Program	B. Pharmacy
Name of Unit	Controlled release drug delivery system , polymers controlled release drug delivery
Subject /Course name	Novel Drug Delivery System
Subject/Course ID	BP 704T
Class: B.Pharm. Semester	7th Semester
Module	1
Course coordinator	Punam Gaba

Learning Outcome of Module 01

LO	Learning Outcome (LO)	Course Outcome Code
LO1	Students will learnt about selection of drug candidates.	BP704.1
LO2	Students will learnt about Approaches to design controlled release formulations	BP704.1
LO3	Students will learnt about Physicochemical and biological properties of drugs relevant to controlled release formulations	BP704.1
LO4	Students will learnt about application of polymers in formulation of controlled release drug delivery systems.	BP704.1

Content Table

Topic
• Introduction, terminology/definitions and rationale, advantages, disadvantages, selection of drug candidates. • Approaches to design controlled release formulations based on diffusion, dissolution and ion exchange principles. • Physicochemical and biological properties of drugs relevant to controlled release formulations • Introduction, classification, properties, advantages and application of polymers in formulation of controlled release drug delivery systems.

INTRODUCTION

The science of controlled release was first originated from the development of oral sustained release products in the 1940s and early 1950s. First of all, the controlled release of marine antifoulants (the 1950s) and controlled release of fertilizer (1970s) were formulated which had only a single application in the soul science. The development of the pharmacology and pharmacokinetics demonstrated the importance of drug release rate in determining therapeutic effectiveness of therapy. This becomes the reason behind the development of controlled release.

The modified release dosage forms are entirely new. The first time Rhozes formulates mucilage coated pills about A.D 900. This technique widely adopted in the10th century by European countries, in the form of gold, silver and pearl coated tablets; this coating modifies the drug release rates. Advancement in the coating technology including sugar & enteric coating on the pills & tablets in the late 1800s. The further coating developed to the enteric coating of tablets followed by incorporation of the second drug to sugar coating layer, this happened near about 1938. However, the first patent for oral sustained release preparation went in the favour of Lipowski; his preparation contained small coated beads that were releasing the drug slowly & constantly. This idea later developed by Blythe and launched the first marketed sustained release product in 1952. Over the past 30 years as the complication involves in the marketing of new drug increased and various advantages recognized of Controlled release drug delivery system (CRDDS), the greater attention is being paid in this field. Today the oral controlled drug delivery system becomes major drug delivery systems mainly drugs having high water solubility and short biological half-life. Other than oral, the various routes like transdermal, ocular, vaginal & parenteral route use for controlled release of various drugs.

The term *modified-release drug product* is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined "as one for which the 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 solutions, ointments, or promptly dissolving dosage forms as presently recognized". Several types of modified-release drug products are recognized.

Extended-release drug products: A dosage form that allows at least a two fold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional)

dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release, and long-acting drug products.

Delayed-release drug products: A dosage form that releases a discrete portion or portions of drug at a time or at times other than promptly after administration, although one portion may be released promptly after administration. Enteric-coated dosage forms are the most common delayed-release products.

Targeted-release drug products: A dosage form that releases drug at or near the intended physiologic site of action. Targeted-release dosage forms may have either immediate or extended-release characteristics.

The term controlled-release drug product was previously used to describe various types of oral extended-release dosage forms, including sustained-release, sustained-action, prolonged-action, long-action, slow-release, and programmed drug delivery.

Conventional Drug Delivery System

Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid/immediate absorption.

As can be seen in the graph (Figure 1), administration of the conventional dosage form by extravascular route does not maintain the drug level in blood for an extended period of time. The short duration of action is due to the inability of conventional dosage form to control temporal delivery.

The conventional dosage forms like solution, suspension, capsule, tablets and suppository etc. have some limitations such as:

1) Drugs with short half-life require frequent administration, which increases chances of missing the dose of drug leading to poor patient compliance.

2) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult. The unavoidable fluctuations in the drug concentration may lead to under medication or over medication as the steady state concentration values fall or rise beyond the therapeutic range.

3) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overdosing occurs.

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.

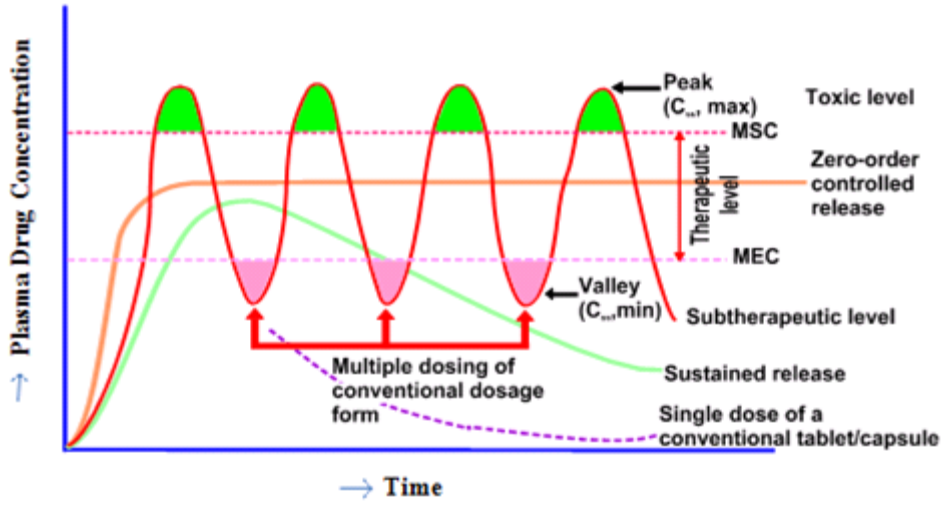


Figure. 1: *A hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations. (MSC = maximum safe concentration, MEC = minimum effective concentration)*

CONTROLLED RELEASE

An ideal dosage regimen of drug therapy is one which rapidly attained the required plasma concentration and maintained for the entire period of treatment. The frequencies of drug administration primarily depend on the biological half-life of the drug and mean residential time (MRT).Conventional drug delivery system often produces over or under medication result in various adverse drug reactions (ADRs) due to unpredictable drug release pattern. The CRDDS alters the drug distribution along with are duction in drug toxicity. The term controlled release (CR) implies the predictability and reproducibility in the drug release kinetics which means the drug release from the delivery system proceed at the rate profile not only expected kinetically but also reproducible from one division to another. CRDDS intended to exercise control drug release in the body; this may be temporal or spatial nature or both. The term sustained release also mentioned during the description of controlled release. Sustained release (SR) used to describe a pharmaceutical dosage form formulated to retard the release of API such a way that its appearance in the systemic circulation is delayed or prolonged and plasma concentration

sustained in duration. The onset of drug action delayed and duration of therapeutic effect is maintained.

Advantages of Controlled Drug Therapy

- ✓ Reduction in dosing frequency easily acceptance of patient.
- ✓ Loss of drug can be reduced by targeting.
- ✓ Decreasing GI side effects and toxicological effects.
- ✓ Fluctuation in plasma drug level minimized.
- ✓ Better patient compliance.
- ✓ Convenient to administration compared to other routes of administration.
- ✓ Stability of drug can be increased.
- ✓ Uniform drug effect achieved.
- ✓ Delivery of drug in the vicinity of site of action.
- ✓ Maintenance of optimal and effective dosage levels for long action.
- ✓ Improve bioavailability of same drugs.
- ✓ Make use of special effects, e.g. sustained release aspect for morning relief of arthritis by dosing before bedtime.

Disadvantages of Controlled Drug

- ✓ They are costly.
- ✓ Unpredictable and often poor in-vitro in-vivo correlations, dose dumping, reduced potential for dosage adjustment and increased potential first pass clearance.
- ✓ Poor systemic availability in general.
- ✓ Effective drug release period is influenced and limited by GI residence time.

Need of Controlled Drug Delivery Systems

Controlled release of active ingredients from oral dosage forms may be required for the following reasons

- ✓ Avoidance of undesirable local side effects.
- ✓ Local treatment of diseases of GI tract.
- ✓ Protection of active ingredients against the influence of digestive fluids.
- ✓ Influencing the pharmacokinetics of active ingredients.

Rationale of Controlled Drug Delivery Systems

The basic rationale for controlled drug delivery is to alter the pharmacokinetic and pharmacodynamics of pharmacologically active moieties by using novel drug delivery systems or by modifying the molecular structure and/or physiological parameters inherent in a selected route of administration. It is desirable that the duration of drug action become more to design properly. Rate controlled dosage form, and less, or not at all, a property of the drug molecules inherent kinetic properties. As mentioned earlier, primary objectives of controlled drug delivery are to ensure safety and to improve efficiency of drugs as well as patient compliance. This achieved by better control of plasma druglevels and frequent dosing. For conventional dosage forms, only the dose (D) and dosing interval (C) can vary and, for each drug, there exists a therapeutic window of plasma concentration, below which therapeutic effect is insufficient, and above which toxic side effects are elicited. This is often defined as the ratio of median lethal dose (LD 50) to median effective dose (ED50).

Selection of drug candidates:

Parameters consider during the drug selectionshow in table 1.

