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REVIEW ARTICLE

Modified Release Dosage Forms

Singh P[1], Ahlawat P*[2]

[1]*Lloyd Institute of Management & Technology, Greater Noida. Affiliated by Gautam Buddh Technical University, Lucknow, India.*

[2]*Ram Gopal College of Pharmacy, Gurgaon. Affiliated by Pt. Bhagwat Dayal Sharma University of Health Sciences, Rohtak, India.*

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ABSTRACT

Modified release dosage forms have been developed to deliver drug to the part of body where it will be absorbed to simplify drug schedules. Recently, several technical advancements have been made which results in new techniques for drug delivery. These techniques are capable of controlling the rate of drug delivery, extending the duration of therapeutic activity and / or targeting the delivery of drug to a tissue. Modified release pharmaceutical dosage forms may offer one or more advantages over conventional dosage forms of the same drug. Modified release dosage forms continue to draw attention in the search for improved patient compliance and decreased incidences of adverse drug reactions and decrease total dose of drug. Ideally, an extended release dosage form will provide a therapeutic concentration of the drug into blood that is maintained throughout the dosing interval with a reduction in a peak concentration ratio. Modified release dosage forms are designed to release their medication in controlled manner at pre determined rate duration and location in body.

KEYWORDS

Modified release, Dosing frequency, Patient Compliance, Immediate release, Extended release

INTRODUCTION

Modified Release Dosage Form

Modified preparations where the rate and/or place of release of the active ingredient are different from that of the conventional dosage form administered by the same route. This deliberate modification is achieved by special formulation design and/or manufacturing method. Modified release dosage forms include prolonged release, delayed release, pulsatile release controlled-release, controlled-delivery, slow-release and sustained-release and accelerated release dosage forms.[1]

***Address for Correspondence:**
Priyanka Ahlawat,
Ram Gopal College of Pharmacy, Gurgaon.
Affiliated by Pt. Bhagwat Dayal Sharma University of Health Sciences, Rohtak, India.
E-Mail Id: Priyankaahlawat15@gmail.com

These preparations, by definition, have a reduced rate of release of active substance.[3]

The *United States Pharmacopoeia* definition of an MR system is that: *"the drug release characteristics of time, course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms."*

Modified release dosage form is the dosage forms whose drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate release dosage form.[2]

The benefits offered by MR systems include reduced dosing frequency with improved patient compliance, better and more

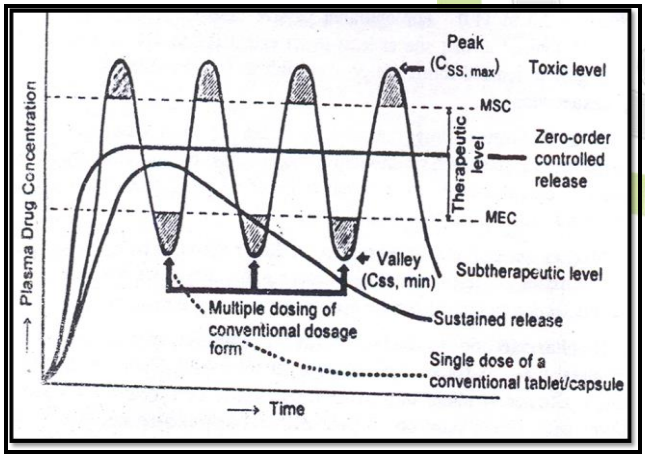
uniform clinical effects with lower incidence of side effects and possible enhanced bioavailability.[3]

Oral solid dosage forms are the preferred route for many drugs and are still the most widely used formulations for new and existing modified release (MR) products. Technologies are available for the formulation, development and production of MR tablets and multi-particulates such as drug-loaded pellets and granules, mini-tablets and drug crystals.

Over many years, approaches and technologies in the area of MR oral drug delivery have been developed:

* Extend the release of drug over a number of hours, an effect accomplished either by combining the drug with release-retardant materials to form a matrix core, or applying release-modifying film coatings to cores containing the drug.

* Delay the release of drug for a period of time, usually through the application of an externally applied enteric coating.



The rational design of MR systems, where biological, physicochemical and physic mechanical considerations have been taken into account during formulation of MR dosage form, has alleviated the risk of 'dose dumping' *in vivo*. In addition to the pharmacological and patient benefits, MR dosage forms offer commercial opportunity through intellectual property, brand differentiation and recognition, plus the potential to license technologies to other companies.

