Novel Approaches in Extended Release Drug Delivery Systems

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ABSTRACT

The prolonged release dosage forms have many advantages in safety and efficacy over immediate release products in that frequency of dosing can be reduced drug efficacy can be prolonged and the incidence of adverse effects can be decreased. Extended release drug formulations have been used since 1960's. These formulations make the drug available over extended time period after oral administration. Extended release drug delivery system which reduce the dosing frequency of certain drugs by releasing the drug slowly over an extended period of time. There are various physiochemical and biological properties which affect the extended release drug delivery system. This article providing the recent literature regarding development and design of extended release tablets.

Keywords: Extended Release, Extended Release Drug Delivery System, Half Life.

INTRODUCTION

In recent years in association with progress and innovation in the field of pharmaceutical technology there has been an increasing effort to develop prolonged release dosage forms. The prolonged release dosage forms have many advantages in safety and efficacy over immediate release products in that frequency of dosing can be reduced drug efficacy can be prolonged and the incidence of adverse effects can be decreased. Extended release drug formulations have been used since 1960's. These formulations make the drug available over extended time period after oral administration. The extended release product will optimize therapeutic effect and safety of a drug at the same time improves patient convenience and compliance, by incorporating the dose in a unit dosage form from which the drug is slowly released for 24 hr. This formulation helps to avoid the side effects associated with low concentration and high concentrations. The ideal drug delivery system should show a constant zero-order release rate and maintain the constant plasma concentrations.[1]

Advantages:

Extended release products having many advantages.

1. The extended release formulations maintain therapeutic concentrations over prolonged periods.

2. The use of extended release formulations avoids the high blood concentration.

3. Extended release formulations have the potential to improve the patient compliance.

4. Reduce the toxicity by slowing drug absorption.

5. Increase the stability by protecting the drug from hydrolysis or other degradative changes in gastrointestinal tract.

6. Minimize the local and systemic side effects.

7. Improvement in treatment efficacy.

8. Minimize drug accumulation with chronic dosing.

9. Minimum drug usage.

10. Improvement the bioavailability of some drugs. Ex: Divalproex sodium

11. Improvement of the ability to provide special effects. Eg: Morning relief of arthritis through bed time dosing.

Disadvantages:

1. High cost of preparation.

2. The release rates are affected by various factors such as, food and the rate transit through the gut.

3. Extended release formulation contains a higher drug load and thus any loss of integrity affects the release characteristics of the dosage form.

4. The larger size of extended release products may cause difficulties in ingestion or transit through gut.

5. Reduced potential for dosage adjustment.

FACTORS AFFECTING THE EXTENDED RELEASE DRUG DELIVERY SYSTEM

I. Physiochemical Properties of the drug:

a) Aqueous Solubility

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 un-dissolved drug and limited solubility at absorption site. So these types of drug are undesirable[1]. 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.[2]

b) 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 ER drug delivery system because more lipid soluble drug will not partition out of the lipid membrane once it gets in the membrane. The optimum n-octanol/water partition coefficient at which maximum flux occurs is approximately 1000.[3]

c) 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. - Nitro-glycerine.[2]

d) Protein Binding

Drug protein binding influences the distribution equilibrium of drugs. Plasma proteins exert a buffer function in the disposition of drugs, especially distribution; the elimination half-life of the drugs will be long, and they may not be qualified to be formulated into controlled release dosage forms. Only the free, nonprotein-bound fraction of the drug can diffuse into the tissue from the blood vessels. The equilibrium between free and bound drug acts as a buffer system and maintains a relatively constant concentration of the drug over a long period of time via the dissociation of the drug protein complex.[4]

e) 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 unionized 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.[5]

f) 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 absorbed by passive diffusion, pore transport and through over the entire length of GIT are suitable candidates for oral ER drug delivery system.[5]

g) Molecular Size and diffusivity

The release of solute or its diffusivity in a polymer is often a complex kinetic parameter that is determined by the properties of the solute such as size and shape and the properties of the polymer. Generally, if permeation occurs via the pore mechanism (i.e., through water-filled pores), the solute size will have an important effect on diffusivity. However, permeation via the partition mechanism is less solute-size dependent. Solute diffusion coefficients in cross-linked polyacrylamide and polyvinylpyrolidone gel show a logarithmic dependence on implant polymer concentration and solute molecular weight. Drug molecular weights less than 500 Dalton do not produce problems with drug absorption and hence may be suitable for oral controlled drug delivery.[6]

h) Dose Size

If a product has dose size >0.5g 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.[2]

