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SUSTAINED RELEASE MATRIX TYPE DRUG DELIVERY SYSTEM - AN OVERVIEW

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ABSTRACT

Oral drug delivery is the most preferred and convenient option as the oral route provides maximum active surface area among all drug delivery system for administration of various drugs. The attractiveness of these dosage forms is due to awareness to toxicity and ineffectiveness of drugs when administered by oral conventional method in the form of tablets & capsules. Usually conventional dosage form produces wide range of fluctuation in drug concentration in the bloodstream and tissues with consequent undesirable toxicity and poor efficiency. The maintenance of concentration of drug in plasma within therapeutic index is very critical for effective treatment. These factors as well as factors such as repetitive dosing and unpredictable absorption lead to the concept of oral Sustained release drug delivery systems. Sustained release drug delivery system works on many different mechanisms to control the release rate of drugs. Developing oral sustained release matrix tablets for drug with constant release rate has always been a challenge to the pharmaceutical technologist. Drug release through matrix system is determined by Water penetration, Polymer swelling, Drug dissolution, Drug diffusion, Matrix erosion have been utilized as formulation approaches. The present article contains brief review on various formulation approaches for Sustained release drug delivery system.

KEYWORDS: Matrix type system, oral drug delivery system, reservoir system, sustains release drug delivery system.

INTRODUCTION

For many decades treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms, including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols, and injectable, as drug carriers. This type of drug delivery system is known to provide a prompt release of drug or immediate release product.[1] Such immediate release products result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects.[2] However, after absorption of drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetics profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity.[3] Before this point is reached another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore, maintain plasma drug concentrations, beyond what is typically seen using immediate release dosage forms. In recent years, various modified release and/ or the time for drug release.[4, 5]

After 20th century investigation of new drug has been retained due to investigation cost of new drug. Therefore, pharmaceutical industries and academic laboratories have been focused on establishment of novel drug delivery system / or modified release dosage form rather investigation and development of new drug.[6]

The basic rationale of a sustained drug delivery system is to optimize the Biopharmaceutic, Pharmacokinetic and Pharmacodynamic properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of condition in the shortest possible time by using smallest quantity of drug, administered by the most suitable route.

The novel system of drug delivery offer a means of improving the therapeutic effectiveness of incorporated drugs by providing sustained, controlled delivery and / or targeting the drug to desired site. The goal of any drug

delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration.[7]

There is a continuously growing interest in the pharmaceutical industry for sustained release oral drug delivery systems. There is also a high interest for design a dosage formulation that allows high drug loading, particularly for actives with high water solubility.

Modified Release Dosage Form and Drug Delivery[8]

Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for many years. Early modified release products were often intramuscular/subcutaneous injection of suspensions of insoluble drug complexes, e.g. Procaine penicillin, protamine zinc insulin, insulin zinc suspension or injections of the drug in oil, e.g. Fluphenazine decanoate. Advance in technology have resulted in novel modified release dosage form. In contrast to conventional (immediate release) forms, modified release products provide either delayed release or extended release of drug.

Extended release products are designed to release their medication in a controlled manner, at a predetermined rate, duration, and location to achieve and maintain optimum therapeutic blood levels of drug.

Sustained Release[9]

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

Sustained release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect. Typically, sustained release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period (Fig 1). The sustained plasma drug levels provide by sustained release products often times eliminates the need for night dosing, which benefits not only the patients but the care given as well.

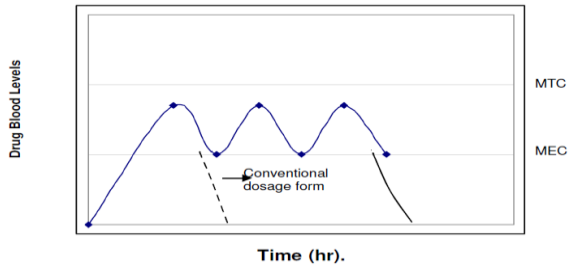

Fig. 1: Hypothetical drug blood level – time coverage for a conventional solid dosage form and a multiple action product.

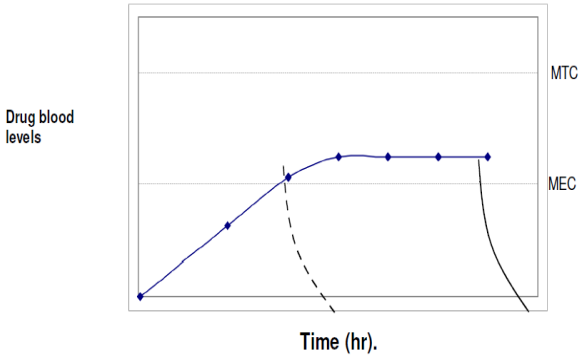

Fig 2: Hypothetical drug blood level – time coverage for a conventional solid dosage form and a controlled release product terminology.

PHARMACOKINETIC SIMULATION OF SUSTAINED RELEASE PRODUCTS[3, 8, 10]

The plasma drug concentration profiles of many sustained release products fits an oral one compartment model assuming first order absorption and elimination. Compared to an immediate release product, the sustained release product typically shows a smaller absorption rate constant, because of the slower absorption of the sustained release product. The time for peak concentration (tmax) is usually longer (fig-3), and the peak drug concentration (Cmax) is reduced. If the drug is properly formulated, the area under the plasma drug concentration curve should be the same, parameters such as Cmax, tmax and AUC conveniently show how successfully the extended release product performs in-vivo. For example, a product with tmax of 3 hours would not be very satisfactory if the product is intended to last 12 hours. Similarly, an excessively high Cmax is a sign of dose dumping due to inadequate formulation. The Pharmacokinetic analysis of single and multiple-dose plasma data has been used by regulatory agencies to evaluate many sustained release products. The analysis is practical because many products can be fitted to this model even though the drug is not released in a first order manner. The limitation of this type of analysis is that the absorption rate constant may not release to the rate of drug dissolution in vivo.

