

## A Brief Review on Sustained Release Matrix Tablets of Baclofen

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### ABSTRACT

The objective of the present study was to focus on sustained release matrix tablets of baclofen, for treatment of spastically resulting from multiple sclerosis, flexor spasm and muscular rigidity. Designing effective therapies for Spinal cord injury (SCI) has been a challenging problem because spinal cord injuries are heterogeneous in causality, severity and location of injury.

Effective drug therapy for Spinal cord injury (SCI) first became a reality in 1990 with the finding that the steroid drug methylprednisolone (MP) can significantly improve recovery. Significant advances in recent year, including an effective drug therapy for acute SCI, have improve recovery. In spinal cord injury, pain persist for longer period i.e., several months, hence the long-term treatment is necessary for maintaining the drug concentration in the therapeutic range.

Hence, there is a need of sustained release dosage form. Baclofen, 4-amino-3-(4-chlorophenyl)-butyric acid is another structural analog of GABA, which is widely used now a days in the treatment of multiple sclerosis, flexor spasms, muscular rigidity. spinal cord injuries and other spinal cord diseases.

**Keywords:** Sustained release, Matrix tablets, Spinal cord injury, Drug therapy

### INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administered among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration belief that by oral administration of the drug is well absorbed.

All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI

physiology, pharmacokinetics, pharmacodynamics and formulation design is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form.<sup>[1]</sup>

### RATIONALE OF SUSTAINED AND CONTROLLED DRUG DELIVERY

The basic rationale for controlled drug delivery is to alter the pharmacokinetic and pharmacodynamics of pharmacological active moieties by using novel drug delivery system or by modifying the molecular structure and physiological parameters inherent in the selected route of administration. It is desirable that the duration of drug action becomes more a design property of a rate controlled dosage form and less or not at all a property of the drug

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molecules inherent kinetics properties. Thus optional design of controlled release systems necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of the drugs.

### **SUSTAINED DRUG DELIVERY SYSTEM** <sup>[2,3,4]</sup>

Over the past 30 years, as the expense and complication involved in marketing new entities have increased with concomitant recognition of the therapeutics advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled drug delivery system.

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.

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.

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.

### **POTENTIAL ADVANTAGE OF SUSTAINED RELEASE DOSAGE FORM** <sup>[5]</sup>

- Avoid patient's compliance problem due to reduced frequency of dosing.
- Blood level oscillation characteristics of multiple dosing of conventional dosage form is 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.

### **MODIFIED RELEASE SYSTEM: [3]**

To overcome the potential problem associated with conventional drug therapy, modified release systems were developed and may be divided into four categories,

- .. Delayed release
- .. Sustained release.
- .. Controlled release.
- .. Prolonged release.
- .. Site specific release
- .. Receptor release

#### **Delayed release system**

Delayed release systems are those are that use, repetitive intermittent dosage form.

#### **Sustained release system**

Sustained release systems are those, which achieves slow release of drug over an extended period of time and in this drug is initially made available to the body in amount to cause the desired pharmacological response.

#### **Controlled release system**

An ideal controlled drug delivery system is that which delivers the drug at predetermined rate, locally or systemically for the predetermined period of time.

#### **Prolonged release system**

Prolonged release system, prolongs the duration of action without maintaining a constant drug blood level. Thus maintaining constant- drug leveling in blood or target tissue.

#### **Site specific and receptor release system**

Site specific and receptor release and targeted release system refers to targeting of the drug directly to a certain biological location.

### **RECENT TRENDS IN SUSTAINED DRUG DELIVERY SYSTEM**

Sustained release dosage forms are categorized as:

- Single unit dosage form.
- Multiple unit dosage form.
- Mucoadhesive system.

#### **Single unit dosage form:**

These refer to diffusion system where the drug is uniformly distributed (dispersed / dissolved) throughout the solid matrix and the release of the drug is controlled or sustained either by incorporating hydrophilic or hydrophobic filler within the matrix or by coating the drug matrix with a swellable or non-swellable polymer film.

These systems can be classified as:

#### **Monolithic system:**

If the release rate is controlled or sustained by incorporating hydrophilic or hydrophobic filler within the matrix then the system is called as Monolithic device where the diffusion of drug through the matrix is rate- limiting step.

