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A CONCISE REVIEW ON CONTROLLED DRUG RELEASE DEVICES: MODELS, DELIVERY DEVICES

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ABSTRACT

Controlled drug release devices have been developed to maintain a constant concentration of the drug in the therapeutic range in the patient's body. There by it helps in reducing the variation in the performance of the active drug. Such systems offer numerous advantages over traditional methods of drug delivery. Targeted delivery systems are also considered as controlled drug delivery systems. These devices have been designed to enhance drug therapy by continuous release after application of single dose to have stability in blood level thereby diminishing side effects. Polymeric membranes are generally used for controlled delivery of drugs. These system works on various mechanisms like osmotic pressure, matrix system, controlled dissolution etc. This article presents a brief review on the preparation of controlled drug release devices, and underlying basic mechanisms effecting release of drug including types of devices for controlled delivery with basic mathematical equations.

KEY WORDS: Drug, Polymer, Stability, Therapy.

INTRODUCTION

Drug delivery is defined as the delivery of an active compound into the body by some technology or approach and maintaining its level within the therapeutic range. Conventionally drug administering methods (oral or injectable formulations) do not provide an effective controlled release and are also not target specific. This also led to an instantaneous increase in the concentration of drug to toxic level within a shorter period of time before declining to the therapeutic level and then followed by a drop in concentration until it is re-administered. In conventional system, drug in the patient's body results in the fluctuation of drug concentration as shown in Figure 1.

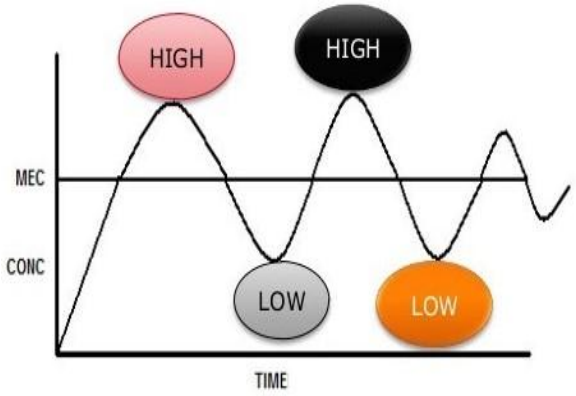


Figure 1: Drug concentration fluctuation with time.

Limitations of conventional drug release (Parashar et al., 2013):

- Only the total mass of drug delivered to patient is controlled
- Attainment of steady-state condition is difficult
- Unavoidable fluctuations of drug concentration leads to under medication or over medication
- Requirement of frequent administration
- Adverse effects due to fluctuation in drug levels

Fluctuation of drug concentration in blood streams and tissues results in unwanted toxicity and poor efficiency (Prescott, 1989). Therefore, it becomes important to maintain drug concentration within the therapeutic index for an effective treatment (Ratnaparkhi and Gupta, 2013). Controlled drug delivery devices (Hoffman, 2008) are developed to enhance the efficiency of drug therapy. Recent advances show remarkable increase of interest in the various types of controlled release drug devices (Yang and Pierstorff, 2012). These have been designed to have prolonged therapeutic effect by continuous release of medication after application of a single dose. Main aim of therapy is to have stable level in blood which is therapeutically effective and nontoxic thus diminishing the side effect. Controlled drug release devices in general are more sophisticated with ability to deliver drug at specific rate within a predetermined time period (Lapidus and Lordi, 1968). This short article focuses on the mechanism involved in the action of controlled drug delivery devices. Their classification on the basis of inherent mechanism is also discussed.

Controlled drug release systems

These systems exercise control over the delivery rate, permit control over the site of release or activity and also protect drug from physiological degradation or elimination (Langer,1990). The common drug delivery products and their manufacturer are summarized in Table 1. (Ratnaparkhi and Gupta Jyoti P, 2013).

Table 1: List of commercially drug delivery products and their manufacturer [adopted Ratnaparkhi and Gupta Jyoti P, 2013].

