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Review Article

An Overview on Classification, Mechanism of Extended Release Drug Delivery of Oral Formulations

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Abstract:

ER is defined as a dosage form designed to release the medication in a controlled manner during an extended period of time, at a predetermined rate, duration, and location following administration. At steady state, the rate of absorption is approximately equivalent to the rate of elimination due to metabolism and excretion. ER (extended release) tablets shows the better patient compliance through reduction of frequency of dose administration and also maintain the therapeutic concentration over a long period of time it help to reduce the side effect of the drug and shows better effect. The ER tablet is very helpful to treat the chronic diseases. The objectives of this review are to discuss their advantages, classification and mechanism of extended drug release systems.

Introduction

Oral administration is usually more preferable compared to other routes of administrations due to its simplicity, safety, high patients' acceptance and efficient absorption through the gastrointestinal tract (GIT) with minimum irritations or pain. Oral formulations account for more than 60% of commercial pharmaceutical dosage forms in the market

Extended-release dosage forms can address this challenge providing they can maintain drug plasma concentrations at therapeutic ranges after just once or twice daily administration.

There are 2 main categories of oral drug delivery systems (DDSs): immediate-release (IR) and modified-release dosage formulations. The latter can be further subdivided into delayed-release (DR) and extended-release (ER) formulations.

The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers

more flexibility in dosage form design than most other routes. The terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

Reasons for Attractiveness of These Dosage Forms: Provides increased bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug.

If one were to develop an ideal drug delivery system, two pre-requisites would be required: Firstly single dose for the duration of treatment whether for day or weeks as with infection, diabetes or hypertension. Second it should deliver the active entity directly to the site of action minimizing the side effects. Weeks as with infection, diabetes or hypertension. Second it should deliver the active entity directly to the site of action minimizing the side effects.

Advantages of Extended Release Delivery System

- The extended release formulations reduce dosing frequency of drugs.
- The extended release formulations may maintain therapeutic concentrations.
- Reduce the toxicity by slowing drug absorption.
- The use of these formulations avoids the high blood concentration.
- Extended release formulations have the potential to improve the patient compliance and convenience.
- Minimize the local and systemic side effects.
- Increase the stability by protecting the drug from hydrolysis or other degradative changes in gastrointestinal tract.
- Improvement in treatment efficacy.
- Minimize drug accumulation with chronic dosing.
- Improve the bioavailability of some drugs.
- Usage of less total drug.
- Improve the ability to provide special effects. For example, Morning relief of arthritis through bed time dosing.

Disadvantages of Extended Release Delivery System

- Extended release formulation contains a higher drug load and thus any loss of integrity of the release characteristics of the dosage form.
- The larger size of extended release products may cause difficulties in ingestion or transit through gut.
- The release rates are affected by various factors such as food and the rate of transit through the gut.
- Some differences in the release rate from one dose to another dose but these have been minimized by modern formulations.
- High cost of preparation.
- Sometimes the target tissue will be exposed to constant amount of drug over extended period results in drug tolerance.

2. Classification of Different types of Drug Delivery Systems

Recently much advancement have resulted in the development of new systems of drug delivery capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and targeting the delivery of the drug to the tissue

Drug delivery systems

1. Conventional drug delivery systems
2. Modified drug delivery systems
3.

Conventional Drug Delivery Systems

Conventional drug therapy requires periodic doses of therapeutic agents. These agents are to produce maximum stability, activity and bioavailability. For most drugs, conventional drug delivery is effective, but some drugs which possess narrow therapeutic window and which cause irritation of gastric mucosa requires modified drug delivery system to achieve desired therapeutic effect. These delivery systems have number of advantages over traditional systems such as improved efficiency, reduced toxicity and improved patient convenience.

Conventional dosage forms are rapidly absorbed, with ascending and descending portions of the concentrations versus time curve reflecting primarily the rate of absorption and elimination. Because of the rapid absorption from conventional dosage forms, drugs are usually administered more than once daily, with the frequency being dependent on the biological half-life and the duration of pharmacological effect. The time of dosing may also be effected by therapeutic index of the drug.

Disadvantages of conventional dosage forms:

- In these system there is little or no control over the release of the drug and effective concentration at the target site.
- The dosing pattern in conventional dosage forms results in constantly changing, unpredictable and often sub- therapeutic plasma concentrations, leading to marked side effects in some cases.
- These are not suitable for the drugs which cause irritation of the gastric mucosa.
- The rate and extent of drug absorption may vary greatly, depending upon factors such as physicochemical properties of the drug, presence of excipients various physiological factors such as presence or absence of food, pH of gastrointestinal tract, gastrointestinal motility and so on.
- Graph showing plasma level versus time profile showing difference between extended release, sustained release and conventional dosage form.