This includes technologies that modify the site of drug delivery. The successful formulation of an MR device requires a comprehensive understanding of the mechanisms of drug release from the macroscopic effects of size, shape and structure through to chemistry and molecular interactions. Multiparticulate dosage forms have been shown to be less prone to food effects than monolithics1 and are often the preferred formulation for extended and/or delayed release.

Film coating is an ideal process for the production of extended release multiparticulate dosage forms. For application in extended release delivery systems, film coats with well-characterized permeability properties are essential.

An important MR technology is delayed release through application of gastro-resistant coatings. In this case, a coating layer is applied to the dosage form, either multiparticulate or monolithic, providing protection to the stomach from the drug or protecting the drug from exposure to acidic gastric fluids. The majority of modern enteric coatings rely on polymers containing carboxylic acid groups as the functional moiety. These groups remain unionized in the low pH environment of the stomach but start to ionize as the dosage form passes into the small intestine. As the pH level rises above the point of dissolution, the polymer is ionized and the drug is released.[4]

These can be grouped in two categories:

a) Immediate Release

The term "immediate release" pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation and/or the absorption of drug, is neither appreciably, nor intentionally, retarded by galenic manipulations. In the present case, immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption.[5]

b) Extended Release

Extended release is designed to slow the rate of release of the active ingredient(s) in the gastrointestinal tract. Some extended-release medications have the letters "XL" or "LA" or "XR" in their name. Extended-release medications have special coatings or ingredients that control how fast the drug is released from the dosage form into body. This may allow you to take certain medications only once a day, instead of more often. The extended release formulations are the type of formulations which will improves the therapeutic index of drug concentration. This formulation makes the drug available over extended time period after oral administration.[6]

Physiochemical Properties of the Drug Effecting Release Pattren[6]

Aqueous Solubility

Lower limit solubility for such product is reported to be 0.1 mg/ml. As the drug must be in solution form before absorption, drug having low aqueous solubility usually suffers oral bioavailability problem due to limited GI transit time of undissolved drug and limited solubility at absorption site. So these types of drug are undesirable.

Drug having extreme aqueous solubility are undesirable for ER because, it is too difficult to control release of drug from the dosage form.

Physiological pH dependent solubility i.e. variation in solubility at different GI pH are undesirable (e.g. Aspirin, which is less soluble in stomach, but more soluble in intestine) as it will yield variation in dissolution rate. A drug with good aqueous solubility, pH independent solubility is desirable for oral new drug delivery system.

Partition Co-Efficient

As biological membrane is lipophilic in nature through which the drug has to pass though, so partition co-efficient of drug influence the bioavailability of drug very much. Drug having lower partition co-efficient values less than the optimum activity are undesirable for oral ER drug delivery system, as it will have very less lipid solubility and the drug will be localized at the first aqueous phase it come in contact e.g. Barbituric acid.

Drug having higher partition co-efficient value greater than the optimum activity are undesirable for oral ERdrug delivery system because more lipid soluble drug will not partition out of the lipid membrane once it gets in the membrane. The value of partition co-efficient at which optimum activity is observed is approximately 1000:1 in 1-octano/water system

Drug Stability In-Vivo

As most of ER Drug delivery system is designing to release drug over the length of the GIT, hence drug should be stable in GI environment. So drug, which is unstable, can't be formulated as oral ER drug delivery system, because of bioavailability problem. E.g. - Nitroglycerine

Protein Binding

The Pharmacological response of drug depends on unbound drug concentration drug rather than total concentration and all drug bound to some extent to plasma and or tissue proteins. Proteins binding of drug play a significant role in its therapeutic effect regardless the type of dosage form as extensive binding to plasma increase biological half-life and thus sometimes ER drug delivery system is not required for this type of drug.

Drug pKa & Ionization at Physiological pH

As we know only unionized drug are absorbed and permeation of ionized drug is negligible, since its rate of absorption is 3 to 4 times less than that of the unionized drug. pKa range for acidic drug where ionization is pH sensitive is around 3.0 – 7.5 and pKa range for basic drug whose ionization is pH sensitive is around 7.0-11.0 are ideal for optimum positive absorption. Drug shall be non-ionized at the site to an extent 0.1 – 5.0%. Drugs existing largely in ionized form are poor candidates for oral ER drug delivery system. e.g.:- Hexamethonium.