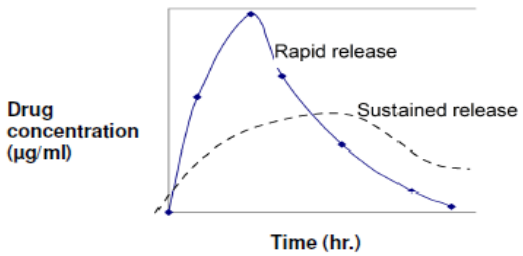

Fig 3: Plasma drug concentration of a SR and a regular release product.

Various other models have been used to simulate plasma drug levels of sustained release product (Wellin, 1983). The plasma drug levels from a zeroorder, sustained release drug product may be simulated with equation (1)

$$C_p = \frac{D_s}{V_D K}\left(1 - e^{-kt}\right) \text{ ---------- (1)}$$

Where, Ds = maintanance dose or rate of drug release (mg/ml),
Cp = plasma drug concentration
K = overall elimination constant, and
VD = volume of distribution

In absence of loading dose, the drug level in the body rises slowly to a plateau with minimum fluctuations.
This simulation assumes that
1) Rapid drug release occurs without delay,
2) Perfect zero-order release and absorption of the drug takes place, and
3) The drug is given exactly every 12 hours.

In practice, the above assumptions are not precise, and fluctuations in drug level do occur.

When a sustained release drug product with a loading dose (rapid release) and a zero-order maintenance dose is given, the resulting plasma drug concentrations are described by.

$$C_p = \frac{D_i Ka}{V_D(Ka - K)}\left(e^{-kt} - e^{-kat}\right) + \frac{D_s}{V_D K}\left(1 - e^{-kt}\right) \text{ -------- (2)}$$

Where, Di = immediate – release (loading dose) and
Ds = maintenance dose (zero-order).

This expression is the sum of the oral absorption equation (first part) and the i.v infusion equation (second part). An example of a zero-order release product with loading dose is shown in fig-4 the contribution due to the loading and maintenance dose is shown by the dashed lines, the inclusion of a built-in loading dose in the extended release product has only limited use.

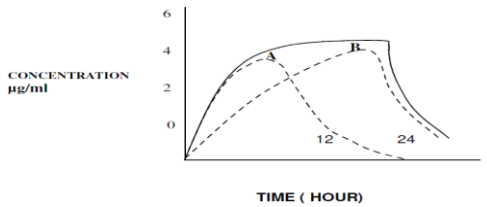

Fig. 4: Simulated plasma drug level of a SR product with a fast release component.
(A) and a maintenance component
(B) The solid line represents total plasma drug level due to the two components.

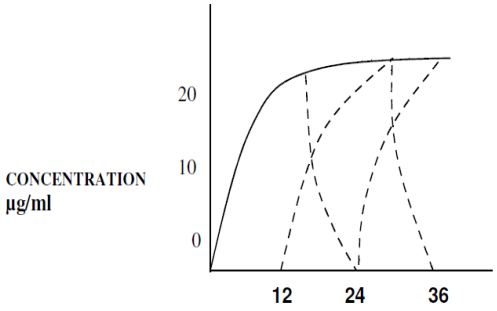

Fig. 5: Simulated plasma drug level of a SR product administered every 12 hrs. The plasma level shows a smooth rise to steady state level with no fluctuations.

With most sustained release product, the patient is given more than one dose and there is no need for a built in loading dose with subsequent doses. Putting a loading dose in the body than necessary, because of the topping, effect in situations where a loading dose is necessary, the rapid – release product is used to titrate a loading dose that will bring the plasma drug level to therapeutic level. A Pharmacokinetic model that assumes first-order absorption of the loading and maintenance dose has also been proposed. This model predicts spiking peaks due to loading dose when the drug is administered continuously fig-9.

Terminology And Sustained Release Concept[11]
Over the years, many terms (and abbreviations), such as sustained release(SR), sustained action (SA), prolonged action (PA), controlled release (CD), extended release (ER), timed release (TR), and long acting (LA), have been used by manufactures to describe product types and features. These are terms used to identify drug delivery systems that are designed to active a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. In the case of injectable dosage form, this period may vary from days to months. Although these terms often have been used interchangeably, individual products bearing these descriptions may differ in design an performance and must be examined individually to as certain their respective features.[12]

Sustained release[13]
In case of sustained release (SR) dosage forms the release of the active agent, although, is lower than in the conventional formulations, however, it is still substantially affected by the external environments into which it is going to be released.

Controlled release[13]
Controlled release (CR) systems provide drug release in an amount sufficient to maintain the therapeutic drug level over extended period of time, with the release profiles of predominantly controlled by the special technological construction and design of the system itself. The release of the active constituent is therefore, ideally independent of exterior factors. Extended release formulation is a controlled release formulation designed

to produce even and consistent release of active ingredient. Extended release (ER) dosage forms are those which due to special technology of preparation provided, soon after a single dose administration, therapeutic drug levels maintained for 8-12 hours.

Prolonged action[14]
Prolonged or long action products are dosage forms containing chemically modified therapeutic substances in order to prolong biological half life (Lee and Robinson, 1987).