Modified Drug Delivery Systems

The term modified release drug product is used to describe products that alter the timing and /or the rate of the drug release.

❖ **Extended release dosage forms**

A dosage form that allows at least twofold reduction in dosing frequency as compared to that drug presented as immediate release form. Ex: Controlled release, Sustained release

A. Controlled release: It includes any drug delivery system from which the drug is delivered at predetermined rate over a long period.

B. Sustained release: It includes any drug delivery system that achieves slow release of drugs over extended period of time not particularly at predetermined rate.

❖ **Delayed release dosage forms**

A dosage form release a discrete portion of the drug at a time or times other than promptly after administration, although one portion may be released promptly after administration. Ex. Enteric coated dosage form.

❖ **Targeted release dosage forms**

A dosage form that releases drug at/near the intended physiological site if action. Targeted release dosage forms may have extended release characteristics.

❖ **Repeated action dosage forms**

It is a modified release drug product that is designed to release one dosage or drug

initially followed by a second dosage of drug at a later time.

❖ **Prolonged release dosage forms**

It is designed to release the drug slowly and to provide a continuous supply of drug over an extended period.

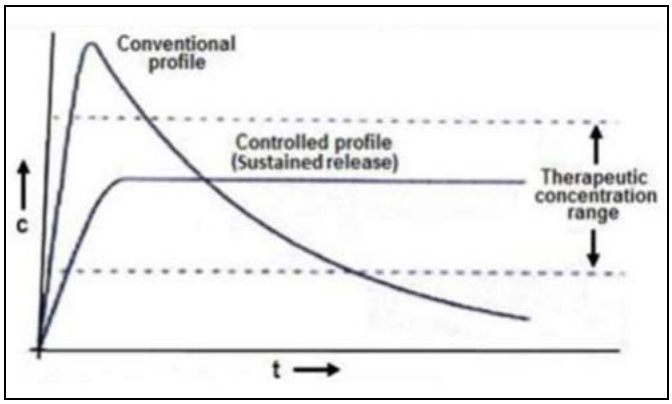

Figure No 1: Comparative release pattern of conventional and modified release dosage forms.

4. Drug Properties of Extended Release Formulations

During Design of Extended Release Delivery Systems, Variables Such As the Route of Drug delivery, the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug, are considered of particular interest to the scientist designing the system are the constraints imposed by the properties of the drug. These properties are classified as:

(a) Physicochemical
(b) Biological properties

Physicochemical Properties

a) Dose Size
b) Aqueous Solubility and pKa
c) Partition Coefficient
d) Drug Stability
e) Molecular Size and Diffusivity
f) Drug Protein Binding

Biological Properties

a) Absorption
b) Distribution
c) Metabolism
d) Elimination and Biological Half-Life

4. Factors Influencing Oral Extended Release Tablets

Physicochemical Factors:

✓ **Dose size**

For orally administered drugs, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5-1.0 is considered as maximal for the conventional dosage form. This also holds for sustained release dosage forms. Those compounds that require large dosing size can sometimes be given in simple amounts or formulated into liquid system. Another consideration is the margin of safety involved in administration of large amounts of a drug with narrow therapeutic range.

✓ **Ionization, pKa and aqueous solubility**

Most of the drugs are weak acid or bases and in order for drug to get absorbed, it must dissolve in the aqueous phase surrounding the site of administration and then partition into the adsorbing membrane. Compounds with low solubility are inherently sustained, since there release over the time course of a dosage form in GI tract will be limited to

dissolution of the drug. The lower limit of the solubility of drug to be formulated in sustained release system has been reported to be 0.1mg/ml, so it is obvious that the solubility of the compound will limit the choice of mechanism to be employed in sustained delivery system. Diffusion systems will be poor choices for slightly soluble drugs, since the driving force for the diffusion, which is the drugs concentration in solution, will be low.