Table. 1-Pharmacokinetic parameters for drug selection

Parameter	Comment
Biological or elimination half-life	Should be between 2 to 6 hrs
Elimination rate constant(KE)	Required for design
Total clearance(CLT)	dose independent
Intrinsic absorption rate	should be greater than the release rate
Apparent volume of distribution (Vd)	Vd effect the required amount of the drug
Absolute bioavailability	Should be 75% or more
Steady state concentration (Css)	lower Css and smaller Vd
Toxic concentration	The therapeutic window should be broader

CLASSIFICATION OF ORAL CONTROLLED RELEASE SYSTEMS

The majority of oral controlled release drug delivery systems depends on, diffusion, dissolution or a combination of diffusion and dissolution mechanisms to produce slow release of drug. Depending upon the manner of drug release these systems are classified as

1. Diffusion controlled release systems
2. Dissolution controlled release systems
3. Dissolution and diffusion controlled release systems
4. Ion exchange resins
5. pH independent formulations
6. Osmotic controlled release systems
7. Altered density release systems
8. Prodrugs
9. Delayed release systems

DIFFUSION-CONTROLLED DELIVERY SYSTEMS

Diffusion process has been utilized in design of controlled release drug delivery systems for several decades. This process is a consequence of constant thermal motion of molecules, which results in net movement of molecules from a high concentration region to a low concentration region. The rate of diffusion is dependent on temperature, size, mass, and viscosity of the environment. Molecular motion increases as temperature is raised as a result of the higher average kinetic energy in the system.

$$E = \frac{kT}{2} = \frac{mv2}{2} \qquad \text{.....1}$$

Where,

E = kinetic energy

k = Boltzmann's constant

T = temperature

m = mass

v = velocity

This equation shows that an increase in temperature is exponentially correlated to velocity ($v2$). Size and mass are also significant factors in the diffusion process. At a given temperature, the mass of molecule is inversely proportional to velocity (Eq. 1). Larger molecules interact more with the surrounding environment, causing them to have slower velocity. Accordingly, large molecules diffuse much slower than light and small particles. The viscosity of the environment is another important parameter in diffusion, since the rate of molecular movement is associated

with the viscosity of the environment. Diffusion is fastest in the gas phase, slower in the liquid phase, and slowest in the solid phase.

Mathematically, the rate of drug delivery in diffusion-controlled delivery systems can be described by Fick's laws. Fick's first law of diffusion is expressed as:

$$J = -D\frac{dC}{dx} \qquad \text{.....2}$$

Where

J = flux of diffusion

D = diffusivity of drug molecule

$\frac{dC}{dx}$ = concentration gradient of the drug molecule across diffusion barrier with thickness dx

According to the diffusion principle, controlled-release drug delivery systems can be designed as a reservoir system or a matrix system. Drugs released from both reservoir and matrix type devices follow the principle of diffusion, but they show two different release patterns as shown in Figure. 2.

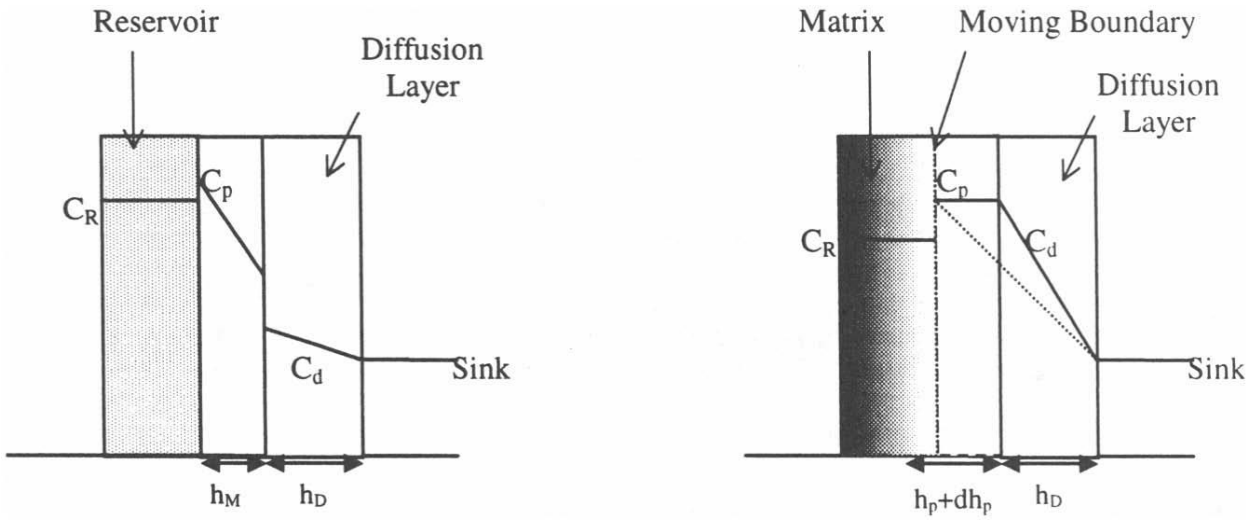


FIGURE 2: *Schematic illustrations of reservoir versus matrix systems.*

In Figure. 2, *CR* is drug concentration in the reservoir or matrix compartment, *CP* is solubility of drug in the polymer phase, *CD* is the concentration in the diffusion layer, *hm* is the thickness of the membrane, *hd* is thickness of the diffusion layer, and *hp* + *dhp* indicates the changing thickness of the depletion zone of matrix. In a reservoir system, if the active agent is in a saturated state, the driving force is kept constant until it is no longer saturated. For matrix

systems, because of the changing thickness of the depletion zone, release kinetics is a function of the square root of time. A typical reservoir system for transdermal delivery consists of a backing layer, a rate-limiting membrane, a protective liner, and a reservoir compartment. The drug is enclosed within the reservoir compartment and released through a rate-controlling polymer membrane (Figure 3).

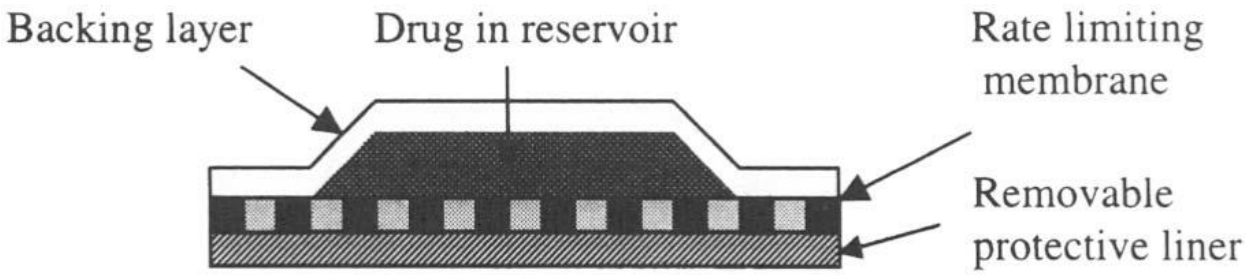


FIGURE 3: Reservoir-type transdermal drug delivery system.

Membranes used to enclose the device can be made from various types of polymers. The rate of release can be varied by selecting the polymer and varying the thickness of the rate-controlling membrane. The drug in the reservoir can be in solid, suspension, or liquid form. Analysis of diffusion-controlled reservoir or matrix drug delivery systems requires a few assumptions:

1. The diffusion coefficient of a drug molecule in a medium must be constant.

2. The controlled drug release must have a pseudo-steady state.

3. Dissolution of solid drug must occur prior to the drug release process.

4. The interfacial partitioning of the drug is related to its solubility in polymer and in solution as defined by

$$K = \frac{Cs}{Cp} \quad \text{.....3}$$

Where

K = partition coefficient of the drug molecule from polymer to solution

Cs = solubility of drug in the solution phase

Cp = solubility of drug in polymer phase

With the above assumptions, the cumulative amount Q of drug released from a diffusion-controlled reservoir-type drug delivery device with a unit surface area can be described as follows:

$$Q = \frac{CpKDdDm}{KDdhm+Dmhd}t - \frac{DdDm}{KDdhm+Dmhd}\int_o^t Cb(t)\ dt \text{.....4}$$

Where

Dm = diffusivity of the drug in a polymer membrane with thickness *hm*

Dd = diffusivity of hydrodynamic diffusion layer with thickness *hd*

Cb = concentration of drug in reservoir side

t = time

Under a sink condition, where $Cb(t) \infty 0$ or $Cs >> Cb(t)$, Eq. (4) is reduced to

$$Q = \frac{CpKDdDm}{KDdhm+Dmhd}t \qquad \text{.....5}$$

This relationship shows that release of drug can be a constant, with the rate of drug release being

$$\frac{Q}{t} = \frac{CpKDdDm}{KDdhm+Dmhd} \text{.....6}$$

In extreme cases, the rate of release may depend mainly on one of the layers, either the polymer membrane layer or the hydrodynamic diffusion layer. If the polymer membrane is the rate-controlling layer, *KDdhm Dmhd*, the equation can be simplified to:

$$\frac{Q}{t} = \frac{CpDm}{hm} \text{.....7}$$

which shows that the release rate is directly proportional to the solubility of the drug in polymer and inversely proportional to thickness of the polymer membrane. Delivery systems designed on this principle can be administered by different routes: intrauterine such as Progestasert, implants such as Norplant, transdermal such as Transderm-Nitro, and ocular such as Ocusert. A matrix system, often described as monolithic device, is designed to uniformly distribute the drug within a polymer as a solid block. Matrix devices are favored over other design for their simplicity, low manufacturing costs, and lack of accidental dose dumping, which may occur with reservoir systems when the rate controlling membrane ruptures. The release properties of the device depend highly upon the structure of the matrix: whether it is porous or nonporous. The rate of drug release is controlled by the solubility of the drug in the polymer and the diffusivity of the drug through the polymer for nonporous system. For a porous matrix, the solubility of the drug in the network and the tortuosity of the network add another dimension to affect the rate of release. In addition, drug loading influences the release, since high loading can complicate the release mechanism because of formation of cavities as the drug is leaving the device. These cavities will

fill with fluids and increase the rate of release. The cumulative amount released from a matrix-controlled device is described by.