Mechanisms and Sites of Absorption

Drug absorption by carrier mediated transport and those absorbed through a window are poor

candidate for oral ER drug delivery system e.g. several B vitamins. Drugs absorbedby passive diffusion, pore transport and through over the entire length of GIT are suitable candidates for oral ER drug delivery system.

Molecular Size and Diffusivity

With large molecular size are poor candidate for oral ER drug delivery system because it the ability of the drug to diffuse polymeric membrane is a function of its diffusivity (or diffusion co-efficient). Diffusivity depends on size shape of the cavities of the membrane. The diffusion co-efficient of intermediate molecular weight drug i.e.-100 to 400 Dalton, through flexible polymer is ranged from 10-6 to 10-9 cm2/sec. For drugs having molecular weight > 500 Daltons the diffusion co-efficient in many polymers are very less i.e. less than 10-12 cm2/sec. Drugs is very difficult to control release rate of medicament from dosage form e.g. proteins and peptides.

Dose Size

If a product has dose size >0.5gm it is a poor candidate for oral ER drug delivery system, because increase in bulk of the drug, thus increases the volume of the product.

Biological Properties of Drug[6]

Absorption

For oral ER drug delivery system the rate of drug absorption (ka) should be more -API than that of the rate of drug release (kr) from the dosage form i.e. kr<<<ka. Drug that are slowly absorbed or absorbed with a variable absorption rate of elimination of drug are poor candidate for oral ER drug delivery system. Some possible reasons for a low extent of absorption are poor water solubility, small partition co-efficient, acid hydrolysis, and metabolism or its site of absorption.

Distribution

Drugs with high apparent volume of distribution, which influence the rate of elimination of the drug, are poor candidate for oral ER drug delivery system e.g. Chloroquine.

Metabolism

Drug, which extensively metabolized is not suitable for ER drug delivery system. A drug capable of inducing metabolism, inhibiting metabolism, metabolized at the site of absorption of first-pass effect is poor candidate for ER delivery, since it could be difficult to maintain constant blood level e.g. levodopa, nitroglycerine.

Half-life of Drug

A drug having biological half-life between 2 to 8 hours is best suited for oral ER drug delivery system. As if biological half-life < 2hrs the system will require unacceptably large rate and large dose and biological half-life >8hours formulation of such drug into oral ER drug delivery system is unnecessary.

Margin of Safety

As we know larger the value of therapeutic index safer is the drug. Drugs with less therapeutic index usually poor candidate for formulation of oral ER drug delivery system due to technological limitation of control over release rates.

Plasma Concentration Response Relationship

Generally pharmacological response of drug depends on plasma drug concentration rather than size and dose. But some drugs pharmacological activity is independent of plasma concentrations, which are poor candidate for oral ER drug delivery system. E.g. Reserpine.

Concentration Dependency on Transfer of Drug

Transfer of drug from one compartment to other by zero kinetic process then such drugs are poor candidate for oral ER delivery system, it should be first order kinetics.

Types of Extended Release Formulation[6]

Many current oral extended release systems are available-

a. Dissolution-controlled release system.
b. Diffusion-controlled release system.
c. Osmotic pump system.

d. Erosion controlled release systems.

Dissolution Controlled Release Systems

In dissolution controlled extended release systems the rate of dissolution in the gastrointestinal juices of the drug or another ingredients is the release controlling process. Sparingly water-soluble drug can form a preparation of a dissolution controlled extended release type. Reduced drug solubility can be accomplished by preparing poorly soluble salts or derivatives of the drug. An alternative means to achieve extended release based on dissolution is to incorporate the drug in a slowly dissolving carrier.

Dissolution controlled extended release systems can also be obtained by covering drug particles with a slowly dissolving coating. The release of the drug from such units occurs in following steps-

1. The liquid that surrounds the release unit dissolves the coating (rate limiting dissolution step).
2. The solid drug is exposed to the liquid and subsequently dissolves sustained release oral products employing dissolution as the rate limiting step are in principle the simplest to prepare.

A drug with a slow dissolution rate is inherently sustained.

Some example of these drugs includes digoxin, griseofulvin, and salicylamide. Others, such as aluminum aspirin, ferrous sulfate, and benzphetaminepaomate, produce such forms when in contact with the absorption pool contents.

