EXTENDED RELEASE FORMULATION: AN OVERVIEW

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ABSTRACT
Recently, controlled release drug delivery has become the standards in the modern pharmaceutical design and intensive research has been undertaken in achieving much better drug product effectiveness, reliability and safety. Oral Extended release drug delivery medication will continue to account for the largest share of drug delivery systems. Hence, in this work to formulate tablets in order to avoid the first pass metabolism and increase the bioavailability. Hence in this work an attempt was made to formulate extended release system in order to achieve plasma concentration profile up to 24 hrs. The extended release formulations are the type of formulations which will improves the therapeutic index of drug concentration. These formulations make the drug available over extended time period after oral administration. The extended release product will optimize therapeutic effect and safety of a drug at the same time improving the patient convenience and compliance. Here an attempt was made to formulate the Delayed Drug release in to the systemic circulation. Which will give detailed information about the formulation and formulation requirements to develop the ideal Delayed drug release formulation.

Key words: Extended release tablets, Oral administration, Pharmaceutical technology, Sustained release tablet, Dosage form, Dose frequency.

INTRODUCTION
If one were to imagine the ideal drug delivery system, two prerequisitdes would be required. First, it would be a single dose for the duration of treatment, whether it is for days or weeks, as with infection, or for the lifetime of the patient, as in hypertension or diabetes. Second, it should deliver the active entity directly to the site of action, thereby minimizing or eliminating side effects. This may necessitate delivery to specific receptors or to localization to cells or to specific areas of the body.\[1],[2]

The advantages of administering a single dose of a drug that is released over an extended period of time, instead of numerous doses, have been obvious to the Pharmaceutical industry for some time. The desire to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy.
of the drug for its intended use. Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of Pharmaceutical technology.

Various drug delivery techniques have been developed to sustain the release of drugs, including triple-layered tablets (Geomatrix® technology) and osmotic pumps with laser drilled holes (OROS® technology). These technologies are intricate and relatively expensive to manufacture. Thus, there remains an interest in developing novel formulations that allow for sustained release of drugs using readily available, inexpensive excipients.

Extended release (ER) dosage form is one of the drug products categorized under the term modified release dosage forms (FDA, 1997). It refers to products, which are formulated to make the drug available over an extended period after ingestion; thus, it allows a reduction in dosing frequency compared to a conventional type i.e. immediate release (IR) dosage form. Several advantages of ER products over IR ones have long been recognized. ER solid oral dosage forms can be classified into two broad groups:

1. Single unit dosage forms (e.g. tablets) and
2. Multiple unit dosage forms or multiparticulate pellet systems.

The systems can be further subdivided into two concepts regarding to the design of dosage forms

1) Matrix systems and
2) Reservoir systems.

Advantages:

Extended release products having many advantages.

1. The extended release formulations may maintain therapeutic concentrations over prolonged periods.
2. The use of extended release formulations avoids the high blood concentration.
3. Extended release formulations have the potential to improve the patient compliance.
4. Reduce the toxicity by slowing drug absorption.
5. Increase the stability by protecting the drug from hydrolysis or other derivative changes in gastrointestinal tract.
6. Minimize the local and systemic side effects.
7. Improvement in treatment efficacy.
8. Minimize drug accumulation with chronic dosing.
9. Usage of less total drug.
10. Improvement the bioavailability of some drugs.
11. Improvement of the ability to provide special effects.

   Ex: Morning relief of arthritis through bed time dosing.

Disadvantages:
2. Dose dumping: Dose dumping may occur with faulty formulations.
3. Need for additional patient education: Patients may need substantial additional information as to the proper use of sustained release products e.g. “Do not crush or chew the dosage unit. Tablet residue may appear in the stools”. In some instances, patients must be started on an immediate release product and then switched over to the extended release products.
4. Possible reduction in systemic availability:
   Reduced systemic availability has been shown for some Sustained release formulations of Theophylline, Procainamide and Vitamin combinations.
5. The release rates are affected by various factors such as, food and the rate transit through the gut.
6. Some differences in the release rate from one dose to another dose but these have been minimized by modern formulations.
7. Extended release formulation contains a higher drug load and thus any loss of integrity of the release characteristics of the dosage form.
8. The larger size of extended release products may cause difficulties in ingestion or transit through gut.

TERMINOLOGY:
Modified release delivery systems may be divided conveniently in to four categories.
A) Delayed release
B) Sustained release
   i. Controlled release
   ii. Extended release
C) Site specific targeting
D) Receptor targeting

A) Delayed Release:
These systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release systems include repeat action tablets and capsules and enteric-coated tablets where timed release is achieved by a barrier coating.