✓ **Partition coefficient**

When a drug is administered to the GI tract it must cross a variety of biological membranes to produce a therapeutic effect in another area of the body. It is common to consider that these membranes are lipidic, therefore, the partition coefficient of oil soluble drugs becomes important in determining the effectiveness of membrane barrier penetration. Partition coefficient is generally defined as the ratio of the fraction of drug in an oil phase to that of an adjacent aqueous phase. Accordingly, compounds with a relatively high partition coefficient is generally defined as the ratio of the fraction of drug in an oil phase to that of the aqueous phase. Accordingly, compounds with a relatively high partition coefficient are predominantly lipid soluble and, consequently, have very low aqueous solubility.

✓ **Stability**

Orally administered drugs can be subject to both acid-base hydrolysis and enzymatic degradation. For drugs that are unstable in the stomach, systems that prolong delivery over the enteric course of transits in the GI tract are beneficial; likewise, for systems that delay release until the dosage form reaches the small intestine. Compound that is unstable in the small intestine may demonstrate decrease bioavailability when administered from a sustaining dosage form. This is because more drugs is delivered in the small intestine and, hence, is subjected to degradation.

Biological Factors:

✓ **Biological Half-Life**

The usual goal of an oral sustained-release product is to maintain therapeutic blood levels over an extended period. The elimination rate is quantitatively described by the half-life. Each drug has its own characteristic elimination rate, which is the sum of all elimination process, including metabolism, urinary excretion, and all other processes that permanently remove drug from the bloodstream.

Therapeutic compound with short half-life are excellent candidates for sustained release preparations, since this can reduce dosing frequency. However, this is limited, in that drug with very short half-lives may require excessively large amounts of drug in each dosage unit to maintain sustained effect, forcing the dosage form itself to become limitingly large. In general, drugs with half-lives shorter than 2 hours are poor candidates for sustained release preparations. Compounds with long half-life more than 8 hours are also generally not used in sustaining forms, since there effect is already sustained.

Absorption

The characteristics of absorption of a drug can greatly affect its suitability as a sustained release product. Since the purpose of forming a sustained release product is place to control on the delivery system, it is necessary that the rate of release much slower than rate of absorption. If we assume that the transit time of most of drugs and devices in absorptive area s of the GI tract is about 8-12 hours, the maximum half-life for absorption should be approximately 3-4 hours, otherwise, the device will pass out of the potential absorptive before drug release

is complete. This corresponds to minimum apparent absorption rate constant of 0.17-0.23 hours-1 to give 80-95% over this time period. This absorption rate constant is apparent rate constant, and should, in actuality be the release rate constant of the drug from the dosage form. Compounds that demonstrate true lower absorption rate constants will probably be poor candidates for sustained release.

Metabolism

The metabolic conversion of a drug to another chemical form usually can be considered in the design of a sustained release system for that drug. As long as the location, rate and extent of metabolism are known and rate constant of the procedures are not too large, successful sustained products can be developed. There are two factors associated with the metabolism of some drugs; however that present problems of their use in sustained release systems. One is the ability of the drug to introduce or inhibit enzyme synthesis; this may result in fluctuating the drug level with chronic dosing. The other is a fluctuating drug level due to intestinal metabolism or through hepatic first pass effect. Drugs that are significantly metabolised especially in the region of small intestine can show decreased level of bioavailability from slower release dosage forms. This is due to saturation of the intestinal wall enzyme systems. The drugs should not have intestinal first pass effect and should not induce or inhibit metabolism are good candidates for sustained release dosage forms.

5. Mechanism of drug release in extended release systems:

The different mechanisms of the drug release in extended release systems are:

1. Dissolution extended release
2. Osmotically extended release
3. Diffusion extended release
4. Erosion extended release
5. Miscellaneous extended release

1. Dissolution extended release

In extended release formulations employing dissolution as the rate limiting step, drug release is extended by dissolution of polymer. Individual particals or granules containing a drug can be uniformly dispersed in the matrix or coated with varying thickness of coating material resulting in dissolution and release of the drug over extended periods of time. If the dissolution is assumed to be diffusion layer extended, in which the rate of diffusion from the solid surface to the bulk solution is rate limiting, the flux is the product of diffusion coefficient and the concentration gradient from the solid surface to the bulk solution side. Flux can also be defined as flow rate of material per unit area. With encapsulated dissolution control, the drug may be coated with slowly dissolving polymeric materials. Once the polymeric membrane has dissolved, the enteric drug inside the membrane is immediately available for dissolution and absorption. Thus drug release can be extended by adjusting the thickness and the dissolution rate of the polymeric membrane.