These are categorized as:

#### **Hydrophobic/Swellable tablet:**

Tablet prepared by mixing the drug with hydrophobic/hydrophilic filler appear to extend the release time of the drug from device within the GI tract after oral administration.

#### **Floating tablet or capsule:**

Designing of Floating tablet or capsule are called hydro-dynamically balanced drug delivery system is based on the principle that device with gravity lesser than that of the gastric juice of stomach and retain the drug in the proximal region of the GIT.

#### **Semisolid matrix system:**

In this system, the hydrophobic carrier occurs in an oily semisolid state where the drug is incorporated and the final mass is usually filled into gelatin capsule to prepare the dosage form.

#### **Coated tablet and Similar Multilayer system:**

Multilayer systems are designed in such a way that the drug has to cross a barrier or membrane on its way from the device to the physiological environment. The nature and the number of barriers control the release process.

In the simplest form coated tablet comprised a core containing the drug and a coating layer, which surrounds the core. The core is usually the drug either alone or loaded on to an inert material (hydrophilic or hydrophobic).

Multilayered tablet having two or more distinct layers usually prepared by dry coating technique have also been used to formulate sustained or controlled preparations for water-soluble drugs. In this case, coating which controls the release process covers the core tablet containing the drug only partially.

#### **Osmotic device:**

In osmotic device usually an osmotic agent (often with an osmotic adjuvant) is contained within a rigid compartment that is separated from the osmotic compartment by a partition. In the physiological environment the aqueous fluid penetrates across the membrane and the increased volume within the osmotic compartment pushes the drug out of the device through a delivery orifice.

#### **Multiple unit dosage forms:**

It represents a combination of subnets of the dosage forms, the source of which may either be homogeneous or heterogeneous. It offers the advantages of releasing one of the drugs or part of the same drug immediately while remaining drug or parts of the same can be sustained release. These are useful where drug-excipients and drug-drug interactions are

inevitable in a single unit dosage form .The various forms are as:

- Micro granules/Spheroids.
- Beads.
- Pellets.
- Microcapsules.

#### **Mucoadhesive systems:**

It utilizes principle of bioadhesion for optimum delivery of the drug from the device. Bioadhesion is definable as the occurrence in which one biological substance is adhered to another substance, which may either, be of biological or non-biological origin. If the substance is mucosal membrane the phenomenon is known as mucoadhesion. Conventional controlled release dosage forms described above are restrained localized in selected regions of GIT. Mucoadhesive systems are suitable to increase the contact time of drug with absorbing membrane and localization of delivery of drug at target sites.

#### **MATRIX SYSTEM <sup>[5]</sup>**

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:

- The chemical nature of support (generally, the support are formed by polymeric net)
- The physical state of drug (dispersed under molecular or particulate form or both)
- The matrix shape and alteration in volume as a function of time.

- The route of administration (oral administration remains the most widely used but other route are adaptable)
- The release kinetic model.

### 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.

#### Hydrophilic matrix:

- Unlimited swelling, delivery by diffusion.
- Limited swelling controlled delivery through swelling.

#### Inert matrix:

- Controlled delivery by diffusion.

#### Biodegradable matrix:

- Non-Lipidic.

### ADVANTAGES OF MATRIX SYSTEM:

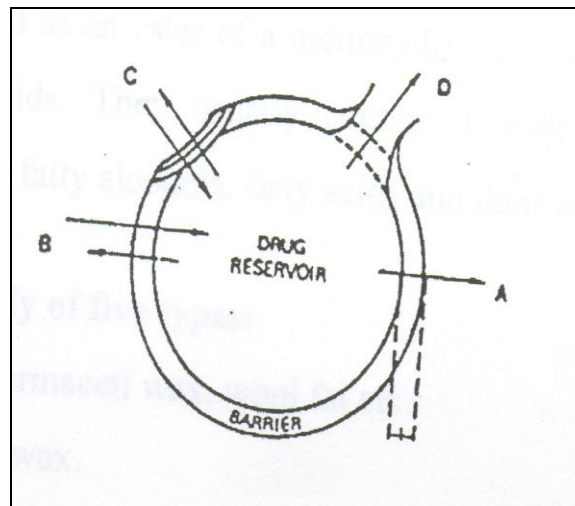
- The interest awakened by matrix system in last few years is completely justified in view of the major advantages. Among these, the following stand out.
- With proper control of manufacturing process, reproducible release profiles are possible.
- There is no risk of "dumping" of a large part of dose, 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

### PRINCIPAL OF MODIFIED DRUG RELEASE

Following either of the two principles can modify drug release:

#### Barrier principal:

In this method the retardant material is imposed between the drug and elution 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.

