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REVIEW ARTICLE

ORAL SUSTAINED RELEASE DOSAGE FORM: A REVIEW

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ABSTRACT

Oral drug delivery system is the most prominent and convenient route of administration of drugs.The maintenance of concentration of drug in plasma within therapeutic index is very critical for effective treatment. Factors associated with conventional dosage forms like wide range of fluctuation in drug concentration in the bloodstream and tissues with consequent undesirable toxicity, poor efficiency in treatment, repetitive dosing and unpredictable absorption leads to the concept of oral Sustained release drug delivery systems.

Sustained release (SR) products provide an advantage over conventional dosage forms by optimizing biopharmaceutics, pharmacokinetic and pharmacodynamic properties of drugs in such a way that it reduces dosing frequency to an extent that once daily do therapeutic management through uniform plasma concentration providing maximum utility of drug with reduction in local and systemic side effects and cure or control condition in shortest possible time by smallest quantity of drug to assure greater patient compliance. Developing oral sustained release matrix tablets for drugs with constant release rate has always been a challenge to the pharmaceutical technologist. Drug release through matrix system is determined by water penetration, drug dissolution, drug diffusion and matrix erosion. Highly water soluble drugs like Deltiazem, Metformin, and Ranitidine has been formulated as sustained release matrix tablets. This article contains the basic information regarding designing and different approaches for sustained release drug delivery systems.

KEYWORDS: Oral drug delivery systems, sustained release, Matrix type systems, patient convenience.

INTRODUCTION:

The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes. The terms sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. There are several reasons for attractiveness of these dosage forms: provides increased bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug. If one were to develop an ideal drug delivery system, two pre-requisites would be required: Firstly, single dose for the duration of treatment whether for days or weeks as with infection, diabetes or hypertension. Secondly, it should deliver the active entity directly to the site of action minimizing the side effects [1].

TERMINOLOGY [2-6]

1. Sustained release:

These are drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose of drug.

2. Controlled-release dosage forms:

They are class of pharmaceuticals or other biologically active products from which a drug is released from the delivery system in a planned, predictable, and slower-than-normal manner for longer period of time.

3. Extended release:

Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate & necessarily reduce the dosage frequency by two folds.

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4. Delayed release:

Delayed release systems are those systems that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form.

5. Repeat action drug delivery system:

These are the alternative system of sustained release which multiple contains doses of drug within the dosage form and each dose is released at regular intervals.

6. Prolonged release system:

They are designed to release the drug slowly and to provide a continuous supply of drug over an extended period. They prevent very rapid absorption of the drug, which could result in extremely high peak plasma drug concentration.

7. Timed release drug delivery system:

Timed release drug delivery system are used to obtain the drug release after a lag time of about 4-5 hrs. Enteric coated dosage forms of cellulose acetate phthalate are designed to provide protection in the stomach. Application of a thick coat causes a delay in the drug release in small intestine and delays the drug release. This time controlled drug release may be retarded up to 5 hrs this targets the drug to the colon.

8. Site-specific and receptor release:

They are designed to target the drug directly to a certain biological location. In the case of site specific release, the drug directly target to a certain organ or tissue, while in receptor release, the target on the particular receptor within an organ or tissue.

ADVANTAGES OF SUSTAINED RELEASE DELIVERY SYSTEMS: [7-14]

1. Decreased local and systemic side effects:
- Reduced gastrointestinal irritation.

2. Better drug utilization:
- Minimum drug accumulation on chronic dosing.
- Improvement in the bioavailability of some drugs

3. Improved efficiency in the treatment:
- More uniform blood concentration
- Maintenance of therapeutic concentrations.
- Reduced toxicity by slowing drug absorption
- Reduction in fluctuation in drug level and hence more uniform pharmacological response
- Increase the stability by protecting the drug from hydrolysis or other degradative changes in gastrointestinal tract.

4. Improved patient compliance:
- Less frequent dosing
- Avoidance in high blood concentration.
- Improvement in treatment efficacy
- Minimization in drug accumulation with chronic dosing.
- Reduced night-time dosing
- Improve the ability to provide special effects.

For example, Morning relief of arthritis through bed time dosing.

5. Economy:
- Although the initial unit cost of sustained release products is usually greater than that of the conventional dosage form because of the special nature of these products, the average cost of treatment over an extended time period may be less.