2. Osmotically extended release

The most commonly used type of membrane material in drug delivery system is homogeneous films of amorphous and semi crystalline polymers above their glass transition temperatures. Drug transport occurs by dissolution in the membrane at one interface, followed by diffusion down a concentration gradient across the membrane and finally release from the second interface into the external medium. The rate of drug permeation through solution diffusion membranes is directly proportional to the product of the drug diffusion coefficient in the polymer and the polymer/solution partition coefficient.

3. Diffusion extended release

In diffusion extended release systems, the transport of solute through the polymer is achieved by molecular diffusion due to concentration gradients. Depending on the molecular structure of the polymer these systems may be classified as porous or nonporous. Porous extended release systems contain pores of large enough size so that diffusion of the solute is accomplished through water, which has filled the pores of the polymer.

In **reservoir (membrane) systems,** the bioactive agent is usually enclosed at relatively high concentrations between two semi permeable membranes and placed in contact with a dissolution medium (water or other biological fluid).

In matrix (monolithic) systems, the bioactive agent is incorporated in the polymer phase either in dissolved or in dispersed form. Therefore, the solubility of the solute in the polymer becomes a controlling factor in the mathematically modelling if these systems.

4. Erosion extended release

Chemically extended systems include all polymeric formulations in which solute diffusion is extended by a chemical reaction, such as the dissolution of the polymer matrix or cleavage of the drug from a polymer backbone. In most chemically extended systems, solute release is extended by the geometric shape of the device. Depending on the type of degradation reaction, these systems may be classified as chemically degradable or biodegradable extended release systems.

5. Miscellaneous forms of extended release

- Ion-exchange resins
- Altered density: Drug coated micro pellets
- pH-independent formulations
- Barrier coating
- Embedment in slowly eroding matrix Embedment in plastic matrix repeated action.

Matrix Formulation:

Definition:

Matrix formulations are defined as a drug or other active ingredient embedded in insoluble excipient in order to achieve release by a continuous leaching of the drug from the inert matrix core.

Classification:

Matrix systems can be divided into three types:

- Monolithic matrix tablets
- Gel forming hydrophilic matrix tablets
- Erodible (hydrophobic) matrix tablets

Inert monolithic matrix tablets:

Probably the simplest method of obtaining sustained release of a drug from an oral dosage form is incorporation of a drug in an inert matrix. In this inert means non-interacting with the biological fluids. The main reason for its popularity is that drug release from plastic matrix tablets is independent on the state and condition of the digestive juices, which may show large inter and intra patient variability (pH, viscosity).

During its transit through the gastro-intestinal tract, the porous matrix tablet does not disintegrate like conventional tablets, but remains intact and the skeleton can be recovered in faeces. The materials used in the preparation of these inert matrices are predominantly (insoluble) polymers and lipophilic compounds. The first polymers to be used for the preparation of matrix tablets were (semi) synthetic polymers such as polyethylene, polyvinyl chloride, polymethyl methacrylate, polystyrene, poly vinyl acetate, cellulose acetate and ethyl cellulose. The fat compounds used included carnauba wax, hydrogenated castor oil and tristearin.

Major drawback of most of the inert polymeric matrix tablets were their inherent

first order drug release characteristics, their poor direct compression characteristics and the problematic cleaning of agglomeration equipment used for the preparation of agglomerates with the required compression characteristics.

❖ **Mechanism of release of inert monolithic matrix tablets:**

Release from inert matrix tablets occurs via a leaching mechanism. Drug particles dispersed in the polymer matrix dissolve in the penetrating gastro-intestinal fluids and are released from the tablet by diffusion through the porous network of already existing pores and pores that created by dissolution of the drug particles. At drug loadings exceeding approximately 10-15 volume %, a continuous structure connecting all drug particles exists (percolating drug network). At considerably lower loadings, a particular fraction of the drug may be completely surrounded by the polymer matrix (trapped fraction), which would result in incomplete release.

a) Gel forming hydrophilic matrix tablets:

Gel forming hydrophilic or swellable matrix systems are homogeneous or heterogeneous systems in which the drug is dispersed in a swellable hydrophilic polymer. These systems have been widely studied by researchers since they offer the possibility to obtain a constant drug delivery over an extended period of time. Drug release is a function of the polymer characteristics.

Upon swallowing gel forming hydrophilic matrix tablets, the hydrophilic polymer is plasticized by the aqueous gastro-intestinal due to which undergoes macromolecular chain relaxation and volume expansion. Consequently, upon penetration of the gastro-intestinal fluids into tablet, a sharp front can be distinguished which separates a dry, glassy core from a hydrated and rubbery gel layer. Release is governed by diffusion of the dissolved drug through the swollen gel layer and generally shows a burst effect, caused by dissolution and leaching of drug particals present at the surface prior to formation of the release controlling gel.