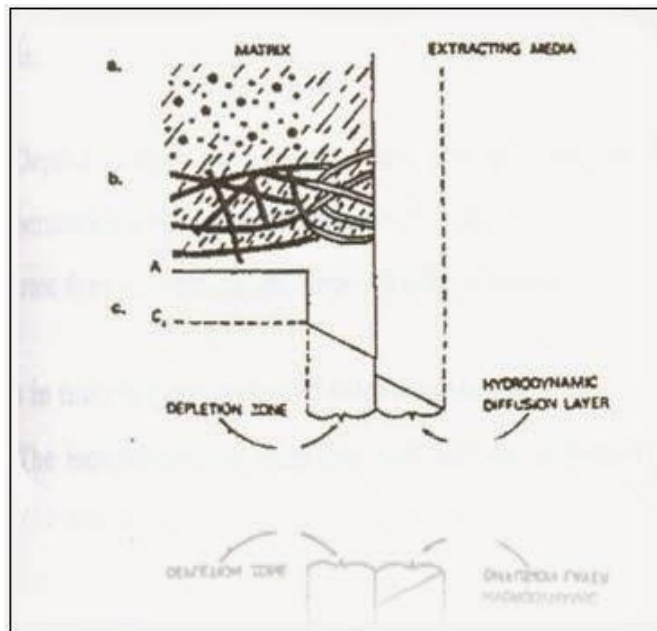


**Figure1.1:** Barrier mediated models of sustained release dosage form regimen

- A. 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 elution media.<sup>12</sup>

#### 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 1.2:** Embedded matrix concept as a mechanism of controlled release in sustained release dosage form design network model

### SWELLABLE MATRICES AS SYSTEM FOR ORAL DELIVERY <sup>6</sup>

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.
- Hydrophilic 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 tablets. They are constituted of a blend of drug and one or more hydrophilic polymers.

The release of drug from swellable matrix tablets 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.

### MECHANISM OF DRUG RELEASE FROM MATRIX DEVICES

#### Dissolution controlled release: <sup>[4]</sup>

Sustained release oral products employing dissolution as the time limiting step are simplest to prepare. If a drug has a rapid rate of dissolution it is possible to incorporate it into a



tablet with a carrier that has a slow rate of dissolution.

In the dissolution process if the dissolution process is diffusion layer control, the rate of diffusion of drug from the solid surface to the bulk solution through an unstirred liquid film, is the rate limiting step. In this case the dissolution process at steady state would be described by Noyes-Whitney equation

$$d_c/d_t = K_D A (C_s - C) \text{-----(1)}$$

Where,

$d_c/d_t$  is dissolution rate.

$K_D$  dissolution rate constant.

$C_s$  is saturation solubility of drug.

$C$  is the concentration of drug in bulk of the solution.

In relation to diffusion expression, that

$$K_D = D/v * I \text{-----(2)}$$

Where,

$D$  is dissolution coefficient

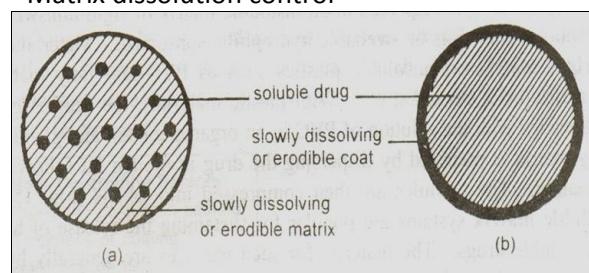
$V$  volume of dissolution media

$I$  is the thickness of unstirred liquid film.

From the above expression it can be seen that the rate of dissolution i.e. availability is approx. proportional to the solubility of the drug in the dissolution media i.e. ( $C_s$ ) provided a constant area and diffusional path length are maintained. This equation predicts constant dissolution rate as long as enough drug is present to maintain  $C_s$  constant, provided surface area does not change.