Disadvantages of Sustained Release Delivery System: [7-14]

1. Extended release formulation contains a higher drug load and thus any loss of integrity of the release characteristics of the dosage form.
2. The larger size of extended release products may cause difficulties in ingestion or transit through gut.
3. The release rates are affected by various factors such as food and the rate of transit through the gut.
4. Some differences in the release rate from one dose to another dose but these have been minimized by modern formulations.
5. High cost of preparation.
6. Sometimes the target tissue will be exposed to constant amount of drug over extended period results in drug tolerance.

Considerations in Sustained release formulations: [15]

There are certain considerations for the preparation of extended release formulations:
1.If the active compound has a long half-life, it is sustained on its own
2.If the pharmacological activity of the active is not directly related to its blood levels
3.If the absorption of the drug involves an active transport
4.If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose. The above factors need serious review prior to design [2].

THE MAJOR DRAWBACKS ASSOCIATED WITH CONVENTIONAL DOSAGE FORMS: [16-19]

• Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.

- The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
- A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady-state condition difficult.
- The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.
- Recently, several advancements in drug delivery system have been made to overcome the drawback of conventional drug delivery system. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity or targeting the delivery of drug to a tissue.

FACTORS TO BE STUDIED IN DOSAGE FORM DESIGN: [1, 17, 18, 20]

The following characteristics of drugs are critical in ensuring their efficacy and safety. Therefore they should be sufficiently studied to fully characterize the drug.

i) Elimination half life: Drugs with long elimination half lives are generally undesirable for prolonged release dosage forms unless designed to prevent toxic effects due to a peaking effect or to reduce the dose.

ii) The first pass effect: Bioavailability may be significantly impaired if the release rate is retarded for drugs that suffer from an extensive first pass effect.

iii) The absorption site: If the absorption site is limited, absorption is likely to decrease and variable bioavailability will occur for typical prolonged release dosage forms.

iv) Adverse reactions: Undesirable adverse reactions may develop by using prolonging drug release.

CHALLENGES IN THE DEVELOPMENT OF SUSTAINED RELEASE DOSAGE FORM: [21, 22]

A. Dose dumping:

Dose dumping is a phenomenon where by relatively large quantities of drug in a sustained release formulation is rapidly released, introducing potential toxic quantities of the drug into the systemic circulation. Dose dumping can lead to fatalities in case of potent drug, which have a narrow therapeutic index.

B. Limited choice of selecting desired dose in the unit:

In conventional dosage forms, dose adjustments are much simpler e.g. tablet can be divided into two fractions. In case of sustained release dosage forms, this appears to be much more complicated. Sustained release property may get lost, if dosage form is fractured.

Design and Fabrication of Oral Sustained Release Systems: [23, 24]

The majority of oral controlled release systems rely on dissolution diffusion or a combination of both mechanisms to generate slow release of drugs into the gastrointestinal milieu.

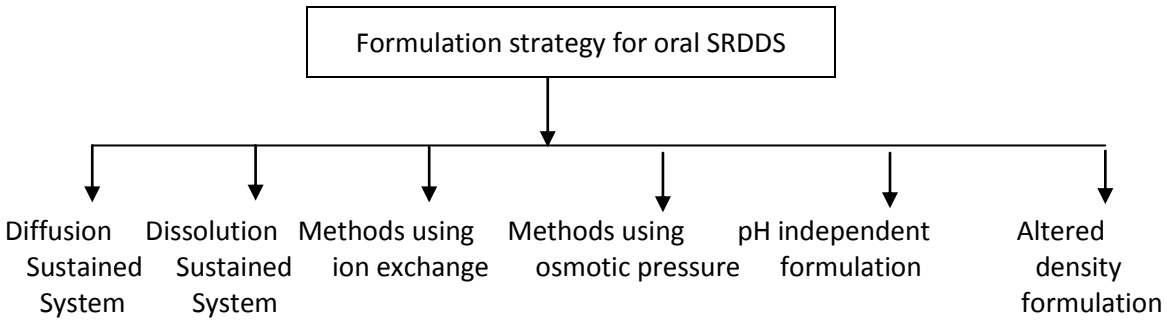

Figure 1: Formulation Strategy for Oral Sustained Release Drug Delivery System

The following techniques are employed in the design and fabrication of oral sustained release dosage forms:

1. Dissolution controlled release
a) Encapsulation dissolution control (Soluble reservoir system)
b) Matrix dissolution control (Soluble matrix system)
c) Multi layer matrix tablet
2. Diffusion controlled release
a) Reservoir devices.
b) Matrix devices.
3. Dissolution and diffusion controlled systems
4. Ion-Exchanges resins
5. PH-dependent formulations
6. Osmotically controlled release
7. Altered density formulations

1.12. Approaches for sustained release: [23, 24]

The different approaches for sustaining the drug release are:

1.Dissolution Controlled System:

It is possible to prepare sustained release product by decreasing the dissolution rate of drug which are highly water soluble. This can be done by preparing appropriate salt or derivatives by coating the drug with slowly dissolving materials, or by incorporating it into tablet with a slowly dissolving carrier.

Most of the formulations relying on dissolution to release the drug fall into three categories:

➢**Encapsulated dissolution systems: (Soluble reservoir system):**

➢Encapsulated dissolution systems can be prepared either by coating particles or granules of drug with varying thickness of slowly soluble polymers, or by microencapsulation. In this system drug is coated with a given thickness coating, which is slowly dissolved in the contents of gastrointestinal tract by alternating layers of drug with the rate controlling coats.

These coated particles can be compressed into tablets called as SPACETABS or placed in capsules as in SPANSULES.

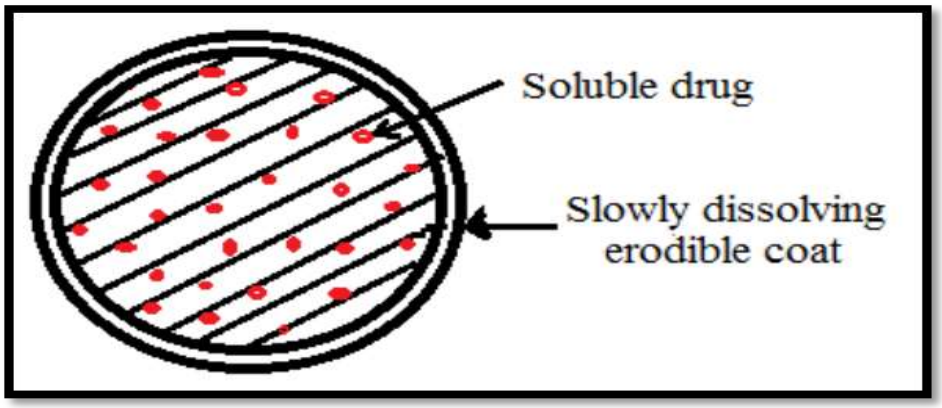

Figure 2: Schematic Representation of Dissolution of Reservoir System

➢**Matrix dissolution systems (Soluble matrix system) :**

It can be either a drug impregnated sphere or a drug impregnated tablet, which will be subjected to slow erosion.

Matrix dissolution devices are prepared by dispersing a dose of micronised drug particles homogeneously throughout a slowly dissolving polymer matrix by congealing or aqueous dispersion methods and compressing into a tablet.

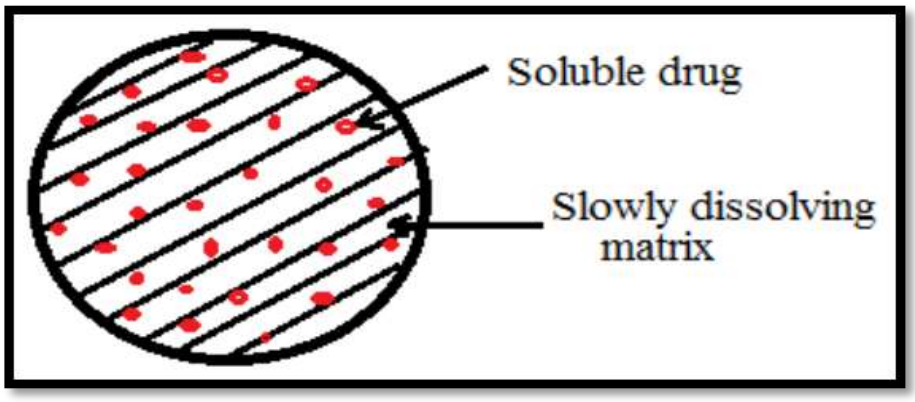

Figure 3: Schematic Representation of Dissolution Matrix System

➢ **Multi- layer matrix tablet:**

Multi-layer matrix tablet provides much diversity in achieving desired release profile by combining various types of subunits in tablets. Usually, an immediate release and sustained release layer.