The mechanism of drug release from swellable devices is determined by the relative position of the rubber-glass interface, the rate at which it penetrates the tablet, the diffusion coefficient of the drug and the erosion rate of the gel. When the penetration rate is high as compared to the drug diffusion rate through the swollen gel layer, release is extended by the diffusion rate of the drug through the gel layer and a diffusion extended (Fickian) release mechanism is observed. If diffusion of drug through the gel layer is fast as compared to the water penetration rate, release of the incorporated drug is governed by the penetration rate of the interface and zero-order drug release with constant release rate may be achieved. Several dimensionless parameters have been developed to characterize drug release from swelling extended dosage forms. The Deborah number (De) represents the ratio of the characteristic relaxation time of the swelling polymer (τ) relative to the characteristic diffusion time of the water into the polymer ($^{\theta}$). The swelling interface number (Sw) represents the ratio of the solvent penetration front velocity (v) to the rate of drug diffusion through the swollen polymer.

$$\mathbf{De = {}^{\theta}/\tau}$$

$$\mathbf{Sw = v.\delta(t) / ID}$$

Where ID is the diffusion coefficient of the drug in the swollen layer and $\delta(t)$ is the thickness of the layer. In order to characterize release behaviour, it is necessary to determine both De and Sw since neither of these values is sufficient by itself. Peppa's and co-workers have extensively investigated diffusion and

solvent extended drug release from swellable polymeric devices with various geometries. Release from swellable tablets can easily be analysed by the following simple equation

$$M_t / M_\infty = kt^n$$

Where,

M_t / M_∞ are the fractional drug release,

k is a constant representing structural and geometrical characteristic of the device, and n gives the type of release mechanism.

When the rate at which the penetration front moves inward into the glassy core is high as compared to the diffusion rate of dissolved drug molecules through the swollen gel layer, release is extended by the diffusion rate of the drug through the gel layer and a Fickian diffusion extended release mechanism with $n \approx 0.5$ is observed. If diffusion of the drug through the gel layer is fast as compared to the solvent penetration rate, release of the incorporated drug is governed by the penetration rate of the interface. For dosage forms with slab geometry, this leads to zero order release (n=1), which is also called non-Fickian, case Π or solvent penetration extended release. Release profiles with intermediate n-values ($0.5 < n < 1$) are classified as anomalous.

Other swellable polymers, which have been applied in swelling extended oral drug delivery systems, which show solvent extended release are guar gums, poly (ethylene oxide) (PEO), poly (vinyl alcohol), ethylene-vinyl alcohol copolymers (EVA) and dextrins.

b) Erodible matrix tablets:

Erodible polymers such as poly anhydrides offer another interesting material platform for zero-order drug release. Like several HPMC grades, upon water penetration, poly anhydrides form a gel layer, which erodes at a specific rate. By choosing the right polymer composition the thickness of the gel-layer may remain constant with time resulting in a constant release rate until depletion of the drug.

In the last two decades, Extended release dosage forms have made significant progress in terms of clinical efficacy and patient compliance. Preparation of drug-embedded matrix tablet that involves the direct compression of a blend of drug, retardant material and additives is one of the least complicated approaches for delivering drug in a temporal pattern into the systemic circulation. The matrix system is commonly used for manufacturing extended release dosage forms because it makes such manufacturing easy. A wide array of polymers has been employed as drug retarding agents each of which presents a different approach to the matrix concept. Polymers forming insoluble or skeleton matrices constitute the first category of retarding materials, also called as plastic matrix systems.

The second class represents hydrophobic and water-insoluble materials, which are potentially erodible; while the third group includes polymers those form hydrophilic matrices.

Plastic matrix systems, due to their chemical inertness and drug embedding ability, have been widely used for controlling the release of the drug. Liquid penetration into the matrix is the rate-limiting step in such systems unless channelling agents are used. The hydrophobic and waxy materials, on the other hand, are potentially erodible and control the release of drug through pore diffusion and erosion. Polymers belonging to hydrophilic matrix systems, when exposed to an aqueous medium, does not disintegrate, but immediately after hydration develops a highly viscous gelatinous surface barrier, which controls the drug release from, and the liquid penetration into the centre of the matrix system.