Dissolution control formulations are categories as

- Encapsulation dissolution control
- Matrix dissolution control



**Figure1.3:** Schematic representation of dissolution controlled release systems –(a) matrix system, and (b) coated/encapsulated system

#### Encapsulation dissolution control:

This method involves coating individual particles or granules of drug with slowly dissolving material. The coated particles can be compressed directly into tablet as in spacetabs or placed in capsule as in spansule products.

#### Matrix dissolution control:

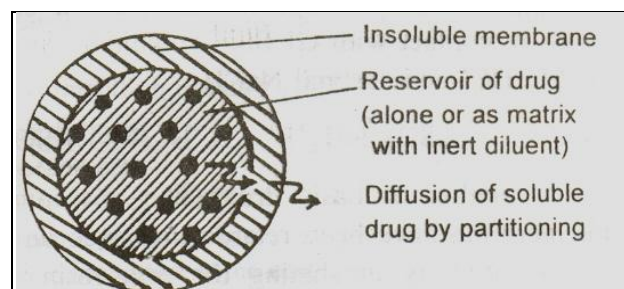
This method involves compression of the drug with a slowly dissolving carrier in a tablet form. Here the rate of drug availability is controlled by the rate of penetration of the dissolution fluid into the matrix. This in turn, can be controlled by porosity of the tablet matrix, the presence of hydrophilic and the wettability of the tablet and particle surface.

#### Diffusion controlled release:

These systems are of two types

#### Encapsulation diffusion control:

In this system water –insoluble polymeric material encases a core of drug. Drug will partition into the polymer membrane and exchange with the fluid surrounding the particle or tablet.



**Figure1.4:** Drug release of diffusion across the insoluble membrane of reservoir device

The rate of drug release is given by the equation.

$$d_m/d_t = Adk\Delta c \text{-----(3)}$$

$\Delta c$  is the concentration difference across the membrane.

Where,

**A** is area

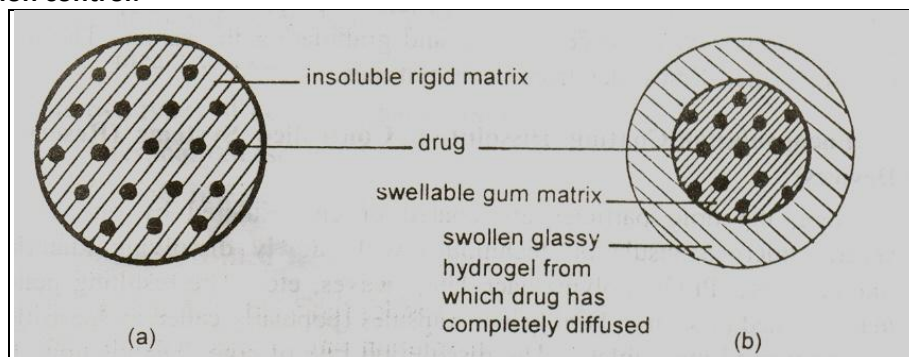
**D** is diffusion coefficient

**K** is the partition coefficient of the drug between the membrane and the drug core

**l** is the diffusional path length

An important parameter in the above eq (3) is the partition coefficient, which is defined as the concentration of the drug in the membrane over the concentration if the drug in core.

#### Matrix diffusion control:



**Figure1.5:** Diffusion controlled devices – (a) rigid matrix, and (b) swellable matrix.

In this system, a solid drug is dispersed in lipophilic or a hydrophilic polymer matrix and the rate of release of drug depends on the rate of drug diffusion and not on the rate of solid dissolution.

#### MATERIAL USE AS RETARDANTS IN MATRIX TABLET FORMULATION<sup>[7,8]</sup>

These classes of retardant materials are used to prepare matrix tablet formulations.

##### Water insoluble inert materials:

e.g. polyethylene, polyvinyl chloride, methyl acrylate, methacrylate copolymer, ethyl cellulose.

##### Insoluble, erodable materials

e.g. Steryl alcohol, stearic acid, polyethylene glycol, carnauba wax, caster wax, polyethylene glycol monosterate, triglycerides.