II. Biological Properties of Drug:

a) Absorption

For oral ER drug delivery system the rate of drug absorption (ka) should be more 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 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.[5]

b) 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.[2]

c) 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.[5]

d) 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 required to maintain study state and drug with biological half-life >8 hours, formulation of such drug into oral ER drug delivery system is unnecessary.[4-5]

e) 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.[6]

f) 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[5]

Drug selection for oral extended release drug delivery systems:

The biopharmaceutical evaluation of a drug for potential use in controlled release drug delivery system requires knowledge on the absorption mechanism of the drug form the G. I. tract, the general absorbability, the drug's molecular weight, solubility at different pH and apparent partition coefficient.[7,10,11]

Table 1: Physicochemical Parameters for drug selection

Parameter	Preferred value
Molecular weight/ size	< 500 daltons
Solubility	> 0.1mg/ml for pH 1 to pH 7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability	From all GI segments
Release	Should not be influenced by pH and enzymes

The pharmacokinetic evaluation requires knowledge on a drug's elimination half- life, total clearance, absolute bioavailability, possible first- pass effect, and the desired steady concentrations for peak and trough.[10]

Table 2: Pharmacokinetic parameters for drug selection.

Parameter	Comment
Elimination half life	Preferably between 2 and 8 h
Total clearance	Should not be dose dependent
Elimination rate constant	Required for design
Apparent volume of distribution V_d	The larger V_d and MEC, the larger will be the required dose size.
Absolute bioavailability	Should be 75% or more
Intrinsic absorption rate	Must be greater than release rate
Therapeutic concentration Css av	The lower Css av and smaller V_d, the loss among of drug required
Toxic concentration	Apart the values of MTC and MEC, safer the dosage form. Also suitable for drugs with very short half-life.

TERMINOLOGY

Modified Release dosage form may be classified as

A. Delayed release

B. Extended release

- Sustained release
- Controlled release
- Prolonged release

C. Site-specific and receptor targeting.

- Organ targeting
- Cellular targeting
- Sub cellular targeting[6]

Delayed release

A delayed-release dosage form is designed to release the drug at a time other than promptly after administration. The delay may be time based or based on the influence of environmental conditions, like gastrointestinal pH.[8]

Extended release

The U.S. Food and Drug Administration (FDA) defines an "extended-release dosage form as one that allows a reduction in dosing frequency from that necessitated by a conventional dosage form, such as a solution or an immediate-release dosage form".[8]

Sustained release

Sustained release indicates an initial release of drug sufficient to provide a therapeutic dose soon after administration, and then a gradual release over an extended period.[8]

Controlled release

Dosage forms release drug at a constant rate and provide plasma concentrations that remain invariant with time.[8]

Prolonged release

Prolonged release indicates that the drug is provided for absorption over a longer period of time than from a conventional dosage form. However, there is an implication that onset is delayed because of an overall slower release rate from the dosage form.[8]

Site-specific and receptor targeting

Targeted release describes drug release directed toward isolating or concentrating a drug in a body region, tissue, or site for absorption or for drug action.[9]

Release rate and dose consideration

The dosage forms can be considered to release their active drugs into an absorption pool immediately. Conventional dosage forms include solutions, capsules tablets, emulsions, etc.
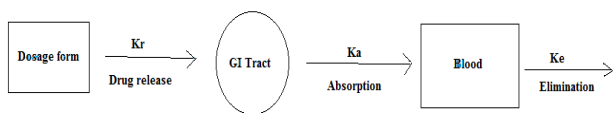
Figure 2: The absorption pool represents a solution of the drug at the site of absorption.

