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A Systematic Review on Drug Delivery Systems Based on Their Mechanism of Drug Release and Their Applications

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ABSTRACT

Oral drug delivery is the most commonly used and preferred route of delivery of pharmaceuticals which has been successfully treating wide number of diseases. The advantages of this method of delivery are patient friendly, cost effective, established delivery system, noninvasiveness and convenient, and In the pharmaceutical field it is the most favored drug delivery system. Oral drug delivery systems along with other effective delivery system types that are effective and promising are discussed in this paper based on the mechanism of drug release.

Keywords- Mechanism of Drug, Oral Drug, Nanoparticles, Fluid.

I. INTRODUCTION

Pharmaceutical drug delivery has wide range of delivery carriers and has dimensions that range from several nanometers like nanotechnology to millimeters like dosage forms -tablets, capsules. In order to treat disease conditions at various sites and targets in animal or human body, these drug delivery systems release a whole array of assemblies to deliver drugs of high potent through several routes of administration.

Typical delivery systems, nanosized active agents and pharmaceutical carries includes dendrimers, and nanoparticles with functionalized surface, nanocrystals, nanoparticle albumin bound system, liposomes. Anti-bodyconjugates, microcapsules, tablets, half antibody functionalized ligand targeted systems, emulsions, oral soluble strips, osmotic pumps, and encapsulated drug delivery systems. Encapsulated drug delivery systems in a capsule carrier, pellets, tablets soluble strips, osmotic pumps, oral soluble strips are most commonly used forms for more than 80% of the commonly used pharmaceuticals in the current pharmaceutical industry. According to US Food and Drug Administration (FDA) and the US Pharmacopeia (USP), delayed or enteric-coated and extended drug release products are encompassed by modified-release solid oral dosage.

Table 1: Approximate fluid flux, pH, and residence time in Gastro intestinal Tract

Section	Fluid	Input per day (mL)	Output per day (mL)	pH	Residence time
Mouth	Water and saliva	1200 to 1500			
Stomach	Fluid in Gastric	2000	1-3.5	0.5-12	
Pancreatic juice		1500	7-8		
Duodenum	Bile	500	7-8	3-4	
Colon	Fluid transfer	500	350	6-8	~10

Modified release dosage forms and its effectiveness depends on transit time through gastro intestinal tract, as it will influence site of drug release. Drug release at different sites and drug absorption require assessment of changing pH and water content (table 1).In the new types of oral modified release products, along with delayed and /or extended release features, there are other features like pulsatile release and combination drugs like single dosage form with immediate release, enteric coated and extended release components, and targeted delivery examples are intestine, oral-mucosa, distal and proximal intestine, and/or colon or the delivery systems that are based on chrono pharmacokinetics and interactions of drugs in the milieu of biological rhythms from a clinical perspective and chrono therapeutics. Design of these dosage forms are done in a way that they release the drug for a prolonged period of time in a controlled manner, and through anatomical routes in the body at the target site. They can be intended for systematic effects or can be targeted to various diseases or organs. Depending on the need of desired effect and product availability the route of administration can be chosen. Administration of drugs can either be done to the organs that are effected directly or drugs can be given systematically to target the affected organ.

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- Gastrointestinal system: Oral, Rectal
- Parenteral: Subcutaneous injection, Intramuscular, and Intravenous injection, Intraarterial injection
- Transmucosal: buccal through lining of the Gastric and the rest of GI tract
- Trans nasal
- Pulmonary: drug delivery by inhalation
- Transdermal drug delivery and Intraosseous infusion
- Different types of drug delivery systems are as follows:
- Controlled release drug delivery system
- Modified release drug delivery system
    1. Delayed release drug delivery systems
    2. Extended release drug delivery systems
    3. Site-specific targeting
    4. 4. Receptor targeting
- Sustained release drug delivery systems
- Targeted release drug delivery system
- Immediate release drug delivery systems

II. CONTROLLED DRUG RELEASE DELIVERY SYSTEM

The drug that is delivered at an already determined rate, for a specific period of time locally is called controlled drug delivery release system. Throughout course of GIT oral frugs are delivered at predictable and reproducible kinetics for a known amount of period. In controlled drug release therapeutic agents are released for longer periods of time at controlled rate, which might range from days to months. These methods has several advantages over traditional drug delivery like protecting fragile drugs, drug release rates tailoring and compliance increase and comfort of patient. When delivering protein and peptide drugs orally, devices that are suitable for delivering the therapeutics agent incorporated microspheres in the form of controlled delivery system is helpful. Sodium alginate at various concentrations is coated on the gelatin capsules and cross linked with calcium chloride at the concentrations requires and is tested in vitro for gastric and intestinal resistance.