These terms are explained in following Fig. 6

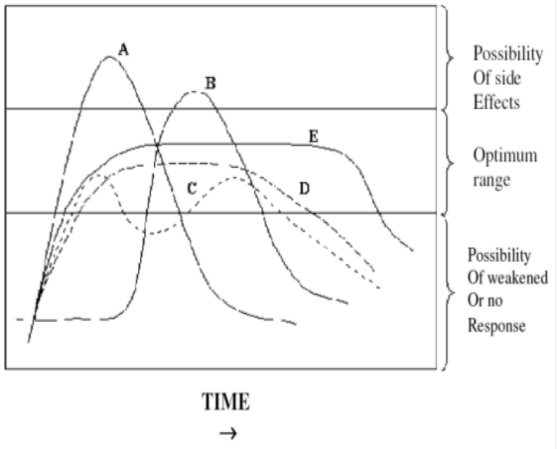

Fig. 6: Relationship between Plasma drug concentration vs Time.

A -Immediate release B -Delayed action C - Repeat action.
D - Prolonged release E - Controlled, sustained release.

In general, the goal of a sustained-release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period. This is usually accomplished by attempting to obtain zero-order release from the dosage form.[15]

Zero-order release constitutes drug release from the dosage form that is independent of the amount of drug in the delivery system (i.e., a constant release rate). Sustained release systems generally do not attain this type of release and usually try to mimic zero-order release by providing drug in a slow first-order fashion (i.e., concentration-dependent). Systems that are designed as prolonged release can also be considered as attempts at achieving sustained-release delivery. Repeat-action tablets are in alternative method of sustained release in which multiple doses of a drug are contained within a dosage form, and each dose is released at a periodic interval.[16, 17] Delayed–release systems, in contrasts, may not be sustaining, since often the function of these dosage forms is to maintain the drug within the dosage form for some time before release.

CLASSIFICATION[10]
Modified Release dosage form may be classified as

A .Delayed release
B. Extended release
B.1: Sustained release
B.2: Controlled release

A. Delayed release[3]
The drug is released at a later time after administration. The delayed action is achieved by the incorporation of a special coat, such as enteric coating, or other time barriers such as the formaldehyde treatment of soft and hard gelatin capsules. The purposes of such preparations are to prevent side effects related to the drug presence in the stomach, protect the drug from degradation in the highly acidic pH of the gastric fluid.

B. Extended release[13-17]
1) Sustained Release System
The idealized objective points to the two aspects most important to drug delivery, namely, spatial placement relates to targeting a drug to a specified organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. An appropriately designed sustained release drug delivery can be a major advance towards solving these two problems. The bulk of research has been directed at oral dosage forms that satisfy the temporal aspect of drug delivery, but many of the new approaches under investigation may allow for spatial placement as well.

The goal of sustained drug delivery are to conserve and maintain effective drug concentration, eliminate night time dosage, improve compliance and decrease side effects thus, optimizing drug therapy.

Compliance with a drug regimen depends among other things on the route and frequency of administration, the type of medication and condition being treated. Oral administration is the most common technique, but patient often forget to take their medication, and the condition, especially when frequent dosing is required.

Products that have been formulated for the purpose of prolonging absorption including oral, parenteral, topical and implants dosage form both for human and veterinary use. Oral sustained release products have gained importance because of the technological advances which achieve zero order release rate of therapeutic substance. Generally the pharmacokinetics of a drug is controlled by its chemical nature. However decreasing the absorption rate by physical means is a useful method to sustain the drug action when it is not feasible to modify the drug compound at its molecular level.

ADVANTAGES OF SUSTAINED RELEASE DRUG DELIVERY[18]
The improvement in drug delivery is represented by several potential advantages as below.
1. It improves patient compliance.
2. It employs lesser quantity of the drug.
3. It may improve the pathophysiology of the diseases.

(a) It minimizes or eliminates local side effects.
(b) It minimizes or eliminates systemic side effects.
(c) It obtains less potentiation or reduction in drug activity with chronic use.
(d) It minimizes drug accumulation with chronic dosing.
4. It improves the efficiency in treatment.
(a) It cures or controls the condition more promptly.
(b) It improves the control of condition i.e. reduces fluctuation in the drug level.
(c) It improves bioavailability of some drugs.
(d) Make use of special effects, e.g., sustained release aspirin for morning relief of arthritis by dosing before bedtime.

5. Economy[19]
(a) In comparison with conventional dosage forms the average cost of treatment over an extended period may be less.
(b) Economy also may results from a decrease in nursing time and hospitalization. Also
_ Reduce blood level oscillation characteristic of multiple dosing of conventional dosage forms.
- Reduce amount of drug administration.
-Maximizing availability with a minimum dose.
-Control of drug absorption; high peak level peaks that may be observed after administration of high availability drug can be reduced.
_ Safety margin of high potency drugs can be increased.
_ Increased reliability of therapy

6. Improved therapy[20]
a) Sustained blood level.
The dosage form provides uniform drug availability / blood levels unlike peak and valley pattern obtained by intermittent administration.

b) Attenuation of adverse effects.
The incidence and intensity of undesirable side effects caused by excessively high peak drug concentration resulting from the administration of conventional dosage forms is reduced.
c) It is seldom that a dose is missed because of non-compliance by the patient.