The absorption pool represents a solution of the drug at the site of absorption.

Where

K_r　　= First order rate constant for drug release

K_a　　= First order rate constant for drug absorption.

K_e　　= First order rate constant for drug elimination.

For immediate release dosage forms $K_r >>> K_a$ or alternatively absorption of drug across a biological membrane is the rate-limiting step in delivery of the drug to its target area.

For non-immediate release dosage forms, $K_r <<< K_a$, that is, release of drug from the dosage form is the rate limiting step. This cause the above kinetics Figure to reduce to.

Figure 3: Drug release from the dosage form.

Thus, the effort to develop a delivery system that release drug slowly must be directed primarily at altering the release rate by affecting the value of K_r. The ideal goal in designing a controlled release system is to deliver drug to the desired site at a rate according to needs of the body, i.e. a self-regulated system based on feedback control but this is a difficult assignment. The pivotal question is at what rate should drug be delivered to maintain a constant blood drug level? This constant rate should be analogous to that achieved by continuous intravenous infusion where a drug is provided to the patient at constants rates just equal to its rate of elimination. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time. That is, release from the dosage form should follow zero-order kinetics, as shown below

$Kr° = $ Rate in = Rate out = $K_e C_d V_d$

where

$Kr°$ = Zero order rate constant for drug release (amount/time)

K_e = First order rate constant for overall drug elimination time.

C_d　　= Desired drug level in the body (amount/volume)

V_d　　=Volume space in which the drug is distributed.

To achieve a therapeutic level promptly and sustain the level for a given period of time, the dosage from generally consist of two parts: an initial primary dose, Di, which release drug immediately and a maintenance or sustaining dose, Dm.

The total dose, W, thus required for the system is

$$W = D_i + D_m$$

To maintain drug blood levels with the therapeutic range over the entire time course of therapy, most controlled-release drug delivery systems are, like conventional dosage forms, administered as multiple rather than single doses. For an ideal controlled-release system that releases drug by zero-order kinetics, the multiple dosing regimens are analogous to that used for a constant intravenous infusion. For those controlled-release systems having release kinetics other than zero-order, the multiple dosing regimens are more complex.[2]

TYPES OF EXTENDED RELEASE FORMULATIONS

Many current oral extended release systems are available

1. Diffusion-controlled release system.

2. Dissolution-controlled release system.

3. Dissolution and diffusion controlled release system.

4. Ion exchange resin-drug complex.

5. Slow dissolving salts and complexes.

6. pH- dependent formulation.

7. Osmotic pump system.

8. Hydrodynamic pressure controlled system.

1. Diffusion-controlled release systems

A number of sustained-release products are based on diffusion of drug. The following discussion, although somewhat naive, will bring into perspective those properties that should be considered in the diffusion approach.

Fick's first law of diffusion states that drug diffuses in the direction of decreasing concentration across a membrane where J is the flux of the drug in amount/area-time.

$$J = -D(dc/dx) \qquad (1)$$

where

D = is the diffusion coefficient in area/time

C = is the concentration,

X = is the distance.

Assuming steady state, equation 1 can be integrated to give

$$J = -D(\Delta C / \ell) \qquad (2)$$

or expressed in more common form when a water-insoluble membrane is employed

$$dM/dt = (ADK\Delta C)/\ell \qquad (3)$$

where

A = is area.

D = is diffusion coefficient.

K = is the partition coefficient of drug into the membrane.

ℓ = is the diffusional path length (thickness of coat in the ideal case).

ΔC = is the concentration gradient across the membrane.

In order to have a constant rate of release, the right-hand portions of equations 2 and 3 must be maintained constant. In other words, the area of diffusion, diffusional path length, concentration increment, partition coefficient, and diffusion coefficient must be invariant. Usually, one or more of the above parameters will change in oral sustained-release dosage forms giving rise to non-zero-order release.