$$Q = \left(CA - \frac{Cp}{2}\right) hp \ldots\ldots\ldots\ldots\ldots\ldots\ldots 8$$

Where

CA is initial amount of drug

CP is solubility of drug in polymer

hp is a time dependent variable defined by

$$\frac{2CpDp}{CA-\frac{Cp}{2}}\, t = h_p^2 + \frac{2(C_A - C_P)Dphdhp}{\left(CA-\frac{Cp}{2}\right) Ddk^{-}K} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 9$$

Where k^- is a constant for relative magnitude of the concentration in the diffusion layer and depletion zone, *Dp* is the diffusivity of drug in the polymer devices, and other parameters are the same as described for Eqs. (3) to (8). At a very early stage of the release process, when there is a very thin depletion zone, the following will be true:

$$h_p^2 \;<< \frac{2(C_A - C_P)Dphdhp}{\left(CA - \frac{Cp}{2}\right) Ddk^{-}K}$$

Equation (9) can be reduced to

$$h \sim \frac{CpDdk^{-}K}{(CA-CP)\, hd} \ldots\ldots\ldots\ldots\ldots\ldots\ldots 10$$

and placing Eq. (10) into Eq. (8) gives

$$\frac{Q}{t} = \frac{CpDdk^{-}K}{hd} \qquad (\text{if } C_A - Cp \sim \left(CA - \frac{Cp}{2}\right) \quad \ldots\ldots\ldots 11$$

Since *KCp* = *Cs*, Eq. (11) becomes

$$\frac{Q}{t} = \frac{CsDdk^{-}}{hd} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 12$$

The k^- term implies that the matrix system is more sensitive to the magnitude of concentration difference between depletion and diffusion layers.

if

$$h_p^2 >> \frac{2(C_A - C_P)Dphdhp}{\left(CA - \frac{Cp}{2}\right) Ddk^{-}K}$$

where the depletion zone is much larger and the system has a very thin diffusion layer, Eq. (9) becomes

$$h_p \sim \left(\frac{2C_p\, Dp}{\left(CA - \frac{Cp}{2}\right)} t\right) \quad \text{.....13}$$

and placing Eq. (13) into Eq. (8) makes

$$\frac{Q}{t^{\frac{1}{2}}} = \lceil (2CA - CP)CPDP \rceil^{1/2} \quad \text{.....14}$$

Equation (14) indicates that after the depletion zone is large enough, the cumulative amount of drug released (Q) is proportional to the square root of time ($t^{1/2}$).

DISSOLUTION/COATING-CONTROLLED DELIVERY SYSTEMS

Controlled release of drug can be achieved by utilizing the rate-limiting step in the dissolution process of a solid drug with relatively low aqueous solubility. The dissolution rate can be quantitatively described by the Noyes-Whitney equation as follows.

$$\frac{dC}{dt} = \frac{DA}{h}(C_o\text{-}C_t) \quad \text{.....(15)}$$

where

$\frac{dC}{dt}$= rate of drug dissolution

D = diffusion coefficient of drug in diffusion layer

h = thickness of diffusion layer

A = surface area of drug particles

C_0 = saturation concentration of the drug in diffusion layer

C_t = concentration of drug in bulk fluids at time t

The surface area A of the drug particle is directly proportional to the rate of dissolution. For a given amount of drug, reducing the particle size results in a higher surface area and faster dissolution rate. However, small particles tend to agglomerate and form aggregates. Using a

specialized milling technique with stabilizer and other excipients, aggregation can be prevented to make microparticles smaller than 400 nm in diameter to improve the dissolution of the drug in the body. The saturation solubility C_0 can also be manipulated to change the rate of dissolution. Both the physical and chemical properties of a drug can be modified to alter the saturation solubility. For example, salt forms of a drug are much more soluble in an aqueous environment than the parent drug. The solubility of a drug can also be modified when the drug forms a complex with excipients, resulting in a complex with solubility different from the drug itself. Controlled or sustained release of drug from delivery systems can also be designed by enclosing the drug in a polymer shell or coating. After the dissolution or erosion of the coating, drug molecules become available for absorption. Release of drug at a predetermined time is accomplished by controlling the thickness of coating. In Spansule® systems, drug molecules are enclosed in beads of varying thickness to control the time and amount of drug release. The encapsulated particles with thin coatings will dissolve and release the drug first, while a thicker coating will take longer to dissolve and will release the drug at later time. Coating-controlled delivery systems can also be designed to prevent the degradation of the drug in the acidic environment of the stomach, which can reach as low as pH 1.0. Such systems are generally referred as *enteric-coated systems.* In addition, enteric coating also protects the stomach from ulceration caused by drug agents. Release of the drug from coatingcontrolled delivery systems may depend upon the polymer used. A combination of diffusion and dissolution mechanisms may be required to define the drug release from such systems.

DISSOLUTION AND DIFFUSION CONTROLLED SYSTEMS

The main characteristic is that the drug reservoir is surrounded with a partially soluble layer. The part of dissolution membrane allow to diffusion of the drug through pores in the polymer membrane. The drug release from these systems explained by following equation:

$$\text{Release rate} = AD(C1-C2)/L$$

Where A = Surface area,

D = Diffusion coefficient

L = Diffusion path length

C1= Concentration of drug in the system

C2= Concentration of drug in the dissolution medium.

BIODEGRADABLE/ERODIBLE DELIVERY SYSTEMS

Biologically degradable systems contain polymers that degrade into smaller fragments inside the body to release the drug in a controlled manner. Zero-order release can be achieved in these systems as long as the surface area or activity of the labile linkage between the drug and the polymeric backbone are kept constant during drug release. Another advantage of biodegradable systems is that, when formulated for depot injection, surgical removal can be avoided. These new delivery systems can protect and stabilize bioactive agents, enable long-term administration, and have potential for delivery of macromolecules.

OSMOTIC CONTROLLED RELEASE SYSTEM

This type of delivery device has a semipermeable membrane that allows a controlled amount of water to diffuse into the core of the device filled with a hydrophilic component. A water-sensitive component in the core can either dissolve or expand to create osmotic pressure and push the drug out of the device through a small delivery orifice, which is drilled to a diameter that correlates to a specific rate. In an elementary osmotic pump, the drug molecule is mixed with an osmotic agent in the core of the device (Fig. 4*a*). For drugs that are highly or poorly water soluble, a two compartment push-pull bilayer system has been developed, in which the drug core is separated from the push compartment (Fig. 4*b*). The main advantage of the osmotic pump system is that constant release rate can be achieved, since it relies simply on the passage of water into the system, and the human body is made up of 70 percent water. The release rate of the device can be modified by changing the amount of osmotic agent, surface area and thickness of semipermeable membrane, and/or the size of the hole.

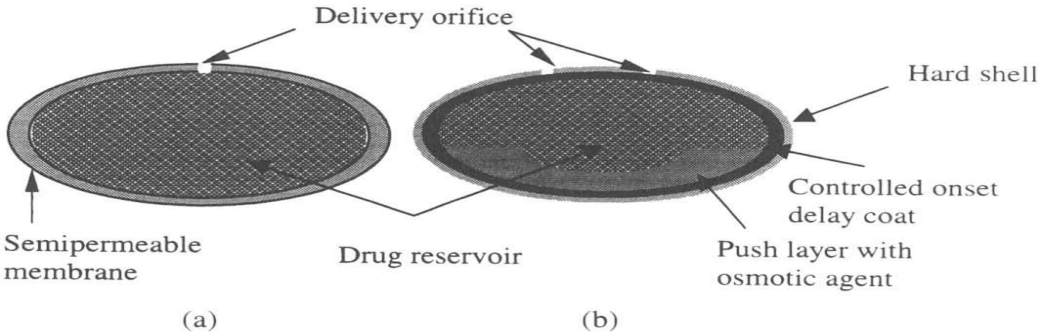


FIGURE 4 Schematic illustration of an elementary osmotic pump (a) and a push-pull osmotic pump device (b).

The rate of water diffusing into the osmotic device is expressed as

$$\frac{dV}{dt} = (\frac{AK}{h})(\Delta\Pi\text{-}\Delta P)$$

where $\frac{dV}{dt}$= change of volume overchange in time

A, *K*, *h* = area, permeability, and thickness of membrane, respectively

ΔΠ = difference in osmotic pressure between drug device and release environment

ΔP = difference in hydrostatic pressure

If the osmotic pressure difference is much larger than the hydrostatic pressure difference (ΔΠ >>ΔP), the equation can be simplified to

$$\frac{dV}{dt} = (\frac{AK}{h})(\Delta\Pi)$$

The rate at which the drug is pumped out the device *dM/dt*, cab be expressed as

$$\frac{dM}{dt} = (\frac{dV}{dt})C$$

where *C* is the drug concentration. As long as the osmotically active agent provides the constant osmotic pressure, the delivery system will release the drug at a zero-order rate. The zero-order delivery rate can be expressed as

$$(\frac{dM}{dt}) = \frac{AK}{h}\Pi_s C$$

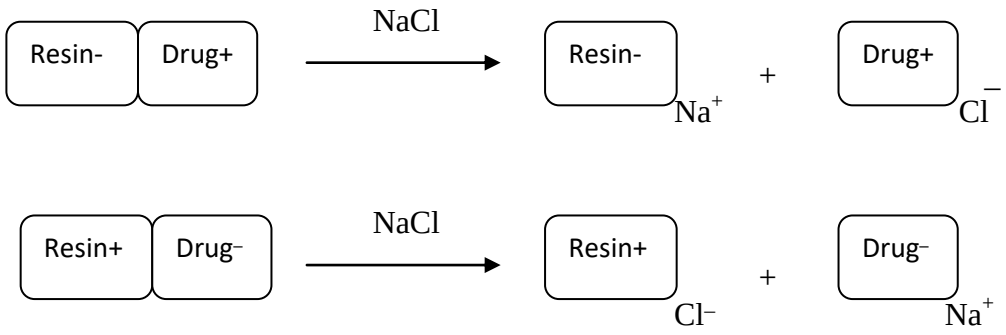
where Πs is osmotic pressure generated by saturated solution and all other symbols are the same as described earlier.