For those drugs with high water solubility and therefore high dissolution rate, one can decrease solubility through appropriate salt of derivative formation.

Unfortunately, forms such as these do not meet the criterion of constant availability rate because their surface area decreases with time. Nevertheless, sustained drug release can be achieved by coating drug particles or granules with materials of varying thickness or by dispersing them in a polymeric matrix.

Principle

If the dissolution process is diffusion layer controlled, where the rate of diffusion from the solid surface through an unstirred liquid film to the bulk solution is rate limiting, the flux J is given by:

$$J = -D (dc/dx) \quad \text{---------- (1)}$$

Where D is the diffusion coefficient and dc/dx is the concentration gradient from the solid surface to the bulk solution. The flux can also be defined as the flow rate to material (dm/dt) through a unit area (A), thus one has the equation:

$$J = (1/A)\, dm/dt \quad \text{---------- (2)}$$

If the concentration gradient is linear and the thickness of the diffusion layer is h,

$$dc/dx = (Cb - Cs)/h \quad \text{---------- (3)}$$

Where Cs is the concentration at the solid surface and Cb is the concentration in the bulk solution. By combining the above equation, the flow rate of material is given by

$$dm/dt = - (DA/h)(Cb–Cs) = kA(Cs – Cb) \quad \text{----(4)}$$

Here, k is the intrinsic dissolution rate constant.

The above equation predicts constant dissolution rate. If the surface area, diffusion co-efficient, diffusion layer thickness, and concentration difference are kept constant.

However, as dissolution proceeds, all of the, parameters the surface area especially may change

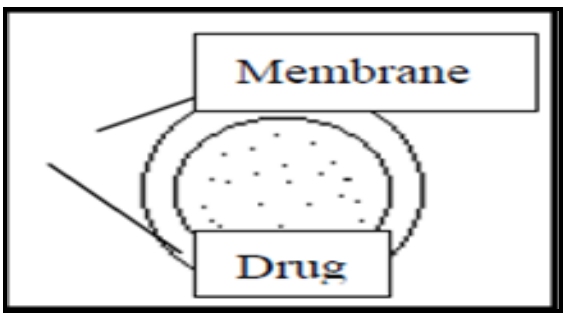


Figure 1: Dissolution control of drug release via thickness and dissolution rate of the membrane barrier coat

Most suitable dosage forms for this mechanism is compressed tablets containing coated particles. E.g. Ethyl cellulose, Nylon and Acrylic resins. Release depends on drug solubility and pore structure membrane. Constant release resulted when GI fluid passes through barrier to dissolve drug.

Diffusion Controlled Release System

There are basically two types of diffusion-controlled systems, which have been developed over the past two decades: reservoir devices and matrix devices. In diffusion controlled extended release systems the transport by diffusion of dissolved drug in pores filled with gastric or intestinal juice or in a solid (normally polymer) phase is the release controlling process. Depending on the part of the release unit in which the drug diffusion takes place, diffusion controlled release systems are divided into matrix systems (also referred to as monolithic systems) and reservoir systems. In matrix systems diffusion occurs in pores located within the bulk of the release unit, and in reservoir systems diffusion takes place in a thin water-insoluble film or membrane, often about 5-20 μm thick, which surrounds the release unit. Diffusion through the membrane can occur in pores filled with fluid or in the solid phase that forms the membrane.

Drug is release from a diffusion controlled release unit in two steps-

1. The Liquid that surrounds the dosage from penetrates the release unit and dissolves the drug. A concentration gradient of dissolved drug is thus established between the interior and the exterior of the release unit.
2. The dissolved drug will diffuse in the pores of the release unit or the surrounding membrane and thus be released, or, alternatively, the dissolved drug will partition into the membrane surrounding the dose unit and diffuse in the membrane.

A dissolution step is thus normally involved in the release process but the diffusion step is the rate-controlling step.

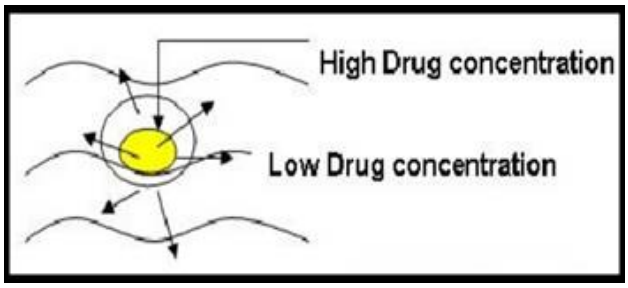


Figure 2: Diffusion release pattern

The rate at which diffusion will occur depends on four variables:

* concentration gradients over the diffusion distance.
* Area.
* Distance over which diffusion occurs.
* The diffusion co-efficient of the drug in the diffusion medium.