2. Diffusion systems:

In diffusion systems, the release rate of drug is determined by its diffusion through a water-insoluble polymer. There are two types of diffusion devices:

➢ **Diffusion reservoir devices:**

In this system, a water insoluble polymeric material covers a core of drug. Drug will partition into the membrane and exchange with the fluid surrounding the particle or tablet. Additional drug will enter the polymer, diffuse to the periphery and exchange with the surrounding media and release of drug is governed by Fick's first law of diffusion.

$$J = -D\, d.Cm / dx$$

Where, J is the flux of drug across a membrane in the direction of decreasing concentration, D is the diffusion coefficient of the drug in the membrane, dCm/ dx is the change in the concentration of the drug in the membrane over a distance x.

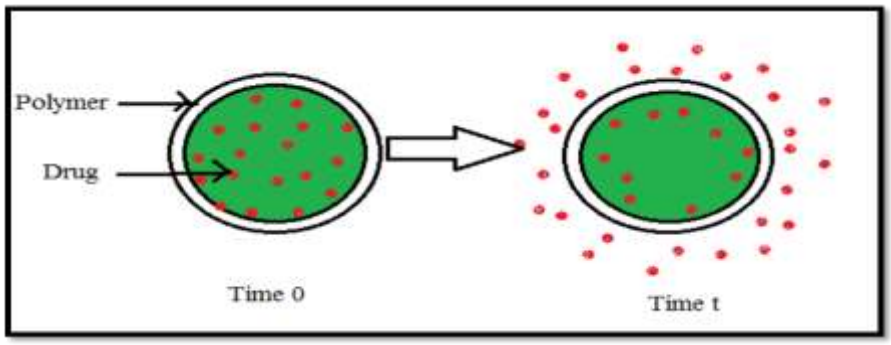

Figure 4: Schematic Representation of Diffusion Type Reservoir System

Reservoir type devices include microencapsulation and press coating the whole tablet.

In matrix devices, the drug is dispersed or dissolved uniformly throughout an inert polymeric matrix. The rate of release of drug is described by Higuchi; the change in amount of drug released per unit area dm, with a change in the depleted zone thickness, dh is,

$$dm = C0\, dh - (Cs/ 2)\, dh$$

Where; C0 is total amount of drug present per unit volume in the matrix. Cs is the saturation solubility of the drug per unit volume in the matrix.

Advantages:

Zero order delivery is possible.

Release rates can be modified with polymer type & concentration

Disadvantages:

Difficult to deliver high molecular weight compound

Generally increased cost per dosage unit.

Potential toxicity if dose dumping occurs.

➢ **Diffusion matrix devices:**

The matrix system is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. Matrix systems are widely used for sustaining the release rate. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed.

The most common method of preparation of matrix devices is to mix the drug with the matrix material and compress the mixture into tablets or multi-layered tablets as per the need of release rate or the drug is dispersed in molten wax or rate controlling material, which is then congealed and compressed into tablets.

The matrix diffusion control devices consist of a solid drug dispersed in an insoluble matrix. The rate of drug release is dependent on the rate of drug diffusion but not on the rate of solid dissolution.

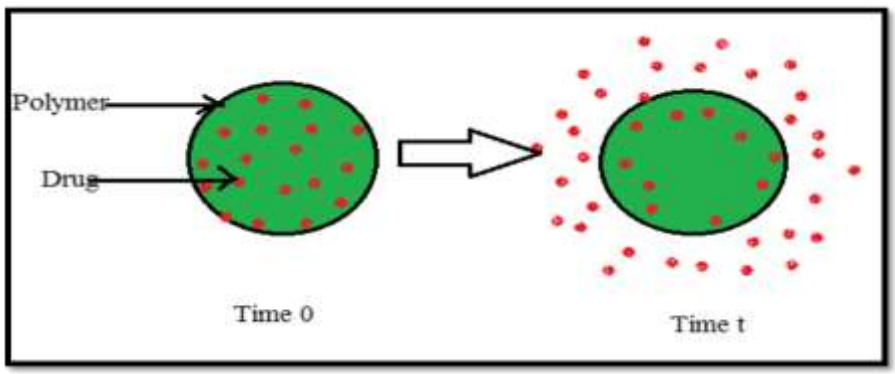

Figure 5: Schematic Representation of Diffusion Type Matrix System

The equation describing drug release from this system has been derived by T – Higuchi. This system has been derived by T – Higuchi

$$Q = D\varepsilon / \tau (2A - \varepsilon Cs) C.st$$

Where;
Q = Weight in grams of drug released per unit surface area.
D = Diffusion coefficient of drug in the release medium.
ε = Porosity of the matrix
τ = Toruosity of the matrix
Cs = Solubility of drug in release medium
A = Concentration of drug in the tablet expressed as g/ml