ION EXCHANGE RESINS

This principle has been used for a long time in analytical and protein chemistry. It is an attractive one of controlled drug delivery because drug release characteristics related to the ionic charges of the resin containing drug and should therefore be less susceptible to environmental conditions like enzyme content and pH at the site of absorption. Drug release can be modified by application of coating on the drug-resin complex.

The ion exchange resin system can be designed by binding drug to the resin. After the formation of a drug/resin complex, a drug can be released by an ion exchange reaction with the presence of

counterions. In this type of delivery system, the nature of the ionizable groups attached determines the chemical behavior of an ion exchange resin (Figure 5).



An ion exchange reaction can be expressed as

$$[A^+] + [R^-][B^+] \longleftrightarrow [B^+] + [R^-][A^+]$$

and the selectivity coefficient is defined as

$$K_B^A = \frac{[A_R^+][B+]}{[A+][B_R^+]}$$

where $[A+]$ = concentration of free counterion

$[B_R^+]$= concentration of drug bound of the resin

$[B+]$ = concentration of drug freed from resin

$[A_R^+]$= concentration of counterion bound to the resin

Factors that affect the selectivity coefficient include type of functional groups, valence and nature of exchanging ions, and nature of nonexchanging ions. Although it is known that ionic strength of GI fluid is maintained at a relatively constant level, first-generation ion-exchange drug delivery systems had difficulty controlling the drug release rate because of a lack of control of exchange ion concentration (Figure. 5*a*). The second-generation ion-exchange drug delivery system (Pennkinetic system) made an improvement by treating the drug-resin complex further with an impregnating agent such as polyethylene glycol 4000 to retard the swelling in water (Figure. 5*b*). These particles are then coated with a water-permeable polymer such as ethyl cellulose to act as a rate-controlling barrier to regulate the drug release.

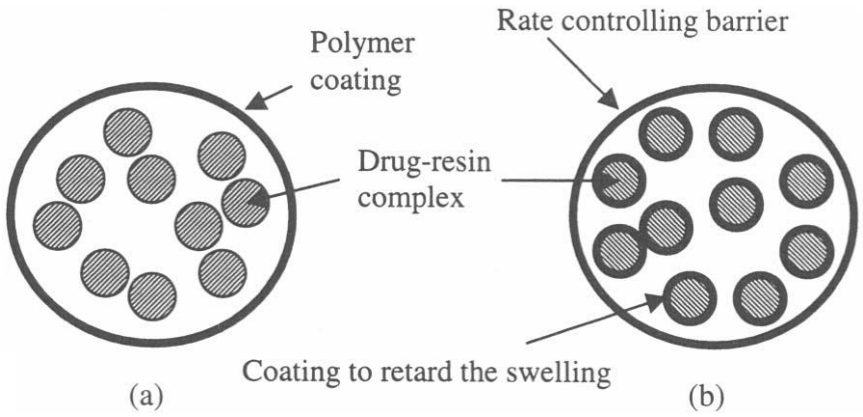


***FIGURE 5: Schematic illustration of first generation (a) and second generation (b) ion exchange drug delivery system*.**

P[H] INDEPENDENT FORMULATIONS

Most of the drug are either weak acid or weak base, the release from sustain release formulation is pH dependent. However, buffer such as salt of citric acid, amino acid, tartaric acid can be added to the formulation, to help to maintain to constant pH their by retarding pH independent drug release. A buffer sustain release formulation is prepared by mixing a basic or acidic drug one or more buffering agent, granulating with appropriate excipients and coating with gastrointestinal fluid permeable film forming polymer. When gastrointestinal fluid permeates through the membrane, the buffering agent adjusts the fluid inside to suitable constant pH there by rendering a constant rate of drug release.

The GI tract presents different features that are not fond in other routes of drug administration. The variable nature of the chemical environment throught the GIT is a constraint on dosage form design. Indeed, drugs administered orally would encounter a spectrum of pH ranging from 1 to 1.6. The pH dependency of drug release from controlled release formulations has been demonstrated by study of papaverine hydrochloride

ALTERED DENSITY CONTROLLED RELEASE SYSTEMS

The GI transit time varies depends on person. In most human subjects, it is the range of 8 to 62 hrs has been found. The specific density of these subunits is found to be a more significant factor than their diameter in influencing their GI transit time, specifically; increasing density from 1to 1.6 increases the average transit time from 7 to 25 hrs. This approach helped in design of floating drug delivery systems and swelling systems.

High Density Approach

In this approach the density of the pellets must exceed that of normal stomach content and should therefore be at least 1-4gm/cm3.

Low Density Approach

Globular shells which have an apparent density lower than that of gastric fluid can be used as a carrier of drug forsustained release purpose.

PRODRUGS

A prodrug is chemically modified one which will liberate the active pharmaceutical ingredient in the body either enzymatic or hydrolytic cleavage. The main objective of a prodrug for oral administration is to increase absorption rate or to reduce local side effects.(i.e. GI irritation by aspirin).

DELAYED RELEASE SYSTEMS

The development of these systems involves release of drug only at a specific site in the GIT. The drugs formulated in such a systems include

1. Known to cause gastric distress,
2. To sensitive of gastric juice or intestinal enzymes,
3. Absorption occurs at a specific intestinal site or
4. To localization at a specific GIT site.

The most common ones are intestinal release systems and colonic release systems.

MATRIX TYPE ORAL CONTROLLED DRUG DELIVERY SYSTEMS

Matrix type drug delivery systems releases drug by both dissolution as well as diffusion controlled mechanisms. Drug release from the system depends on different solubility properties of drug dispersed in polymers. One of the simplest method involves the fabrication of sustained release dosage forms involve the direct compression of blended drug, polymer and additives. To develop tablet formulation in which the drug is dispersed in a matrix of the polymer. In another way drug and polymer may be granulated prior to compression.

Advantages of matrix tablets

1. Minimize the local and systemic side effects
2. Improvement efficacy in treatment
3. Minimization of drug accumulation

4. Improvement the bioavailability of the some drugs
5. It is a versatile and low cost
6. Reducing toxic effects by slowing absorption
7. Increase stability of drug by protection from hydrolysis
8. The ability to provide special effects

Disadvantages of matrix tablets

1. The release rate can be effected by various factors like food, GI transit time, etc
2. The matrix must be removed from the body after releasing the drug
3. The drug release rate vary with square root of time

Classification of matrix tablets

Matrix drug delivery systems broadly divided into two classes are

Reservoir type matrix systems – in this system drug release controlled with membrane.

Monolithic matrix systems – in this systems drug dispersed in a matrix or encapsulated.

Depending on the type of polymer

Matrix tablets classified into following types

Lipophilic matrices (Plastic matrices)

This concept was first discovered in 1959. In method of oral sustained release systems, drug is blended with polymer and compressed into a tablet. In fact sustained release produced by the dissolved drug has diffused through a net work of channels of matrix. The rate controlled step involves liquid penetration into the matrix.

E.g.: Polyvinyl chloride (PVC), Polyethylene (PE), Ethyl cellulose (EC), Acrylate polymers and their copolymers.

Wax matrices

These are prepared by using lipid waxes and their derivatives. In this systems release of drug occurred through pore diffusion and erosion. Release characteristics are more sensitive to digestive fluids than to insoluble polymers matrix. E.g.: Carnauba wax with stearyl alcohol or stearic acid is commonly used.

Hydrophilic matrices

These are widely employed in oral controlled drug delivery system due to their flexibility. The drug is formulated into gelatinous capsules or in tablets, polymers with high gelling capacities. In

fact a matrix means mixing of one or more drugs with a polymer that leads to swelling when exposed to liquid environment. Commonly used polymers are as follows

Natural or semi synthetic polymers include agar-agar, alginates, molasses, carob gum, and polysaccharides such as mannose, galactose and chitosan, modified starches.

Cellulose derivatives are Hydroxylpropylmethyl cellulose (HPMC), Methyl cellulose 400&4000cps, Hydroxyethyl cellulose (HEC), and Sodium carboxymethyl cellulose (NaCMC).

Polymers of acrylic acid, carbopol-934 commonly used.

Mineral matrices

The polymers extracted from seaweed species for system development. E.g.: Alginic acid obtained from brown sea weeds by using alkali.

Biodegradable matrices

These consist of polymers those comprised of monomers through cross linking between functional groups in the back bone. These are biodegraded into oligomers by metabolically with the help of enzymes. E.g.: Proteins, Polysaccharides, Polylacticacid, Polyglycolicacid etc.

Depending on porosity of matrix

Matrix systems also classified according to its intrinsic character i.e. porous nature. They are

1. **Micro porous system:** Size range of pores is 50 to 200Ao slightly larger than diffusant molecule size.
2. **Macro porous system:** Size range of pores is 0.1 to 1micrometers, which is larger than diffusant molecule size.
3. **Non porous system:** There is no pores and drug diffuse through the network of matrix.

