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Design and Fabrication of Extended Release Formulation

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***Abstract*: Extended release formulation is an approach to deliver the drug for extend period of time after oral administration. By the help of extended release approach, the dose can be incorporated in one capsule or tablet for 24 hrs from which drug release slowly for prolong period of time. Extended release products improve the patient compliance and convenience and reduce the risk of side effects that associated with high or low concentrations. It optimizes the therapeutic effect also. Extended release formulation reduce the risk of drug accumulation with chronic dose and it also reduce the frequency of dose and it employs less amount of drug and also improves the bioavailability of drug. Extended release formulation avoids the high concentration of drug in the blood and it slows the absorption of drug and thus reduce the toxicity.**

***Keywords*: Extended release, Polymers.**

1. Introduction

A. Extended release dosage forms [1]-[3]

Extended release dosage forms are the formulations which is use to deliver the drug for long period of time in controlled manner with pre-determined rate. It also maintains the optimum therapeutic level of drug in blood. Oral administration of drugs is consider as the most preferable route of drug delivery. There are many reason due to which oral route is consider as preferred route like this route has ease of administration, more patient compliance and more flexible to formulate. Extended-release oral drug formulations have been used since the 1960s to enhance performance and increase patient compliance. By incorporating the dose for 24 h into one tablet from which the drug is slowly released, peaks of high plasma concentration and troughs of low plasma concentration can be prevented. This helps to avoid the side-effects associated with high concentrations and the low concentrations lead lack of activity and gives better overall therapy. In biopharmaceutics, scientists generally are faced with an engineering problem; to develop drug delivery systems that hit a desired target. Plasma/blood drug concentration is the main target in biopharmakokinetics and it is lies between the minimum effective concentration (MEC) and minimum toxic concentration (MTC).

Oral Drug Delivery Systems is the system that is most widely used as a therapeutic agent in human body. Oral drug delivery system is technique which covers large range of therapeutic active ingredient and it is a most widely used conventional dosage form. The main aim of drugs to cure patient ailments. Drugs are never administered in human body in their pure form but are converted in a suitable form so that we can check its onset and intensity of action as well as total duration of action. There are many various routes of drug delivery but oral route is most widely used route among all drug delivery system. But as far as we know that conventional dosage form also offers few limitations and these limitation can be overcome by modifying the existing dosage form [3]-[5].

There are many limitations of conventional oral dosage form:

- Patient compliance may be poor.
- Increase the chances of dose missing.
- See-saw fluctuations.
- Multiple drug therapy may enhances the risk of toxicity.
- Treatment cost may be increase.

B. Approaches to overcome these limitations

- Development of new, better and safer drugs having long half-life and large therapeutic indices.
- Effective and safer use of existing drugs by using the concepts and techniques of controlled and targeted drug delivery systems.

The first approach has many disadvantages; however, we can use second approach. An ideal controlled drug delivery system is that which delivers the drug with specific rate locally or systemically for a specified period of time having minimum fluctuation in plasma drug concentration, and it also reduces the toxicity and maximize efficiency.

The ideal objective points that are most important to drug delivery is targeting of a drug to a specified organ or tissue and second is the control the rate of drug delivery to target tissue. Extended release drug design is a strategy which can offer major advantage towards the above two ideal properties.

Those products which are formulated for the purpose of increasing the range of absorption includes oral, topical, parentral for both vertinary as well as human use. Extended release products have their importance in medical field because of their zero order release rate of therapeutic substances. We can control the pharmacokinetics of the drug by adjusting their chemical nature. However, by using the physical means absorption rate can be decrease and the drug action can be extended.

C. Goal of extended release drug delivery system

The goal of extended release drug delivery system is to deliver the drug for long period of time in controlled manner with pre-determined rate. It also maintains the optimum therapeutic level of drug in blood. This helps to avoid the side-effects associated with high concentrations and the lack of activity associated with low concentrations giving better overall therapy.

- They are used in the chronic conditions as compare to the acute conditions because acute conditions requires the adjustment of dosage which can be adjusted by the physician but in case of extended release approach there is no need of adjustment.

Advantage of extended release dosage form [4], [5], [9], [10]

- It helps in reducing the dosage frequency of drug.
- It reduces the toxicity of drug.
- It maintains the therapeutic concentration of the drug in the blood.
- It minimizes the chances of drug accumulation of those having chronic dose.
- Improves the efficacy of treatment.
- Also helps in improving the bioavailability of drugs.
- These formulations also avoids the high concentration in blood.
- It reduces the local and systemic side effects.
- It protects the drug from hydrolysis and other degradative changes in GIT and make it stable.
- Increase the patient's compliance.
- It also reduces the health care cost.
- Decrease the chances of dose dumping.
- Safety margin can be increased of those drugs which have high potency.
- It is economical approach as it decreases nursing time and hospitalization.
- It also increases the reliability of therapy.
- It includes lesser quantity of drug.
- It reduces the dose administration frequency.