CONVENTIONAL DRUG THERAPY[4, 21]
In most cases of conventional dosage form the dosing interval is much shorter than the half-life of the drug resulting in a number of limitations.
1. Unless the dosing interval is relatively short, depending on biological half-life of the drug, large peaks and valleys (Fig.7) in the drug level will occur.
2. Success by this approach is dependent on patient compliance with the dosing regimen. Numerous studies have documented that lack of compliance is an important reason for drug therapy inefficiency or failure.
3. During the early periods of dosing there may be insufficient drug to generate a favorable biological response, which may be a significant problem in certain disease states.
4. For drugs with short biological half-lives, frequent dosing is needed to maintain relatively constant therapeutic levels of drugs.

There are two ways to overcome such a situation[22]
Development of new, better and safer drugs with long half-lives and large therapeutic indices. Effective and safer use of existing drugs through concepts and techniques of controlled and targeted delivery systems. The first approach has many disadvantages, which therefore resulted in increased interest in the second approach.

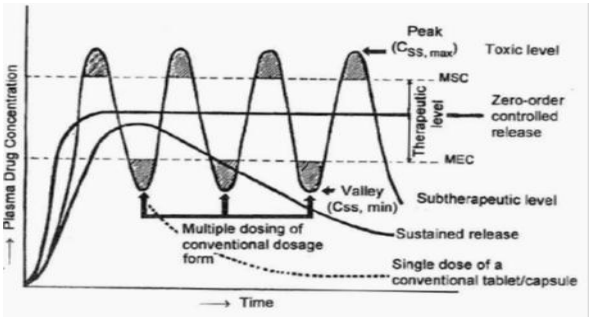

Fig 7: A hypothetical plasma concentration – time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations.

1.3 THEORY OF SUSTAINED RELEASE[23, 17]
Sustained release dosage form may contain:
a) Maintenance dose, and
b) Loading dose

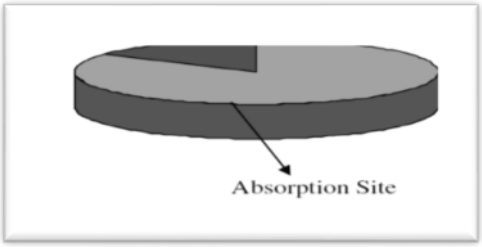

Fig. (8): Schematic representation of sustained release dosage system.

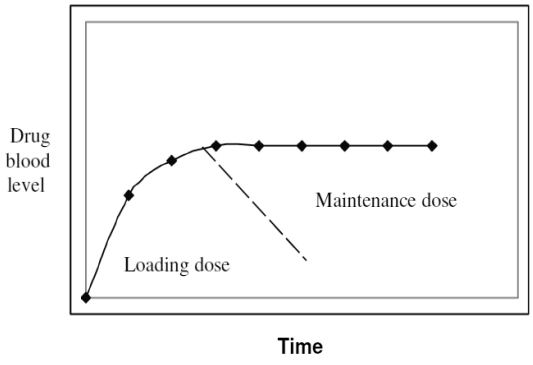

Fig. (9): A hypothetical plasma concentration time profile from sustained drug delivery formulation.

The maintenance dose or slowly available portion will release the drug slowly and maintain the therapeutic level for an extended period of time. While the loading dose or immediately available portion will held obtaining the therapeutic level quickly after administration. The rate of release of the drug from the maintenance dosage should be zero order (independent of the concentration) if the drug at the absorption site is to remain constant. The release of the drug from the loading dose should follow first order kinetics.

Sustained action curve is possible only when the drug from the dosage form is supposed for absorption into the blood, at a constant rate equal to the rate constant for the elimination of the drug. From the blood, mathematically this relationship is given as.

$$K_2B=R=K_dG\text{------ (3)}$$

Where, K2: Rate constant for elimination of drug from blood.
B : Quantity of drug to be maintained to the blood
R : Replacement rate
Kd : Constant relating the amount that can be absorbed under standard volume and concentration conditions
G : Quantity of drug that the dosage form must supply (maintain) in the depot.

When a fraction, f, of the drug is available because of irreversible binding or degradation, the amount available for absorption must be increased by 1/f.

The value for B is usually known or can be ascertained if the drug and its effect can be measured. It is often possible to obtain a value for K2 by plotting a log of the concentration of the drug remaining in blood versus time. The negative slope of the elimination rate is constant for design purpose.

When the initial dose (Dn) is estimated from the multiple dose data, the dose (Dn) is quantity needed to produce B (quantity of drug that must be maintained at receptor site). The correction for irreversible binding and / or degradation of the drug in depot (1/f) is not required when Dn is obtained from multiple dose data. Ideally, knowledge of the absorption rate constant K1, the elimination rate constant (K2) and the distributive rate constant (K12, K 21) should enable the formulation scientist to construct a curve similar to that given for a single dose. Number of methods for determining absorption rate constant has been reported.

The total dose of drug, Dt, in a prolonged action preparation comprises of the normal dose, Dn, and the sustaining dose Ds i.e.

$$D_t = D_n + D_s\text{---------- (4)}$$

For the system where the maintenance dose Ds provides drug via a zeroorder process the total dose is

$$D_t = D_n + K_r^0 T_d\text{ ---------- (5)}$$

Where, Kr
0 is the zero-order rate constant for drug release and Td is the total time desired for sustained release corresponding to one dosing interval. If the maintenance dose begins releasing drug at time zero it will add on to that which is provided by the initial dose, thus pushing the drug level too high.

In this case a correction factor is needed to account for the added drug from the maintenances dose

$$D_t = D_n - K_r^0 T_p + K_r^0 T_d\text{ ------(6)}$$

Where the correction factor is the amount of drug provided, during the time period t = 0 to the time of the peak drug level, Tp. Naturally, if the dosage form is constructed such that the maintenance dose not begin to release drug until the peak blood drug level, no correction factor is needed.