In vitro the most promising one is gelatin coated with 20% w/v of polymer, and this is in the volunteers who are humans for their gastro intestinal tract behavior. Uncoated gelatin capsules are observed in radio graphical studies and it disintegrates in stomach within 15 minutes of injecting it.

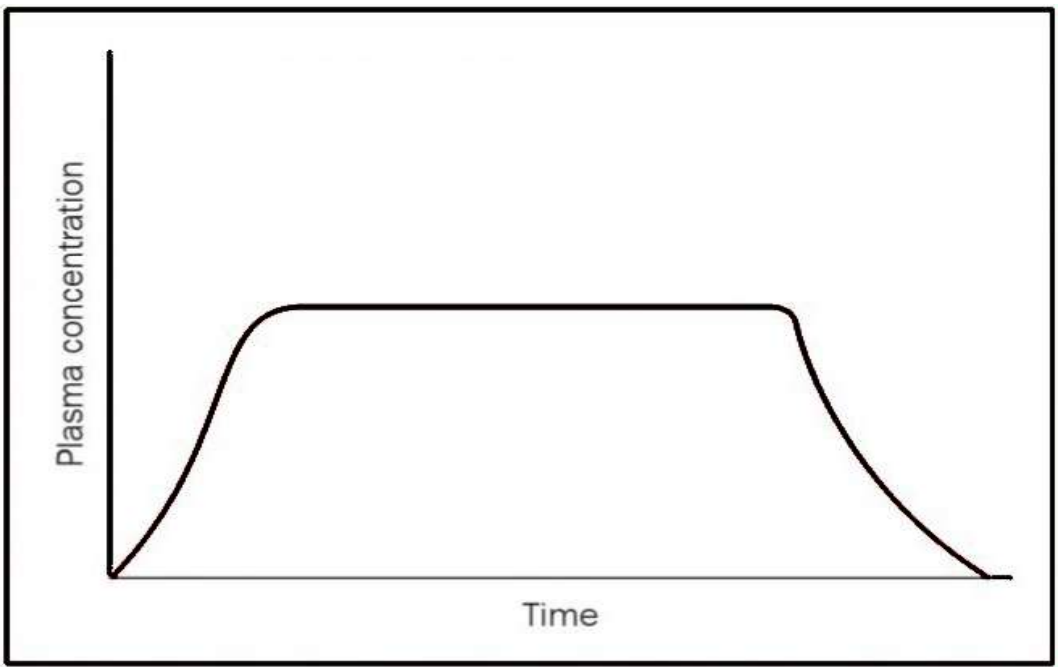

Figure 1: Idealised plasma concentration versustime profile of a controlled release dosage form

The gelatin capsule that is coated with alginate remained intact in the stomach as long as it is retained which is for about 3h, and then moved to ileocecal region and disintegrates. [1,2,3,4] Authors has prepared 1mm size of pellets and prochlorperazine of 1.65mm size using the palletization technique. ethyl cellulose is used to coat the pellets and are evaluated for in vitro release using USP apparatus. They observed that with the increase in amount of ethyl cellulose the release of PCPM is being reduced. Nicotinic acid NA is good

cholesterol lowering agent which can be used in treating dyslipidemia. The half-life of NA is 1-3 hours. By encapsulating NA with natural phenolic antioxidant polymer the dissolution controlled system is developed for NA. Using this approach a stable drug levels in plasma are achieved by slowly releasing drug over a longperiod. Encapsulation efficiency and drug release were achieved good using F4 and F5 formulations [5].

Maintaining drug level with in desired range, need for only few administrations, usage of drug in question, patient compliance re included in controlled drug delivery systems are provided in controlled drug delivery system. Due to the toxicity of the materials used and non-biocompatibility, the potential disadvantages cannot be ignored even though there are good advantages. Some other disadvantages include degradation by products that are undesirable, to remove or implant the system any surgery that is required, and the discomfort to the patient from the device used for surgery, and it is expensive compared to traditional pharmaceutical formulations.

