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A REVIEW ON AN EXTENDED RELEASE DRUG DELIVERY SYSTEM

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ABSTRACT:

In recent years pharmaceutical industries are focusing on the development of extended release dosage forms due to its various advantages. The drugs which are having the shorter duration of therapeutic action (half-life) and a multiple dosing frequency, are suitable for the transform into extended release dosage forms. The extended release dosage form is a type of dosage forms which can reduce the dosing frequency of dosage forms upto once in a day. This formulations can minimize the side effects of low systemic concentrations and high systemic concentrations in systemic circulation. The extended release Dosage forms can regulate the drug release over a specified time period. The extended release dosage form can reduce low dose side effects. The extended release formulations can also improve the patient compliance by reducing the dosing frequency and dosing strength. Also it can improve the bioavailability of the drugs. Developing oral extended release tablets for drug at constant release rate has always been a challenge to the pharmaceutical technologist. There are various physicochemical and biological properties which affect the extended release dosage form. This article discusses the recent literature regarding development and design and fabrication of extended release system and in-vitro performance of extended release formulation.

KEYWORDS: Extended Release Dosage form, Oral Drug Delivery System, Design of Extended Release Dosage forms.

Introduction:

Extended release dosage forms are the dosage forms which are used for the longer duration of therapeutic effect of particular drug. Means this are specifically used for the longer duration of action of dosage forms upto 6-12 hrs. And it can be extended upto 24 hrs. of the therapeutic effect. In this type of dosage forms we can control the release of the API from the dosage form upto desired time.[(01)] The design of oral extended release delivery systems is subjected to several interrelated variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug. Matrix tablets are considered to be the commercially feasible extended action dosage forms that involve the least processing variables, utilize the conventional facilities and accommodate large doses of drug. These remains an interest in developing novel formulations that allow for extended the drug release using readily available, inexpensive excipient by matrix based formulation.[(2,3)] During the last two decades there has been remarkable increase in interest in extended release drug delivery system. This has been due to various factors like the prohibitive cost of developing new drug entities, expiration of existing international patients, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. The basic

goal is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage form is an important element to accomplish this goal.[4,5] Extended release, extended action, prolonged action, controlled release, extended action, timed release and depot dosage form are term used to identify drug delivery system that are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. In the case of oral extended released dosage form, an effect is for several hours depending upon residence time of formulation in the GIT. Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges.[6,7,8]

Advantages:

Advantages of extended release drug delivery system:

1. The concentration of the API during the longer duration of time is maintained in this type of dosage forms.
2. The use of extended release formulations avoids the high blood concentration.
3. The patients are convenient for the administration frequency of the dosage forms.
4. Due to the lower absorbance in the systemic circulation the side effects can be reduced.
5. Increase the stability by protecting the drug from hydrolysis or other degradative changes in gastrointestinal tract.
6. It can minimize the local and systemic side effects.
7. Improvement in treatment efficacy.
8. It can minimize drug accumulation with chronic dosing.
9. Minimum drug usage.
10. It can improve the bioavailability of some drugs. Ex: Divalproex sodium
11. Improvement of the ability to provide special effects.

Ex: Morning relief of arthritis through bed time dosing.

Disadvantages:

1. This kind of dosage forms can be costly to manufacture.
2. The drug release can be affected by some factors.
3. Extended release formulation contains a higher drug load and thus any loss of integrity affects the release characteristics of the dosage form.
4. The larger size of extended release products may cause difficulties in ingestion or transit through gut.
5. Reduced potential for dosage adjustment.

For extended release formulation some drug properties has be followed : [9,10]

A) Physiochemical Properties of the drug:

1. Partition co-efficient: (1000:1 octanol:water system).
2. Aqueous solubility: (>0.1mg/ml).
3. Drug stability *in vivo*: (High enough, so drug remain stable during release from system).
4. Protein binding: (Drug with high protein binding will not required release modification).
5. Drug pKa and ionization at physiological pH: (pKa for acidic Drug= 3.0 - 7.5, pKa for Basic Drug = 7.0 - 11.0).
6. Mechanisms and sites of absorption: (Mechanism of absorption should not be active type and absorption window should not be narrow).
7. Molecular size and diffusivity: (Molecule size should be small (100-400 D so it can be easily diffused through polymer matrix).
8. Dose size: (<300mg).

B) Biological Properties of Drug

1. Distribution: (Drug. with large volume of distribution is not suitable).
2. Metabolism: (Drug. should be metabolized with intermediate speed).