If drug is released via a first-order process, no correction factor is needed.

$$Dt = Dn + \frac{KeCd}{K^1_r}Vd \text{ --------- (7)}$$

Where Ke is the total elimination constant for the drug, Cd is the desired blood drug level and K1 r is the first-order drug release rate constant. The last term in equation (13) results from the approximation.

$$Ds = \frac{KeCd}{K^1_r}Vd \text{ --------- (8)}$$

If the maintenance dose begins release of drug from time zero, a correction factor is required similar to the zero-order case. In this case the correct expression is

$$Dt = Dn - DsK^1_rT_p \frac{K_eC_d}{K^1_r}V_d \text{ --------- (9)}$$

B-2: Controlled release formulation[24]

The controlled release systems is to deliver a constant supply of the active ingredient, usually at a zero-order rate, by continuously releasing, for a certain period of time, an amount of the drug equivalent to the eliminated by the body.

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

Repeat action preparations

A dose of the drug initially is released immediately after administration, which is usually equivalent to a single dose of the conventional drug formulation. After a certain period of time, a second single dose is released. In some preparation, a third single dose is released after a certain time has elapsed, following the second dose. The main advantage is that it provides the convenience of

supplying additional dose(s) without the need of re-administration.
It has disadvantage that the blood levels still exhibit the "Peak and valley" characteristic of conventional intermittent drug therapy.

ORAL CONTROLLED RELEASE SYSTEM[10, 25, 26]
Oral route has been the most popular and successfully used for controlled delivery of drug because of convenience and ease of administration, greater flexibility in dosage form design(possible because of versatility of GI anatomy and physiology) and ease of production and low cost of such a system. The controlled release systems for oral use are mostly solids and based on dissolution, diffusion or a combination of both mechanisms in the control of release rate of drug.

A. Continuous release systems
These systems release the drug for a prolonged period of time along the entire length of GIT with normal transit of the dosage form.

The various systems under this category are.
1. Dissolution controlled release system
2. Diffusion controlled release system
3. Dissolution and diffusion controlled release system
4. Ion exchange resin – drug complexes
5. Slow dissolving salts and complexes
6. pH – dependant formulation
7. Osmotic pressure controlled systems
8. Hydrodynamic pressure controlled system

B. Delayed transit and continuous release system
These systems are designed to prolong their residence in the GIT alon with their release systems included in this category are;
1. Altered density systems
2. Mucoadhesive systems
3. Size- based systems

C. Delayed release systems
The design of such systems involves release of drug only at a specific site in the GIT. The two types of delayed release systems are;
1. Intestinal release systems
2. Colonic release systems

The drugs contained in this system are those that are.
i. Destroyed in the stomach or intestinal site.
ii. Known to cause gastric distress
iii. Absorbed from a specific intestinal site, or
iv. Meant to exert local effect at a specific GI site.

CONTINUOUS RELEASE SYSTEMS[9, 27]
Diffusional System
Diffusional systems are characterized by the release rate of drug being dependent on its diffusion through an inert membrane barrier usually; this barrier is an insoluble polymer. There are basically two types of diffusion devices: reservoir devices and matrix devices.

(a) Reservoir devices
Reservoir devices, as the name implies, are characterized by a core of drug, the reservoir, surrounded by a polymeric membrane. The nature of the membrane determines the rate of release of drug from the system. The release of drug from a reservoir device is governed by **fick's first law of dissolution**.[25, 27]

The **fick's first law** states that the amount of drug passing across a unit area is proportional to the concentration difference across that plane. The equation is given as.

$$J = -D\frac{dC}{dX} \quad \text{- - - - - - - - - - - - - - (10)}$$

Where, J = flux in units of amount/area-time,
D = diffusion coefficient,
dC/dX= change in concentration C relative to distance X in the membrane.

(b) Matrix devices
A matrix device, as the name implies consists of drug dispersed homogeneously throughout a polymer matrix as represented in following figure.

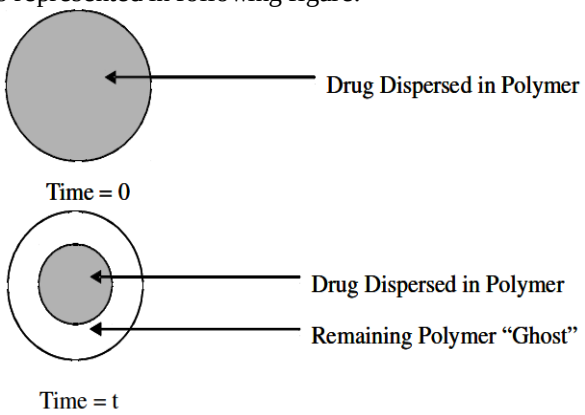

Fig 10: - Matrix Diffusion system before drug release (time = 0) and after partial drug release (time = t).

In this model, drug in the outside layer exposed to the bathing solution is dissolved first and then diffuse out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior.

Derivation of the mathematical model to describe this system involves the following assumptions: (a) a pseudo-steady state is maintained during drug release, (b) the diameter of the drug particles is less than the average distance of drug diffusion through the matrix, (c) the bathing solution provides sink conditions at all times, (d) the diffusion coefficient of drug in the matrix remains constant.