For a drug delivery system to be ideal, it should be mechanically strong, inert and biocompatible, patient should feel comfortable, the drug should achieve high drug loading, should be safe from accidental release, it should be easy to administer and remove, and should be easy to sterilize and fabricate. The main goal of a controlled delivery system is to yield high blood level delivery profile for the drug over a long time period. In the traditional drug delivery systems, after each administration the drug level raises in the blood and goes down until next dose is administered. One of the important factors with traditional delivery systems is that drug level should remain within the range of maximum value, at which drug reaches toxic levels and below which drug is not effective.

Advantages of Controlled Release dosage Forms:

- Frequency in which drug administered can be reduced.
- Improved patient compliance
- Fluctuation of drug level in the blood can be reduced.
- The total amount of drug used can be reduced when compared to conventional therapy.
- Accumulation of the drug can be reduced with chronic therapy.
- Toxicity of the drug can be greatly reduced.
- Medical condition of the patient can be greatly stabilized due to the uniform levels of the drug.
- Limitations of Controlled Release dosage Forms:
- The onset of drug action is delayed.
- With the formulation strategy being poor there is a risk of dose dumping.
- There is a potential increase in the first pass metabolism.
- Dependency on the Gastrointestinal residence time of dosage form might have greater influence.
- The accuracy of dose adjustment is possibly less in some cases.

As we already discussed, In the controlled drug delivery systems the drug is released at an already determined rate depending on required therapeutic concentration as well as pharmacokinetic characteristics of the drug, and they are as follows:

Biological half-life (t ½):

The fluctuations between the maximum steady state concentration are larger depending on the shorter the t ½ of a drug is and maximum steady state concentration upon repetitive dosing. So drug product needs to be administered more often.

Minimum effective concentration (MEC): IN minimum effective concentration MEC, controlled release preparation or frequent dosing of conventional drug product is chosen.

Molecular weight or size: Through small pores of membrane molecules of smaller size may pass by convective transport. This applies to biologic membrane as well as the drug released from dosage form. The limit for biological membrane is by molecular weight if 150 to 400 respectively for chain compounds and spherical molecules.

Solubility: The drug should be available in the form of solution, at the location of absorption for all the mechanisms. It is important to determine the solubility of drug at different pH levels during the preformulating study. Reduced bioavailability can be expected and also variable when the solubility is less than 0.1 µg/ml in acidic medium. The availability will become dissolution limited if the solubility is less than 0.01 µg/ml absorption. So the diffusion driving force may be inadequate. Up on oral administration absorption of drug is good from the small intestine using passive diffusion.

III. DELAYED RELEASE DRUG DELIVERY SYSTEMS

This drug dosage form is released at a time other than the time of administration either by some or discrete portion, but one other portion is promptly released as soon as administered. Common delayed release products are enteric coated dosage forms [7].

In the low pH environments like stomach, to protect the drug from degradation or to lower the stomach irritation caused by drug, delayed release systems are used. In situations like these until the dosage form reaches small intestine the release of drug must be delayed. An to achieve this purpose polymers are used. Suitable polymer can be used to coat the dosage form. From the low pH environments like stomach when the dosage form moves to high pH environments like small intestine the drug is released by the polymer coat being dissolved.

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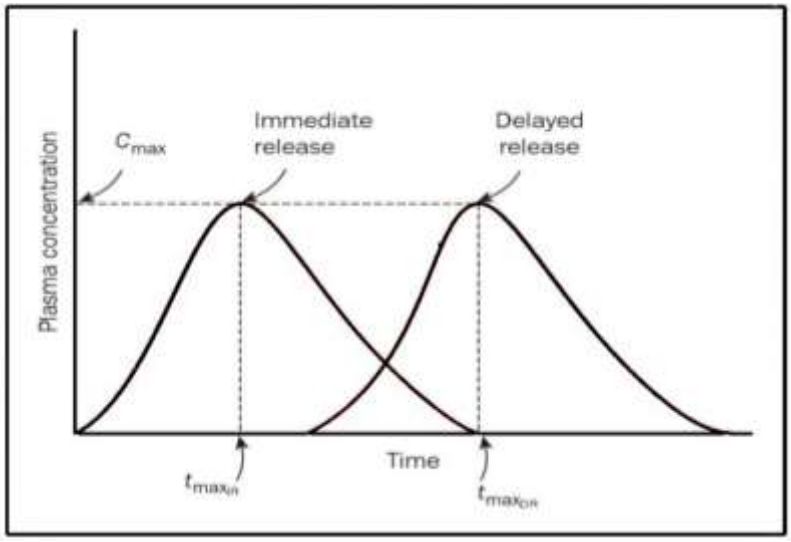

Figure 2: Idealized concentration of plasma vs time profile of delayed oral dosage form, which is compared to an immediate dosage form. For the immediate release dosage form the time at which maximum concentration of plasma is release is called T_{maxIR}. For the delayed release dosage, form the time at which maximum concentration of plasma is release is called T_{maxDR}.