3. Half-life of drug: (2 - 8 hrs).
4. Margin of safety: (High enough so dose dumping does not cause any serious side effect).
5. Plasma concentration response relationship: (Drug. having linear relationship is better candidate).

Drug selection for oral extended release drug delivery systems:
The biopharmaceutical evaluation of a drug for potential use in controlled release drug delivery system requires knowledge on the absorption mechanism of the drug form the G.I. Tract, the general absorbability, the drug's molecular weight, solubility at different pH and apparent partition coefficient.[11,12,13]

Table-1 Physicochemical Parameters for drug selection

Sr. No.	Parameter	Preferred Value
1	Molecular weight/ size	500 Daltons
2	Solubility	> 0.1mg/ml for pH 1 to pH 7.8
3	Apparent partition coefficient	High
4	Absorption mechanism	Diffusion
5	General Absorbability	From all GI segments
6	Release	Should not be influenced by pH and enzymes

For the pharmacokinetic evaluation, we need a proper knowledge on a drug's elimination half- life, total clearance, absolute bioavailability, possible first- pass effect, and the desired steady concentrations for peak and trough.[12]

Table 2: Pharmacokinetic parameters for drug selection

Sr. No.	Parameter	Preferred Value
1	Elimination Half life	Preferably between 2 and 8 h
2	Total clearance	Should not be dose dependent
3	Elimination rate constant	Required for design
4	Apparent volume of distribution Vd	The larger Vd and MEC, the larger will be the required dose size.
5	Absolute Bioavailability	Should be 75% or more
6	Intrinsic absorption rate	Must be greater than release rate
7	Therapeutic concentration Css av	The lower Css av and smaller Vd, the loss among of drug required
8	Toxic concentration	Apart the values of MTC and MEC, safer the dosage form. Also suitable for drugs with very short half-life.

Terminology:
Modified Release dosage forms can be classified as follows:
A. Delayed release
B. Extended release
- Sustained release
- Controlled release
- Prolonged release

C. Site-specific and receptor targeting.
- Organ targeting
- Cellular targeting
- Sub cellular targeting[14]

Delayed release:
A delayed-release dosage form is designed to release the drug at a time other than promptly after administration. The delay may be time based or based on the influence of environmental conditions, like gastrointestinal pH.[15]

Extended release:

The U.S. Food and Drug Administration (FDA) defines an "extended-release dosage form as 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". [15]

Sustained release:

Sustained release indicates an initial release of drug sufficient to provide a therapeutic dose soon after administration, and then a gradual release over an extended period. [15]

Controlled release:

Dosage forms release drug at a constant rate and provide plasma concentrations that remain invariant with time. [15]

Prolonged release:

Prolonged release indicates that the drug is provided for absorption over a longer period of time than from a conventional dosage form. However, there is an implication that onset is delayed because of an overall slower release rate from the dosage form. [15]

Site-specific and receptor targeting:

Targeted release describes drug release directed toward isolating or concentrating a drug in a body region, tissue, or site for absorption or for drug action. [16]

Release rate and dose consideration:

The dosage forms can be considered to release their active drugs into an absorption pool immediately. Conventional dosage forms include solutions, capsules, tablets, emulsions, etc.

Extended (zero-order) drug release has been attempted to be achieved with various classes of extended drug delivery system:

1. Diffusion extended system.
   a) Reservoir type.
   b) Matrix type.
2. Dissolution extended system.
   a) Reservoir type.
   b) Matrix type.
3. Methods using Ion-exchange.
4. Methods using osmotic pressure.
5. pH independent formulations.
6. Altered density formulations.

Diffusion Extended 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.

$$J = - D \, dc/dx.$$

Where,

D = diffusion coefficient in area/ time

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 dm/ dt is given by.

$$dm/dt = ADK\Delta C/L$$

Where,

A = Area.

K = Partition coefficient of drug between the membrane and drug core.
L= Diffusion path length (i.e. thickness of coat).
Δc= Concentration difference across the membrane.[17]

Reservoir Type
In the system, a water insoluble polymeric material encases 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.

Description:
Drug core surrounded by polymer membrane which controls release rate.

Advantages:
Zero order delivery is possible, release rates variable with polymer type.

Disadvantages:
System must be physically removed from implant sites. Difficult to deliver high molecular weight compound, generally increased cost per dosage unit, potential toxicity if system fails.[18]

Matrix Type
A solid drug is dispersed in an insoluble matrix. And the rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution.
Higuchi has derived the appropriate equation for drug release for this system

$$Q = D\varepsilon/ T [2 A - \varepsilon Cs] Cst^{1/2}$$

Where;
Q = Weight in gms of drug released per unit area of surface at time t.
D = Diffusion coefficient of drug in the release medium.
ε = Porosity of the matrix.
Cs = Solubility of drug in release medium.
T= Tortuosity of the matrix.
A = Concentration of drug in the tablet, as gm/ ml.[19]

Description:
Homogenous dispersion of solid drug in a polymer mixture.