B) Sustained release:
During the last two decades there has been remarkable increase in interest in sustained release drug delivery system. This has been due to various factor viz. the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. Now-a-days the technology of sustained release is also being applied to veterinary products. These systems also provide a slow release of drug over an extended period of time and also can provide some control, whether this be of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells.

1) Controlled Release:
These systems include any drug delivery system that achieves slow release of drug over an extended period of time.

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

C) Site specific targeting:
These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.

D) Receptor targeting:
These systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue. Site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be sustained drug delivery systems.\cite{5,6}

**DRUGS, WHICH ARE SUITABLE FOR, EXTENDED RELEASE FORMULATION:**

I. Physiochemical Properties of the drug:

a) Aqueous Solubility:
Lower limit solubility for such product is reported to be 0.1 mg/ml. As the drug must be in solution form before absorption, drug having low aqueous solubility usually suffers oral bioavailability problem due to limited GI transit time of undissolved drug and limited solubility at absorption site. So these types of drug are undesirable.

Drug having extreme aqueous solubility are undesirable for ER because, it is too difficult to control release of drug from the dosage form. Physiological pH dependent solubility i.e. variation in solubility at different GI pH are undesirable (e.g. Aspirin, which is less soluble in stomach, but more soluble in intestine) as it will yield variation in dissolution rate. A drug with good aqueous solubility, pH independent solubility is desirable for oral new drug delivery system.

b) Partition Co-efficient:
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 co-efficient 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
co-efficient at which optimum activity is observed is approximately 1000:1 in 1-octano/water system.

c) Drug Stability in-vivo:
As most of ER Drug delivery system is designing to release drug over the length of the GIT, hence drug should be stable in GI environment. So drug, which is unstable, can’t be formulated as oral ER drug delivery system, because of bioavailability problem.

  e.g.- Nitroglycerine.

d) Protein Binding:
The Pharmacological response of drug depends on unbound drug concentration drug rather than total concentration and all drug bound to some extent to plasma and or tissue proteins. Proteins binding of drug play 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.

  e) Drug pKa & Ionization at Physiological pH:
As we know only unionized drug are absorbed and permeation of ionized drug is negligible, since its rate of absorption 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 – 7.5 and pKa range for basic drug whose ionization is pH sensitive is around 7.0-11.0 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.

  f) Mechanisms and Sites of Absorption:
Drug absorption by carrier mediated transport and those absorbed through a window are poor candidate for oral ER drug delivery system e.g. – several B vitamins. Drugs absorbed by passive diffusion, pore transport and through over the entire length of GIT are suitable candidates for oral ER drug delivery system.

g) Molecular Size and diffusivity:
With large molecular size are poor candidate for oral ER drug delivery system because it 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 i.e.-100 to 400 Dalton, through flexible polymer range from 10-6 to 10-9 cm²/sec. For drugs having molecular weight > 500 Daltons the diffusion co-efficient in many polymers are very less i.e. less than 10-12 cm²/sec. Drugs is very difficult to control release rate of medicament from dosage form e.g. proteins and peptides.

h) Dose Size:
If a product has dose size >0.5g it is a poor candidate for oral ER drug delivery system, because increase in bulk of the drug, thus increases the volume of the product.

II. Biological Properties of Drug:

a) Absorption:
For oral ER drug delivery system the rate of drug absorption (ka) should be more -API than that of the rate of drug release (kr) from the dosage form i.e. kr << ka. Drug that are slowly absorbed or absorbed with a variable absorption rate of elimination of drug are poor candidate for oral ER drug delivery system. 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:
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.

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 of first-pass effect is poor candidate for ER delivery, since it could be difficult to maintain constant blood level e.g. levodopa, nitroglycerine.

d) Half-life of Drug:
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 < 2hrs the system will require unacceptably large rate and large dose and biological half-life >8hours formulation of such drug into oral ER drug delivery system is unnecessary.
e) Margin of safety: As we know, larger the value of therapeutic index safer is the drug. Drugs with less therapeutic index usually a poor candidate 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 size and dose. But some drugs pharmacological activity 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 by zero kinetic process then such drugs are poor candidate for oral ER delivery system, it should be first order kinetics. [7], [8], [9]

CLASSIFICATION OF DRUG DELIVERY SYSTEMS (DDS)

