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EXTENDED RELEASE ORAL DRUG DELIVERY SYSTEM – AN UPDATED OVERVIEW

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ABSTRACT

Extended release formulations, make the drug available over extended time period administration. Extended release will decrease the side effects of the drug by preventing the fluctuation of therapeutic concentration of the drug in the body. As Incorporating the dose for 24hrs into one tablet or capsule from which the drug is released slowly. These formulations have the potential to improve the patient compliance, reduce the toxicity by slowing drug absorption, and minimize drug accumulation with chronic dosing. Having improvement in bioavailability of some drugs. Usage of the less total drug and reduce the dose frequency. The article provides information about the overview of the design of the extended release system and different types of extended release system.

Key words: Extended release oral drug delivery system,Design,Therapeutic concentration.

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 the therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose [1].

Extended release formulations are two types:

1) Sustained release (SR)
2) Controllled release (CR), Which is based on drug release kinetics mechanism.

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. Second, it should deliver the active entity directly to the site of action minimizing the side effects.

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

Advantages of Extended Release Delivery System.

- The extended release formulations reduce dosing frequency of drugs.
- The extended release formulations may maintain therapeutic concentrations.
- Reduce the toxicity by slowing drug absorption.
- The use of these formulations avoids higher blood concentration.
- Extended release formulations have the potential to improve the patient compliance and convenience.
- Minimize the local and systemic side effects.
- Increase the stability by protecting the drug from hydrolysis or other degradative changes in the

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gastrointestinal tract.

- Improvement in treatment efficacy.
- Minimize drug accumulation with chronic dosing.
- Improve the bioavailability of some drugs.
- Usage of less total drug.

Disadvantages of Extended Release Delivery System.

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

Rationale of Extended Drug Delivery.

The main objective to formulate an API in an extended drug delivery system is related to its pharmacokinetics parameters. An appropriate formulation can make the absorption, distribution, metabolism and elimination (ADME) profile of a drug much more favorable. This change of the ADME can have a profound impact on many aspects of the clinical use of the drug from patient compliance and convenience to its very efficacy, tolerance and safety parameters [4].

Fig.1 indicates characteristic representation of plasma concentratin of a conventional immediate release dosage form (IR),a sustain release dosage form(SR) , and a idealized zero order controlled release dosage form

MECHANISM OF DRUG RELEASE FROM MATRIX DEVICES

Dissolution controlled release

Sustained release oral products employing dissolution at the time limiting step were simple to prepare. If a drug has a rapid rate of dissolution it is possible to incorporate it into a tablet with a carrier that has a slow rate of dissolution. In the

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

$$dc/dt = DA / h (Cs - C_b) \text{ ---------- (1)}$$

Where *D* is the diffusion coefficient of the solute, *A* is the surface area of the solid undergoing dissolution, h is the thickness of the diffusion layer, *C*s is the concentration of the solvent at saturation and *C*b is the concentration of the drug in the bulk solution phase at time *t*.

Dissolution control formulations are categories as

Encapsulation dissolution control

Matrix dissolution control

Encapsulation dissolution control

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

Matrix dissolution control

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

Diffusion controlled release

These systems are of two types;

Encapsulation diffusion control

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

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The rate of drug release by a diffusion mechanism given by the Ficks first law.

$$dm/dt = ADK / I (\Delta c) \text{ ---------- (2)}$$

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Where, A = Area of the membrane
D = Diffusion coefficient
K = The partition coefficient of the drug between the membrane and the drug cure
I = The diffusional path length
Δc = The concentration difference across the membrane.
An important parameter in the above eq. (2) Is the partition coefficient, which is defined as the concentration of the drug in the membrane over the concentration if the drug in core.

Matrix diffusion control

In this system, a solid drug is dispersed in lipophillic or a hydrophilic polymer matrix and the rate of release of drug depends on the rate of drug diffusion and not on the rate of solid dissolution [5].

MATERIALS USE AS RELEASE RETARDANTS IN MATRIX TABLET FORMULATION

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

Water insoluble inert materials

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

Insoluble, erodable materials

e.g. Sterile alcohol, stearic acid, polyethylene glycol, carnauba wax, castor wax, polyethylene glycol monosterate, triglycerides.

