of the lower viscosity grade of matrix tablet may be affected.

Table 1.3: Different Fillers Used In CR Hydrophilic Matrix Tablets:

<table>
<thead>
<tr>
<th>Solubility in water</th>
<th>Examples</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>WATER SOLUBLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monosaccharides</td>
<td>Glucose (dextrose), mannitol, xylitol, etc.</td>
<td>Cause faster hydration of hydrophilic polymer and thus faster release profiles due to channeling effect.</td>
</tr>
<tr>
<td>Disaccharides</td>
<td>Sucrose, lactose, etc</td>
<td></td>
</tr>
<tr>
<td>WATER INSOLUBLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulose derivatives</td>
<td>Microcrystalline cellulose</td>
<td>Slower release than soluble diluents. Wicking effect but lack of channeling</td>
</tr>
<tr>
<td>Mineral salts</td>
<td>Dicalcium phosphate,</td>
<td>May interact with certain drugs due to alkaline nature and also being ionic in nature.</td>
</tr>
<tr>
<td>PARTIALLY SOLUBLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starch derivative</td>
<td>Partially pregelatinized starch</td>
<td>Acts synergistically with HPMC to enhance gel strength</td>
</tr>
</tbody>
</table>

4. Matrix modifiers: Incorporated into matrix to modify the diffusional characteristics of gel layer, usually to speed-up the dissolution. e.g. Sugars, polyols and soluble salts.
5. **Solubilizers and pH modifiers:** Improve dissolution e.g., PEGs, polyols, surfactants etc.) The only restriction is that the formulation can be formed into a tablet and that the material is acceptable. Many drugs are ionizable. The inclusion of appropriate counter-ions can facilitate release from the system. Some materials can act as both dissolution enhancer and matrix modifier; the amount needed will be determined by the amount of drug.

6. **Lubricants:** They
   - Reduce inter-particulate friction during compression and compaction.
   - Reduce die wall friction
   - Prevent sticking to the punches
   - Improve flow of the formulation on the machine and into the die.

### Table 1.4: Concentration Of Lubricants Used In Hydrophilic Matrix Systems:

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Lubricants</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hydrophilic lubricants</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a. Magnesium stearate</td>
<td>0.25-2</td>
</tr>
<tr>
<td></td>
<td>b. Calcium stearate</td>
<td>0.25-2</td>
</tr>
<tr>
<td></td>
<td>c. Stearic acid</td>
<td>1-4</td>
</tr>
<tr>
<td></td>
<td>d. Hydrogenated vegetable oil</td>
<td>1-4</td>
</tr>
<tr>
<td>2</td>
<td>Hydrophilic lubricants (the later 2 are partially soluble in water)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a. Glyceryl palmitostearate</td>
<td>0.5-5</td>
</tr>
<tr>
<td></td>
<td>b. Glyceryl behenate</td>
<td>2-5</td>
</tr>
<tr>
<td></td>
<td>c. Sodium stearyl fumarate</td>
<td>0.25-2</td>
</tr>
<tr>
<td>3</td>
<td>Inorganic lubricants</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a. Colloidal silicon dioxide</td>
<td>0.05-0.25 as glidant</td>
</tr>
<tr>
<td></td>
<td>b. Talc</td>
<td>0.2-1.0 as anti-adherent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-4 as anti-adherent</td>
</tr>
</tbody>
</table>

1.8.1.2: **Mechanism of Drug Release from Hydrophilic Matrices:**

After oral administration and exposure to aqueous medium, the polymer in hydrophilic matrix tablet quickly hydrates on the surface and forms a gel layer around the tablet. This phenomenon is also referred to glassy to rubbery state transition of polymer. The outermost layer of gelled polymer reaches a dilution point where it no longer has structural integrity and the polymer finally is entangles and leaves the surface of the matrix. This phenomenon is referred to as erosion.

On a molecular level, a highly coiled long chain and branched molecule when comes in contact with water, starts uncoiling due to formation of hydrogen bond with water, Figure
1.11. This initial hydration of the polymeric molecule is seen as a viscous gel layer formation, causing an increased in the volume of the matrix (this mechanism is referred to as swelling). As time progresses and more and more polymeric molecular chain gets uncoiled due to hydration, weaker the gel becomes on the outer region of the gel structure. Finally when the entire polymeric molecule is uncoiled, (fully hydrated, mechanism referred to as relaxation), it finally disentangles from the surface of the matrix (referred to as erosion or dissolution).