The more common diffusional approaches for sustained drug release are shown in Figures 4 and 5. In most cases, the drug must partition into a polymeric membrane of some sort and then diffuse through the membrane to reach the biological milieu. When the tablet or microcapsule contains excess drug or suspension, a constant activity of drug will be maintained until the excess has been removed, giving rise to constant drug release.

In Figure 4 the polymer is water insoluble, and the important parameter is solubility of drug in the membrane, since this gives rise to the driving force for diffusion. In Figure 5 either the polymer is partially soluble in water or a mixture of water-soluble and water-insoluble polymers is used. The water-soluble polymer then dissolves out of the film, giving rise to small channels through which the drug can diffuse. The small channels would presumably give a constant diffusional path length, and hence maintain constant conditions as described earlier.
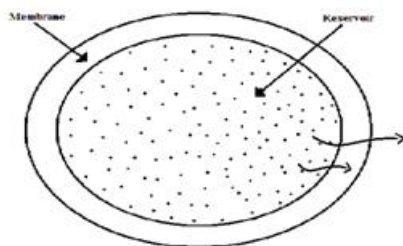

Figure 4: Diffusion control of drug release by a water-Insoluble polymer.

Although diffusion through the channels should be much more rapid than diffusion through the membrane noted in Figure 4, it is possible to have a situation whereby membrane diffusion, being quite rapid in this ease, is within an order of magnitude of pore diffusion. In this event, both types of diffusion, membrane and pore, will provide contributions to the overall diffusion rate and the

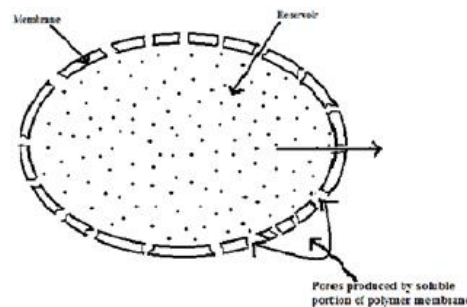equations would have to be modified to account for these combined effects.[2]

Figure 5: Diffusion control of drug release by a partially water-soluble polymer.

2. Dissolution-controlled release system

In this case, the drug is embedded (coated) in a polymeric material and the dissolution rate of the polymer dictates the release rate of drug. The drug release rate, if governed by erosion or dissolution, can be expressed as

$$dM/dt = A(dx/dt)f(C) \qquad (4)$$

where

dx/dt   = the erosion rate,

f(C)   = the concentration profile in the matrix,

A   = area.

A constant erosion rate can produce zero-order release kinetics, provided the drug is dispersed uniformly in the matrix and area is maintained constant. Oftentimes, swelling of the system or a significant change in area produces non-zero-order release. The common forms of dissolution control are shown in Figures 6 and 7.
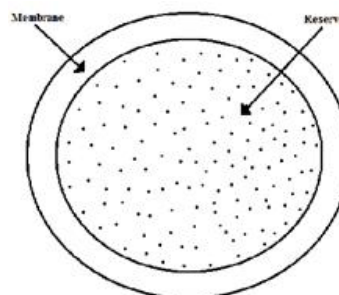

Figure 6: Dissolution control of drug release via thickness and dissolution rate of the membrane barrier coat.
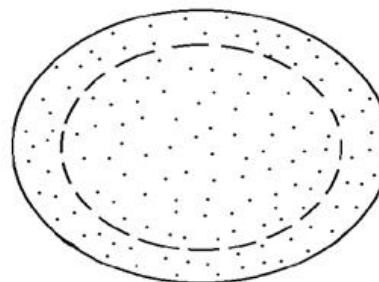

Figure 7: Dissolution control of drug release via polymer core erosion or polymer-coating erosion.