The following assumptions were made in delivering the above equation:

(i) A Pseudo – steady state is maintained during release
(ii) A>> Cs i.e., excess solute is present
(iii) C=O in solution at all times (perfect sink condition)
(iv) Drug particles are much smaller than those in the matrix
(v) The diffusion coefficient remains constant
(vi) No interactions between the drug and the matrix occur

The above equation can be reduced to Q = Kt½. Therefore, a plot of amount of drug release versus the square root of time should be linear if drug release from the matrix is diffusion controlled.
One may control drug release from a homogenous matrix by varying the following parameters.
(i) Initial concentration of drug in the matrix.
(ii) Drug solubility.
(iii) Porosity
(iv) Tortuosity
(v) Leaching solvent composition.
(vi) Polymer system making up matrix

Advantages:

a) Easier to produce than reservoir or encapsulated devices.
b) Versatile, effective and low cost.
c) Possible to formulate high molecular weight compounds.
d) Increased the stability by protecting the drug from hydrolysis or other derivative changes in gastrointestinal tract.

Disadvantages:

i) The ghost matrix must be removed after the drug has been released.
ii) The release rates are affected by various factors such as, food and the rate transit through the gut.
iii) Cannot provide pure zero order release.

Sustained release Matrix Tablets: [25]

One approach to the manufacture of sustained release dosage forms (matrix tablets) is the direct compression of blends of drug, retardant materials and additives to form a tablet in which drug is embedded in a matrix core of the retardant. Alternatively, retardant drug blends may be granulated prior to compression. Matrix tablets are considered to be the commercially feasible sustained action dosage form that involves the least processing variables, utilize the conventional facilities and accommodate large doses of drug.
A major disadvantage of matrix tablets or devices is that drug release rate continuously decreases with time. This is consequence of increased diffusional distance and decreased surface area at the penetrating solvent front. Consequently, to achieve zero-order release from matrix devices, it is necessary to select a geometry that compensates the increase in diffusional distance with a corresponding increase in surface area for dissolution .Additives such as poly vinyl pyrrolidone or hydrophilic polymers also control drug release from materials and apparent zero-order release can be obtained.
There are three classes of retardant materials used -
i) The first class consists of retardant that form insoluble "Skeleton" matrices;
ii) The second class represents water insoluble materials that are potentially erodible;
iii) The third class consists of polymers that form hydrophilic matrices

POLYMERS USED IN THE MATRIX: [26, 27]

The polymers most widely used in preparing matrix system include both hydrophilic and hydrophobic polymers.

(A) Hydrophilic Polymers:

Hydroxyl propyl methyl cellulose (HPMC), hydroxyl propyl cellulose(HPC), hydroxyl ethyl cellulose (HEC), Xanthan gum, Sodium alginate, poly(ethylene oxide), and cross linked homopolymers and co-polymers of acrylic acid.

(B) Hydrophobic Polymers:

This usually includes waxes and water insoluble polymers in their formulation.

(C) Waxes:

Carnauba wax, bees wax, candelilla wax, micro crystalline wax, ozokerite wax, paraffin waxes and low molecular weight polyethylene.

(D) Insoluble polymers:

Ammoniomethacrylate co-polymers (Eudragit RL100, PO, RS100, PO), ethyl cellulose, cellulose acetate butyrate, cellulose acetate propionate and latex dispersion of meth acrylic ester copolymers.