##### Hydrophilic materials:

e.g. Hydroxy propyl methylcellulose, sodium CMC, methylcellulose, hydroxy ethyl cellulose.

Natural gums: Galactomannose (guargum), chitosan, gum acacia, locust bean gum, sodium alginate, karaya gum, pectins, xanthan gum.

##### Natural polymers:

e.g. Ispaghula husk, tamarind seed polymer.

#### ADVANTAGES OF HYDROPHILIC MATRIX TABLETS:

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 nonexpensives 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.

#### 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 tablets.
- Tablet shape and size.
- Drug particle size.
- Solubility of drug in aqueous phase
- Surfactants and other additives

#### TABLET MANUFACTURING METHODS: <sup>[8]</sup>

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

##### 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 tablets.

##### 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 tablets.

##### Direct compression

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

#### DRUG PROPERTIES RELEVANT TO CONTROLLED RELEASE FORMULATION <sup>[9,10,11]</sup>

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 constraints 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.

##### Physicochemical properties:

##### 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 play an influential role in the performance of controlled release systems.

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<sub>D</sub>** = Dissolution rate constant.

**A** = Total surface area of the drug particles.

**C<sub>s</sub>** = 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 C<sub>s</sub>

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 pK<sub>a</sub> of the compound and pH of the medium.<sup>13</sup>

For weak acid.

$$S_t = S_o (1 + K_a / [H^+]) = S_o (1 + 10^{pH - pK_a}) \dots \dots \dots (1)$$

Where

**S<sub>t</sub>** = Total solubility (both ionized and un-ionized forms) of the weak acid

**S<sub>o</sub>** = Solubility of the un - ionized form

**K<sub>a</sub>** = Acid Dissociation constant

**H<sub>+</sub>** = hydrogen ion concentration of the medium.

Equation (1) predicts that the total solubility, S<sub>t</sub> of a weak acid with a given pK<sub>a</sub> can be affected by the pH of the medium.

For a weak base,

$$S_t = S_o (1 + [H^+] / K_a) = S_o (1 + 10^{pK_a - pH}) \dots \dots \dots (2)$$

Where, **S<sub>t</sub>** = Total solubility (both conjugate acid and free base forms) of the weak base.

**S<sub>o</sub>** = Solubility of the free base form

**K<sub>a</sub>** = Acid dissociation constant of the conjugate acid.

So total solubility, S<sub>t</sub> of a weak base whose conjugate acid has a given pK<sub>a</sub>, 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.

### 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

$$K = C_o / C_w$$

Where, **C<sub>o</sub>** = Equilibrium concentration of all forms of the drug  
e.g ionized and unionized in an organic phase at equilibrium.

**C<sub>w</sub>** = 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.

### 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 release 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 uniformly 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.

### Protein Binding

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

If a drug 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.

### 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, its 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

$$\log D = -S_v \log V + K_v = -S_M \log M + K_m$$

**V** = molecular Volume.

**M** = molecular weight.

**S<sub>v</sub>, S<sub>m</sub>, K<sub>v</sub>, K<sub>m</sub>** = constant

### Pharmacokinetic Properties

#### Absorption:

The rate, extent and uniformity of absorption of a drug are important factors when considering its 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  $K_r \lll K_a$  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, (ie.,  $K_a \gg 0.23 \text{ hr}^{-1}$ ), the above discussion implies that a first order release rate constant  $K_r < 0.17 \text{ hr}^{-1}$  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  $K_r \lll K_a$  must be met.

#### 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.

#### 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.

#### 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 limitingly large.

#### 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, (TI).

$$TI = \frac{TD_{50}}{ED_{50}}$$

Where,  $TD_{50}$  = median toxic 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.

#### Dose Size:

Since a controlled-release system is designed to alleviate repetitive dosing, it is naturally contain

greater amount of drug that an 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.<sup>13</sup>

#### CONCLUSION

It was concluded that an oral sustained released dosage form offer many advantages for drugs having absorption from the upper gastrointestinal tract and improves the bioavailability of medications that are characterized by the narrow absorption window. A Gastro retentive sustained released floating matrix tablets was developed with polymers like HPMC (K4 M), K100 M and Xanthan gum.

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