Some of these variables are used to modulate the release rate in the formulation.

Osmotic Pump System

The rate of drug release in these products is determined by the constant inflow of water across semi permeable membrane into a reservoir, which contains an osmotic agent. The drug is either mixed with the agent or is located in a reservoir. The dosage form contains a small hole from which dissolved drug is pumped at a rate determined by the rate of entrance of water due to osmotic pressure.

The advantage of this type of product is that the constant release is unaltered by the environment of the gastrointestinal tract. The rate of release can modify by altering the osmotic agent and the size of the hole.

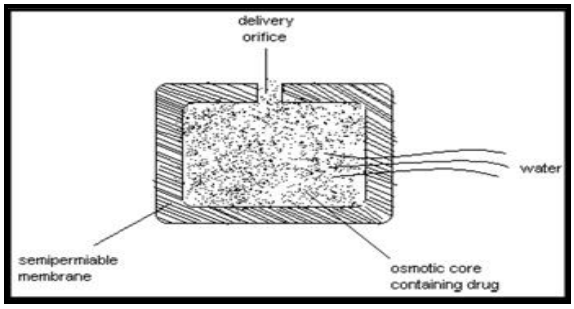


Figure 3: Osmotic pressure controlled by size of hole and concentration of osmotic agent in the core system

$$dm/dt = Ak(Cs-C)/h \quad \text{---------- (5)}$$

Where, A = membrane area, k = membrane permeability, h = membrane thickness, (Cs-C) is conc. Gradient and dm/dt is diffusion rate

Erosion Controlled Release Systems

In erosion controlled extended release systems that rate of drug release is controlled by the erosion of a matrix in which the drug release is controlled by the erosion of a matrix in which the drug is dispersed. The matrix is normally a tablet, i.e. the matrix is formed by a tab letting operation, and the system can thus be described as a single unit system.

The erosion in its simplest form can be described as a continuous liberation of matrix material (both drug and excipients) from the surface of the tablet, i.e. surface erosion. The consequence will be a continuous reduction in tablet weight during the course of the release process.

Mechanism of Drug Release from an Erosion Based Matrix Tablet

1. Drug release from an erosion system can thus be described in two steps. Matrix material, in which the drug is dissolved or dispersed, is liberated from the surface of the tablet.
2. The drug is subsequently exposed to the gastrointestinal fluids and mixed with (if the drug is dissolved in the matrix) or dissolved in (if the drug is suspended in the matrix) the fluid.

The eroding matrix can be formed from different substances. One example is lipids or waxes, in which the drug is dispersed. Another example is polymers that gel in contact with water (Hydroxy ethyl cellulose). The gel will subsequently erode and release the drug dissolved or dispersed in the gel. Diffusion of the drug in the gel may occur in parallel.

a) Release is Controlled by Ion Exchange

Ion exchangers are water insoluble resinous materials containing salt forming anionic or cationic groups. While manufacturing, the drug solution is mixed with resin and dried to form beads which are tableted.

The drug release depends upon high concentration of charged ions in gastro intestinal tract where, the drug molecules are exchanged and diffused out of the resin into the surrounding fluid.

This mechanism relies upon the ionic environment of resin and not pH or enzyme on absorption site.

Extended Release Solid Oral Dosage Forms[7]

Extended release (ER) dosage form is one of the drug products categorized under the term modified release dosage forms (FDA, 1997). It refers to products, which are formulated to make the drug available over an extended period after ingestion; thus, it allows a reduction in dosing frequency compared to a conventional type i.e. immediate release (IR) dosage form.

Several advantages of ER products over IR ones have long been recognized. ER solid oral dosage forms can be classified into two broad groups:

(i) Single unit dosage forms

(ii) Multiple unit dosage forms or multi particulate pellet systems.

The systems can be further subdivided into two concepts regarding to the design of dosage forms:

(i) Matrix System

(ii) Reservoir system

Matrix Systems

Matrix or monolithic devices consist of drug dispersed homogenously throughout a continuous phase of polymer or lipid.