FACTORS AFFECTING DRUG RELEASE FROM MATRIX TABLETS: [28]

1. Swelling characteristics of polymers
2. Polymer erosion
3. Drug loading
4. Drug solubility

FACTORS AFFECTING SUSTAINED RELEASE FORMULATION:

I. Physicochemical Properties of Drug: [2, 27, 29]

a) Aqueous Solubility:

Generally drugs are weak acids or weak bases, since the unchanged form of a drug preferentially permeates across lipid membranes, drugs aqueous solubility will be decreased by conversion to an unchanged form. Drugs with low water solubility will be difficult to incorporate into extended release mechanism. The lower limit on solubility for such product has been reported 0.1 gm/ml. Drugs with extreme water solubility are equally difficult to incorporate in extended release system because it is difficult to control release of drug from dosage form. pH dependent solubility, particularly in the physiological pH range, would be another problem because of the varied pH of gastro intestinal tract, which ultimately gives variation in dissolution profile. e.g. Aspirin, which is less soluble in stomach, but more soluble in intestine.

b) Partition coefficient:

Partition coefficient is generally defined as the fraction of drug in an oil phase to that of an adjacent aqueous phase. As biological membrane is lipophilic in nature through which the drug has to pass though, so partition co-efficient of drug influence the bioavailability of drug very much. Drug having lower partition coefficient values less than the optimum activity are undesirable for oral ER drug delivery system, as it will have very less lipid solubility and the drug will be localized at the first aqueous phase it come in contact e.g. Barbituric acid. Drug having higher partition co-efficient value greater than the optimum activity are undesirable for oral ER drug delivery system because more lipid soluble drug will not partition out of the lipid membrane once it gets in the membrane. The value of partition coefficient at which optimum activity is observed is approximately 1000:1 in 1-octanol/water system.

c) Drug pKa and Ionization at Physiological pH:

As we know only unionized drugs are well absorbed and permeation of ionized drug is negligible, since its rate of absorption of ionized drug is 3 to 4 times less than that of the unionized drug. pKa range for acidic drug where ionization is pH sensitive is around 3.0 to 7.5 and pKa range for basic drug whose ionization is pH sensitive is around 7.0 to 11.0 are ideal for optimum positive absorption. Drug shall be non-ionized at the site to an extent 0.1 – 5.0%. Drugs existing largely in ionized form are poor candidates for oral ER drug delivery system. e.g. Hexamethonium.

d) Drug stability:

Drugs when administered orally can undergo both acid/base hydrolysis and enzymatic degradation. The degradation will proceed at the reduced rate for drugs in the solid state. For the drugs that are unstable in stomach, formulation systems that prolong delivery to the entire GI tract are beneficial. Compounds that are unstable in the small intestine may demonstrate decreased bioavailability when administered in extended release dosage form. This is happening due to the fact that a greater quantity of drug is delivered in small intestine and is being subjected to more degradation.

e) Molecular size and diffusivity:

With large molecular size are poor candidate for oral sustained release (SR) where it is first time drug delivery system because the ability of the drug to diffuse polymeric membrane is a function of its diffusivity (or diffusion co-efficient). Diffusivity depends on size shape of the cavities of the membrane. The diffusion co-efficient of intermediate molecular weight drug is 100 to 400 Daltons; through flexible polymer range is 10-6 to 10-9 cm2/sec. For drugs having molecular weight > 500 Daltons, the diffusion coefficient in many polymers are very less i.e. less than 10-12 cm2/sec. The examples of drugs which are difficult to control release rate of medicament from dosage form are proteins and peptides.

f) Protein binding:

The Pharmacological response of drug depends on unbound drug concentration rather than total concentration and almost all drugs bind to some extent to plasma and or tissue proteins. Protein binding plays a significant role in its therapeutic effect regardless the type of dosage form as extensive binding to plasma increase biological half life and thus sometimes ER drug delivery system is not required for this type of drug.

II. Biological Properties of Drug: [17, 18]

a) Absorption:

The absorption behaviour of a drug can affect its suitability as an extended release product. The aim of formulating an extended release product is to place a control on the delivery system. It is essential that the rate of release is much slower than the rate of absorption. If we assume the transit time of most drugs and devices in the absorptive areas of GI tract is about 8-12 hours, the maximum half-life for absorption should be approximately 3-4 hours. Otherwise the device will pass out of absorptive regions before drug release is complete. Therefore the compounds with lower absorption rate constants are poor candidates for extended release systems. Some possible reasons for a low extent of absorption are poor water solubility, small partition co-efficient, acid hydrolysis, and metabolism or its site of absorption.

b) Distribution:

The distribution of drugs in 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 on time course of drug disposition. Drugs with high apparent volume of distribution, which influence the rate of elimination of the drug, are poor candidate for oral ER drug delivery system e.g. Chloroquine. For design of extended release products, one must have information on disposition of the drug.

c) Metabolism:

Drug, which extensively metabolized is not suitable for ER drug delivery system. A drug capable of inducing metabolism, inhibiting metabolism, metabolized at the site of absorption or first-pass effect is poor candidate for ER delivery, since it could be difficult to maintain constant blood level e.g. Levodopa, Nitroglycerine. Drugs that are metabolized before absorption, either in lumen or the tissues of the intestine, can show decreased bioavailability from the extended releasing systems. Most intestinal walls are saturated with enzymes. As drug is released at a slow rate to these regions, lesser drug is available in the enzyme system. Hence the systems should be devised so that the drug remains in that environment to allow more complete conversion of the drug to its metabolite.

d) Biological half-life:

The main target of an oral extended release product is to maintain therapeutic blood levels over an extended period. To implement this, drug must enter in the circulation approximately with the same rate at which it is eliminated. The elimination rate is quantitatively described by half-life (t1/2). Therapeutic compounds with short half-lives are excellent candidates for extended release preparations because this can reduce dosing frequency. A drug having biological half-life between 2 to 8 hours is best suited for oral ER drug delivery system. As if biological half-life < 2 hours the system will require unacceptably large rate and large dose and biological half-life > 8 hours formulation of such drug into oral ER drug delivery system is unnecessary.

e) Margin of safety:

Larger the value of therapeutic index, safer is the drug. Drugs with less therapeutic index are usually poor candidates for formulation of oral ER drug delivery system due to technological limitation of control over release rates.

f) Plasma Concentration Response Relationship:

Generally pharmacological response of drug depends on plasma drug concentration rather than dose. But pharmacological activity of some drugs is independent of plasma concentrations, which are poor candidate for oral ER drug delivery system e.g. Reserpine.

g) Concentration Dependency on Transfer of Drug:

Transfer of drug from one compartment to other if follows zero kinetic process then such drugs are poor candidate for oral ER delivery system, it should be first order kinetics.

Dissolution Profile: [30- 33]

This test is to check the amount of drug available, which can be estimated based on the amount of drug dissolved in the dissolution medium. The drug concentration in plasma can be exemplified via dissolution rate, extent and time. The method involves placing the tablet in a hemispherical cylinder vessel filled with the dissolution medium and a mechanical stirrer attached with a rotator to move the stirrer at variable speeds, which can be set at a fixed speed. The samples are withdrawn at specific time intervals and the drug content is calculated. The amount of the drug available in the body is estimated by in-vitro in-vivo correlation. Several reviews have been published reporting the research that has gone into the development of extended release tablets. This review is aimed at understanding novelty and feasibility of design

approach in the development of extended release formulation by matrix technology.

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PRINCIPAL OF RELEASE RATE AND DOSE CONSIDERATION: [5]

The objective in designing a sustain release system is to deliver drug at a rate necessary to achieve and maintain a constant drug level. This rate should be analogous to that achieved by continuous IV infusion where drug is provided at a constant rate equal to its rate of elimination. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time that is release from the dosage form should follow zero order kinetics. Shown by following equation.

kr0 = Rate In = Rate out = ke. Cd. Vd

Where,

kr_0 – Zero order rate constant for drug release.
Ke - First order rate constant for overall drug elimination.
Cd - Desirable drug level in the body.
Vd - Volume space in which drug is distributed/volume of distribution.

To achieve a therapeutic level promptly and sustaining the level for a given period of time, the dosage form generally consists of two parts, an initial priming dose, Di, that release drug immediately and a maintenance or sustaining dose, Dm. The total dose, W, thus required for the system is –

W = Di + Dm ..... (1)

For a system where the maintenance dose release drug by a zero order process for a specified period of time, the total dose is

W = Di + Kr0 Td ..... (2)

Where,
Kr0 is the zero order rates constant and
Td is the total time desired for sustained release form and dose.

EVALUATION OF SUSTAINED RELEASE TABLETS [34-35]

Before marketing a sustained release product, it is must to assure the strength, safety, stability and reliability of a product by forming in-vitro and in vivo analysis and correlation between the two. Various authors have discussed the evaluating parameters and procedures for sustained release formulations.