Hydrophillic materials

E.g. Hydroxy propyl methylcellulose, sodium CMC, methylcellulose, hydroxy ethyl cellulose. Natural gums: Galactomannose (guargum), chitosan, gum acacia, locust bean gum, sodium alginate, karaya gum, pectins, xanthan gum [6].

Natural polymers

Eg. Ispaghula husk, tamarind seed polymer [7]

Biopharmaceutical aspects of route of administration

Oral and parental (i.m.) routes followed by transdermal are most popular. Routes of minor importance in sustained drug delivery are buccal/sublingual, nasal, rectal, ocular and pulmonary [8-12]. A detailed knowledge of ADME characteristics of drug is essential in the design of sustained release product. An optimum range of given pharmacokinetic parameter of a drug is necessary beyond which controlled/sustained delivery is difficult [13-17] (Tables 1 and 2).

Sustained-release oral drug product forms can be grouped according to their release mechanism.

Coated beads or granules produce a blood level profile similar to that obtained with multiple dosing.

A solution of the drug substance in a no aqueous solvent (e.g., alcohol) is coated on small, inert beads, or granules, made of a combination of sugar and starch. When the drug dose is large, the starting granules may be composed of the drug itself.

Some of the granules are left uncoated to provide an immediate release of the drug.

Coats of a lipid material (e.g., beeswax) or a cellulosic material (e.g., ethyl cellulose) is applied to the remaining granules. Some granules receive few coats, and some receive many. The various coating thicknesses produce a sustained-release effect.

Microencapsulation is a process by which solids, liquids, or gases are encased in microscopic capsules. Thin coatings of a wall material are formed around the substance to be encapsulated.

Coacervation and phase separation method is the most common method of microencapsulation. It occurs when a hydrophilic substance is added to colloidal drug dispersion and causes layering and the formation of microcapsules.

Film-forming substances that are used as the coating material include a variety of natural and synthetic polymers. These materials include shellacs, waxes, gelatin, starches, cellulose acetate phthalate, and ethyl cellulose. After the coating material dissolves, all of the drug inside the microcapsule is immediately available for dissolution and absorption. The thickness of the wall can vary from 1 to 200 mm, depending on the amount of coating material used (3% to 30% of total weight).

Matrix tablets use insoluble plastics (e.g., polyethylene, polyvinyl acetate, polymethacrylate), hydrophilic polymers (e.g., methylcellulose, hydroxyl propyl methylcellulose), or fatty compounds (e.g., various waxes, glyceryl tristearate). Examples include Gradumet (Abbott) and Dospan (Aventis).

- The most common method of preparation is mixing of the drug with the matrix material followed by compression of the material into tablets.
- The primary dose, or the portion of the drug to be released immediately, is placed on the tablet as a layer, or coat. The rest of the dose is released slowly from the matrix.

Osmotic systems include the Oros system (Alza), which is an oral osmotic pump composed of a core tablet and a semi permeable coating that has a small hole (0.4 mm in diameter) for drug exit. The hole is produced by a laser beam. Examples include Glucotrol XL (glipizide extended-release tablets, Pfi zer) and Procardia XL (nifedipine extended-release tablets, Pfizer)

- This system requires only osmotic pressure to be effective. It is essentially independent of pH changes in the environment.
- The drug-release rate can be changed by changing the tablet surface area, the nature of the membrane, or the diameter of the drug-release aperture.

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Ion-exchange resins can be complexed with drugs by passage of a cationic drug solution through a column that contains the resin. The drug is complexed to the resin by replacement of hydrogen atoms. Examples include Ionamin capsules and the Penn kinetic system, which incorporates a polymer barrier coating and bead technology in addition to the ion-exchange mechanism.

- After the components are complexed, the resin–drug complex is washed and tableted, encapsulated, or suspended in an aqueous vehicle.
- Release of the drug from the complex depends on the ionic environment within the gastrointestinal tract and on the properties of the resin. Usually, release is greater in the highly acidic stomach than in the less acidic small intestine.

Complex formation is used for certain drug substances that combine chemically with other agents. For example, hydroxypropyl - cyclodextrin forms a chemical complex that can be only slowly soluble from body fluids, depending on the pH of the environment. Tannic acid(i.e., tannates) complexes with the amino groups of weak bases dissolve at a slow rate in the gastrointestinal tract, thereby providing for a prolonged release of the drug. Examples of the latter include brompheniramine tannate and chlorpheniramine /phenylephrine tannates [15].