Advantages:
Easier to produce than reservoir or encapsulated devices, can deliver high molecular weight compounds.

Disadvantages:
Cannot provide zero order release, removal of remaining matrix is necessary for implanted system. Diffusional mechanism is the system where a partially soluble membrane encloses a drug core. Dissolution of part of membrane allows for diffusion of the constrained drug through pores in the polymer coat. The release rate can be given by following equation.

$$\text{Release rate} = AD / L = [C1 - C2]$$

Where;
A = Area.
D = Diffusion coefficient.
C1 = Drug concentration in the core.

C2 = Drug concentration in the surrounding medium.
L = Diffusional path length.

Thus diffusion extended products are based on two approaches the first approach entails placement of the drug in an insoluble matrix of some sort. The eluting medium penetrates the matrix and drug diffuses out of the matrix to the surrounding pool for ultimate absorption. The second approach involves enclosing the drug particle with a polymer coat. In this case the portion of the drug which has dissolved in the polymer coat diffuses through an unstirred film of liquid into the surrounding fluid.[20]

Dissolution Extended Systems:
A drug with a slow dissolution rate is inherently extended and for those drugs with high water solubility, one can decrease dissolution through appropriate salt or derivative formation. These systems are most commonly employed in the production of enteric coated dosage forms. To protect the stomach from the effects of drugs such as Aspirin, a coating that dissolves in natural or alkaline media is used. This inhibits release of drug from the device until it reaches the higher pH of the intestine. In most cases, enteric coated dosage forms are not truly sustaining in nature, but serve as a useful function in directing release of the drug to a special site.

Reservoir Type:
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 as a pulsed delivery can be achieved. If the outer layer is quickly releasing bolus dose of the drug, initial levels of the drug in the body can be quickly established with pulsed intervals. Although this is not a true extended release system, the biological effects can be similar. An alternative method is to administer the drug as group of beads that have coating of different thickness. The maintenance of drug levels at late times will be achieved from those with thicker coating.

Matrix Type:
These are common type of dissolution extended dosage form. It can be either a drug impregnated sphere or a drug impregnated tablet, which will be subjected to slow erosion. Two types of dissolution extended pulsed delivery systems.

a) Single bead type device with alternating drug and rate-controlling layer.
b) Beads containing drug with differing thickness of dissolving coats. Amongst extended release formulations, hydrophilic matrix technology is the most widely used drug delivery system due to following advantages.
c) Provide desired release profiles for a wide therapeutic drug category, dose and solubility.
d) Simple and cost effective manufacturing using existing tableting unit operation equipment.
e) Broad regulatory and patient acceptance.
f) Ease of drug release modulation through level and choice of polymeric systems and function coatings.[21]

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 osmotically extended systems are:-
Type A contains an osmotic core with drug.
Type B contains the drug in flexible bag with osmotic core surrounding.[22]

pH– Independent Formulations
The gastrointestinal tracts present some unusual features for the oral route of drug administration with relatively brief transit time through the gastrointestinal tract. Since most drugs are either weak acids or weak bases, the release from extended release formulations is pH dependent. A buffered extended 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 thereby rendering a constant rate of drug release.[23]

Altered Density Formulations:
It is reasonable to expect that unless a delivery system remains in the vicinity of the absorption site until most, if not all of its drug content is released. Several approaches have been developed to prolong the residence time of drug delivery system in the GI.

High Density Approach:
In this approach the density of the pellets must exceed that of normal stomach content and should therefore be at least 1-4gm/cm3.

Low Density Approach:
Globular shells which have an apparent density lower than that of gastric fluid can be used as a carrier of drug for extended release purpose. [24]

Types of Polymers Used in Preparations of Extended Release Dosages:
Hydrogels

- Polyhydroxyethylmethylacrylate (PHEMA)
- Cross-linked polyvinyl alcohol (PVA)
- Cross-linked polyvinylpyrrolidone (PVP)
- Polyethyleneoxide (PEO)
- Polyacrylamide (PA)

Soluble Polymers

- Polyethyleneglycol (PEG)
- Polyvinyl alcohol (PVA)
- Polyvinylpyrrolidone (PVP)
- Hydroxypropylmethylcellulose (HPMC)