1. In-Vitro Methods:

These are:-

a. Beaker method
b. Rotating disc method
c. Rotating Bottle method
d. Rotating Basket method
e. Stationary Basket Method
f. Oscillating tube method
g. Dialysis method
h. USP dissolution method.

2. In–Vivo Methods

Once the satisfactory in-vitro profile is achieved, it becomes necessary to conduct in-vivo evaluation and establish in-vitro in-vivo correlation. The various in-vivo evaluation methods are-

a. Clinical response
b. Blood level data
c. Urinary excretion studies
d. Nutritional studies.
e. Toxicity studies
f. Radioactive tracer techniques

3. Stability Studies:

Adequate stability data of the drug and its dosage form is essential to ensure the strength, safety, identity, quality, purity and in-vitro in-vivo release rates that they claim to have at the time of use. A sustained release product should release a predetermined amount of the drug at specified time intervals, which should not change on storage. Any considerable deviation from the appropriate release would render the sustained release product useless. The in-vitro and in-vivo release rates of sustained release product may be altered by atmospheric or accelerated conditions such as temperature and humidity. The stability programmes of a sustained release product include storage at both nominal and accelerated conditions such as temperature and humidity to ensure that the product will withstand these conditions.

In vitro - In vivo Correlations:

The requirement of establishing good *in vitro - in vivo* correlation in the development of sustained release delivery systems is self-evident. To make a meaningful in-vitro in-vivo correlation one has to consider not only the pharmaceutical aspect of sustained release drug delivery system but also the biopharmaceutics and pharmacokinetics of the therapeutic agent in the body after its release from the drug delivery system and also the pharmacodynamics of therapeutic agent at the site of drug action. A simple in vitro-in vitro relationship can be established by conducting in-vitro and in-vivo evaluations of a potential drug delivery system simultaneously to study and compare the mechanism and rate profiles of sustained drug release. When the in-vivo drug release mechanism is proven to be in good agreement with that observed in the invitro drug release studies, then in-vitro invivo correlation factor is derived. For capsule type drug delivery system the factor can be represented as:

(Q/t) *In-vivo*

Q= (Q/t) *In-vitro*

Where,
Q/t = Rate of release
'Q' values are dependent profiles of drug delivery systems.

Upon the sites of administration and environmental conditions to which the animals are exposed during treatment (study).

The above relationship can be used for optimization of sustained release Levy has classified *In-vitro- In-vivo* correlation in to:

A. Pharmacological correlations based on clinical observations;
B. Semi-quantitative correlations based on blood levels or urinary excretion data;
C. Quantitative correlation arising from absorption kinetics. While most of the published correlations are of semi quantitative nature, the most valuable are those based on absorption kinetics.

Bioavailability Testing: [28]

Bioavailability is generally defined as the rate and extent of absorption of unchanged drug from its site of application to the general circulation. Bioavailability is defined in terms of a specific drug moiety, usually active therapeutic entity, which may be the unchanged drug or as with prodrug, for instance, a metabolite. In contrast, the term "absorption" often refers to net transport of drug related mass from its site of application into the body. Hence, a compound may be completely absorbed but only partially bioavailable as would occur, when low bioavailability is caused by incomplete absorption. Pharmaceutical optimization of the dosage form may be warranted to improve absorption characteristics of the drug and thereby also its bioavailability.
Bioavailability studies are ordinarily single dose comparisons of tested drug product in normal adults in a fasting state. A crossover design, in which all subjects receive both, the product and reference material on different days, is preferred. Guidelines for clinical testing have been published for multiple dose studies. Correlation of pharmacological activity or clinical evidence of therapeutic effectiveness with bioavailability may be necessary to validate the single significance of sustained release claims. While single dose studies are usually sufficient to establish the validity of sustained release dosage form design; multiple dose studies are required to establish optimum dosing regimen. They are also required when difference may exist in the rate but not the extent of absorption. When there is excessive subject-to subject variation or when the observed blood levels after a single dose are too low to be measured accurately.
A sufficient number of doses must be administered to attain steady state blood levels. According to an extensive study of sustained release Theophylline products; for example, encapsulated forms howed less peaking during multiple dosing and therefore better control of blood level within the desired limits.

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. More over all these comes with reasonable cost. The dosage form is easy to optimize and very helpful in case of the antibiotics in which irrational use of the same may result in resistance.

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