The next equations, which describe the rate of release of drugs dispersed in an inert matrix system, have been derived by **Higuchi.**[27]

The following equation can be written based on Fig 4.

$$\frac{dM}{dh} = C_0\, dh - \frac{Cs}{2} \quad \text{----------} \quad (11)$$

Where, dM = Change in the amount of drug released per unit area,
dh = Change in the thickness of the zone of matrix that has been depleted of drug,
C0 = Total amount of drug in a unit volume of the matrix,
Cs = Saturated concentration of the drug within the matrix.

From diffusion theory,

$$dM = \frac{D_m C_s}{h}\, dt \quad \text{----------} \quad (12)$$

Where, Dm is the diffusion coefficient in the matrix, Equating Eqs. (1) and (2), integrating, and solving for h gives

$$M = [C_s D_m (2C_0 - C_s)t]^{1/2} \quad \text{----------} \quad (13)$$

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

$$M = (2C_s D_m C_0 t)^{1/2} \quad \text{----------} \quad (14)$$

Which indicates that among the drug released is a function of the square root of time. In a similar manner, the drug release from a porous or granular matrix can be described by

$$M = \left[D_s C_a \frac{P}{T} (2C_0 - pC_a)t \right]^{1/2} \quad \text{----} \quad (15)$$

Where, P = porosity of the matrix,
Ca = solubility of the drug in the release medium
T = tortuosity
Ds = diffusion coefficient in the release medium.

This system is slightly different from the previous matrix system in that the drug is able to pass out of the matrix through fluid-filled channels and does not pass through the polymer directly. For purposes of data treatment, Eq. (14) or (15) can be reduced to.

$$M = kt1^{/2} \quad \text{----------} \quad (16)$$

Where k is a constant, so that plot of amount of drug released versus the square root of time will be linear, if the release of drug from the matrix is diffusion controlled. If this case, then by the Higuchi model, one may control the release of drug from a homogeneous matrix system by varying the following parameters26, 27: (a) initial concentration of drug in the matrix. (b) Porosity, (c) tortuosity, (d) polymer system forming the matrix, and (e) solubility of the drug.

E.g. Procan SR.

MATRIX SYSTEMS[9, 26, 27]

A matrix is a uniform mixture of drug and excipients. e.g. polymer that is homogeneously fixed in solid dosage form. The drug substance, which has a solubility S gm /cm3 in the dissolution medium, is dispersed in the matrix which is insoluble in the dissolution medium, The concentration of drug in the matrix is 'A' gm / cm3. The matrix is porous, with a porosity of '€' and diffusion coefficient of 'Dm'. The drug release from such system can be described by dQ/dt = 2SDmAt. Liquid will intrude from the bulk liquid. The rate and extent of intrusion will follow the following equation.

$$\frac{dL}{dt} = \frac{-Qr2}{8\eta L} = -\frac{q}{L} \quad \text{----------} \quad (17)$$

Where, L is the length of the intrusion at time t, r is the average radius of the pores, _ is the viscosity of the liquid and Q is a constant.

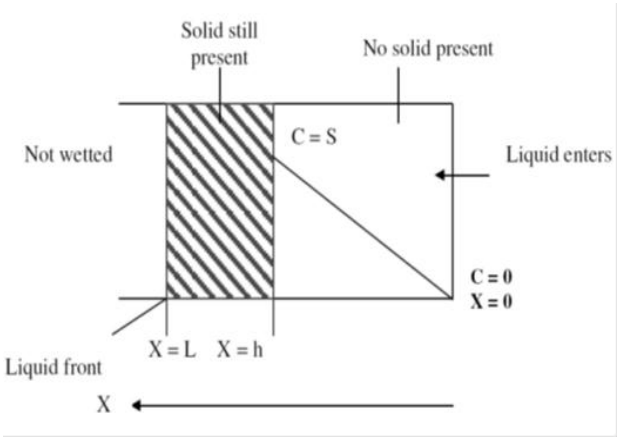

Fig. (11): Dissolution of drug from a solid matrix.

Hydrophillic matrix system[28]

A hydrophilic matrix controlled release system is a dynamic system composed of polymer wetting, polymer hydration and polymer dissolution. At the same time other soluble excipients or drug will also wet, dissolve and diffuse out of the matrix while insoluble materials will be hold in place until the surrounding polymer/ excipients / drug complex erodes or dissolves away.

The main principle is that a water-soluble binder, present throughout the tablet, partially hydrates on the outer tablet "**sink**" to form a gel layer.[29] Throughout the life of ingested tablet the rate of drug diffusion (if soluble) out of the wet gel and the rate of tablet erosion control the overall dissolution rate and drug availability.

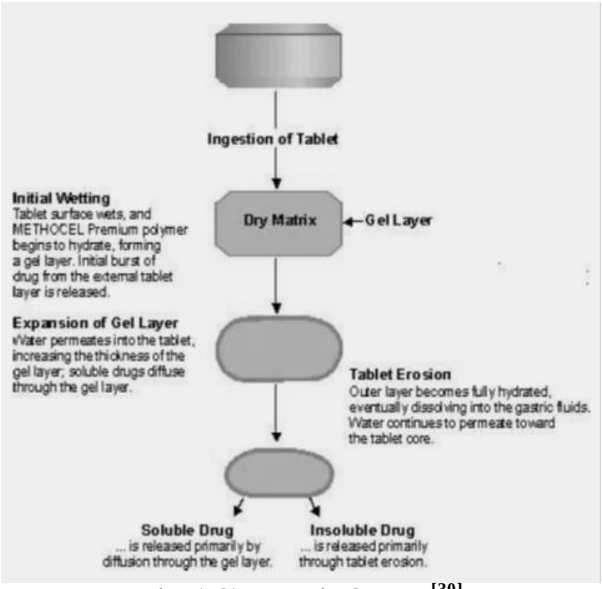

Fig. (12): Matrix System[30]