As soon as this happens, the rate of release is then similar to immediate release dosage forms, which means release is immediate and the resulting plasma concentration versus time curve is same [9].

One of the examples of delayed release type of modified release dosage form is enteric coated tablet, which is designed to release drug in small intestine. For example the gastric mucosal of the stomach is irritated by aspirin. Aspirin has enteric coating on its surface, which will prevent the dosage form from being dissolved and release the drug in low pH environment like stomach. The drug is released in the high pH areas if the duodenum where the coating and the tablet dissolves, and the drug is absorbed at a rapid rate with less irritation to the mucosal membrane.

IV. MODIFIED RELEASE DRUG DELIVERY SYSTEMS

In this form of drug release some elements like time course and /or location are selected to achieve therapeutic objectives and the drug is released in these areas. This is not offered by conventional dosage forms like ointments, solutions and dissolving dosage forms [11].

In modified drug release system drugs are released either by extended drug delivery release system or by sustained drug release drug delivery system.

V. EXTENDED RELEASE DRUG DELIVERY SYSTEMS

In this form of drug release the drug is released over a prolonged period of time. Releasing drug for an extended period of time can reduce the frequency at which it is administered. Extended release products are commonly used method medication delivery methods. Using this form of release have certain advantages over other forms of release as well as disadvantages. We will discuss advantages and disadvantages with examples as below:

- One of the main important benefit of extended release drug delivery system is patient can take the medication less frequently. When you tell a patient to take the medication number of times per day the likelihood of nonadherence is increasing. Diltiazem is the example of extended release drug delivery system. When immediate release is used, it is required to administer multiple doses per day, but when we use, extended release delivery we have to take only once per day.
- Along with adherence, multiple people get annoyed with the polypharmacy and the multiple number of tablets they need to take. Reducing the number of pills one must take is the solution in this case, for example we can switch metoprolol XL once per day instead of metoprolol IR BID.
- When it comes to extended release drugs cost is one of the major disadvantages. For example if we take Namenda XR, the immediate release version is a lot cheaper by hundred dollars compared to extended release, and some people argue that the advantage of is of no help or minimal help compared to immediate release.
- Slower start of action is seen in extended release formulations. Example of extended release formulations are patches of Fentanyl. As the method of delivery is very slow, we should not use these types of drugs for acute pains.

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- These extended release formulations may have slower onset action. One example here is Fentanyl patches, because of the delivery method being very slow onset of action, we should not use this drug for acute pain.
- In case of adverse reactions, the extended release products will have adverse effects with extended release and these effects may linger for a longer period compared to immediate release.

Sustained release drug delivery system:

The rate of drug release is maintained over a period of time for sustained release drug delivery system, for example if the drug dosage form release is sustained so that the release takes place throughout the GI tract [8], can be reduced, and the time interval of drug concentration can be prolonged in the therapeutic range. This in turn helps with reduction in number of times administering doses, form three times a day to one time a day. By using suitable polymers this is achieved by sustained release drug delivery system, and they are used to coat the capsules if granules in which the drug is dispersed. The release kinetics of this drug release may differ.

- Zero order kinetics is followed by reservoir system.
- Linear release as a function of the square root of time is followed by Matrix systems.