The use of hydrophilic polymers is actually the most used method in controlling the release of drugs in the formulation of oral pharmaceutical dosage forms. Hydroxy propyl methyl cellulose has been extensively used since the early 1960s as a rate controlling polymer in oral extended-release dosage forms.

Hydrophilic matrix systems are popular and versatile extended release system. Amongst polysaccharide derivatives used to produce such systems, these are a range of cellulose ethers, e.g. hydroxy propyl methyl cellulose (HPMC) and a diverse range of other materials, including sodium alginate, carrageenan, chitosan and xanthan gum.

Materials used as Retardants in matrix tablets:

Various polymers have been investigated as drug retarding agents, each presenting a different approach to the matrix system. Based on the features of retarding polymer, matrix systems are usually classified into three main groups. They are:

A. Insoluble, Inert

- Polyethylene
- Polyvinylchloride
- Ethyl cellulose
- Methyl acrylate

B. Insoluble, Erodible

- Carnauba wax
- Stearyl alcohol
- Stearic acid
- Polyethylene glycol
- Castor wax
- Triglycerides

C. Hydrophilic

- Methyl cellulose
- Hydroxy ethyl cellulose
- Hydroxy propyl methyl cellulose
- Carboxy methyl cellulose sodium
- Carboxy polyethylene
- Xanthan gum
- Sodium alginate
- Chitosan

❖ **Mechanism of drug release from matrix tablets:**

The below figure shows the schematic drug release from matrix diffusion extended release drug delivery systems in which the drug homogenously dispersed in hydrophilic matrices, formation of the gel layer and its dynamics as a function of time determines the drug release. Gel layer thickness, which determines the diffusion path length of the drug, corresponds to the distance between the diffusion and erosion fronts. As the swelling process proceeds, the gel layer gradually becomes thicker, resulting in progressively slower drug release rates; however, due to continuous hydration, polymer disentanglement occurs from the surface of the matrix, resulting in a gradually decreasing depletion zone and an increased dissolution rate.

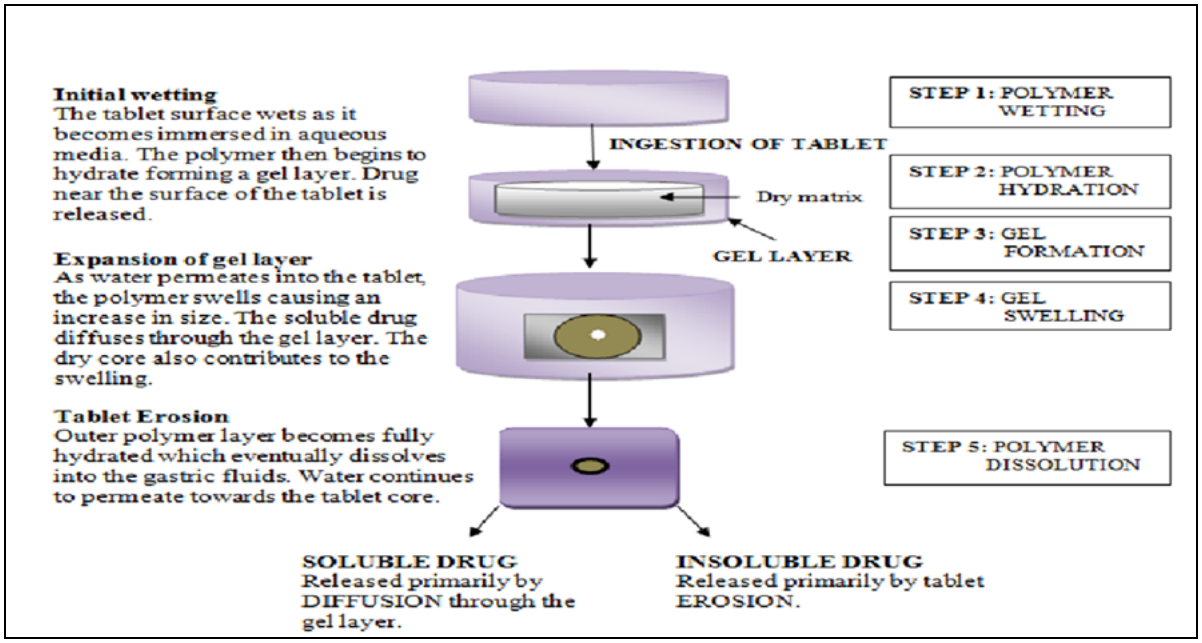

Figure no.2: Drug release from matrix tablets

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