The most common controlled delivery system has been the matrix type such as tablets and granules, where the drug is uniformly dissolved or dispersed throughout the polymer, because of its effectiveness, low cost, ease of manufacturing and prolonged delivery time period. Hydrophilic polymers are becoming more popular in formulating oral controlled release tablets, it is well documented that the dissolution curve of drug release from a hydrophilic matrix shows a typical time dependent profile.[31, 32] The release of a dissolved drug inherently follows near first order diffusion either an initially high release rate, due to the dissolution of the drug present at the surface of the matrix followed by a rapidly declining drug release rate.[33, 34] The enhanced release rate observed at the beginning for the short time of release process is known as '**burst effect**',[35] and is many a time undesirable since it may, have negative therapeutic consequences. After this burst effect, hydration and consequent swelling and/or erosion of related polymer occur. These phenomenons control the release process but with time, the diffusion path length increases and saturation effect is attained, resulting in a progressively slow release rate during the end of dissolution span.[36, 37, 38]

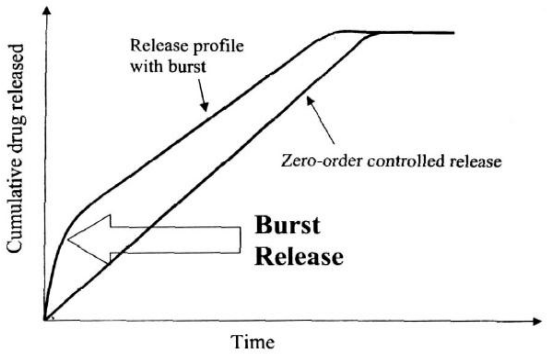

Fig.(13): Schematic showing the burst effect in a zero-order Drug delivery system.

In many controlled release formulations immediately upon placement in release medium, an initial large bolus of drug is released before the release rate reaches a stable profile.[39,40] This phenomenon is referred to as '**burst release**'.

SWELLABLE MATRICES AS SYSTEMS FOR ORAL DELIVERY[41-42]

Monolithic devices or matrices represent a substantial part of the drug delivery systems. Matrices containing swellable polymers are referred to as hydro gel matrices, polymeric matrices involving moving boundaries, hydrocolloid matrices, swellable controlled release systems or hydrophilic matrix tablets. Swellable matrices for oral administration are commonly manufactured as tablets by the compression of hydrophilic micro particulate powders.

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 polymer. In general drug release from swellable matrix tablets is based on glassy-rubbery transition of polymer as a result of water penetration into the matrix. Whereas interactions between water, polymer and drug are the primary factors for release control, various formulations 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. However the central element of the mechanism of drug release is the gel layer (rubbery polymer), which is formed around the matrix.[43]

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 the phenomena determining gel layer thickness. Finally, drug release is controlled by drug diffusion through the gel layer and/or by erosion of the gel layer. In order to follow gel layer dynamics during drug release in swellable matrices, the boundaries of such a layer have to be defined. It is well known that gel layer is physically delimited by two sharp fronts that separate-different matrix states, i.e. the boundaries separating swollen matrix from solvent and glassy from rubbery polymer.[44]

However the possibility of the presence of a third front inside the gel layer has been described. This additional front was termed undissolved drug front or diffusion front and turned out to be a function of drug solubility and loading. Its presence can create conditions such that the release will be more controlled by drug dissolution than by polymer swelling.[45]

Thus in swellable matrix tablet three fronts could be expected[46]

1. The swelling front, the boundary between the still glassy polymer and its rubbery state,

2. The diffusion front, the boundary in the gel layer between the solid, as yet undissolved drug and the dissolved drug and
3. The erosion front, the boundary between the matrix and the dissolution medium.

The measurement of front positions gives the possibility to determine three important parameters related to the behavior of the matrix, i.e. the rate of water uptake, the rate of drug dissolution and the rate of matrix erosion, associated with the movements of the swelling front, diffusion front and erosion front respectively.[47] These parameters are strictly linked to the drug release kinetics from matrix. Many attempts have been made in order to control the movement of the fronts and therefore the drug release kinetics.[48] The more successful consists in the reduction of the matrix-swelling rate by partially coating the matrix surface with impermeable or slowly permeable polymeric layer. In this way drug release can be modulated and the release kinetics can be shifted toward the linearity.[49, 50]

MECHANISM OF DRUG RELEASE FROM MATRIX SYSTEM[31, 51]

When a hydrophilic matrix system containing a swellable glassy polymer comes in contact with an aqueous medium, the fall in glass transition temperature leads to an abrupt change from a glassy to a rubbery state, causing swelling of the polymer on the surface and formation of a hydrated gel. Drug release is controlled by this gel diffusional barrier and/or by surface erosion of the gel. Surface leaching of the drug can lead to an initial burst, especially with highly soluble drugs.

Hydration of individual polymer chains leads to expansion in their end to end distance and radius of gyration to a new solvated state due to lowering of the polymer transition temperature, a sharp distinction between glassy and rubbery region is observed and the matrix increases in volume because of swelling.[52]

As water infiltrates deep in to the core, the thickness of the gel layer increases with simultaneous dissolution and erosion occurring at the outer layer due to complete hydration.