Disadvantage of extended release dosage form [11]

- Extended release products having the large size may create problem in ingestion or transit through gut.
- Release of the drug can be affected by the food.
- High chances of dose dumping.
- Patients variation difficulties also arise in such kind of formulations, like the time period of absorption of the dosage may vary from person to person, which also give rise to variation in patients compliance.
- We cannot take it by crushing or chewing because by crushing or chewing slow release characteristic of drug may be lost and toxicity can be occur.

D. Drug properties influencing the dosage form [14]-[16]

1) Physicochemical properties

- *Ionization, aqueous solubility and pKa:*

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

- *Partition coefficient:*

Partition coefficient influence the bioavailability of the drug, as the biological membrane lipophilic in nature transport of drug across the membrane largely depends upon the partition coefficient of the drug. Drugs having low partition coefficient are considered for the CR formulation as it will be localized in the aqueous phase.

- *Stability of the drug:*

When the drugs are administration orally, they come across acid-base hydrolysis and enzymatic degradation. Drugs that undergo enzymatic degradation and those drugs that are not good or unsuitable in stomach, in such case we preferred those medication that release drugs extended period , and in case of those drug that are unstable in intestine will show less bioavailability.

- *Size of the dose:*

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

- *Molecular size and diffusivity:*

High molecular weights of the drugs are expected to display very slow release kinetics in controlled release devices were diffusion through polymeric membrane or matrix is the release mechanism.

2) Biological properties

- *Absorption:*

Absorption rate of the formulation that are sustain is depends upon release rate constant of the drug from the dosage form and absorption rate of those drugs that absorbed by active transport it's absorption is limited to intestine.

- *Distribution:*

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

- *Metabolism:*

Drug metabolism can result in either inactivation of an active drug or transfer from inactive drug to an active metabolite. Metabolism process can occur in variety of tissues but the main organ that is responsible for metabolism is liver because liver contain variety of enzymatic systems and thus when drug

absorbed in systemic circulation after its absorption metabolic alteration of drugs take place. And the metabolism pattern of drug is the factor that influence the selection of the route of administration. There are two factors responsible for the limit controlling release product design and these factors associated with metabolism. First, it will be difficult to maintain uniform blood levels of drug upon chronic administration if a drug is capable of either inducing or inhibiting enzyme synthesis. And drug blood level can also be fluctuating when drug undergoes intestinal or other tissue metabolism or hepatic first pass metabolism.

- *Biological half-life:*

For CR dosage form drug with biological half-life of 2-8 hours are considered suitable candidate, since this can reduce dosing frequency. Though this is limited in that drugs with very short biological half-lives may require excessive large amounts of drugs in each dosage form to maintain controlled effects, forcing the dosage form itself to become limitingly large.

Safety considerations and side effects:

To measure the margin of safety of a drug the most widely used parameter is its therapeutic index which is defined as

Therapeutic index = median toxic dose / median effective dose

In general, the drug is safer if the value of TI is larger. A drug is considered safe if its TI value occur greater than 10.

Drug candidate suitable for extended release products:

- Drug should not have very fast rate of absorption.
- Drug should not exhibit in very fast rate of excretion.
- Drug should have good aqueous solubility.
- It should be able to maintain the gastric residence time in gastro intestinal tract.
- Drugs that are used frequently in multiple dosing manner, can also be a suitable candidate for extended release formulation, as it can decrease the chances of missed dose and inconvenient of the patient.

Table 1
Physicochemical parameters for drug selection

Parameters	Criteria
Molecular size	< 1000 Daltons
Apparent partition coefficient	High
Absorption mechanism	Diffusion
Aqueous solubility	>0.1 mg/ml at pH 1 to pH 7.8
Absorbability from all GIT	Release should not be effected by enzymes and Ph

Table 2
Pharmacokinetics parameters for drug selection

Parameters	Comment
Elimination half-life	Between 2 to 8 hours
Absolute bioavailability	Should be 75% or more
Absorption rate constant (Ka)	Must be higher than release rate
Apparent volume of distribution (Vd)	Larger Vd and MEC, larger will be the required dose.
Total clearance	Not depend on dose
Therapeutic concentration (Css)	The lower Css and smaller Vd, the loss among of drug required.
Toxic concentration	Apart the value of MTC and MEC safer the dosage form[30,31,32]

2. Design and fabrication of extended release system [17]

A. Diffusion controlled drug delivery system [18]

It is the system where the diffusion of the dissolved drug molecules occur through the rate controlling element. The rate controlling system is such that it is insoluble and non-degradable and non-erodible. It is porous in nature so it allows diffusion of dissolved drug. Depending upon the mechanism it can be classified in to two categories:

1) Porous matrix controlled systems

It is the system where the rate controlling membrane is water swellable material or non-swellable water insoluble polymer.