1. Diffusion-Controlled Drug Delivery System
   1. Oral
   2. Matrix-type systems
   3. Hydrophobic matrix systems
   4. Hydrophilic matrix systems
   5. Reservoir-type systems
   6. Transdermal
   7. Drug in adhesive systems
   8. Monolithic adhesive systems
   9. Multilaminate adhesive systems
   10. Inert matrix systems
   11. Semisolid matrix systems
   12. Reservoir matrix systems
   13. Other diffusion controlled systems
   14. Intrauterine devices and intravaginal rings
   15. Intraocular inserts
   16. Subcutaneous implants

2. Dissolution-Controlled Drug Delivery System
1. Based on dissolution-controlled release of solid particles
2. Based on dissolution-controlled release coated technologies
3. Based on dissolution-controlled release matrix technologies

3. Osmotic Controlled Drug Delivery System
   a) Osmotic delivery systems for solids
      Type I: Single compartment
      Type II: Multiple compartments
   b) Osmotic delivery systems for liquids

4. Biodegradable Polymeric Drug Delivery System
   1. Microparticles
   2. Nanoparticles
   3. Implants

5. Ligand-Based Targeting Drug Delivery System

6. Programmable Drug Delivery System
   1. Pulsatile systems
   2. Feedback-controlled systems

7. Stimulus Responsive
   1. Physically modulated: Temperature
   2. Chemically modulated: pH dependent \[^{[10]}\]

1] Diffusion Sustained System

Basically diffusion process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration. The flux of the drug \( J \) (in amount / area - time), across a membrane in the direction of decreasing concentration is given by Fick’s law.

\[
J = - D \frac{dc}{dx}.
\]

\( D = \) diffusion coefficient in area/ time
\( \frac{dc}{dx} = \) change of concentration ‘c’ with distance ‘x’

In common form, when a water insoluble membrane encloses a core of drug, it must diffuse through the membrane.

The drug release rate \( \frac{dm}{dt} \) is given by
\[
\frac{dm}{dt} = ADK \frac{C}{L}
\]

Where;

\( A \) = Area.

\( K \) = Partition coefficient of drug between the membrane and drug core.

\( L \) = Diffusion path length (i.e. thickness of coat).

\( \Delta c \) = Concentration difference across the membrane.\,[11],[12] [13]

2) Dissolution controlled release systems:

In dissolution controlled extended release systems the rate of dissolution in the gastrointestinal juices of the drug or another ingredients is the release controlling process. Sparingly water-soluble drug can form a preparation of a dissolution controlled extended release type. Reduced drug solubility can be accomplished by preparing poorly soluble salts or derivatives of the drug. An alternative means to achieve extended release based on dissolution is to incorporate the drug in a slowly dissolving carrier.

The rate of dissolution (\( \frac{dm}{dt} \)) can be approximated by equation,

\[
\frac{dm}{dt} = ADS/h
\]

Where,

\( S \) = Aqueous solubility of the drug.

\( A \) = Surface area of the dissolving particle or tablet.

\( D \) = Diffusivity of the drug.

\( h \) = Thickness of the boundary layer.\,[14],[15]

3) Methods using osmotic pressure: A semi permeable membrane is placed around a tablet, particle or drug solution that allows transport of water into the tablet with eventual pumping of drug solution out of the tablet through a small delivery aperture in tablet coating.

Two types of somatically sustained systems are:-

a. Osmotic delivery systems for solids

Type I: Single compartment

Type II: Multiple compartment

b. Osmotic delivery systems for liquids\,[16],[17]
4) pH-Independent formulations:
The gastrointestinal tract present some unusual features for the oral route of drug administration with relatively brief transit time through the gastrointestinal tract, which constraint the length of prolongation, further the chemical environment throughout the length of gastrointestinal tract is constraint on dosage form design. Since most drugs are either weak acids or weak bases, the release from sustained release formulations is pH dependent. However, buffers such as salts of amino acids, citric acid, ophthalmic acid phosphoric acid or tartaric acid can be added to the formulation, to help to maintain a constant pH thereby rendering pH independent drug release. A buffered sustained release formulation is prepared by mixing a basic or acidic drug with one or more buffering agent, granulating with appropriate pharmaceutical excipients and coating with gastrointestinal fluid permeable film forming polymer. When gastrointestinal fluid permeates through the membrane, the buffering agents adjust the fluid inside to suitable constant pH. There by rendering a constant rate of drug released.\[17]\[18]

REFERENCES


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