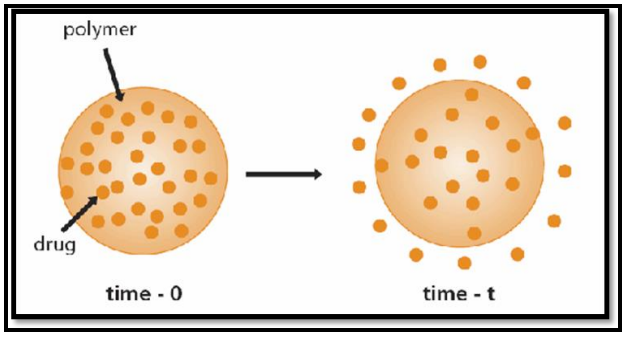


Figure 4: Matrix system for single unit dosage form

The devices can be prepared either by the compression of a polymer/drug mixture or by the dissolution or melting, resulted in the molecularly dispersed drug. The drug transport often results from a combination of several mechanisms included dissolution, diffusion, swelling and erosion.

Water-Soluble Matrix Formers

Water-soluble or hydrophilic matrices are a well-known type of ER oral dosage forms. While hydroxyl propyl methylcellulose (HPMC) is the most important hydrophilic carrier material, several others are also available including:

1. Cellulose derivatives: hydroxyl propyl cellulose (HPC), carboxy methylcellulose sodium (NaCMC).
2. Natural polymers: sodium alginate, carrageenan, chitosan.
3. Synthetic polymers: polymerized acrylic acid (Carbopol), polyvinyl alcohol (PVA) polyethylene oxide (PEO). It has been suggested, however, that the term 'swell matrices' is more appropriate as it better explains the characteristic of the systems.

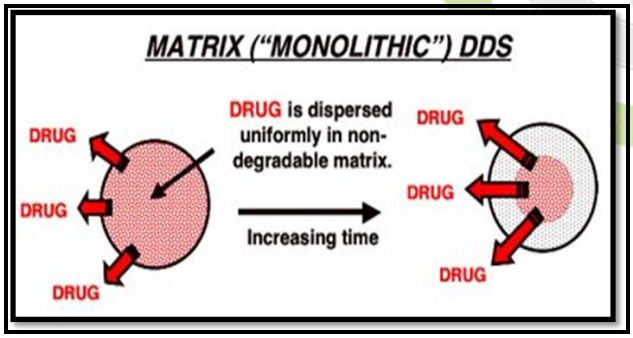


Figure 5: Monolithic matrix system

Water-Insoluble Matrix Formers

Water-insoluble carrier materials include:

(i) Lipid-base excipients: white wax, carnauba wax, glycerylmonostearate, hydrogenated vegetable oil, paraffin.

(ii) Polymer-based excipients: ethylcellulose (EC), cellulose acetate. In comparison to the hydrophilic matrices, the system has a greater physical stability, resulting in the less variable drug release and the lower incidence of 'dose dumping' in presence of food.

B) Reservoir Systems

Reservoir systems are characterized by a drug-containing core surrounded by release-rate controlling polymer(s). The mechanism of the drug transport across the polymeric membrane has been extensively described by Lecomte (2004).

Coated Tablets

An example of technology for ER coated tablet is MODAS (Multiporous Oral Drug Absorption System; Elan Corporation, Ireland). The tablet core consists of the mixture of active drug and other excipients, subsequently coated with a solution of water-insoluble polymers and water-soluble excipients. Upon exposure to aqueous media, the surrounded coating is transformed into a semi-permeable membrane through which drug diffuses in a rate-limiting manner.