Table 1. Physicochemical parameters for drug selection

Parameter	**Criteria**
Molecular size	Less than 600 Daltons
Aqueous solubility	More than 0.1 mg/ml
Partition coefficient	1-2
Dissociation constant	Acidic drugs, pka >2.5 Basic drugs, pka <11.0
Absorption mechanism	Passive
Stability of GI	Stable at both gastric and intestinal pH
Ionization at physiological pH	Not more than 95%

Table 2. Pharmacokinetic parameters for drug selection

Parameters	**Comment**
Elimination Half-life	Between 2-6 hrs
Absolute bioavailability	> 75% or more
Absorption rate constant (Ka)	High
Metabolism Rate	Not too High
Total clearance	Should not depend on dose
Therapeutic concentration (Css)	Lower Css and small Vd

Fig 1. Plasma Concentration Verses Time

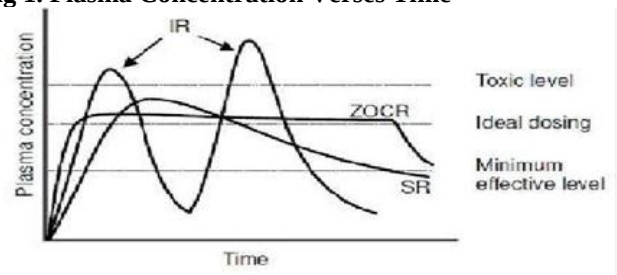


Fig 2. Schematic representation of dissolution controlled release systems
Matrix system, and (b) coated/encapsulated system

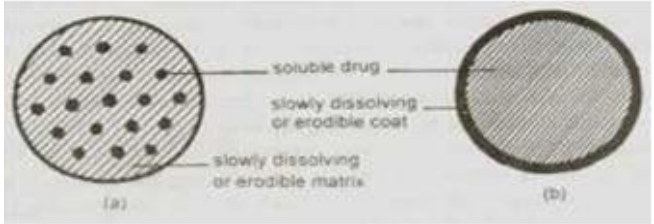


Fig 3. Drug release of diffusion across the insoluble membrane of reservoir device

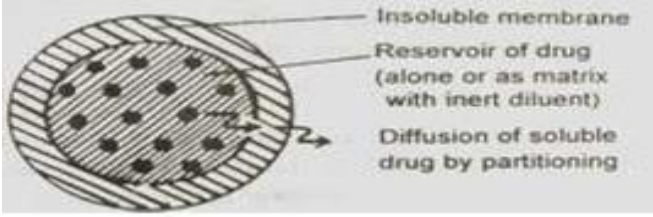
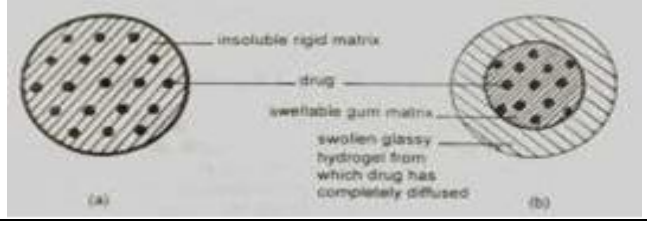


Fig 4. Diffusion controlled devices (a) rigid matrix, and (b) swellable matrix.



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CONCLUSION

Extended release pharmaceutical products became a very useful tool in medical practice, offering a wide range of actual and perceived advantages to the patients. Number of drugs are now marketed in a variety of different extended release products. It concludes that the extended release dosage form are a drug delivery system which by virtue of formulation and product design, provide drug release in a modified form distinct from that of the conventional dosage forms. Drug release can either be delayed or extended in nature. It is an effective tool for drugs that are not inherently long lasting and require multiple daily dosing to achieve the desired therapeutic effects; when compared to conventional dosage form it provides improved patient compliance. Extended release drug delivery system is the preferred dosage form for the drugs having short half-life, so as to maintain the drug plasma level in therapeutic index for a prolonged period of time.

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CONFLICT OF INTEREST

No interest

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