In Figure 6 we have a barrier coat across a microcapsule or nonpareil seed containing drug, and the release of drug is dictated by the dissolution rate and thickness of the barrier coat. Varying the coating thickness, or layering concentric spheres of coating material and drug reservoir material, gives rise to different release times, producing the repeat action dosage form. Once the polymer has dissolved, the entire drug contained in the capsule or seed is available for dissolution and absorption. In Figure 7 the drug is either embedded in a polymer or coated with a water soluble polymer, which in turn is compressed into a slowly dissolving tablet. The release rate is controlled by the dissolution rate of the polymer or tablet.[2]

3. Dissolution and diffusion controlled release system

In this system the drug core is encased in a partially soluble membrane. Pores are thus created due to dissolution of parts of membrane which permits entry of aqueous medium into the drug core and hence drug dissolution allows diffusion of dissolved drug out of the system. An example of obtaining such a coating is using a mixture of ethyl cellulose with PVP or methyl cellulose; the latter dissolves in water and creates pores in the insoluble ethyl cellulose membrane.[5]
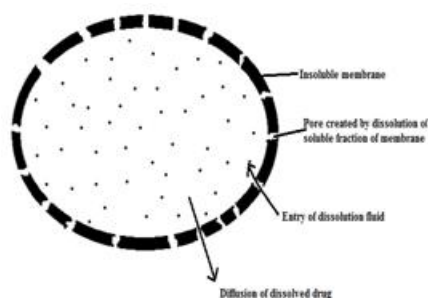

Figure 8: Dissolution and diffusion control release system.

4. Ion exchange resin-drug complex

Controlled delivery of ionizable acid and basic drug can be obtained by complexing them with insoluble nontoxic anion exchange and cation exchange resin respectively. The drug is released slowly by diffusion through the resin particle structure. The following equation represent the release of basic drug NH_2R, from the cation exchange resin RSO3H when in contact with GI fluid containing an ionic compound A+B$^-$ (either gastric HCl or intestinal NaCl)

$$RSO_3^- NH_3^+R' + A^-B^- \longrightarrow RSO_3^- A^+ + NH_3^+ R'B^- \quad (5)$$
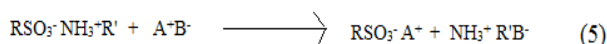
A number of basic drugs like noscapine, phenylpropanolamine and phentermine have been retarded by such an approach. The complex can be prepared by incubating the drug-resin solution or passing the drug solution through a column containing ion-exchange resin. The drug resin complex can be coated with cellulose and or hard paraffin and formulated as ion free suspension of pediatric use.[5]

5. Slow dissolving salts and complexes

Salts and complexes of drug which are slowly soluble in GI fluids can be used for control release of active principle. Amine drugs can be reacted with tannic acid to form poorly soluble complexes that can be formulated as long acting tablets. Penicillin G has been complexes with N,N'-dibenzyl ethylenediamine to give benzathine penicillin G that can be formulated as oral suspension. Such complexes can be obtained by simple acid-base reaction on mixing together the solution of individual compounds.[5]

6. pH- dependent formulation

Such system are designed to eliminate the influence of changing the gastrointestinal pH on dissolution and absorption of drugs by formulating them with sufficient amount of buffering agents (salts of phosphoric, citric or tartaric acids) that adjust the pH to the desired value as the dosage form passes along the GIT and permit drug dissolution and release at a constant rate independent of gastrointestinal pH. The dosage form containing drug and buffer is coated with a permeable substance that allows entry of aqueous medium but prevents dispersion of tablets.[5]

7. Osmotic pump system

Placement of a semipermeable membrane around a tablet, particle, or drug solution, which allows creation of an osmotic pressure difference between the inside and outside of the tablet and hence "pumps" drug solution out of the tablet through a small orifice in the coat, can be used as a sustained- release mechanism. The key component of the system is the ability of a drug solution to attract water through a semipermeable membrane by osmosis. Since the drug solution is contained within a fairly rigid system, drug solution can be pumped out of the tablet or particle at a controlled constant rate if a small hole is created in the coating surface and a constant activity of drug, that is, excess drug, is maintained. Controlling the rate of water imbibition thus controls the rate of drug delivery. This can be seen in the following expression

$$dV/dt = k (A/\ell) (\Delta\pi - \Delta P) \quad (6)$$

where

dV/dt = is the flow rate of water,

k, A, and ℓ = the membrane permeability, area, and thickness respectively.