![Figure 1.11: Hydrophilic polymer dissolution](image)

1.8.1.3: Key attributes for a successful CR hydrophilic matrix include:

1. Fast hydration of surface polymer and gel formation (to prevent burst release of soluble to highly soluble drugs).
2. Uniform distribution of polymer in the matrix (to give consistent swelling / erosion intra and inter tablet batch)
3. Sufficient polymer concentration on the tablet surface as well as inside the tablet to prevent pre-mature tablet disintegration (extremely crucial to prevent dose-dumping)
4. Smaller particle size of polymer (in order to have uniform distribution within the tablet and also to hydrate faster due to high surface area)
5. High / sufficient gel strength of the polymer to prevent variation in drug release in fasted or fed state
6. Inert to different gastro-intestinal fluid conditions (especially pH, osmotic pressure, ionic content in fasted and fed state).

Drug release from the hydrophilic matrices, takes place via:

1. Diffusion of water soluble drugs through the hydrated gel layer
2. Diffusion and erosion of insoluble drug
3. A combination of above for most drugs

As solubility of the drug reduces, the erosion mechanism becomes more prominent.
1.8.1.4: Effect of release limiting parameters on drug release:
The mechanistic analysis of CR of drug reveals that partition coefficient; diffusivity; diffusional path thickness and other system parameters play various rate determining roles in the CR of drugs from either capsules, matrix or sandwich type DDS.

A. Polymer hydration:
It is important to study polymer hydration/swelling process for the maximum number of polymers and polymeric combinations. The most important step in polymer dissolution include absorption/adsorption of water in more accessible places, rupture of polymer-polymer linking with the simultaneous forming of water-polymer linking, separation of polymeric chains, swelling and finally dispersion of polymeric chain in dissolution medium.

B. Drug solubility:
Molecular size and water solubility of drug are important determinants in the release of drug from swelling and erosion controlled polymeric matrices. For drugs with reasonable aqueous solubility, release of drugs occurs by dissolution in infiltrating medium and for drugs with poor solubility release occurs by both dissolution of drug and dissolution of drug particles through erosion of the matrix tablet.

C. Solution solubility:
In view of in vivo (biological) sink condition maintained actively by hemoperfusion; it is logical that all the in vitro drug release studies should also be conducted under perfect sink condition. In this way a better simulation and correlation of in vitro drug release profile with in vivo drug administration can be achieved. It is necessary to maintain a sink
condition so that the release of drug is controlled solely by the delivery system and is not affected or complicated by solubility factor.

D. Polymer diffusivity:
The diffusion of small molecules in polymer structure is energy activated process in which the diffusant molecules moves to a successive series of equilibrium position when a sufficient amount of energy of activation for diffusion $E_d$ has been acquired by the diffusant which is dependent on length of polymer chain segment, cross linking and crystallinity of polymer.

The release of drug may be attributed to the three factors as Polymer particle size, Polymer viscosity and Polymer concentration.

i. Polymer particle size: When the content of hydroxyl propyl methyl cellulose is higher, the effect of particle size is less important on the release rate of drug, the effect of this variable is more important when the polymer content is low.

ii. Polymer viscosity: With cellulose ether polymers, viscosity is used as an indication of matrix weight. Increasing the molecular weight or viscosity of the polymer in the matrix formulation increases the gel layer viscosity and thus slows drug dissolution. Also, the greater viscosity of the gel, the more resistant the gel is to dilution and erosion, thus controlling the drug dissolution.

iii. Polymer concentration: An increase in polymer concentration causes an increase in the viscosity of gel as well as formulation of gel layer with a longer diffusional path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore reduction in drug release. The mechanism of drug release from matrix also changes from erosion to diffusion as the polymer concentration increases.

E. Thickness of polymer diffusional path:
The CR of a drug from both capsule and matrix type polymeric drug delivery system is essentially governed by Fick’s law of diffusion:

$$J_D = D \frac{dc}{dx}$$
Chapter 1

Introduction

J_D - Flux of diffusion across a plane surface of unit area; D - Diffusibility of drug molecule; dc/dx - Concentration gradient of drug molecule across a diffusion path with thickness dx.

F. Thickness of hydrodynamic diffusion layer:

It was observed that the drug release profile is a function of the variation in thickness of hydrodynamic diffusion layer on surface of matrix type delivery devices. The magnitude of drug release value decreases on increasing the thickness of hydrodynamic diffusion layer $\delta_d$.

G. Drug loading dose:

The loading dose of drug has a significant effect on resulting release kinetics along with drug solubility. The effect of initial drug loading of the tablets on the resulting release kinetics is more complex in case of poorly water soluble drugs, with increasing initial drug loading the relative release rate first decreases and then increases, whereas, absolute release rate monotonically increases.