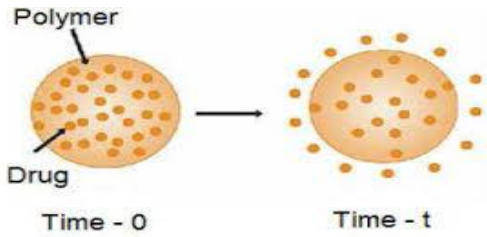

Fig. 1. Porous matrix controlled system

2) Porous membrane controlled system

It is the system where the rate controlling element is non swellable water insoluble polymer. Eg-Ethylcellulose or polymethacrylate which control drug release through micropores that is present in the membrane.

Two major types of materials are used in the pharmaceutical industry to control the drug release from matrix devices; insoluble plastics and fatty compounds. E.g.; Insoluble plastics: methylacrylatemethyl methacrylate copolymers, polyvinyl chloride, polyethylene. Fatty compounds: carnuba wax and glyceryl tristearate.

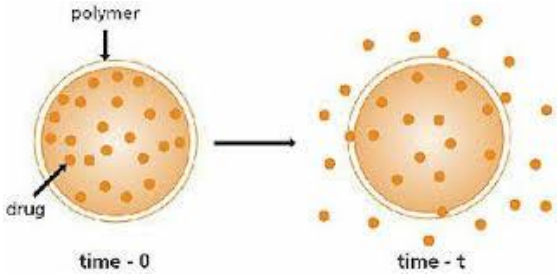

Fig. 2. Porous membrane controlled system

B. Dissolution controlled extended release formulations

It is the formulations in which involves and the slow dissolution or erosion of the release controlling element in the formulation and through dissolution drug is released. The system can be formulated into reservoir type in which drug is encapsulated within slowly soluble polymeric membrane in the form of tablets or capsules. We can also use hydrophilic swellable polymers. E.g. Hydroxypropyl cellulose, Hydroxypropyl methyl cellulose, Methyl cellulose, Sodium carboxymethyl cellulose to formulate the drug into a matrix system.

A major drawback in the dissolution controlled system,

It is difficult to maintain a constant drug release rate because as the size of dosage form diminishes with time, the release rate also changes.

Dissolution controlled extended release system is sub divided in to two types,

1) Encapsulation Dissolution control system
2) Matrix Dissolution control system

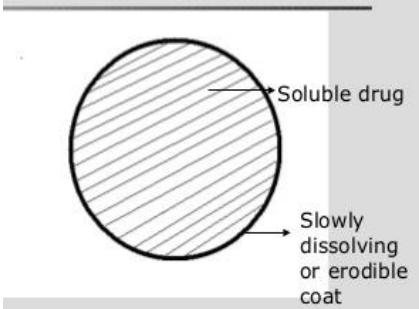

Fig. 3. Encapsulation dissolution control system

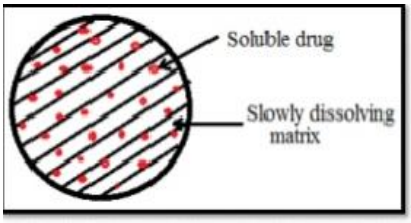

Fig. 4. Matrix dissolution system

C. Osmotic extended release formulations controlled system

It is the system in which osmotically active agents are incorporated (if the drug itself is not osmotically active) in the formulations. The dosage form consists of semi permeable membrane coating in which through which pores occur. Gastrointestinal fluid enters through the membrane and osmotic agent(s) gets dissolve and it creates high osmotic pressure inside the reservoir. Subsequently, osmotic pressure differences arised and water convicts out of the reservoir through the hole(s). Drug release follows zero order kinetics and do not depend on the pH of the gastrointestinal tract. E.g. Semi permeable membranes: Polyvinyl alcohol, Polyurethane, Cellulose acetate, Ethyl cellulose, Polyvinyl chloride.

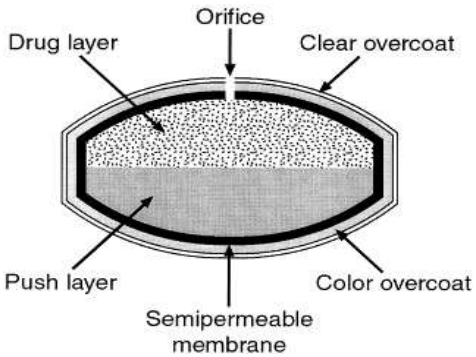

Fig. 5. Osmotic extended release system

D. Extended release formulation based on ion exchange resin

Ion exchange resins are water insoluble, and cross-linked polymers which containing salt forming group in repeating positions on the polymer chain. Drug bound with resin and the release of drug will depend on the properties of the resin, ionic environment and pH and electrolyte concentration of the gastrointestinal tract. A cationic drug bound with resin which contain SO_3^- and anionic drug bound with the resin which contain $N(CH_3)_3^+$ group.

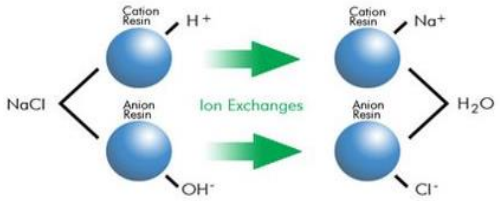

Fig. 6. Extended release formulation based on ion exchange resin

E. Multi particulate as oral extended release drug delivery system [19]-[23]

It consists particles of different size which includes pellets, granules, micro-capsules, micro-particles, nanocapsules, nano-particles. In this each unit dose is comprised of many entities together shape the drug release profile. It describes the coated and coated pellets having the size range between 0.1-1 mm.

Multi particulates system gained much attention due to their flexibility and therapeutics benefits, like it reduces the side effects and maximize the absorption, reduces inter and intra-patient variability and prevent the risk of local irritation.

In this the gastric emptying time is less variable. Pellets can be loaded with different types of drugs, it may allow the administration of two or more types of drugs and at the same or different sites within the gastro-intestinal tract, that may or not be chemically compatible.

Pellets can be loaded with different drugs and then it can be formulate in single dosage form. This allows the administration combined in a single unit dosage form in order to achieve the desired drug release profile. They have low surface area to volume ratio, because of this ideal shape for film coating, good flowability, low friability, narrow particle size distribution, uniform and reproducible batches are obtained. After coating of the pellets, these can be compressed into tablets or filled into hard gelatin capsules as final dosage form. Pellets can be directly coated or prepared with a polymer to achieve control release of drug.

F. Matrix Systems [24]-[29]

In matrix systems a polymer and drug is mixed to form solution or dispersion. Then excipient is added and then it is granulated to form pellets or sprayed onto pellets in order to achieve controlled drug release. The drug is dissolved within the polymer. Matrix systems offers many advantages like it is easy to manufacture and decrease the cost, decrease the chances of dose dumping (if the coating accidentally ruptures) and the

aqueous solubility of drug can also be improved. But the main disadvantages of this system is that initially the drug releases so fast and release is incomplete in a defined time. And due to the coating sugar cores with different polymer: drug ratios, the latter release of drug could be avoided.

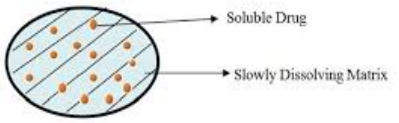

Fig. 7. Matrix Systems

Types of Matrix Systems: The matrix system can be divided into two categories depending on the types of retarding agents or polymeric materials.

1) Hydrophobic matrix system
2) Hydrophilic matrix system

1) Hydrophobic Matrix System [30], [31]

This is the system in which insoluble polymer is employed this is the only system in which for control release of drug use of polymer is not essential. In this system the rate controlling membrane is hydrophobic which is water insoluble. To modulate drug release, it may be necessary to incorporate soluble ingredients such as lactose into formulation. In the formulation insoluble ingredients also used because at the time of drug release it is helpful to maintain the physical dimension of hydrophobic matrix.

2) Hydrophilic matrix system [32], [33]

In this system the polymer is used which is hydrophilic in nature and when it comes in contact with aqueous solution it gets swells a gel layer is formed on the surface of the system.

The solvent penetrates into the free spaces between macromolecular chains. Due to the penetration of the solvent, the polymer undergoes in relaxation process and the polymer chains become more flexible and the matrix get swells. As the matrix get swells it allows the encapsulated drug to diffuse more rapidly out of the matrix. On the other hand, diffusion of the drug from the matrix would take long time because due to the swelling of the matrix the diffusion path become lengthens and drug would take more time to cross this path. It is known that swelling and diffusion are not the only factors which determine the drug release rate.

For dissolvable polymer matrix, polymer dissolution is another important mechanism that can modulate the drug delivery rate. While either swelling or dissolution can be the predominant factor for a specific type of polymers, in most cases drug release kinetics is a result of a combination of these two mechanisms.

Table 3
Marketed products of extended release tablet

Product	Company Name
Pantosec	Cipla
Volix	Ranbaxy
Urocit	Orphan Australia
Ovarine – F	Matrix Pharma

3. Conclusion

This paper presented design and fabrication of extended release formulation.

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