Biodegradable Polymers

- Polylactic acid (PLA)
- Polyglycolic acid (PGA)
- Polycaprolactone (PLA)
- Polyanhydrides
- Polyorthoesters

Non-Biodegradable Polymers

- Polyethylene vinyl acetate (PVA)
- Polydimethylsiloxane (PDS)
- Polyetherurethane (PEU)
- Polyvinyl chloride (PVC)
- Cellulose acetate (CA)

Mucoadhesive Polymers

- Polycarbophil
- Sodium carboxymethyl cellulose
- Polyacrilic acid
- Tragacanth
- Methyl cellulose
- Pectin
- Natural gums
- Xanthan gum

- Guar gum
- Karaya gum[25]

***In vitro* performance of oral ER formulations:**

Dissolution testing

Dissolution testing is an official evaluation method for solid oral dosage forms. Several Pharmacopoeial standard dissolution media and apparatuses are well documented. The method was initially developed for IR solid oral dosage form and then extended to modified release solid oral dosage forms as well as other novel/special dosage forms.[26]

The application of dissolution testing was conventionally known as a tool for ensuring batch to batch consistency. It is also an essential mean for deciding on a candidate formulation in product development. The tests should be sensitive enough to demonstrate any small variable in manufacturing of a product as well as the type and level of excipients used. Therefore, it is possible that an over discriminatory test, although in vivo irrelevance might be suitable for these purposes.[27]

The value of dissolution test was later shifted to bioavailability prediction. Challenges in selecting the test conditions which reflect *in vivo* drug release have been of interested to many researchers.[28,29] The tests may not be Pharmacopoeial standard, they should, however, be sensitive, reliable and discriminatory with regard to the *in vivo* drug release characteristics.[27,30] The ultimate goal of the dissolution test is to predict the *in vivo* performance of products from *in vitro* test by a proper correlation, so called *in vitro/in vivo* correlation (IVIVC).[31]

In certain cases, dissolution tests can be used for providing bio-waivers for lower strengths of a product once the higher strength is approved. The waivers can also be granted to some categories of postapproval changes, based on the appropriate bioavailability/ bioequivalence test procedure. [32,33]

Bio-relevant dissolution testing:

A) Physiological properties of the gastrointestinal tract

Physiological conditions vary wildly along the gastrointestinal (GI) tract. Not to mention inter subject variability, various factors within an individual, such as disease states, physical activity level, stress level and food ingestion, considerably influence the GI conditions.[34] The effects of this variability on the performance of ER systems are even more pronounced given that the dosage forms are designed to remain in the GI tract for the substantially longer period of time and transit through various conditions compared with IR systems. Inhomogeneous distribution of fluid in the small and large intestine is one of many factors that potentially contribute to the variability of drug release and absorption.

Gastric emptying time of a solid dosage form changes dramatically with the effect of co administered food. One out of twelve capsules taken three hrs before meal and all twelve capsules taken immediately after meal remained in the stomach for at least one hrs, while in the fasted state, the majority of the capsules had left the stomach within one hrs.[35] The total time for a dosage form to empty from the stomach in the fasted state depends on the size of the dosage form, i.e. the longer time is needed for the larger, as well as the motility cycle of the stomach which is two hrs in average. The emptying for most non-disintegrating solid dosage forms with larger than one millimetre diameter occurred in the late phase II or phase III of the cycle. Co-administered food even further altered the emptying time depending on the calorie content. A delay for several hrs to empty a relatively large solid dosage form can also occur as the food will be first cleared from the stomach and return to the normal gastric motility cycle in the fasted state. The dosage form is then emptied under the phase III activity.[34] Unlike the gastric emptying, transit time in the small intestine in both fasted and fed states are not significantly different, regardless of the type of dosage forms.[34,36] The pH and osmolality of the stomach and the upper small intestine is greatly influence by coadministered food. In healthy humans, their values for the stomach increased from pH 1.7/ 140 mOsm kg-1 up to pH 6.4/559 mOsm kg-1 within thirty minutes postprandial and then gradually decreased to pH 2.7/217 mOsm kg-1 after 3.5 hrs. Composition and quantity of the meal significantly affected the time require to re-establish the fasting gastric pH more than did the pH value of the meal.

Conclusion:

As per above discussion we can conclude that these oral extended release dosage forms can be useful and convenient to the patients. As it can reduce the dosing frequency upto once a day so that the patient compliance can be improved in this manner. Also the therapeutic efficacy can also be improvised by reducing the rate of absorption of the drug molecule. Also on the contrary of price, these dosage forms can be chip as compared to conventional dosage forms.

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