The present work is planned to prepare and evaluate novel drug delivery systems of highly soluble drugs alfuzosin hydrochloride and citicoline using hydrophilic and hydrophobic polymers. Alfuzosin is indicated for treatment of BPH. Citicoline is used in the treatment of neurodegenerative disorders like alzheimer's disease, parkinson's disease and head injuries with improve patient mental ability.

FACTORS INFLUENCING THE DESIGN AND ACT OF CONTROLLED RELEASE PRODUCTS

A. Biological factors

1. Biological Half-life

Drug molecules with short half-life are excellent candidate for sustained-release formulation, since this can reduce dosing frequency. However, this is limited, in that drugs with very short half-lives may require excessive large amounts of drug in each dosage unit to maintain sustained effects, forcing the dosage form itself to become limitingly large.

Compounds with relatively long half-lives, generally greater than 8 hrs are not used in the sustained release dosage forms, since their effect is already sustained and also GI transit time is 8-12 hrs. So the drugs, which have long -half life and short half- life, are poor candidates for sustained release dosage forms.

Some examples of drug with half-lives of less than 2 hours are ampicillin, cephalexin, cloxacillin, furosemide, levodopa, penicillin G and propylthiouracil. Examples of those with half-lives of greater than 8 hours are dicumarol, diazepam, digitoxin, digoxin, guanethidine, phenytoin and warfarin.

2. Absorption

The absorption rate constant is an apparent rate constant, and should, in actuality, be the release rate constant of the drug from the dosage form. Compounds that demonstrate the absorption rate constant will probably be poor candidates for sustaining systems. If a drug is absorbed by active transport, or transport is limited to a specific region of intestine, sustained-release preparations may be disadvantageous to absorption.

3. Metabolism

The metabolic conversion of a drug to another chemical form usually can be considered in the design of a sustained-release system for that drug. As long as the location, rate and extent of metabolism are known and the rate constants for the processes are not too large, successful sustained-release products can be developed.

There are two factors associated with the metabolism of some drugs; however that present problems of their use in sustained-release systems. One is the ability of the drug to induce or inhibit enzyme synthesis; this may result in a fluctuating drug blood level with chronic dosing. The other is a fluctuating drug blood level due to intestinal (or other tissue) metabolism or through a hepatic first-pass effect. Examples of drugs that are subject to intestinal metabolism upon oral dosing are hydralazine, salicylamide, nitroglycerine, isoproterenol, chlorpromazine

and levodopa. Examples of drugs that undergo extensive first-pass hepatic metabolism are propoxyphene, nortriptyline, phenacetine, propranolol and lidocaine.

Drugs that are significantly metabolized especially in the region of the small intestine can show decreased bioavailability from slower releasing dosage forms. This is due to saturation of intestinal wall enzyme systems. The drugs should not have intestinal first pass effect and should not induce (or) inhibit metabolism are good candidates for sustained release dosage forms.

4. Therapeutic window: The drugs with narrow therapeutic index are not suitable for CRDDS. If the delivery system failed to control release, it would cause dose dumping and ultimate toxicity.

5. Absorption window: The drugs which show absorption from the specific segment in GIT, are a poor candidate for CRDDS. Drugs which absorbed throughout the GIT are good candidates for controlled release

6. Patient physiology: The Physiological condition of the patient like gastric emptying rate, residential time, and GI diseases influence the release of the drug from the dosage form directly or indirectly.

B. **Physiological properties**

1. Dose size

In general, single dose of 500-1000 mg is considered maximal for a conventional dosage form. This also holds true for sustained-release dosage forms. Another consideration is the margin of safety involved in administration of large amounts of drug with a narrow therapeutic range.

2. Ionization, PKa & Aqueous Solubility

The pH Partition hypothesis simply states that the unchanged form of a drug species will be preferentially absorbed through many body tissues. Therefore it is important to note the relationship between the PKa of the compound and its absorptive environment. For many compounds, the site of maximum absorption will also be the area in which the drug is least soluble.

For conventional dosage forms the drug can generally fully dissolve in the stomach and then be absorbed in the alkaline pH of the intestine. For sustained release formulations much of the drug will arrive in the small intestine in solid form. This means that the solubility of the drug is likely to change several orders of magnitude during its release.

Compounds with very low solubility are inherently controlled, since their release over the time course of a dosage form in the GIT will be limited by dissolution of the drug. The lower limit for the solubility of a drug to be formulated in a sustained release system has been reported to be 0.1mg/mL. Thus for slightly soluble drugs, diffusion systems will be poor choice, since the concentration in solution will be low.

For example Tetracycline has maximum solubility in the stomach and least solubility in the intestine where it is maximally absorbed. Other examples of drugs whose incorporation into sustained release systems are limited because of their poor aqueous solubility and slow dissolution rate are digoxin, warfarrin, griseofulvin and salicylamide. Very soluble drugs are also good candidates for the sustained release dosage forms.

3. Molecular size and diffusivity

The ability of drug to diffuse through membrane is called diffusivity & diffusion coefficient is function of molecular size (or molecular weight). Generally, values of diffusion coefficient for intermediate molecular weight drugs, through flexible polymer range from 10-8 to 10-9 cm^2 / sec. with values on the order of 10-8 being most common for drugs with molecular weight greater than 500, the diffusion coefficient in many polymers frequently are so small that they are difficult to quantify i.e. less than 16-12 cm2/sec. Thus high molecular weight drugs and / or polymeric drugs should be expected to display very slow release kinetics in sustained release device using diffusion through polymer membrane.

4. Partition coefficient

The compounds with a relatively high partition coefficient are predominantly lipid soluble and easily penetrate membranes resulting high bioavailability. Compounds with very low partition coefficient will have difficulty in penetrating membranes resulting poor bioavailability. Furthermore partitioning effects apply equally to diffusion through polymer membranes.

5. Drug Stability

The drugs, which are unstable in stomach, can be placed in a slowly soluble form and their release delayed until they reach the small intestine. However, such a strategy would be detrimental for drugs that either are unstable in the small intestine (or) undergo extensive gut wall metabolism, as pointed out in the decrease bioavailability of some anticholinergic drugs from controlled /sustained release formulation. In general the drugs, which are unstable in GIT environment, are poor candidates for oral sustained release forms.

6. Protein Binding

It is well known that many drugs bind to plasma proteins with a concomitant influence on the duration of drug action. Since blood proteins are mostly recirculated and not eliminated drug protein binding can serve as depot for drug producing a prolonged release profile, especially if a high degree of drug binding occurs.

POLYMERS

The constantly changing needs, shortened product life cycle and image build of new pharmaceutical commodities require the new product development for new chemical entities, new formulation development as well as new indication for existing drugs. The application of product development starts with new concepts, preformulation, formulation, scale up, quality control/assurance, packaging and marketing of a wide range of new and life cycle management of existing or generic drugs. The polymer sciences have been the backbone of product development in the modern pharmaceutical industry.

The word polymer is derived from the Greek words means ‘many’ and meros means ‘units or parts’. Polymers are compounds with high molecular masses formed by monomers and compressed of a large number of repeating units.

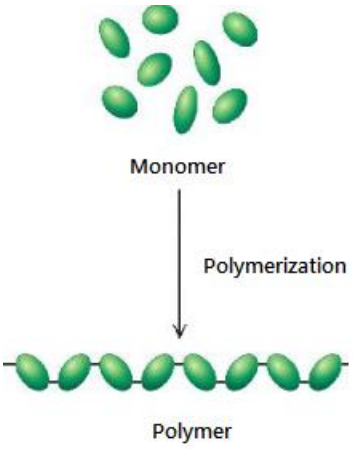


Figure 1: Shown in polymerization

Polymers can form particles of solid dosage form and also can change the flow property of liquid dosage form. Polymers are the backbone of pharmaceutical drug delivery systems. Polymers have been used as an important tool to control the drug release rate from the formulation. They are also mostly used as stabilizer, taste-making agent, and proactive agent. Modern advances in drug delivery are now predicated upon the rational design of polymers tailored specific cargo and

engineered to exert distinct biological functions. Polymers are both naturally occurring and synthetic. Natural polymeric materials such as shellac, amber and natural rubber have been in use for centuries. Biopolymers such as proteins and nucleic acids play crucial roles in biological processes. A variety of other natural polymers exist such as cellulose which is the main.

constituent of wood and paper. Synthetic polymers are produced on a large scale and have a many properties and used. A proper selection selection of surface and bulk properties can help in the designing of polymers for various applications in pharmacy. These are used as pharmaceutical aids (suspending agent, emulsifying agent, adhesives, coating agents, adjuvants etc.), packaging materials and medical devices both in conventional and controlled drug delivery systems. The polymers with specific properties (such as stimuli sensitivity, biodegradability, film forming nature) offer interesting possibilities.

HISTORICAL BACKGROUND

The use of polymers in the medical field is not a novelty - natural polymers have been used as components of herbal remedies for centuries. When it comes to synthetic polymers however the situation is very different. Because polymer science is a relatively recent area of research synthetic water-soluble polymers as macromolecular drugs or as part of drug delivery systems related to inoculation can be considered a modern achievement. The first polymer-drug conjugates appeared around 1955, being mescaline-N-vinylpyrolidine conjugate one of the first.

About ten years later Frank Davis and Abraham Abuchowski were able to foresee the potential of conjugating poly(ethylene glycol) (PEG) to proteins causing the birth of a technique called PEGylation. PEGylation consists in the covalent bond of poly(ethylene glycol) polymer chains to another molecule usually a drug or a protein with therapeutic effects.