S No.	Technology	Brand name	Drug	Manufacturer
1	Diffusion controlled	Welbutrin XL	Bupropion	GlaxoSmithKline
2	Matrix system tablet	Ambien CR	Zolpidem Tartarate	Sanofi-Aventis
3	Method using ion Exchange	Tussionex Pennkinetic ER suspension	Hydrocodone Polistirex & Chlorpheneramine Polistirex	UCB Inc.
4	Methods using osmotic pressure	Efidac 24®	Chlorpheniramine Maleate	Novartis

The major advantages of controlled drug release devices vis-à-vis conventional drug administration methods are: (Ratilal et al., 2013 and Bhowmik et al., 2012):

- ❖ Eliminate over or under dosing
- ❖ Maintain drug levels in desired range
- ❖ Permit less dosing
- ❖ Increased patient compliance
- ❖ Prevention of side effects
- ❖ Site specific targeting
- ❖ Increased contact time hence improved bioavailability

Their major disadvantages are:

- ❖ Higher cost per unit dose compared to conventional doses
- ❖ Dose dumping if administered drug has long half-life
- ❖ Less accurate dose adjustment for drugs having narrow therapeutic index
- ❖ Lower bioavailability under high first pass clearance

With advent of polymer science and technology, concept of smart drug delivery system was came because earlier drug was introduced to entire body which may cause drug toxicity due to long term treatment of chronic diseases (Bhandari, 2004). Drug released from these system is based on diffusion, degradation, swelling and affinity based mechanism (Wang, 2011). Some of the advantages of smart drug delivery as intelligent delivery system

- Ease of manufacture and characterization
- Biodegradable polymer as drug delivery system
- Thermos magnetic targeted drug delivery
- Thermos sensitive targeted liposomes
- Application in biometric actuators
- Bio separation strategy in drug delivery

DRUG RELEASE CHARACTERIZATION MODELS

The mechanisms used to achieve goals of controlled drug release systems are diverse and complex, and depend on the particular application. Several mechanisms exist (Khan, 2009) so it is desirable to understand these mechanisms when designing and manufacturing controlled drug release systems. These models are of different mathematical function defining concentration profile (Kakar, 2014). Different types of mathematical model for controlled drug delivery are defined below.

Zero Order Delivery Model

Ideal drug delivery would follow "zero order kinetics" (Ummadi et al., 2013) where it becomes important to maintain drug level constant throughout the delivery period as in case of antibiotic delivery, heart and blood pressure maintenance, pain control. Zero order (constant rate release of drug) is desirable in order to reduce the fluctuation in the drug concentration in the blood which may lead to underexposure or overexposure. In simple form zero order release is mathematically represented as,

$Q = Q_o + K_o t$ ……i)

Where,

Q=amount of drug release after drug dissolve

Q_o= initial amount of drug

K_o = zero order release constant

Figure 2 illustrates the drug concentration profile over a time. A rapid increase in concentration is followed by a rapid decrease with small residence time in the therapeutic range and then below it till the next dose is administered. The drug concentration on an average fluctuates with in the maximum desired level (MDL) and a

minimum level indicated by the minimum effective concentration (MEC) so as to maintain concentration frequent dosing is required but their control is difficult. However, dosage forms that prolong release can maintain drug concentration within the therapeutic range. As shown in figure 2 controlled release leads, in principle, to the best control of concentration. Such control permits constant drug delivery without causing toxicity due to overdose.

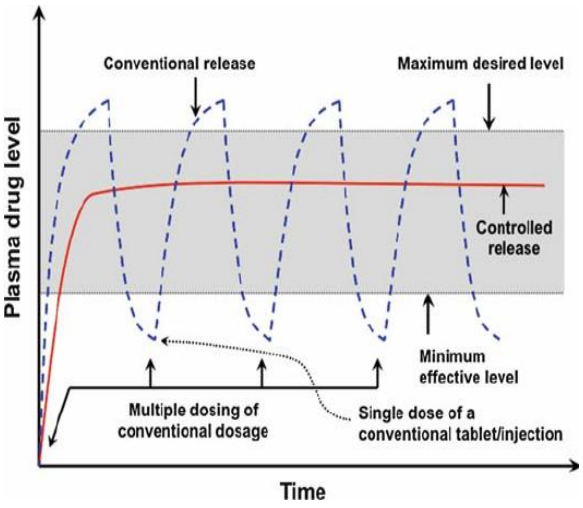


Figure 2: Conventional drug Vs Controlled Release Drug concentration profile (Huynh and Lee 2014).