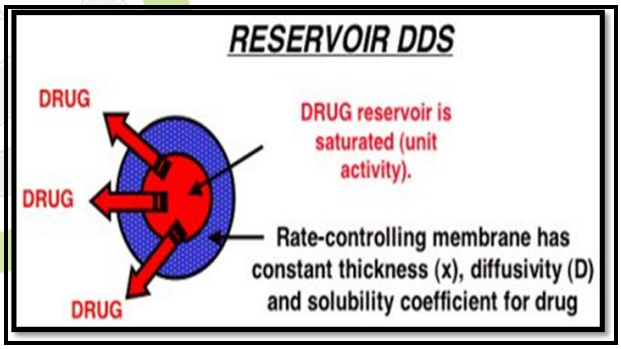


Figure 6: Reservoir system

Osmotic Pump Systems

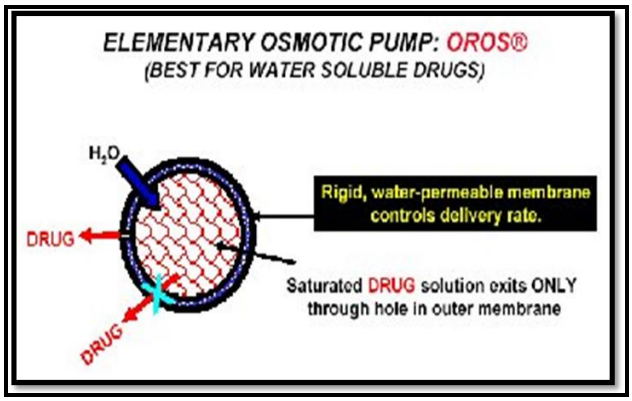


Figure 7: Osmotic Pump Reservoir System

Osmotic device is a special type of the reservoir systems, where the release rate of the drug is controlled dynamically by an incorporated osmotic agent in the active drug core. The rigid surrounding semi-permeable membrane consists for example of cellulose acetate. The drug is released through a defined, laser drilled delivery orifice in the membrane.

Multiparticulate Pellet Systems

Several advantages of multiparticulate systems over the single unit ones have been well documented. Following a proper preparation method, the ER pellets are either filled into a capsule or are compressed into a tablet.

Matrix Systems

The matrix type of multiparticulate systems can be prepared by several techniques such as extrusion/spheronisation, spherical crystal agglomeration and melt-solidification. Although, the production of multiparticulate matrix systems is considered to be easier than that of the reservoir systems, their extent of retardation is limited because of pellet geometry.

Reservoir Systems

Coated pellets as a mean to control drug delivery are widely used in the pharmaceutical industry, although the development and optimization of the systems are rather complex. Numerous aspects of the system performance have been investigated, for instance, the influence of formulation and coating technique, the effect of drug solubility and core material, the use of polymer blends, in vitro/in vivo evaluation and the influence of release medium.

Modified Release Tablet

The main aim behind formulation of this dosage form is to release the medicament slowly for long time duration after administration of a single tablet. Moreover, these types of formulations are generally used to target the site specific releases.

A widespread use of this type of tablet is seen in present scenario, as well as many researchers have concentrated their attention in this direction. This is mainly because of improvement in patient's compliance as the dosage frequency is reduced, patient can take an undisturbed sleep at night, it's also beneficial for psychiatric patients who forget to take their tablets regularly and the dose related side effects and toxicities are reduced.

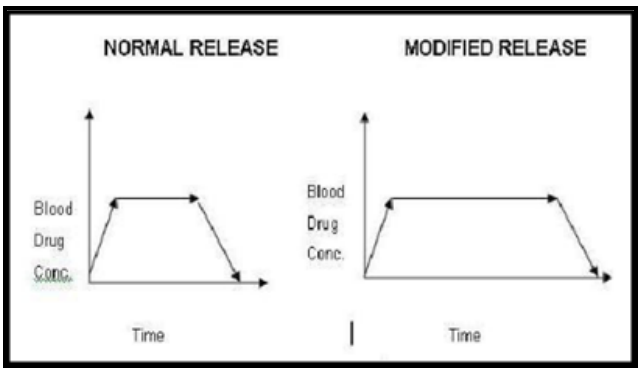


Figure 8: Graphical comparison of blood concentration v/s time

Any adjuvant that can alter water uptake rate, swelling, and gelling characteristics of matrixing agents can alter the release rate of API example like electrolytes in HPMC matrix tablet.

It's also possible to achieve pulsed drug release.

Weakly basic drugs exhibit good solubility at low pH while less soluble at high pH conditions, which can result in incomplete drug release for sustained release formulations. The drug release can be modified by providing suitable micro environmental pH in the tablet e.g., acidic polymer, succinic acid, etc.

Similarly, inclusion of alkaline polymers results in desirable drug release of acidic drugs. On the other hand, formulation of this type of dosage form presents challenge for the formulator: increases the cost of manufacturing, chances of burst drug release and drop in drug release rate in terminal phase and thus incomplete release on API. In case of accidental poisoning, the doctor has to deal with special treatment problems. Due to large size, patient may feel difficulties in swallowing as the matrixing agent to drug ratio is high.

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