In 1994, the first synthetic polymer-drug conjugate (as shown in figure 1b) designed to treat cancer was clinically tested. It consisted on an HPMA (N-(2-hydroxypropyl) methacrylamide) copolymer conjugate of doxorubicin. Targeted release of anticancer agents can also be made using block copolymer micelles which have the ability to entrap the drug or to covalently link to it.

In the 2000s, two polymer-protein conjugates, (as shown in figure 2a) PEG-interferon-α (an antiviral drug intended to treat chronic hepatitis C and hepatitis B) and PEG-GCSF (PEG granulocyte colony-stimulating factor) were placed in the market and five years later the first therapeutic nanoparticles (albumin-entrapped paclitaxel) was approved as a treatment for

metastatic breast cancer. All the above achievements and researches were the core element that led to the development of polymer based pharmaceuticals namely polymeric drugs, polymer-drug conjugates and polymer-protein conjugates. The clinical trials of these new technologies eventually lead to the resolution of many other unexpected challenges that quickly appeared, such as the manufacturing of the polymers at an industrial scale and the quick and total solubilization of the pharmaceuticals for safe inoculation. The optimization of these clinical tests (in terms of dosage and frequency) is still being evaluated today for a large variety of products.

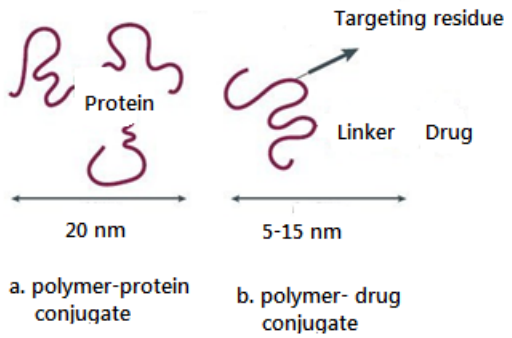


Figure 2: The families of polymer constructs called polymer therapeutics

An important contribution to synthetic polymer science was made by Italian chemist Giulio Natta and German chemist Karl Ziegler, who were honored with the Nobel Prize in chemistry in 1963 for the development of the Ziegler- Natta catalyst. Further recognition of the importance of polymers came with the award of the Nobel Prize in chemistry in 1974 to Paul Flory, whose work on polymers included the kinetics of step- growth polymerization and of addition polymerization, chain transfer, excluded volume, the Flory Huggins solution theory and the Flory convention. Synthetic polymer materials such as nylon, polyethylene, Teflon and silicone have formed the basis for a burgeoning polymer industry. Most commercially important polymers today are entirely synthetic and produced in high volume on appropriate scaled organic synthetic techniques. Synthetic polymers today find application in nearly every industry and area of life.

Advantages

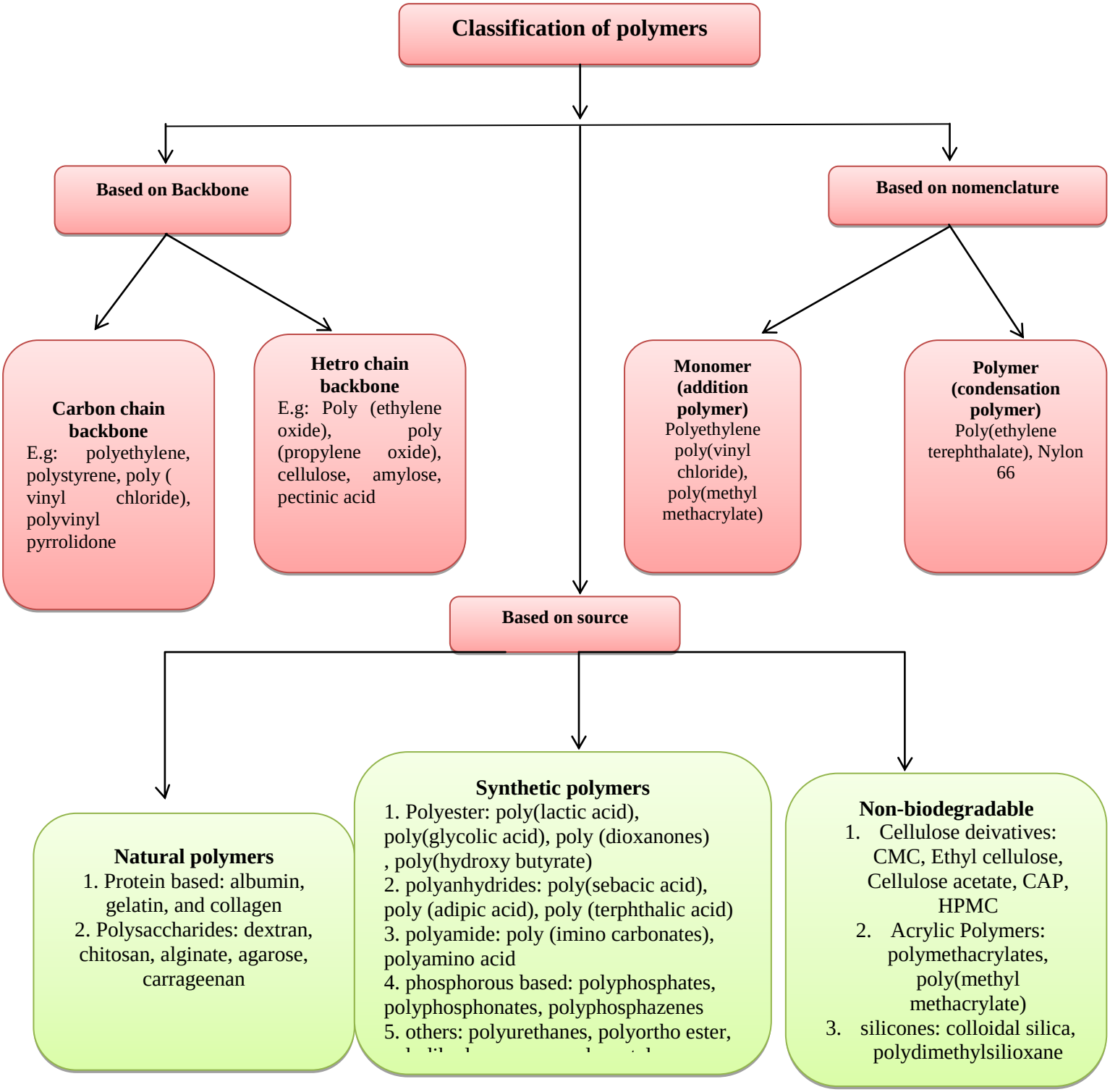
- The product can be implanted directly at the site where drug action is needed and hence systemic exposure of the drug can be reduced. Especially for toxic drugs which are related to various systemic side effects.
- The drug encapsulated is released over extended period and hence eliminates the need for multiple injections. This feature can improve patient compliance especially for drugs for chronic indications, requiring frequent injection.
- The polymer can protect the drug from the physiological environment and hence improve its stability in vivo. This feature makes this technology attractive for the delivery of labile drugs like proteins.
- Cheap to make
- Many uses because of their different properties.
- Provide jobs in firms which make the polymer and the product.
- Some polymers can be recycled, melted down and made into something else which saves valuable natural resources.
- Products relatively pure due to minimum contamination.
- Enhanced yield per reactor volume.
- If polymers are used instead of wood, fewer trees will have to be cut down.

Disadvantages

- People do not like to live near polymer-producing industrial works.
- Some people think plastic products look cheap compared with natural materials.
- Made from oil, a non-renewable resource.
- Most plastics are not biodegradable so there is a problem of how to get rid of them.
- Landfill sites are ugly.
- Give off toxic fumes when they burn.
- Sorting types of polymers for recycling can be expensive.

CLASSIFICATION OF POLYMERS

The polymers for the drug delivery system are classified on the following characteristics:-



APPLICATIONS IN CONVENTIONAL DOSAGE FORMS

In Solid Dosage Forms,

1. Tablets
2. Capsules
3. Film Coatings of Solid Dosage Forms
4. Disperse Systems
5. Gels
6. Transdermal Drug Delivery Systems (Patches)

Tablets

In tablet the polymer are used as a Binder and Disintegrants. Binders which bind the powder particle in a damp mass various polymer are used are Ethyl cellulose, HPMC, Starch, Gelatin, polyvenylpyrrolidine. Alginic acid, Glucose, Sucrose. Disintegrates like Starch, cellulose, Alginates, polyvenylpyrrolidine, sodium CMC which decrease the time of dissolution and gives fast action of drug.

Capsules

The various polymer are used in the capsule as the plasticizer on which the flexibility and strength of the Gelatin are depend on it .The release rate of the Capsule are controlled by using the various type of polymer.

Natural coating agents

Natural polymer like Shellac and zein, although still used from time to time, are hardly able to meet present-day requirements. Organic solvents should be reserved for special applications only and chlorinated hydrocarbons such as methylene chloride and chloroform are avoided altogether, since they impose a heavy load on the environment. Low-molecular-weight types of methylcellulose and hydroxypropyl methylcellulose can also be processed as aqueous solutions. Ethyl cellulose and cellulose acetate phthalate are available as aqueous dispersions, so-called pseudolatexes. An overview of the most widely used cellulosic's is presented, the structure and properties of acrylic polymers.

The solubility properties of EUDRAGIT® acrylic polymers are adjusted to the conditions of the digestive tract. They satisfy particularly stringent requirements in terms of purity. Further quality characteristics are the high stability to environmental influences during storage and absolute skin

friendliness, i.e. indifference to bodily tissue and fluids. The amount of acrylic polymer consumed with the active ingredient is very small, only a few milligrams in the case of coated tablets and approximately 150 mg per day with specific sustained-release preparations. The average polymer quantity taken up by an adult is thus about 2 mg per kg of body weight.