When the system is hydrated to the core, the drug concentration falls below its solubility value and the release rate of the drug begins to decline.[53] A concurrent increase in the thickness of the barrier layer with time increases the diffusion path length, further reducing the release rate. Drug release kinetic associated with this gel layer dynamics, range initially from Fickian to anomalous (Non-Fickian) and subsequently from quasi-constant (near zero order) to constant. Matrices of highly molecular weight polymers rarely shows all three regimens (Fickian, Non-Fickian and quasi-constant) of drug release because of a low chain disentanglement rate and insufficient external polymeric mass transfer.[54]

Soluble drugs are primarily released by diffusion through aqueous filled porous network formed in the inert matrix former due to dissolution and erosion of the polymer from the surface. Far poorly soluble drugs dispersed in inert polymer systems erosion is the primarily release mechanisms.

There are two major processes that control the drug release from swelling controlled matrix systems, these include[55]
1. Ingress of aqueous medium into the matrix followed by a hydration, gelation or swelling and
2. Matrix erosion.

Simultaneous occurrence of these processes leads to the formation of two fronts within the hydrating matrix, this are- **a swelling front**, at the junction of the anhydrated glassy matrix and the hydrated matrix and **an eroding front** where the polymer is completely hydrated. Thickness of the diffusion layer, i.e. the distance between the two fronts, depends on the relative rates at which the swelling and erosion occurs.[56]

If the polymer gels slowly, solvent can penetrate deep into the glassy matrix, thus dissolving the drug; therefore, gel layer thickness and its stability are crucial in controlling drug release. Numbers of techniques have been used to study the swelling of matrix tablets and to characterize the gel layer and front movement such as, optical imaging, 1H- NMR, pulsed –filled gradient spin echo NMR, co focal laser scanning microscopy, cryogenic scanning electron microscopy and texture analysis. The gel layer thickness is determined by the relative position of the swelling and erosion front.[57, 58]

ADVANTAGES OF HYDROPHILIC MATRIX SYSTEM[59, 60]

A hydrophilic matrix system essentially consists of a drug dispersed in a water swelling viscous polymer. These systems offer a number of advantages over other sustained release technologies namely.
1. Simplicity of formulation.
2. High drug loading as high as 80 % is possible in many cases.
3. The system is usually inexpensive as the rate-controlling agent is usually a GRAS (generally accepted as safe) food polysaccharides.
4. Number of matrix former is available allowing development of formulations that meet special needs and avoid patent infringement.
5. The systems are eroded as they pass the GIT thus there are no accumulation of "Ghosts" or empty shells.
6. As system depends on both diffusion and erosion for drug release, release is not totally dependent on GI motility.
7. No specialized equipment is required which substantially reduces manufacturing costs.
8. Offer easy scalability and process validation due to simple manufacturing processes.

The above listed advantages overshadow the undesirable property of reducing release rates with time. Alternatively drug and retardant blend may be granulated prior to compression.

FACTORS AFFECTING THE ORAL SUSTAIN RELEASE DOSAGE FORM DESIGN[61-64]

A) Pharmacokinetics and pharmacodynamics factor.

1. Biological half-life

Drug with biological half-life of 2-8 hours are considered suitable candidate for sustain release dosage form, since this can reduce dosing frequency. However this is limited in that drugs with very short biological 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.

2. Absorption

Rate of absorption of a sustained formulating depends upon release rate constant of the drug from the dosage form, and for the drugs that are absorbed by active transport the absorption is limited to intestine.

3. Distribution

The distribution of drugs into tissues can be important factor in the overall drug elimination kinetics. Since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibrium with blood and extra vascular tissue, consequently apparent volume of distribution assumes different values depending n the time course of drug disposition. Thus for design of sustain release products, one must have information of disposition of drug.

4. Metabolism

The metabolic conversion to a drug is to be considered before converting into another form. Since as long as the location, rate, and extent of metabolism are known a successful sustain release product can be developed.

B) Drug properties relevant to sustain release formulation

1. Dose size

A dose size of 500-1000mg is considered maximal for a conventional dosage form. This also holds true for sustain release dosage forms. Since dose size consideration serves to be a parameter for the safety involved in administration of large amounts with narrow therapeutic range.

2. Ionization, pKa and aqueous solubility

Most drugs are weak acids or bases and in order for a drug to get absorbed, it must dissolve in the aqueous phase surrounding the site of administration and then partition into the absorbing membrane.

3. Partition coefficient

Bioavailability of a drug is largely influenced by the partition coefficient, as the biological membrane is lipophilic in nature transport of drug across the membrane largely depends upon the partition coefficient of the drug. Drugs having low partition coefficient are considered as poor candidate for the sustain release formulation as it will be localized in the aqueous phase e.g.: Barbituric acid and vice a versa.

4. Drug stability

When drugs are orally administered, they come across acid-base hydrolysis and enzymatic degradation. In this case, if the drug is unstable in stomach, drug release system which provides medication over extended period of time is preferred, whereas in contrast the drug unstable in intestine will face problem of less bioavailability.

CONCLUSION

By the above discussion, it can be easily concluded that sustained-release formulation are helpful in increasing the efficiency of the dose as well as they are also improving the patient's compatibility matrix forming polymers can be successfully used to prepare Matrix tablets, releasing drug in a controlled manner. Preparatory procedures easily allow adaptation of release kinetics to delivery needs. This suitability of matrix forming polymers, to various drug delivery systems preparation confirms the importance of these specialized excipients in pharmaceutical application. They represent the choice solution for many oral delivery problems like fluctuating drug plasma levels, low bioavailability, more frequent dose administration etc. So matrix tablets can overcome the above problems of conventional oral drug delivery.

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