$\Delta\pi$ = is the osmotic pressure difference,

ΔP = is the hydrostatic pressure difference.

Keeping the hydrostatic pressure small relative to the osmotic pressure, equation 6 reduces to

$$dV/dt = k (A/\ell) (\Delta\pi) \quad (7)$$

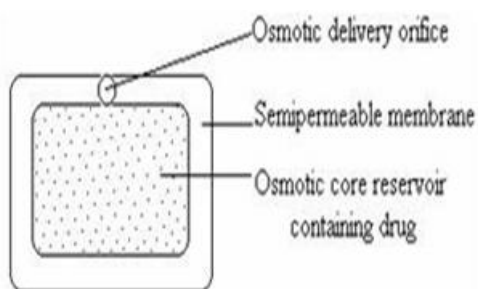By maintaining the right-hand side of equation 7 constant, a zero-order release system will result.[2]

Figure 9: Osmotic pump release system.

8. Hydrodynamic pressure controlled system

A hydrodynamic pressure-activated drug delivery system can be fabricated by enclosing a collapsible, impermeable container, which contains a liquid drug formulation to form a dug reservoir compartment, inside rigid shape retaining housing. A composite laminate of an absorbent layer and swellable, hydrophilic polymer layer is sandwiched between the drug reservoir compartment and the housing. In the GI tract the laminate absorb the gastrointestinal fluid through the annular opening at the lower end of the housing and become increasingly swollen, which generates hydrodynamic pressure in the system. The hydrodynamic pressure thus created forces the drug reservoir compartment to reduce in volume and causes the liquid drug formulation to release through the delivery orifice at the specific rate. Such systems are also called as push-pull osmotic pumps.[5]
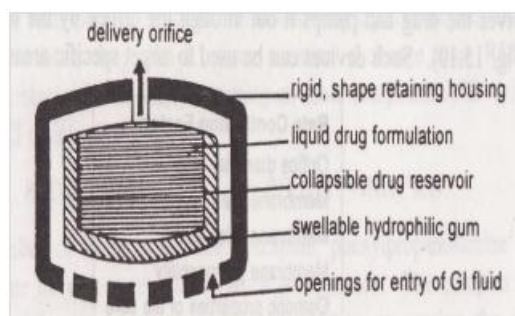

Figure 10: Hydrodynamic pressure controlled system.

MECHANISM OF DRUG RELEASE FROM MATRIX TABLET

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 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.

Derivation of the mathematical model to describe this system involves the following assumptions:

➢ A pseudo-steady state is maintained during drug release.

➢ The diameter of the drug particles is less than the average distance of drug diffusion through the matrix.

➢ The bathing solution provides sink conditions at all times.

The release behavior for the system can be mathematically described by the following equation:

$$dM/dh = (C_0.dh) - C_s/2 \qquad (8)$$

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.

Additionally, according to diffusion theory:

$$dM = (Dm. Cs / h) dt \qquad (9)$$

Where,

Dm = Diffusion coefficient in the matrix.

h = Thickness of the drug-depleted matrix.

dt = Change in time

By combining equation 8 and equation 9, integrating and solving for h gives:

$$M = [Cs.Dm (2Co - Cs) t]^{1/2} \qquad (10)$$

When the amount of drug is in excess of the saturation concentration, that is Co>>Cs, then.

$$M = [2Cs.Dm.Co.t]^{1/2} \qquad (11)$$

Equation 10 and equation 11 relate the amount of drug release to the square-root of time. Therefore, if a system is predominantly diffusion controlled, then it is expected that a plot of the drug release vs. square root of time will result in a straight line. Drug release from a porous monolithic matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through tortuous interstitial channels and pores. The volume and length of the openings must be accounted for the drug release from a porous or granular matrix can be describe as

$$M = [Ds. Ca. p/T. (2Co - p.Ca) t]^{1/2} \qquad (12)$$

Where,

p = Porosity of the matrix.

t = Tortuosity.

Ca = solubility of the drug in the release medium.

Ds = Diffusion coefficient in the release medium.

T = Diffusional path length.