In case of freely water soluble drugs, the porosity of matrix upon drug depletion increases with increasing initial drug loading. This effect leads to increased absolute drug transfer rate. But in case of poorly water soluble drugs another phenomenon also has to be taken in to account. When the amount of drug present at certain position within the matrix, exceeds the amount of drug soluble under given conditions, the excess of drug has to be considered as non dissolved and thus not available for diffusion. The solid drug remains within tablet, on increasing the initial drug loading of poorly water soluble drugs, the excess of drug remaining with in matrix increases.

H. Surface area and volume:

The dependence of the rate of drug release on the surface area of drug delivery device is well known theoretically and experimentally. Both the in vitro and in vivo rate of the drug release, are observed to be dependent upon surface area of dosage form. Siepman et al. found that release from small tablet is faster than large cylindrical tablets.

I. Diluents effect:

The effect of diluents or fillers depends upon the nature of diluents. Water soluble diluents like lactose cause marked increase in drug release rate and release mechanism is also shifted towards Fickian diffusion; while insoluble diluents like dicalcium phosphate reduce the Fickian diffusion and increase the relaxation (erosion) rate of matrix.
reason behind this is that water soluble filler in matrices stimulate the water penetration in to inner part of matrix, due to increase in hydrophilicity of the system, causing rapid diffusion of drug, leads to increased drug release rate.

J. Additives:
The effect of adding non-polymeric excipients to a polymeric matrix has been claimed to produce increase in release rate of hydro soluble active principles. These increases in release rate would be marked if the excipients are soluble like lactose and less important if the excipients are insoluble like tricalcium phosphate.

1.8.2 FAT-WAX MATRIX TABLET-
Here the drug is incorporated into fat-wax granulations by-
- spray congealing in air
- blend congealing in an aqueous media with or without surfactants
- spray-drying techniques
- suspension of drug and melted fat-wax is allowed to solidify and is then comminuted for granulation

Melting is done in fluidized-bed and steam jacketed blender or granulating with a solution of waxy material or other binders, granules obtained thus above are compressed by direct compression technique where the drug embedded into a melt of fats and waxes is released by leaching and/or hydrolysis as well as dissolution of fats under the influence of enzymes and pH change in the gastrointestinal tract.

Thus, nonporous (homogeneous) matrix is the one in which the release retarding matrix material is first melted and drug is then incorporated in it by thorough mixing followed by congealing mass while stirring. Two types of hydrophobic matrix systems are as –
- Dissolved drug nonporous system: is the one where the drug is dissolved in the molten release retarding matrix material.
- Dispersed drug nonporous system: is the one where the quantity of drug is greater than its solubility in molten matrix material.

The surface erosion of a fat-wax matrix depends upon the nature and percent of fat-wax and extender in matrix; other factors such as drug particle size and drug concentration. Surfactants if added affects release of the drug from the matrix system. Polyethylene, ethyl cellulose, bees wax, carnuba wax, cetyl alcohol and glyceryl esters of hydrogenated resins have been added to modify the drug – release pattern.
1.8.3 PLASTIC MATRIX TABLETS (Hydrophobic Matrices)

The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. In this method of obtaining CR from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed into a tablet. CR is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles. These types of hydrophobic matrices are also known as porous (heterogeneous) matrices.

Examples of materials that have been used as inert or hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers. The rate-controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion. Such types of matrix tablets become inert in the presence of water and GI fluid.

1.8.4 BIODEGRADABLE MATRICES:

These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. They are biologically degraded or eroded by enzymes generated by surrounding living cells or by non-enzymatic process into oligomers and monomers that can be metabolized or excreted. Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

1.8.5 MINERAL MATRICES:

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

1.9 GASTRORETENTIVE DOSAGE FORMS:

CRDFs have been extensively used to improve therapy with several important drugs. However, the development processes are faced with several physiological difficulties such as the inability to restrain and localize the system within the desired region of the GIT and the highly variable nature of the gastric emptying process. This variability may lead to unpredictable bioavailability and time to achieve peak plasma level. On the other hand, incorporation of the drug in a CR Gastroretentive dosage forms (CR-GRDF) which can remain in the gastric region for several hours would significantly prolong the gastric
residence time of drugs and improve bioavailability, reduce drug wastage, and enhance the solubility of drugs that are less soluble in high pH environment. Gastroretention would also facilitate local drug delivery to the stomach and proximal small intestine. Thus, gastroretention could help to provide greater availability of new products and consequently improved therapeutic activity and substantial benefits to patients.\textsuperscript{19}

GRDFs are designed on the basis of one of the several approaches like,

- Formulating low-density dosage form that remains buoyant above gastric fluid (floating dosage form).
- High-density dosage form that is retained at the bottom of the stomach.
- Imparting bioadhesion to the stomach mucosa.
- Reducing the motility of the GI tract by concomitant administration of drugs or pharmaceutical excipients.
- Expanding the dosage form by swelling or unfolding to a large size, this limits emptying of the dosage form through the pyloric sphincter.
- Utilizing ion-exchange resin which adhere to mucosa.
- Using modified shape system.