Disperse Systems

The biphasic system are like emulsion, suspension use various polymer for disperse one phase into another phase i.e. water phase disperse in oil phase or vice versa the polymer like poly vinyl pyrolidine, ethyl cellulose etc. Dispersed Systems consist of particulate matter known as the dispersed phase, distributed throughout the dispersion medium with the help of dispersing agent polymer mentioned above. In the oil in water in oil type emulsion the dispersion of drug content is very difficult but it is easily produced by using polymer as a dispersing agent.

Film Coatings of Solid Dosage Forms

Chitosan's film forming abilities lend itself well as a coating agent for conventional solid dosage forms such as tablets. Furthermore its gel- and matrix-forming abilities make it useful for solid dosage forms, such as granules, micro particles, etc. Sakkinen and coworkers studied microcrystalline chitosan as gel-forming excipients for matrix-type drug granules. Crystallinity, molecular weight, and degree of deacetylation were seen to be factors that affected the release rates from the chitosan-based granules. Combination of positively charged chitosan with negatively charged biomolecules, such as gelatin, alginic acid, and hyalouronic acid, has been tested to yield novel matrices with unique characteristics for controlled release of drugs

Taste masked by spray drying:

Chitosan and drug are dissolved in suitable solvent. Sonication done by ultracentrifuge, after stirring 24 hrs with magnetic stirrer, after completely loading drug to polymer, complex dried by spray drying and evaluated for taste masking, Threshold concentration of bitterness. Complexes characterization done with the help of XRPD, FT-IR, DSC and SEM. If Complexation was achieve, % of drug content was determine and equivalent weight of complexes taken and formulate it. Dissolution of the chitosan – drug complexes tablet give sustain released effect.

Transdermal Drug Delivery Systems (Patches)

In the formulation of Transdermal Patches various polymer are used. The baking material also prepared from the polymer for supporting of drug in drug reservoir.

APPLICATIONS IN CONTROLLED DRUG DELIVERY

1. Reservoir Systems
2. Ocusert System
3. Matrix Systems
4. Swelling Controlled Release Systems
5. Biodegradable Systems
6. Osmotically controlled Drug Delivery
7. Introduction: Principles of Controlled Drug Delivery
8. The Progestasert System
9. Reservoir Designed Transdermal Patches
10. Matrix Systems
11. Stimulus Responsive Drug Release
12. Ultrasound Responsive Drug Release
13. Temperature Responsive Drug Release
14. pH Responsive Drug Release
15. Electric Current Responsive Drug Release
16. Polymer-Drug Conjugates

POLYMERS IN BIOMEDICAL APPLICATIONS

Water-Soluble Synthetic Polymers

- Poly (acrylic acid) Cosmetic, pharmaceuticals, immobilization of cationic drugs, base for Carbopol polymers
- Poly (ethylene oxide) Coagulant, flocculent, very high molecular-weight up to a few millions, swelling agent
- Poly (ethylene glycol) *M*W <10,000; liquid (*M*W <1000) and wax (*M*W >1000), plasticizer, base for suppositories
- Poly (vinyl pyrrolidone) Used to make betadine (iodine complex of PVP) with less toxicity than iodine, plasma replacement, tablet granulation
- Poly (vinyl alcohol) Water-soluble packaging, tablet binder, tablet coating Polyacrylamide Gel electrophoresis to separate proteins based on their molecular weights, coagulant, absorbent.
- Poly (isopropyl acrylamide) and poly (cyclopropyl methacrylamide)

- Thermogelling acrylamide derivatives, its balance of hydrogen bonding, and hydrophobic association changes with temperature

Cellulose-Based Polymers

- Ethyl cellulose Insoluble but dispersible in water, aqueous coating system for sustained release applications
- Carboxymethyl cellulose Super disintegrant, emulsion stabilizer
- Hydroxyethyl and hydroxypropyl celluloses
- Soluble in water and in alcohol, tablet coating
- Hydroxypropyl methyl cellulose Binder for tablet matrix and tablet coating, gelatin alternative as capsule material
- Cellulose acetate phthalate Enteric coating

Hydrocolloids

- Alginic acid Oral and topical pharmaceutical products; thickening and suspending agent in a variety of pastes, creams, and gels, as well as a stabilizing agent for oil-in-water emulsions; binder and disintegrant
- Carrageenan :- Modified release, viscosities
- Chitosan :- Cosmetics and controlled drug delivery applications, mucoadhesive dosage forms, rapid release dosage forms
- Hyaluronic acid Reduction of scar tissue, cosmetics
- Pectinic acid Drug delivery

Water-Insoluble Biodegradable Polymers

Lactide-co-glycolide polymers Microparticle–nanoparticle for protein delivery.

Starch-Based Polymers

Starch Glidant, a diluent in tablets and capsules, a disintegrant in tablets and capsules, a tablet binder Sodium starch glycolate Super disintegrant for tablets and capsules in oral delivery

Plastics and Rubbers

- Polyurethane Transdermal patch backing (soft, comfortable, moderate moisture transmission), blood pump, artificial heart, and vascular grafts, foam in biomedical and industrial products Silicones Pacifier, therapeutic devices, implants, medical grade adhesive for transdermal delivery.
- Polycarbonate Case for biomedical and pharmaceutical products

- Polychloroprene Septum for injection, plungers for syringes, and valve components.
- Polyisobutylene Pressure sensitive adhesives for transdermal delivery.
- Polycyanoacrylate Biodegradable tissue adhesives in surgery, a drug carrier in nano- and microparticles.Poly (vinyl acetate) Binder for chewing gum
- Polystyrene Petri dishes and containers for cell culture
- Polypropylene Tight packaging, heat shrinkable films, containers
- Poly (vinyl chloride) Blood bag and tubing.
- Polyethylene Transdermal patch backing for drug in adhesive design, wrap, packaging, containers
- Poly (methyl methacrylate) Hard contact Lenses Poly (hydroxyethyl methacrylate) Soft contact lenses

APPLICATION IN PARENTERAL

In Parenteral the various polymer like Methacrylic acid act as an Interferon inductor which induce to the interferon in cancer like disease. Methacrylic acid alkyl amide is act as plasma expander which increase the plasma level in body when admixture of drug with polymer present in body. Some Vaccines are transpired by using polymer because which disintegrate in GIT tract, example Methyl methacrylate.

In the disease diabetes the insulin are administered by using different polymer reservoir which form bond with insulin and release at target site.

NUTRITIONAL APPLICATION

Cholesterol lowering effect

Chitosan bind cholesterol, fat and initiate clotting of RBC. Fibers with a range of abilities to perturb cholesterol homeostasis were used to investigate how the serum cholesterol-lowering effects of insoluble dietary fibers are related to parameters of intestinal cholesterol absorption and hepatic cholesterol homeostasis in mice. Cholestyramine, chitosan and cellulose were used as examples of fibres with high, intermediate and low bile acid-binding capacities, respectively. The serum cholesterol levels in a control group of mice fed a high fat/high cholesterol (HFHC) diet for 3 weeks increased about 2-fold to 4·3mM and inclusion of any of these fibres at 7·5% of the diet prevented this increase from occurring. In addition, the amount of cholesterol accumulated in hepatic stores due to the HFHC diet was reduced by treatment with these fibres. The three kinds of fibres showed similar hypocholesterolaemic activity; however, cholesterol

depletion of liver tissue was greatest with cholestyramine. The mechanisms underlying the cholesterol-lowering effect of cholestyramine were,

1) Decreased cholesterol (food) intake,

2) Decreased cholesterol absorption efficiency, and

3) Increased faecal bile acid and cholesterol excretion.

The latter effects can be attributed to the high bile acid-binding capacity of cholestyramine. Incontrast, incorporation of chitosan or cellulose in the diet reduced cholesterol (food) intake, but did not affect either intestinal cholesterol absorption or faecal sterol output. The present study provides strong evidence that above all satiation and satiety effects underlie the cholesterol-lowering.

Weight loss effect

Chitosan use to replace calories in blood and food, which increase the body weight.

CUTANEOUS APPLICATION

Carpool, Meth acrylic acid, Methyl Meth acrylic acid, Methyl Meth acrylic acid are used in the Ointment, Gel, Transversalsystem, WoundSpray, MucosalOintment. The polymer like In terms of structure and electronics, melanins are "rigid-backbone" conductive polymerscomposed of polyacetylene, polypyrrole, and polyaniline "Blacks" and their mixed copolymers. The simplest melanin is polyacetylene, and some fungal melanins are pure polyacetylene. *synthetic* melanin (commonly referred to as BSM, or "black synthetic matter") is made up of 3-6 oligomeric units linked together — the so-called "protomolecule" — there is no evidence that *naturally occurring* biopolymer (BCM, for "black cell matter") mimics this structure. Evidence exists in support of a highly cross-linked heteropolymerbound covalentlyto matrix scaffolding melanoproteins. It has been proposed that the ability of melanin to act as an antioxidantis directly proportional to its degree of polymerization or molecular weight.

APPLICATION IN COSMETICS

Cosmetic compositions are disclosed for the treatment of hair or skin, characterized by a content of new quaternary chitosan derivatives of the formula. The chitosan derivatives have a good substantively, particularly to hair keratin, and prove to have hair strengthening and hair conditioning characteristics. e.g.; Hair setting lotion, Oxidation Hair-coloring Composition, Hair toning Composition, Skin Cream, Hair-treatment Composition, Gel-form.

GENERAL PHARMACEUTICAL APPLICATIONS

Increase stability of drug:

Chitosan is use to increase the stability of the drug in which the drug is complexes with chitosan and make slurry and kneading for 45 minutes until dough mass. This dough mass is pass-through sieve no.16 and make a granules is completely stable at different condition.

Orthopaedic patients:

Chitosan is a biopolymer that exhibits osteo conductive, enhanced wound healing and antimicrobial properties which make it attractive for use as a bioactive Coating to improve Osseo integration of orthopedic and craniofacial implant devices. It has been proven to be useful in promoting tissue growth in tissue repair and accelerating wound-healing and bone regeneration.

Enhanced bone formation by transforming growth factor

Chitosan composite microgranules were fabricated as bone substitutes for the purpose of obtaining high bone-forming efficacy. The microgranules have the flexibility to fill various types of defect sites with closer packing. The interconnected pores formed spaces between the microgranules, which allowed new bone in growth and vascularization. In addition, the transforming growth factor-beta 1 (TGF-pl) was incorporated into the microgranules in order to improve bone-healing efficacy. The chitosan microgranules were fabricated by dropping a mixed solution into a NaOH/ethanol solution. TGF-pl was loaded into the chitosan microgranules by soaking the microgranules in a TGF-pl solution.

Dental Medicine

Chitin / chitosan have been recognized to accelerate wound healing to attain an aesthetically valid skin surface, and to prevent excess scar formation. In dental medicine, chitin / chitosan is also applied as a dressing for oral mucous wound and a tampon following radical treatment of maxillary sinusitis. Furthermore, it is being investigated as an absorbing membrane for periodoental surgery. Chitin / chitosan has a variety of biological activities and advertised as a healthy food that is effective for improvement and/or care of various disorders, arthritis, cancer, diabetes, hepatitis, etc. In Japan , it is renowned since a three-year old Russian boy whose skin was burnt 90 % in total area

For oral drug delivery: Preliminary study on film dosage form

The potential of chitosan films containing diazepam as an oral drug delivery was investigated inrabbits. The results indicated that a film composed of a 1:0.5 drug-chitosan mixture might be

an effective dosage form that is equivalent to the commercial tablet dosage forms. The ability of chitosan to form films may permit its use in the formulation of film dosage forms, as an alternative to pharmaceutical tablets. The pH sensitivity, coupled with the reactivity of the primary amine groups, make chitosan a unique polymer for oral drug delivery applications.

Permeation Enhancer:

It has been reported that chitosan, due to its cationic nature is capable of opening tight junctions in a cell membrane. This property has led to a number of studies to investigate the use of chitosan as a permeation enhancer for hydrophilic drugs that may otherwise have poor oral bioavailability, such as peptides. Because the absorption enhancement is caused by interactions between the cell membrane and positive charges on the polymer, the phenomenon is pH and concentration dependant. Furthermore increasing the charge density on the polymer would lead to higher permeability.

Mucoadhesive Excipient:

Bioadhesivity is often used as an approach to enhance the residence time of a drug in the GI tract, thereby increasing the oral bioavailability. A comparison between chitosan and other commonly used polymeric excipients indicates that the cationic polymer has higher bioadhesivity compared to other natural polymers, such as cellulose, Xantham gum, and starch.

Ophthalmic Drug Delivery:

Chitosan exhibits favorable biological behavior, such as bioadhesion, permeability-enhancing properties, and interesting physico-chemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles. Due to their elastic properties, chitosan hydro gels offer better acceptability, with respect to solid or semisolid formulation, for ophthalmic delivery, such as suspensions or ointments, ophthalmic chitosan gels improve adhesion to the mucin, which coats the conjunctiva and the corneal surface of the eye, and increase precorneal drug residence times, showing down drug elimination by the lachrymal flow. In addition, its penetration enhancement has more targeted effect and allows lower doses of the drugs. In contrast, chitosan based colloidal system were found to work as transmucosal drug carriers, either facilitating the transport of drugs to the inner eye (chitosan-coated colloidal system containing indomethacin) or their accumulation into the corneal/conjunctival epithelia (chitosan nanoparticulate containing cyclosporine). The micro particulate drug- carrier (micro spheres)

seems a promising means of topical administration of acyclovir to the eye. The duration of efficacy of the ofloxacin was increased by using high MW (1930 kd) chitosan.

Gene Delivery:

The course of many hereditary diseases could be reversed by gene delivery. In addition, many acquired diseases such as multigenetic disorders and those diseases caused by viral genes could be treated by genetic therapy. Gene delivery systems include viral vectors, cationic liposomes, polycation complexes, and microencapsulated systems. Viral vectors are advantageous for gene delivery because they are highly efficient and have a wide range of cell targets. However, when used in vivo they cause immune responses and oncogenic effects. To overcome the limitations of viral vectors, non-viral delivery systems are considered for gene therapy. Non-viral delivery system has advantages such as ease of preparation, cell/tissue targeting, low immune response, unrestricted plasmid size, and large-scale reproducible production. Chitosan has been used as a carrier of DNA for gene delivery applications. Also, Chitosan could be a useful oral gene carrier because of its adhesive and transport properties in the GI tract. MacLaughlin et al. Showed that plasmid DNA containing cytomegalo virus promoter sequence and a luciferase reporter gene could be delivered in vivo by Chitosan and depolymerized Chitosan oligomers to express a luciferase gene in the intestinal tract.

Preparation of micro spheres:

A novel cellulose acetate/chitosan multimicrospheres (CA/CM) was prepared by the method of w/o/w emulsion. The concentration of cellulose acetate (CA) and the ratio of CA/chitosan (CS) had influence on the CACM size, and appearance. Ranitidine hydrochloride loading and releasing efficiency in vitro were investigated. The optimal condition for preparation of the microspheres was CA concentration at 2% and the ratio of CA/CS at 3:1. The microspheres size was 200–350 μm. The appearance of microspheres was spherical, porous, and non aggregated. The highest loading efficiency was 21%. The ranitidine release from the CACM was 40% during 48 hr in buffers.

Polymethacrylates for pharmaceutical purposes

Neutral poly(meth)acrylates are pharmacologically inactive. Good compatibility with the skin and mucous membranes prompted their use for wound sprays and ointment bases. Crosslinked copolymers based on methacrylic acid serve as ion exchangers for adsorption of active ingredients in the manufacture of sustained-release formulations in the form of tablets and

suspensions. For sustained release, active ingredients can also be embedded in water-insoluble polymers, e.g. by compression to tablets together with polymer powders or by extrusion at the softening temperatures of the polymers between 120 and 200 °C. Probably the most important role of poly (meth) acrylates in pharmaceutical manufacture is that of special excipients for coating oral dosage forms and for ensuring controlled release of the active ingredient. Coating of tablets, sugar-coated products, capsules, granules, pellets, crystals and other drug-loaded cores serves to ensure their physical and chemical stability, to enhance patient compliance and to further improve their therapeutic efficacy. Acknowledging the fact that the efficiency of a pharmaceutical dosage form depends not only on the active ingredients it contains but also, and critically so, on the formulation and processing technique, scientists and engineers alike have devoted increasing attention to these parameters in recent years.

Pharmaceutical applications of Chitosan polymer in various dosage forms:

Due to its good biocompatibility and low toxicity properties in both conventional exciepient applications as well as in novel application, chitosan has received considerable attention as a pharmaceutical exceipient in recent decades.

Medical

The polymer Polyvenylpyrolidin was used as a blood plasma expander for trauma victims after the first half of the 20th century. It is used as a binder in many pharmaceutical tablets; it simply passes through the body when taken orally. However, autopsies have found that crosspovidone does contribute to pulmonary vascular injury in substance abusers who have injected pharmaceutical tablets intended for oral consumption. The long-term effects of crosspovidone within the lung are unknown. PVP added to iodine forms a complex called povidone-iodine that possesses disinfectant properties. This complex is used in various products like solutions, ointment, pessaries, liquid soaps and surgical scrubs. It is known for instance under the trade name Betadine. It is used in pleurodesis (fusion of the pleura because of incessant pleural effusions). For this purpose, povidone iodine is equally effective and safe as talc, and may be preferred because of easy availability and low cost.

QUESTION BANK

SHORT ANSWER (2MARKS)

1. Define and differentiate between controlled and novel drug delivery systems.
2. Compare the advantages and disadvantages of controlled release dosage forms.
3. What are the different factors that influence desiging of sustained release dosage forms.
4. Write note on therapeutic index, volume of distribution.
5. Write the criteria followed to select polymers for Controlled release drug delivery systems
6. Write factors affecting formulation of Controlled release drug delivery systems
7. State Hixson Crowell model
8. State Higuchi model
9. Define absolute bioavailability
10. Write note on matrix diffusion system
11. Write biological factors influencing controlled release drug delivery systems.
12. Write any four applications of polymers in pharmaceuticals.
13. What are ideal characters of polymers
14. What are smart polymers?
15. Write the two polymerization techniques

LONG ANSWER (5 MARKS)

1. Describe the various physicochemical and pharmaceutical factors to be considered in selection of a drug candidate for controlled delivery formulations.
2. Write the concept of controlled drug delivery systems. Explain the approaches for the Controlled release formulations based on dissolution.
3. Write the concept of controlled drug delivery systems. Explain the approaches for the Controlled release formulations based on dissolution.
4. Explain the principle involved in the design of controlled drug delivery systems.

VERY LONG ANSWER (10 MARKS)

1. Write about reservoir and matrix type of controlled release formulations.
2. What are biodegradable and non- biodegradable polymers?
3. Explain mechanisms involved in drug release retardation using polymers.
4. Write shortly about types of polymers with their applications in pharmaceuticals.
5. Write about controlled release polymers and their applications