For pseudo steady state, the equation can be written as:

$$M = [2D.Ca .Co (p/T) t] \tfrac{1}{2} \qquad (13)$$

The total porosity of the matrix can be calculated with the following equation:

$$p = pa + Ca/\rho + Cex/\rho ex \qquad (14)$$

Where,

p = Porosity.

ρ = Drug density.

pa = Porosity due to air pockets in the matrix.

ρex = Density of the water soluble excipients.

Cex = Concentration of water soluble excipients.

For the purpose of data treatment, equation 11 or 12 can be reduced to:

$$M = k. \, t^{1/2} \qquad (15)$$

Where, k is a constant, so that the amount of drug released versus the square root of time will be linear, if the release of drug from matrix is diffusion-controlled. If this is the case, the release of drug from a homogeneous matrix system can be controlled by varying the following parameters:

- Initial concentration of drug in the matrix
- Porosity
- Tortuosity
- Polymer system forming the matrix
- Solubility of the drug.[4 & 7]

Delayed Transit and Continuous Release System:

These systems are designed to prolong their residence in the GIT along with their release. Often, the dosage form is fabricated to detain in the stomach and hence the drug present therein should be stable to gastric pH. Systems included in this category are as follows:

Altered Density System

The transit time of GI contents is usually less than 24 hours. This is the major limiting factor in the design of oral controlled release formulation which can reduce the frequency of dosing to a time period little more than the residence time of drug. If the residence time of drug in the stomach or intestine is prolonged in some way the frequency of dosing can be reduced. There are 3 ways by which this can be achieved such as altering the density ofdrug particles use of mucoadhesive polymer and altering the size of the dosage form.

Mucoadhesive System

A bioadhesive polymer such as cross-linked polyacrylic acid, when incorporated in a tablet, allows it to adhere to the gastric mucosa or epithelium. Such a system continuously releases a fraction of drug into the intestine over prolonged periods of time.

Size-Based System

Gastric emptying of a dosage form can be delayed in the fed state if its size is greater than 2 mm. Dosage form of size 2.5 cm or larger is often required to delay emptying long enough to allow once daily dosing. Such forms are however to swallow.

Delayed Release System:

Intestinal Release System

A drug may be enteric coated for intestinal release for several known reasons such as to prevent gastric irritation, prevent destabilization in gastric pH, etc. Certain drugs are delivered to the distal end of small intestine for absorption via peyer's patches or lymphatic system. Peyer's patches are mucosal lymphoid tissues that are known to absorb macromolecules like proteins and peptides and antigens by endocytosis. Selective release of such agents to peyer's patch region prevents them from getting destroyed/digested by the intestinal enzymes. Such a site can be utilized for oral delivery of insulin.

Colonic Release System

Drugs are poorly absorbed through colon but may be delivered to such a site for two reasons – Local actions as in the treatment of ulcerative colitis with mesalamine and systemic absorption of protein and peptide drugs like insulin and vasopressin. The advantage is taken of the fact that pH sensitive bioerodible polymers like polymethacrylates release the medicament only at the alkaline pH of colon or use of divinylbenzene cross-linked polymer that can be cleaved only by the azoreductase of colonic bacteria to release free drug for local effect or systemic absorption.[12, 13]

POLYMERS USED IN PREPARATIONS OF CRDDS

Hydrogels:

- ➢ Polyhydroxyethylmethylacrylate (PHEMA)
- ➢ Cross-linked polyvinyl alcohol (PVA)
- ➢ Cross-linked polyvinylpyrrolidone (PVP)
- ➢ Polyethyleneoxide (PEO)
- ➢ Polyacrylamide (PA)

Soluble Polymers:

- ➢ Polyethyleneglycol (PEG)
- ➢ Polyvinyl alcohol (PVA)
- ➢ Polyvinylpyrrolidone (PVP)
- ➢ Hydroxypropylmethylcellulose (HPMC)

Biodegradable Polymers:

- ➢ Polylactic acid (PLA)
- ➢ Polyglycolic acid (PGA)
- ➢ Polycaprolactone (PLA)

- Polyanhydrides
- Polyorthoesters

Non Biodegradable Polymers:

- Polyethylene vinyl acetate (PVA)
- Polydimethylsiloxane (PDS)
- Polyetherurethane (PEU)
- Polyvinyl chloride (PVC)
- Cellulose acetate (CA)

Mucoadhesive Polymers :

- Polycarbophil
- Sodium carboxymethyl cellulose
- Polyacrilic acid

- Tragacanth
- Methyl cellulose
- Pectin
- Natural gums
- Xanthan gum
- Guar gum
- Karaya gum14

Extended Release Tablets Available in National and International Markets

There are so many ER Tablets of different drug molecule by different manufacturers are available in the market. Some of their name is depicted in table 3.

Table 3: Various Extended release marketed dosage form and there manufacturers.

Brand Name	Active Ingredient(s)	Manufacturer
Metapure-XL Tab	Metoprolol Succinate	Emcure, Mumbai
Etomax – ER Tab	Etodolac	Ipca, Mumbai
Betacap –TR Cap	Propranolol HCl	Sun Pharma, J and K
Metaride Tab	Glimipiride and Metformin HCl	Unichem, Mumbai
Augmentin – XR Tab	Amixicillin and Potassium Clavulanate	Glaxosmithkline, Mumbai
Wellbutrin - XL Tab	Buprorion HCl	Glaxosmithkline, Mumbai
Revelol – XL Tab	Metoprolol Succinate	Ipca, Mumbai
Dayo – OD Tab	Divolproex Sodium	Lupin, Baddi(HP)
Sentosa – ER Tab	Venlafaxine	Nicholas Piramal, Baddi(HP)
Zanocin – OD Tab	Ofloxacin	Ranbaxy, Ponta Sahib.
Glizid – MR Tab	Gliclazide	Panacea Biotech, Lalru(CHD).
Metzok Tab	Metoprolol Succinate	USV, Mumbai
Tegritol - CR Tab	Carbemezapine	Novartis, Goa
Glimestar PM Tab	Glimipride,Pioglitazone and metformin	Discovery Mankind, Ponta Sahib
Supermet – XL Tab	Metoprolol Succinate	Piramal Healthcare, Baddi(HP)
Gabaneuron – SR Tab	Gabapentin and Methylcobalamin	Aristo, Baddi(HP)
Cefoclox – XL Tab	Cefpodoxime Dicloxacillin and Lactic acid bacillus	Khandelwal
Zen Retard Tab	Carbemezapine	Intas, Ahemdabad
Tolol AM Tab	Metoprolol Succinate	Unichem, Mumbai
Exermet GM 502 Tab	Glimepiride and Metformin HCl	Cipla, Baddi(HP)
Mahacef – XL Tab	Cefpodoxime Dicloxacillin and Lactic acid bacillus	Discovery Mankind, Ponta Sahib
Gluconorm PG Tab	Glimepiride, Pioglitazone and Metformin HCl	Lupin, Baddi (HP)
Minipress –XL Tab	Parazocin HCl	Pfizer, Goa
Pomed – EX Tab	Pantaprozol and domperidone	Panjon
Riomet – Trio 2 Tab	Metformin HCl	Ranbaxy, Ponta Sahib
Divaa – OD Tab	Divalproex Sodium	Intas, Ahemdabad

CONCLUSION

We concluded from the above discussion that extended release formulations are very much helpful in increasing the effectiveness of the drugs with short half life and also improve patient compliance by decreasing the dosing frequency. Now, a wide range of drugs are formulated in a variety of different oral extended release dosage forms. However, only those which result in a significant reduction in dose frequency and a reduction in toxicity resulting from high concentration in the blood or gastrointestinal tract are likely to improve therapeutic outcomes. To be a successful extended release product, the drug must be released from the dosage form at a predetermined rate, dissolve in the gastrointestinal fluids, maintain sufficient gastrointestinal residence time, and may be absorbed at a rate and will replace the amount of drug being metabolized and excreted.

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