First Order Model

This model is basically used to define adsorption and elimination of drugs as reported by (Dash et. al, 2010). The kinetics of first order release drug is expressed as

$dC/dt = - KC$ …….ii)

K= first order rate constant ($time^{-1}$)

C = concentration of drug

This type of model is generally used in water soluble drugs in porous matrix.

Hixson and Crowell model

This model expresses rate of dissolution based on cube root of particle where radius of particle is not treated as constant (Ramteke et. al, 2014). Model equation describing rate equation based on size particle is:

$M_0^{1/3} - M_t^{1/3} = Kt$ …….iii)

M_0 = initial amount of drug

M_t = remaining amount of drug

K = proportionality constant

Such model is used where a dosage is from tablet in a plane parallel to drug surface.

Higuchi model

These models are used to study release of low soluble from semisolid or solid matrices (Salome et. al, 2013). Higuchi in 1961 derived a model for dissolution from a planar homogenous matrix:

$Q = [D(2C-C_s) C_s t]^{1/2}$ …….iv)
Model for dissolution from a planar spherical heterogeneous matrix
$Q = D \varepsilon/\tau (2C- \varepsilon C_s) C_s t$ …….v)
Q = amount of drug released in time t per unit area,
C = initial drug concentration,
Cs = drug solubility in the matrix
D is the diffusivity of drug molecules

These relation are valid for all t except when total depletion of the drug in the therapeutic system is achieved.

Korsmeyer-Peppas model (the power law)

(Lokhandwala, 2013)

Korsmeyer et al. (1983) define drug release from polymeric system where diffusion is main drug release mechanism as given by

$A_t/ A_0 = at^n$ ……..vi)

a = constant (structural and geometrical characteristic of dosage form)

n = release exponent

A_t/ A_0 = fraction of drug release at time t

In 1985 Peppas characterizes different release mechanism using release exponent value

n	**Diffusion**
0.5	Fickian diffusion
0.5-1.0	Non Fickian diffusion

Weibull Model

This model relates accumulated fraction of drug 'm' in solution at time't' (Singhavi, 2011 and Costa, 2001)

$C= C_0[1-\exp[\frac{-(t-T)^b}{a}]]$ ……vii)

Where,

C= amount of dissolved drug as a function of time.

C_0= total amount of drug being released.

T= lag time measured.

a= scale parameter describing time dependency.

b= shape of dissolution curve. These are applied when comparing release profile of drug release of matrix type.

Hopfenberg Model

These are applied for the release of drug from surface eroding polymer such that area remains constant during process (Shaikh et al, 2015). These models are used to identify the type of drug released from the optimized oilisphere.

The model equation for cumulative fraction of drug released is given as:

$C_t/ C_i = [1-K_0t/ C_La]^n$ ……viii)

K_0 is the zero order rate constant

C_L is the initial drug loading

a=system half thickness (that is radius for a sphere or cylinder.)

n=exponent that varies with geometry, n=1, 2, 3 for slab (flat, cylindrical and spherical geometry. From the above described model selection of best suitable model is difficult. However few criteria still exist for selection which has highest coefficient of determination (R), Analysis of Variance (ANOVA) and Multivariate analysis of Variance (MANOVA). An ideal drug system should deliver precise amount of drug at specific rate to have necessary drug level to treat the disease.

Polymers used in the drug delivery systems (Langer, 1993)

Polymers are extremely important in the field of drug delivery. Controlled drug delivery occurs when a polymer (natural or synthetic) when judiciously combined with a drug or active agent results in release of active component form the material in a predesigned manner. Release can be constant or cyclic over long period (Bhowmik et al., 2012). The characteristics of polymers that make them versatile in drug delivery systems include polymers having wide molecular weight distributions, variety of visco-elastic properties, ability to contract when heated, variety of dissolution times, specialized chemical reactivity, tolerance to a variety of manufacturing methods (Liechty, 2010). Example: poly (2-hydroxy ethyl methacrylate), poly (N-vinyl pyrrolidone) (Shaikh et. al, 2012 and Uhrich et. al, 1999).