From the formulation and technological point of view, FDDS is considerably easy and logical approach in the development of GRDFs. FDDS remains in the stomach or upper part of GI tract for a prolonged period of time due to their floating capabilities. To make the system float in stomach, the density of dosage form should be less than gastric content i.e. 1.0 g/cm. However, the bulk density of a dosage form is not a sole measure to describe its buoyant capabilities, because the magnitude of floating strength may also vary as a function of time and gradually decreases after immersion of the dosage form into the fluid as a result of the development of its hydrodynamic equilibrium.

Three major requirements for FDDS formulations are:

1. It must form a cohesive gel barrier
2. It must maintain specific gravity lower than gastric contents (1.004-1.01 g/cc)
3. It should release contents slowly to serve as a reservoir.

1.9.1 Effervescent Floating Drug Delivery System:

These floating delivery systems employ matrices from swelling polymers and effervescent components – gas generating materials such as carbonates are incorporated. These materials react with gastric acid or organic acids in formulation and produce
carbon dioxide, which allows them to float. The matrices are prepared in such a manner
that when they come in contact with stomach fluid, carbon dioxide is generated and
retained entrapped in the hydrocolloid gel. This leads to an upward drift of the dosage
form and maintains it in a floating condition.

A single layer tablet can be prepared by intimately mixing the carbon dioxide generating
component in tablet matrix. A bilayer tablet may be compressed in which gas liberating
component is present in hydrocolloid layer and the drug is compressed in other layer for
CR. It is worth mentioning here that carbonates apart from imparting buoyancy to the
dosage form also provide initial alkaline microenvironment for polymers to form gel.
Furthermore, the liberated carbon dioxide helps to accelerate the hydration of the floating
system, which is important for the formation of a bio-adhesive hydrogel. The bio-
adhesion helps retention of dosage form in stomach.

1.10 FORMULATION OF MATRIX TABLETS:

Conventional Matrix tablets for CR can be formulated by –

1. Granulation – Wet granulation, Dry granulation or Melt granulation
2. Direct compression

1. Granulation:

Granulation technique includes wet granulation and dry granulation/slagging methods
wherein binders are added in solution/suspension form and in dry form respectively.
Powders/Granules intended for compression into tablets must possess two essential
properties: flow property and compressibility. Flow property/Fluidity is required to
produce tablets of a consistent weight and uniform strength. Compressibility is required
to form a stable, intact compact mass when pressure is applied. These two objectives are
obtained by adding binder to tablet formulation and then proceeding for granulation
process. Granules so formed should possess acceptable flow property and
compressibility. Some drugs exhibit poor fluidity and compressibility. In such cases
binders have to be added for improving flow property and compressibility.

Other reasons for Granulation process are to improve appearance, mixing properties, to
avoid dustiness, to densify material, to reduce segregation, in general to either eliminate
undesirable properties or to improve the physical and chemical properties of fine
powders.
2. **Direct Compression:**
Dry methods and particularly direct compression is the simplest method of tablet manufacturing. In Direct Compression, binders possessing direct compressibility characteristics are used. Binder when used in liquid form gives better binding action as compared to when used in dry form.

**Advantages of Direct Compression Technique:**

1. Economical: Economical savings can occur in a number of areas
2. Reduced processing time:
   a. Reduced labor costs
   b. Fewer manufacturing steps and equipments needed
   c. Fewer Less process validation and documentation
   d. Low consumption of power
3. Processing without moisture and heat which is inherent to wet granulation.
4. Avoidance of high compaction pressure in slugging and roll compaction process.
5. Changes in dissolution profiles are less likely to occur in tablets made by direct compression than in those made from granulations.

**Melt Granulation:** An interesting approach to develop CR formulations is based on melt granulation, which is a very short one-step technique converting fine powders into granules. For any CR dosage form, it is very important that both the number of excipients in the formula and the processing steps are kept to the minimum, in order to reduce tablet-to-tablet and batch-to-batch variations.

Hence, melt granulation is a suitable and easily scalable technique for this purpose. Powder agglomeration is promoted by the addition of a low melting point binder, which is solid at room temperature and melts at relatively low temperatures (50–80°C). In recent years, the interest in melt granulation has increased due to the advantages of this technique over traditional wet granulation. Since it is a solvent-free process, the drying phase is eliminated and thus it becomes less consuming in terms of time and energy.

Thus in the present investigation major approach for formulation of matrix tablets for controlled drug delivery system was direct compression.
1.11 BIBLIOGRAPHY FOR INTRODUCTION:


