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MATRIX TABLETS AS ORAL SUSTAINED RELEASE DOSAGE FORMS: AN OVERVIEW

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ABSTRACT

Oral route of drug administration is oldest and safest mode of drug administration. It posses several advantage. It does not pose the sterility problem and minimal risk of damage at the site of administration. It provides accurate dosing without assistantship of administration. In conventional oral drug delivery system, there is little or no control over release of drug, and effective concentration at the target site can be achieved by administration of grossly excessive dosage form. This kind of dosing pattern result in constantly changing, unpredictable and often sub or supra therapeutic plasma concentration, leading to marked side effects in some cases. Moreover, the rate and extent of absorption from conventional formulation may vary greatly, depending on factor such as physiochemical properties of drug, presence of excipients, various physiological factors such as presence or absence of food, pH of gastrointestinal tract, G.I. motility etc. These problems can be minimized by oral controlled drug delivery systems.

KEYWORDS: Drug release, drug delivery system, controlled drug delivery, sustained release, matrix tablets.

1. INTRODUCTION[1]

In oral controlled drug delivery the amount of drug release is constantly predetermined and these constant releases of drug provide a constant blood plasma level of drug for a therapeutic response. The oral controlled drug delivery have many advantage to conventional delivery- it decrease the fluctuation of drug plasma concentration, it reduce toxicity, provide a sustained effects, reduced the dosing frequency. Apart from other advantage it reduces total amount of drug used, improve patient compliance and reduced patient care time.

The disadvantage of oral controlled release product are longer time to achieve therapeutic blood concentration, possible increase variation in bioavailability after oral administration, enhanced first pass effect, dose dumping, sustained concentration in oral dose case, lack of doses flexibility and usually grater expense.

Hydrophilic polymers are widely used in oral controlled drug delivery due to their flexibility to produce desirable drug release profile, cost effectiveness, and broad regulatory acceptance. Among the hydrophilic polymers, HPMC (hydroxyproylmethylcellulose) is the most widely used carrier for the preparation of oral controlled drug delivery system due to its properties such as its ability to swell upon jellification once contact with water, and its very low toxicity and easy of manufacture, the gel becomes a viscous layer acting as a protective barrier to both influx of water and efflux of drug in the solution. On the other hand, hydrophobic polymer, such as EC can be alternative to the swelling polymers by forming an inert matrix with no physiological action and stable at different pH values and moisture levels when a tablet with hydrophobic matrix is placed in the dissolution medium, the drug at surface is released quickly, with a possible burst effects, requiring its replacement drug from inner layers that must diffuse through the pores until it reaches the surface.

Physician can achieve several desirable therapeutics advantages by prescribing sustained release dosage form. Since, the frequency of drug administration is reduced, patient's compliances can be improved and the drug administration can be made more convenient as well. The blood level oscillation characteristics of multiple dosing form of conventional dosage form is reduced, because more even blood level is maintained in the design of sustained release dosage form. The total amount of drug administered, thus maximum availability with a minimum dose. In addition, the safety margin of high potency drug can be increased and the incidence of both local and systemic adverse effects can be reduced in sensitive patients. Overall, increased administration of sustained release dosage form gives increased reliability.

Sustained release technology is relatively new field and as a consequence, research in the field has been

extremely fertile and has produced many discoveries. With many drugs, the basic goal is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage form is an important element to accomplish this goal. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release and depot dosage form are term used to identify drug delivery system that are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. In the case of oral sustained released dosage form, an effect is for several hours depending upon residence time of formulation in the GIT.

Not all the drugs are the suitable candidates for the sustained release dosage form. Ideal characteristic of the drug for the sustained release dosage form are;

- Drug should have a shorter half-life as drug with a longer half-life are inherently long acting drugs.
- Drug should be absorbed from large portion of gastrointestinal tract, since absorption must occur through the gut.
- Drug should be having a good solubility profile to be a good candidate for sustained release dosage form.
- Dose of the drug should not be too large, as a larger dose is to be incorporated into sustained release dosage form.

1.1 Potential Advantage of Sustained Release Dosage Form[2]

- Avoid patient's compliance problem due to reduced frequency of dosing.
- Blood level oscillation characteristics of multiple dosing of conventional dosage form are reduced because a more even blood level is maintained.
- Employ a less total drug.
- Minimize or eliminate local or systemic side effects.
- Minimize drug accumulation with chronic dosing.
- Obtained less potential of reduction in drug activity with chronic use.
- Improved efficiency in treatment.
- Cure or control condition more promptly.
- Improved control of condition i.e. reduced fluctuation in drug level.
- Improved bioavailability of some drugs.
- Make a use of special effects, e.g. sustained release aspect for relief of arthritis by dosing before bedtime.
- Economy.
  Overall, administrations of sustained release form enable increased reliability of therapy.

1.2 Matrix System[3,4]

The matrix system is most often used for a drug-controlled release from a pharmaceutical dosage form. Among the innumerable method used in controlled release drug from pharmaceutical dosage form, the matrix system is the most frequently applied; it is release system for delay and control of the release of the drug that is dissolved or dispersed in a resistant supports to disintegration. To define matrix, it is necessary to know the characters that differentiate it from other controlled release dosage forms. Hence the following must be considered:

a. The chemical nature of support (generally, the support are formed by polymeric net)
b. The physical state of drug (dispersed under molecular or particulate form or both)
c. The matrix shape and alteration in volume as a function of time.
d. The route of administration (oral administration remains the most widely used but other routes are adaptable)
e. The release kinetic model.

1.3 The Classification Of Matrix System

Mineral matrix
Drug retained in the support.
Drug adsorbed on the support

Lipidic matrix
Delivery by diffusion.
Delivery by surface erosion

Hydrophillic matrix
Unlimited swelling, delivery by diffusion.
Limited swelling controlled delivery through swelling

Inert matrix
Controlled delivery by diffusion

Biodegradable matrix
Non-Lipidic.

1.4 Advantages of Matrix System

The interest awakened by matrix system in last few years is completely justified in view of the major advantages. Among these, the following stand out. With proper control of manufacturing process, reproducible release profiles are possible.

There is no risk of "dumping" of a large part of dose, through the structure makes the immediate release of a small amount of active principle unavoidable.

Their capacity to incorporate active principle is large, which suits them to delivery of large dosage.

1.5 Principles of Modified Drug Release[5,6]

Following either of the two principles can modify drug release:

1.5.1 Barrier principle

In this method the retardant material is imposed between the drug and elusion medium. Drug release is by diffusion of the drug through the barrier and /or erosion of the barrier or permeation of the barrier by moisture.

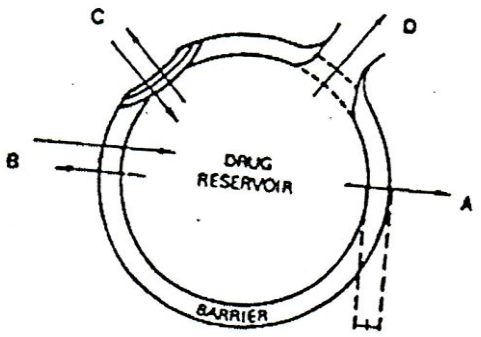

Figure 1: Barrier mediated models of sustained release dosage form regimen. Drug diffusion through the barrier, B. permeation of barrier by elution media followed by drug dissolution, C. Erosion of barrier releasing drug, D. rupture of permeation of elutiomedia.

1.5.2 Embedded matrix

In this drug is dispersed/embedded in a matrix of retardant material that may be encapsulated in a particulate form or compressed into the tablet. Drug release occurs by permeation of water leaching extraction of diffusion of drug from the matrix and erosion of matrix material.

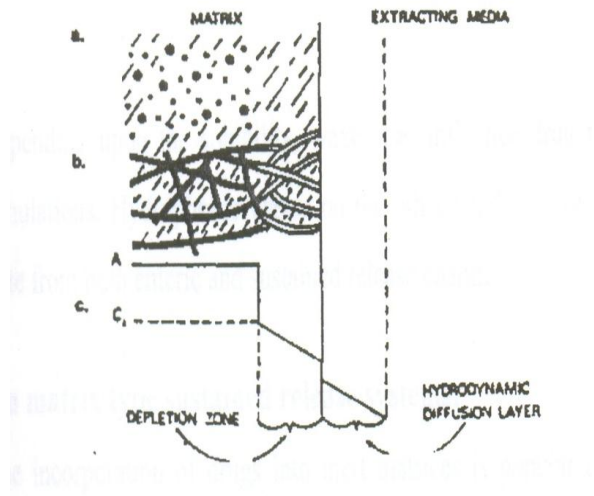

Figure 2: Embedded matrix concept as a mechanism of controlled released in sustained release dosage form design network model a drug is insoluble in the retardant material. B Drug is soluble in the retardant material. Diffusion profile etc. Characterize drug release from matrix system.

1.6 Swellable Matrices As System For Oral Delivery[7]

Monolithic devices or matrices represent a substantial part of drug delivery systems. Matrices containing swellable polymers are referred to as

- Hydrogel matrices
- Swellable control release systems.
- Hydrophillic matrix tablet

Swellable matrices for oral administration are commonly manufactured as tablet by compression of hydrophilic microparticulate polymers. Therefore, the most appropriate classification for these systems is swellable matrix tablet. They are constituted of a blend of drug and one or more hydrophilic polymers.

The release of drug from swellable matrix tablet is based on glassy-rubbery transition of polymer as a result of water penetration into the matrix. The interaction between water, polymer and drug are the primary factors for drug release. However, various formulation variables such as polymer grade, drug–polymer ratio, drug solubility and drug and polymer particle size, can influence drug release rate to greater or lesser degree. The central element of the mechanism of drug release in the gel layer (rubbery polymer), which is formed around the matrix. The gel layer is capable of preventing matrix disintegration and further rapid water penetration.Water penetration, polymer swelling, drug dissolution and diffusion and matrix erosion are phenomenon determining gel layer thickness. Finally drug release is controlled by drug diffusion through the gel layer and/or by erosion of the gel layer.

1.7. Mechanisms of Drug Release From Matrix System[8,9]

The release of drug from controlled devices is via dissolution of the matrix or diffusion of drug through the matrix or a combination of the two mechanisms.

1.7.1. Dissolution controlled systems

A drug with slow dissolution rate will demonstrate sustaining properties, since the release of the drug will be limited by the rate of dissolution. In principle, it would seem possible to prepare extended release products by decreasing the dissolution rate of drugs that are highly water-soluble. This can be done by:

- Preparing an appropriate salt or derivative
- Coating the drug with a slowly dissolving material – encapsulation dissolution control
- Incorporating the drug into a tablet with a slowly dissolving carrier – matrix dissolution control (a major disadvantage is that the drug release rate continuously decreases with time).

The dissolution process can be considered diffusion-layer-controlled, where the rate of diffusion from the solid surface to the bulk solution through an unstirred liquid tablet is the rate-determining step. The dissolution process at steady-state is described by the Noyes-Whitney equation:

$$Dc/dt = k_D A(C_s\text{-}C) = D/hA(C_s\text{-}C)$$

dC - dissolution rate
kd - the dissolution rate constant (equivalent to the diffusion coefficient
Divided by the thickness of the diffusion layer D/h)
D - Diffusion coefficient
Cs - saturation solubility of the solid
C - Concentration of solute in the bulk solution

Equation 1 predicts that the rate of release can be constant only if the following parameters are held constant: surface area, diffusion coefficient and diffusion layer thickness and concentration difference. However, under normal conditions, it is unlikely that these parameters will remain constant, especially surface area, and this is the case for combination diffusion and dissolution systems.

1.7.2. Diffusion controlled systems

Diffusion systems are characterized by the release rate of a drug being dependent on its diffusion through an inert membrane barrier, which is usually a water-insoluble polymer. In general, two types or subclasses of diffusion systems are recognized: reservoir devices and matrix devices.

1.7.2.1. Reservoir devices

In these formulations where tablet coating constitutes the main factor in controlling drug release. Examples of materials used to control drug release include hardened gelatin, methyl or ethyl cellulose, polyhydroxymethacrylate, methacrylate ester copolymers, and various waxes. Ethyl cellulose and methacrylate ester copolymers are the most commonly used systems in the pharmaceutical industry.

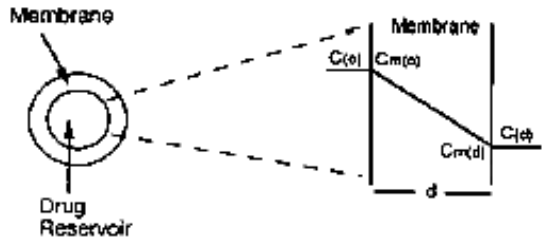

Figure 3: Schematic representation of a matrix release system.

1.7.3 Bioerodible and combination diffusion and dissolution system

Bioerodible devices constitute a group of system for which mathematical description of release kinetics can be quite complex. Bioerodible matrix system consists of the drug dispersed in an erodible matrix.

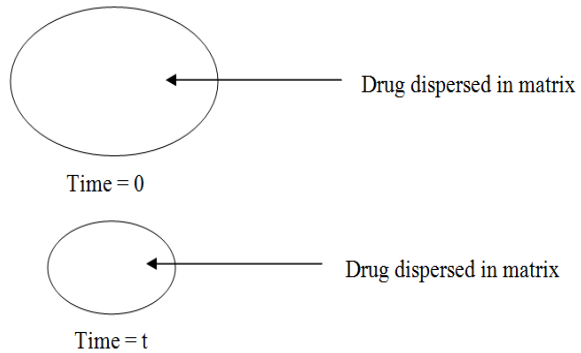

Figure 4: Representation of a bioerodible matrix system.

Drug dispersed in the matrix before release at time = 0. At time = t release by drug diffusion or matrix erosion has occurred.

The mechanism of release from simple erodible slab, cylinders, and sphere has been described. by Eq. A simple expression describing release from all three of these erodible devices is

$$M_1/M = 1- (1-K_0t/C_0a)^n$$

Where n=3 for a sphere, n=2 for a cylinder and n=1 for a slab. The radius of a sphere, or cylinder, or the half-height of a slab is represented by a. M_t is the mass of a drug released at infinite time. As a further complication, these systems can combine diffusion and dissolution of both matrix material and the drug. Not only can drug diffuse out of the dosage form, but also the matrix itself undergoes a dissolution process. The complexity of the system can arise from the fact that, as the polymer dissolves, the diffusional path-length for the drug changes. These usually result in a moving boundary diffusion system. Zero order release can occur only if surface erosion occurs and surface area does not change with time. The inherent advantage of such a system is that bioerodible property of the matrix dose not result in a ghost matrix. The disadvantages of these matrix systems are that release kinetics is often hard to control, since many factors affecting to both the drug and the polymer must be considered. Another method for the preparation of bioerodible system is to attach the drug directly to the polymer by a chemical bond. Generally, the drug is released from the polymer by hydrolysis or enzymatic reaction. This makes control of the rate of release somewhat easier. Another advantage of the system is the ability to achieve very high drug loading, since the amount of drug placed in the system is limited only by the available sites on the carrier.

A third type, which in this case utilizes a combination of dissolution and diffusion, is that of a swelling controlled matrix. In this the drug is dissolved in the polymer, instead of an insoluble or erodible polymer. This allows entrance of water which causes dissolution of drug and diffusion out of the swollen matrix. In these systems the release rate is highly dependent on polymer-swelling rate, drug solubility, and the amount of soluble fraction in the matrix. This system usually minimizes burst effects, since polymer swelling must occur before drug release.

1.8 Advantages of Hydrophilic Matrix Tablet[10,11,12]

1. With proper control of the manufacturing process, reproducible release profiles are possible. The variability associated with them is slightly less than that characterizing coated release form.
2. Structure allows an immediate release of small amount of active principle there is no risk of dose dumping.
3. Their capacity to incorporate active principle is large, which suits them to delivery of large doses.

4. The manufacturing processes are notably simple. Tablet formulation can be done via direct compression or by wet granulation techniques.
5. Large variety of non expensive gelling agents is approved for oral use by the Competent official organization.
6. The safety margin of high-potency drugs can be increased.
7. The drug release from hydrophilic matrices show a typical time dependent profile i.e. decreased drug release with time because of increased diffusion path length.

1.9 FACTORS INFLUENCING THE DRUG RELEASE FROM MATRIX

- Choice of matrix material.
- Amount of drug incorporated in the matrix.
- Viscosity of the hydrophilic material in aqueous system at a fixed concentration.
- Drug: matrix ratio.
- Tablet hardness, porosity, and density variation.
- Entrapped air in tablet.
- Tablet shape and size.
- Drug particle size.
- Solubility of drug in aqueous phase.
- Surfactants and other additives.

1.10 Tablet Manufacturing Methods[4]

Tablets are manufactured by wet granulation, Dry granulation or direct compression method.

1] Wet Granulation

Wet granulation is the process in which a liquid is added to a powder in a vessel equipped with any type of agitation that will produce agglomeration or granules. These granules after drying are compressed to form tablet.

2] Dry Granulation

In this technique, there is no use of liquids. The process involves the formation of slugs. Then the slugs are screened or milled to produce granules. The granules formed are then compressed to form tablet.

3) Direct compression

The term direct compression is used to define the process by which tablet is compressed directly from powder blends of active ingredient and suitable excipients, which will flow uniformly in the die cavity and forms a firm compact.

1.11 Drug Properties Relevent To Controlled Release Formulations[6,9,13]

The design of controlled - release delivery systems is subject to several variables of considerable importance. Among these are the route of drug delivery, the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug. Each of these variables are interrelated and this imposes certain constrains upon choices for the route of delivery, the design of the delivery system and the length of therapy. Properties of drugs are very important for designing a sustained release dosage form mainly physicochemical and biological properties of the drug are most important.

1.11.1 Physicochemical properties

a) Aqueous solubility and pKa

A drug to be absorbed it must be dissolved in the aqueous phase surrounding the site of administration and then partition into the absorbing membrane. Two of the most important physicochemical properties of a drug that influence its absorptive behavior are its aqueous solubility and if it is a weak acid or base its pKa. These properties pay an influential role in the performance of controlled release systems.[14]

The aqueous solubility of a drug influences its dissolution rate, which in turn establishes its concentration solution and hence the driving force for diffusion across membrane.

Dissolution rate is related to aqueous solubility as shown by the Noyes-Whitney equation that, under sink condition is:-

$$dc/dt = K_D A C_S$$

Where

dc/dt = Dissolution rate

K_D = Dissolution rate constant.

A = Total surface area of the drug particles.

C_s = Aqueous saturation solubility of the drug.

The dissolution rate is constant only if surface area 'A' remain constant, but the important point to note is that the initial rate is directly proportional to aqueous solubility Cs. Therefore, aqueous solubility of a drug can be used as a first approximation of its dissolution rate. Drugs with low aqueous solubility have low dissolution rates and usually suffer oral bioavailability problems.

Aqueous solubility of weak acids and bases is governed by the pKa of the compound and pH of the medium.

For weak acid.

$$S_t = S_o (1+ka/[H^+]) = S_o(1+10^{pH-pKa}) \text{.....(1)}$$

Where S_t = Total solubility (both ionized and un-ionized forms) of the weak acid

S_o = Solubility of the un - ionized form

K_a = Acid Dissociation constant

H^+ = hydrogen ion concentration of the medium.

Equation (1) predicts that the total solubility, s_t of a weak acid with a given pKa can be affected by the pH of the medium.

For a weak base,

$$S_t = S_o (1+[H^+] / Ka = S_o (1+10^{Pka-PH}) \text{ ..... (2)}$$

Where St = Total solubility (both conjugate acid and free base forms) of the weak base.

S_o = Solubility of the free base form

K_a= Acid dissociation constant of the conjugate acid.

So total solubility, S_t of a weak base whose conjugate acid has a given pKa, which can be affected by the pH of the medium.

In general, extremes in the aqueous solubility of a drug are undesirable for formulation into controlled release product. A drug with very low solubility and a slow dissolution rate will exhibit dissolution limited absorption and yield an inherently sustained blood level.

Formulation of such a drug into a controlled - release system may not provide considerable benefits over conventional dosage forms. Any system upon diffusion of drug through a polymer as the rate - limiting step in release would be unsuitable for a poorly soluble drug, since the driving force for diffusion is the concentration of drug in the polymer or solution, and this concentration would be low. For a drug with very high solubility and a rapid dissolution rate, it is often quite difficult to decrease its dissolution rate to slow its absorption. Preparing a slightly soluble form of a drug with normally high solubility is, however, one possible method for preparing controlled release dosage forms.[14]

b) Partition Coefficient

Between time that a drug is administered and the time is eliminated from the body, it must diffuse through a variety of biological membranes that act primarily as lipid like barriers.

A major criteria in evaluation of the ability of a drug to penetrate these lipid membranes is its apparent oil / water partition coefficient defined as

$$\mathbf{K = C_0/C_W}$$

Where

C_o = Equilibrium concentration of all forms of the drug e.g ionized and unionized in an organic phase at equilibrium.

C_w= Equilibrium concentration of all forms in aqueous phase.

In general, drugs with extremely large values of 'K' are very oil soluble and will partition into membrane quite readily. According to Haunch correlation, the logarithm of the activity of a drug or its ability to be absorbed and the logarithm of its partition coefficient having parabolic relationship. The explanation for this relationship is that the activity of a drug is a function of its ability to cross membranes and interact with the receptor. The more effectively a drug crosses membranes, the greater its activity. The optimum partition coefficient value of a drug in which it most effectively permeates membranes and thus shows the greatest activity.

The value of K at which optimum activity is observed is approximately 1000/1. Drugs with a partition coefficient that is higher or lower than the optimum is, in general, poorer candidates for formulation into controlled-release dosage forms.

C) Drug stability

One important factor for oral dosage forms is the loss of drug through acid hydrolysis and/or metabolism in the GI tract. Since a drug in the solid state undergoes degradation a much slower rate than a drug in suspension or solution. It is possible to improve significantly the relative bioavailability of a drug that is unstable in the stomach; the most appropriate controlling unit would be one that releases its content only in the intestine. The reverse in the case for those drugs that are unstable in the environment of the intestine, the most appropriate controlling unit in this case would be one that releases its contents only in the stomach, so, drugs with significant stability problems in any particular area of the GI tract are less suitable for formulation into controlled release systems that deliver their content uniformity over the length of the GI tract. Controlled drug delivery systems may provide benefits for highly unstable drugs because the drug may be protected from enzymatic degradation by incorporation into a polymeric matrix.

d) Protein Binding

There are some drugs which having tendency to bind with plasma proteins (e.g. Albumin) and causes retention of the drug in the vascular space. The main force of attraction responsible for binding is vander waal's forces, hydrogen bonding and electrostatic forces. In general, charged compounds, because of electrostatic effects.

If a drug binds with protein then the distribution of the drug into the extravascular space is governed by the equilibrium process of dissociation of the drug from the protein. The drug-protein complex can serve therefore as a reservoir in the vascular space for controlled drug release to extravascular tissues, but only for those drugs that exhibit a high degree of binding. Thus, the protein binding characteristics of a drug can play a significant role in its therapeutic effect, regardless of the type of dosage form.

Extensive binding to plasma proteins will be evidenced by a long half-life of elimination for the drug and such drugs generally does not required a controlled-release dosage form, however, drugs that exhibit a high degree of binding to plasma protein also might bind to biopolymers in the GI tract, which could have an influence on controlled-drug delivery.

e) Molecular size and diffusivity

Drugs in many controlled-release systems must diffuse through a rate controlling membranes or matrix. The ability of a drug to diffuse through membranes, it's so called diffusivity [diffusion coefficient), is a function of its molecular size (or molecular weight). An important influence upon the value of the diffusivity. 'D', in polymers is the molecular size for molecular weight) of the diffusing species. For most polymers, it is possible to relate logD empirically to some function of molecular size as

$$\mathbf{Log\ D = -S_v \log V + K_v = - S_M \log M + K_m}$$

V = molecular Volume.
M = molecular weight.
S_V, S_m, K_v, K_m = constant

The value of 'D' thus is related to the size and shape of the cavities as well as size and shape of drugs. Generally, values of the diffusion coefficient for intermediate molecular, weight drugs, i.e. 150 to 400, through flexible polymers range from $10^{-6 \text{ to }} 10^{-9}$ cm^2 / sec, with values on the order of 10^8 being most common. A value of approximately 10^{-6} is typical for these drugs through water as the medium. For drugs with a molecular weight greater than 500, the diffusion co-efficient in many polymers frequently are so small that they are difficult to quantify, i.e., less than 10-^{12} cm^2/sec. Thus, high molecular weight drugs and/or polymeric drugs should be expected to display very slow release kinetics in controlled release devices using diffusion through polymeric membranes or matrices as the releasing mechanism.[15]

1.11.2 BIOLOGICAL PROPERTIES

i) Absorption

The rate, extent and uniformity of absorption of a drug are important factors when considering it's formulation into a controlled - release system. Since the rate limiting step in drug delivery from a controlled-release system is its release from a dosage form, rather than absorption, a rapid rate of absorption of drug relative to its release is essential if the 'system is to be successful. In case of controlled release dosage form $K_r <<< K_a$ this becomes most critical in the case of oral administration. Assuming that the transit time of a drug through the absorption half-life should be to 4 hrs. This corresponds to a minimum absorption rate constant K_a of 0.17 to 0.23 hr necessary for about 80 to 95 % absorption over a 9 to 12 hr transit time. For a drug with a very rapid rate of absorption, (i.e. $K_a >> 0.23$ hr^{-1}), the above discussion implies that a first order release rate constant $K_r < 0.17$ hr^{-1} is likely to result in unacceptable poor bioavailability in many patients. Therefore, slowly absorbed drugs will be difficult to formulate into controlled release systems where the criteria that $K_r <<< K_a$ must be met.

ii) Distribution

The distribution of a drug into vascular and extravascular spaces in the body is an important factor in its overall elimination kinetics. Two parameters that are used to describe the distribution characteristics of a drug are its apparent volume of distribution and the ratio of drug concentration in the tissue is that in plasma at the steady state called T/P ratio. The magnitude of the apparent volume of distribution can be used as a guide for additional studies and as a predictor for a drug dosing regimen and hence there is a need to employ a controlled-system.

iii) Metabolism

Drugs that are significantly metabolized before absorption, either in the lumen or: tissue of the intestine can show decreased bioavailability from slower-releasing dosage forms. Most intestinal wall enzyme systems are saturable. As the drug is released at a slower rate to these regions, less total drug is presented to the enzymatic process during a specific period allowing more complete conversion of drug to its metabolite. Formulation of these enzymatically susceptible compounds as prodrug is another viable solution.

iv.) Biological Half Life

The usual goal of an oral sustained release product is to maintain therapeutic blood levels over an extended period. To this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life. Each drug has its own characteristics elimination rate, which is the sum of all elimination processes including metabolism, urinary excretion and all other processes that permanently remove drug from blood stream. Therapeutic compounds with short half-life are excellent candidates for sustained-release preparations, since this can reduce dosage frequency. However, this is limited, in that drugs with very short biological half life as it may require excessively large amounts of drug in each dosage unit to maintain sustained effect, forcing the dosage form itself to become limiting large.

In general, drugs with half-life shorter than two hrs are poor candidates for sustained release preparations. Drugs with long half-life, more than 8 hrs, are also generally does not be used in sustaining forms, since their effect is already sustained.

v.) Side Effects and Safety Considerations

There are very few drugs whose specific therapeutic concentrations are known. Instead, a therapeutic concentration range is listed, with increasing toxic effects expected above this range and a fall off in desired therapeutic response observed below the range.
The most widely used measure of the margin of safety of a drug is its therapeutic index, (Tl).

$$\mathbf{TI = LD_{50} / ED_{50}}$$

Where, LD_{50} = median lethal dose
ED_{50} = median effective dose

For very potent drugs, whose therapeutic concentration range is narrow, the value TI is small. In general, larger the value of TI, Usually are poor candidates for formulation into controlled-release product. A drug is considered to be relatively safe if its TI value exceeds 10.

vi.) Dose Size

Since a controlled-release system is designed to alleviate repetitive dosing, it is naturally contain greater amount of drug that a corresponding conventional dosage form. For lose drugs requiring large conventional doses, the volume of sustained dose may be so large so to be

impractical or unacceptable, depending on the route of administration. The same may be true for drugs that require a large release rate from the controlled-release system, e.g., drugs with shorter half-life. For oral route, the volume of the product is limited by patient acceptance.

REFERENCES

1. Bret Berner and Steven M. Dinh; "Fundamental Concepts in Controlled Release" in "Treatise on Controlled Drug Delivery"; Marcel Dekker Publication, 1992; 1-4.
2. Robinson M., Sustained Action Dosage Forms: Lachman L., Lieberman H, Kanig J., The Theory and Practice of Industrial Pharmacy. Philadelphia, 2nd edition, Lea and Febiger, 1970; 666.
3. Vyas S.P., Khar R.K., Controlled Drug Delivery Concepts and Advances, Delhi, India; 1st edition Vallabh Prakashan, 2002; 155-195.
4. Liberman, H. A. "Pharmaceutical Dossage Form; Tablets," second Edn, I: 201-213.
5. Chin, Y.W. Novel Drug Delivery Systems, Ed. 2nd, Vol. 50, Revised and Expanded Marcel Dekker, 140-155.
6. Lachman Leon, Liberman H.A.and Kanig J.L. "The Theory and Practice of Industrial Pharmacy" (3rd Edn),Varghese publishing House Bombay, 443-453.171
7. Howard C. Ansel "Pharmaceutical Dosage Form And Drug Delivery Systems", (7th edition), 229-243.
8. Jain N.K., "Controlled And Novel Drug Delivery" CBS Publishers and distributors, New Delhi, 2002; 1-2: 676-698.
9. Remington, "The Science and Practice of pharmacy", 20th Edn, I: 903-913.
10. Banker GS, Rhodes CT, Modern Pharmaceutics, Ed. 4th, Revised and Expanded Marcel Dekker, 121: 501-573.
11. Brahmankar D. M. and Jaiswal S. B. in "Biopharmaceutics and Pharmacokinetics", Vallabh Prakashan, 1st edn, 1995; 347-352.
12. Colombo P., R. Bettini, Manima, in "Journal Of Pharm. Sci." 1991-1992; 08: 86.
13. V. H. Lee, J. R. Robinson in, "Sustained and Controlled Release Drug Delivery System," Marcel Dekker, New York, 71-121.
14. Garg Ayush, Singhvi Indrajeet, "Concepts of Sustained Release Dosage Forms", International Journal of Applied Pharmaceutical and Biological Research, 2016; 1(1): 22-43.
15. Garg, Ayush, and Amul Mishra. "Sustained Release Dosage Forms: A Review." Annals of Pharma Research, 2021; 9: 9.