Polymers used in devices are classified broadly into two categories (Gavasane and Pawar, 2014):

a) Natural polymer for e.g.

- ✓ Protien-based polymer: Collagen, Albumin, Gelatin
- ✓ Polysaccharides: Alginate, Cyclodextrin

b) Synthetic polymer for e.g.

Biodegradable polymers

- Polyester: Poly lactic acid, Poly glycolic acid
- Polyanhydride: Poly adepic acid, Poly sebacic acid, Poly terpthalic acid

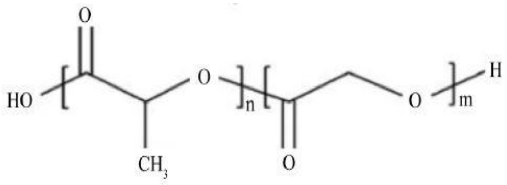
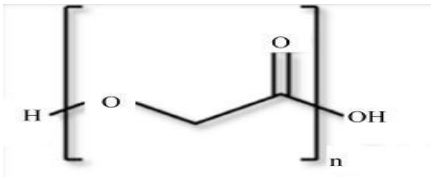
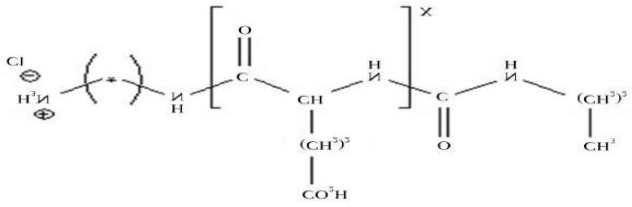
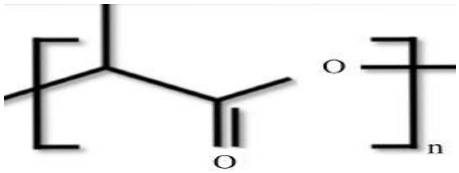
Non-Biodegradable polymers

- Cellulose derivative: Carboxy methyl cellulose, Ethyl cellulose, Cellulose acetate hydroxyl propyl methyl cellulose
- Silicons: Polydimethyl siloxane, Colloidal silica, Polymethacrylate

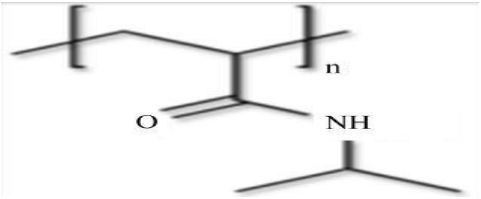
Similar other polymer are enlisted in Table 2 with their chemical structure.

Polymer are having better circulation time than conventional drug releasing molecule and are target specific (Srivastava et. al, 2016). Some of the polymer with name of drug released by them is listed in table 2 (Vilar et. al, 2012). Drug delivery systems are classified according to the physico-chemical mechanism controlling the release of the drug. Some of the basic systems are described below.

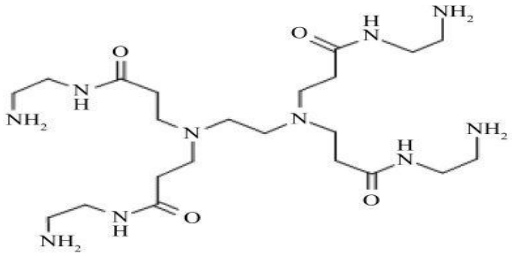
Table 2: Polymer and its structure (Srivastava et. al, 2016).

S. No.	Polymer	Structure
1	poly lactic-co-glycolic acid	
2	poly glycolic acid	
3	Poly-l-glutamic acid	
4	Poly lactic	

5 Poly(*N*-isopropylacrylamide)



6 Poly (amidoamine)



TYPES OF DEVICES

1) DIFFUSION CONTROLLED DELIVERY SYSTEM

Diffusion control release of biologically active compound is one the most common and important method (Tongwen and Binglin, 1998). Drug release can be in solid, suspension or liquid form. Mathematically rate of drug delivery in diffusion-controlled delivery systems in simple form can be described by Fick's laws (Shaikh et al., 2015).

J= -D (dC/dx) …….ix)

Where J = flux of diffusion or amount of substance passing per unit area per unit time (mg/m^2 h). D = diffusivity of drug molecule (cm^2/sec)

dC/dx = concentration gradient across diffusional barrier of thickness dx. According to diffusion principle the design of delivery system is divided into a) reservoir and ii) matrix configuration but they have two different release pattern as shown in Figure 3.

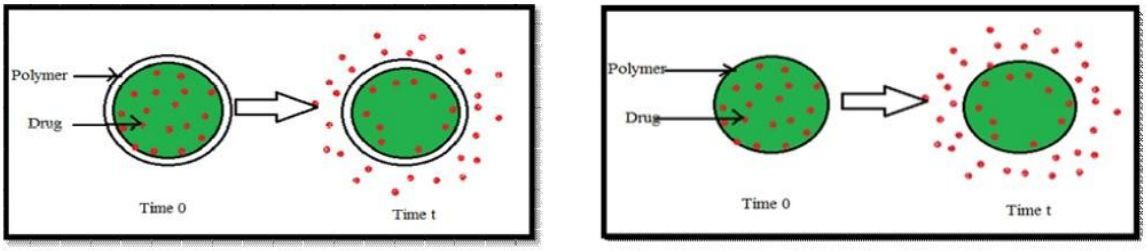


Figure 3: Schematic representation of reservoir and matrix system devices (Ratnaparkhi and Gupta Jyoti, 2013).

i) Diffusion Reservoir System

In these systems drug reservoir is covered with a water insoluble polymer. Drug will partition through membrane and exchange with fluid surrounding tablet. Here drug release takes place through diffusion mechanism (Modi et al., 2013).

Advantages:

- Zero order delivery is possible

- Release rate can be enhanced with use of different polymer types

Disadvantages:

- Difficult to deliver to high molecular weight compound and
- Potential toxicity if system fails

ii) Diffusion Matrix Systems

In these devices the drug is uniformly distributed within a polymer as a solid block and is released by diffusion out of a polymer matrix. For this system release kinetics is function of square root of time. The diffusion depends on the solubility of the drug in the polymer. They are non-biodegradable matrix with a dispersed drug diffusing out through the matrix (Lyu and Siegel, 2016). The cumulative amount released from a matrix-controlled device is described by (Steve et al., 2003)*:*

$$\frac{Q}{t^{0.5}} = [\frac{2C_a - C_P}{D_P C_P}]^{0.5} \quad \ldots\ldots\ldots\ldots\ldots x)$$

where

C_p = solubility of drug in polymer (g/cm^3).
C_a= initial amount of drug (g/cm^3)
D_p = diffusivity in polymer (cm^2/s)
Q = cumulative amount released (g/sec)
Rate can be controlled by choice of matrix:

- glassy matrix: (they have diffusion coefficients in range of D~10^{-10}-10^{-12} cm^2/s)
- rubbery matrix: (they have diffusion coefficients in range of D ~ 10^{-6}-10^{-7} cm^2/s)

Advantage:

- Easier to produce as compared to reservoir
- Versatile, effective and low cost.
- Stability is increased by protecting it from hydrolysis.

Disadvantage:

- Matrix needs to be removed after release of drug
- Pure zero order release is not possible

2) MEMBRANE CONTROLLED DRUG RELEASE DEVICES

These are constant flux devices where drug release rate is controlled by semi-permeable membranes which can be of two types

2.a) Nonporous semi-permeable membranes

Diffusion occurs through swollen polymer membrane as shown in figure 4

$$M = \frac{DkA}{\delta}(C_2 - C_1)t \ldots\ldots\ldots\ldots\ldots\ldots xi)$$

where

K= membrane partition coefficient
δ= thickness
C_1, C_2= concentration outside and inside membrane respectively (g/cm^3).

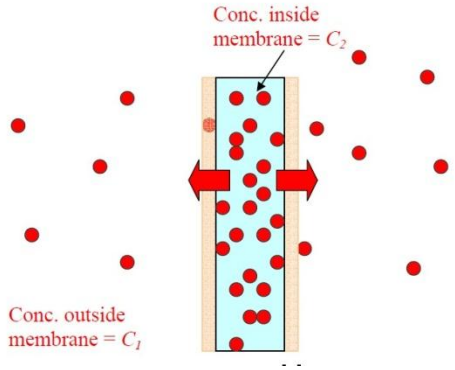


Figure 4: Schematic representation of non-porous membrane (Oct.mig.edu, 2006)

2.b) Porous semi-permeable membranes

Diffusion of drug molecules occurs through membrane pores. An equation similar to eq iv) can be used to describe the drug release process by replacing D with an effective D_{eff} defined as:

$$D_{eff} = D_{pore}\varepsilon/\tau$$

ε = porosity, τ= tortuosity.

3) OSMOTIC CONTROLLED DRUG RELEASE DEVICES

These devices use semipermeable membranes that allow controlled amount of water to diffuse into the core of device filled with particle hydrophilic component. The transport of water into the device exercises a pressure on the drug solution within the device and pumps (Gupta et. al, 2011) it out through a small opening in the tablet as shown in figure 5. It offers advantage of constant release rate (Herbig et. al, 1995). The release rate is affected by the amount of osmotic agent, surface area, thickness of semipermeable membrane, size of hole. This technique permits zero order release.

The release rate is proportional to the change in volume of drug reservoir [Kim, 2000]

$$\frac{dM_t}{dt} = \frac{dV}{dt}C = \frac{Ak\Delta\pi C}{\delta} \dots\dots\dots\dots\dots\dots\text{xii)}$$

Where,
A = membrane area (cm^2)
C = drug concentration (g/cm^3)
K = membrane permeability
$\Delta\pi$ = osmotic pressure differential (atm)
δ = membrane thickness (µm)

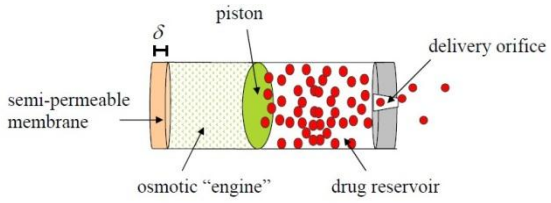


Figure 5: Schematic representation of osmotic controlled pump (Oct.mig.edu, 2006)

4) DISSOLUTION CONTROLLED DRUG RELEASE DEVICES

These types of system are commonly used for the production of enteric coated dosage form Costa P et. al, 2001). To protect stomach from the effect of drugs such as aspirin, a coating that dissolves in alkaline solution is used. Controlled release of drug is obtained by using rate limiting step in dissolution process of solid drug with low solubility.

The dissolution rate can be quantitatively described by the Noyes-Whitney equation as follows [Steve et al., 2003]:

$$\frac{dC}{dt} = \frac{DA}{h}(C_0 - C_l) \dots\dots\dots\dots\dots\text{xiii)}$$

where

$\frac{dC}{dt}$= Rate of dissolution
D= diffusion coefficient of drug (cm^2/sec)
A= area of drug particle (cm^2)
C_o= saturation concentration of drug in diffusion layer (g/cm^3)
C_1= concentration of drug in bulk fluid at time t (g/cm^3)

5) PULSATILE DRUG RELEASE DEVICES

These systems deliver drug at specific time as per the need leading to improvement in patient therapeutic efficacy. They are used in treating asthma, peptic ulcer, cardiovascular disease etc. (Survase et. al, 2007). The drug release is controlled by delivery system for example stimuli induced pdds, where stimuli is controlling factor for delivery.

6) FLOATING DRUG RELEASE DEVICES

Floating or Hydrodynamically controlled system have sufficient buoyancy to float over gastric component without affecting empty rate of gastric (Gopalakrishnan et. al,

2011). Since the system is floating so drug is released slowly but at desired rate. Along with buoyancy rating principal a minimum floating force is also desirable to keep the dosage form reliably buoyant on the surface of the meal.

7) ION EXCHANGE CONTROLLED DRUG RELEASE RESINS

They are cross linked water insoluble polymers having ionisable functional groups (Anand et. al, 2001). After formation of drug/resin complex the drug is released by ion exchange with the presence of counter ion (Srikanth et al., 2010) and (Jeong and Park, 2008).

Rate of drug release is governed by the area and length of diffusion pathway and the amount of cross linked polymer in resin (Conaghey et. al, 1998).

Ion exchange reaction is expressed as
$[A^+] + [R^-][B^+] \longleftrightarrow [B^+] + [R^-][A^+]$
Hence selectivity coefficient is described as

$$K_B^A = \frac{[A_R^+][B^+]}{[B_R^+][A^+]} \quad \text{..... xiv)}$$

Where,
$[A^+]$ = concentration of free counter ion
$[B_R^+]$ = concentration of drug bound of resin
$[B^+]$ = concentration of drug freed from resin
$[A_R^+]$ = concentration of counter ion bound to resin.

8) BIODEGRADABLE / ERODIBLE DELIVERY SYSTEM

It involves degradation of polymer into smaller fragments inside the body to release drug in a controlled manner. Zero order release can effectively be obtained. These delivery systems protect and stabilize bioactive agents enabling long term administration. In this system drug is incorporated inside a dissolvable or erodible matrix. Common erodible systems are based on poly (lactic acid) or poly (lactic acid-co-glycolic acid) polymers. The selection of matrix is controlled by its dissolvable nature and non-toxic erosion fragments or products.

These drug delivery devices can be bulk eroding and surface eroding type a shown in figure 6 (Baker, 2004). In former case water invasion is rapid whereas in the latter case hydrolysis is fast.

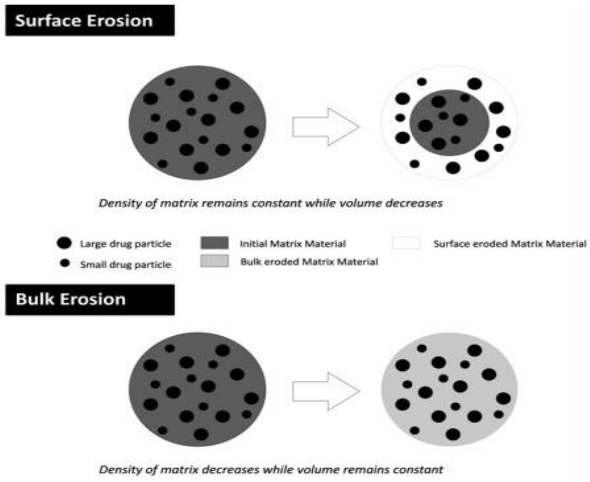


Figure 6: Erosion mechanism found in matrix system (Holowaka and Bhatia, 2014)

CONCLUSION

The most important quality for any drug delivery device is to release drug at specific site and in controlled manner. This objective is fulfilled by controlled drug delivery devices (Langer, 1998). The controlled release devices have maximum efficiency with minimum side effects and fluctuation in drug concentration (Huynh and Lee 2014). These devices work on different mechanisms to control the release rate which include osmotic pressure, matrix system, etc. Concept of smart drug delivery helps in reduction in cost due to minimization of doses, making medicine universally affordable and helps in ensuring patient compliance. Mathematical modeling of the drug release under different governing mechanisms has helped in the design and development of better devices. These systems provide many clinical applications and depending on the specific site to be treated most suitable controlled release devices can be opted. Such systems offer numerous advantages over traditional drug delivery methods, however, it should be recognized that development of these devices can be expensive and more complete understanding of factors need to be carried out for optimal designing of control release devices and reduce the cost.

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