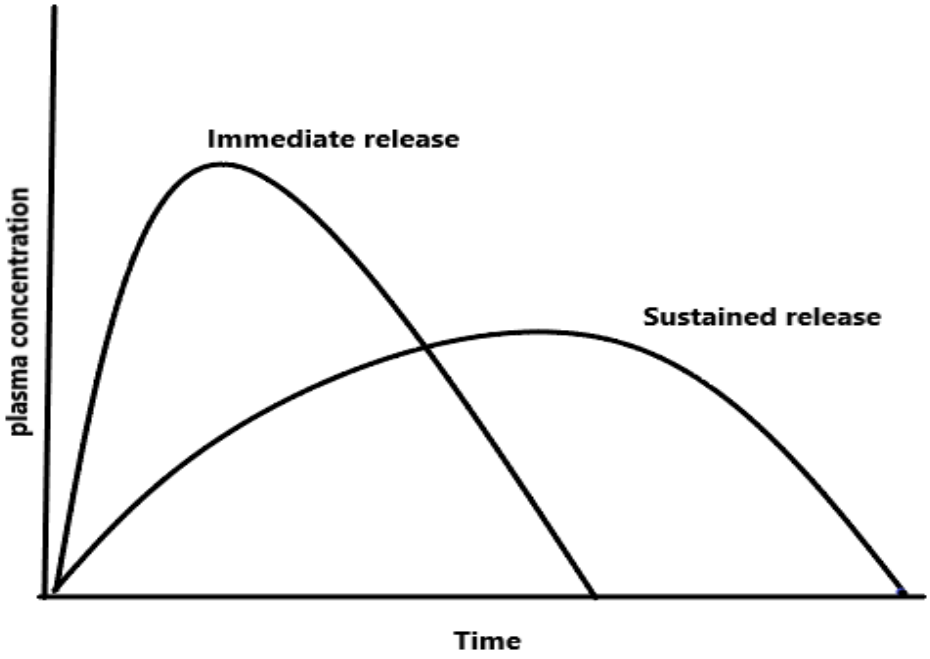

Fig 3: Ideal concentration of plasma versus time profile of a sustained release oral dosage in comparison with immediate release dosage form

VI. DRUG SELECTION PARAMETERS FOR ORAL SUSTAINED DRUG DELIVERY SYSTEMS

Table 2: Drug selection parameters

Parameter	Preferredvalue
Molecular weight/ size	< 1000
Solubility	> 0.1 µg/ml for pH 1 to pH 7.8
P_{ka}	Non ionized moiety > 0.1% at pH 1 to pH 7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability	From all GI segments
Release	Should not be influenced by pH and enzymes

Table 3: Pharmacokinetic parameters that need to be considered for drug selection

Parameter	Comment
Elimination half life	Preferably between 0.5 and 8 h
Total clearance	Should not be dose dependent
Elimination rate constant	Required for design
Apparent volume of distribution V_d	The larger V_d and MEC, the larger will be the required dose size.
Absolute bioavailability	Should be 75% or more
Intrinsic absorption rate	Must be greater than release rate
Therapeutic concentration Css av	The lower Css av and smaller V_d, the loss among of drug required
Toxic concentration	Apart the values of MTC and MEC, safer the dosage form. Also suitable for drugs with very short half-life.

The knowledge of certain factors is required for biopharmaceutical evaluation of a drug to use in controlled drug delivery system. Those factors include drug's mechanism from the gastrointestinal tract, general absorbability, molecular wight of the drug, p_{ka}, solubility of the drug at various pH levels and apparent partition coefficient. Half life of a drug, bioavailability, clearance, first pass effect, are needed to evaluate pharmacokinetic features of the drug[13-20].

Site-specific targeting*:* In this type of targeting, certain biological location is targeted. The target is in the diseased tissue or organ or is next to a diseased organ in site specific targeting.

Receptor targeting: Target for the drug in the receptor targeting is the receptor that is in a tissue. These two systems satisfy the drug delivery's spatial aspect and are also called as controlled drugdelivery systems.

VII.TARGETED DRUG DELIVERY SYSTEMS

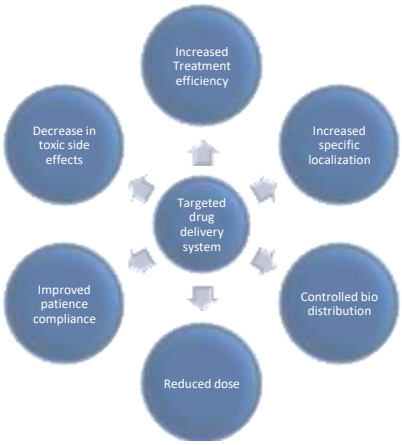

Figure 4: Advantages of a targeted drug delivery system

Targeted drug delivery system is also called as smart drug delivery systems, and in this method of drug delivery treatment is given by increasing medication in one or few body parts compared to other parts. By following this, the medication will be delivered to only areas that needs the treatment. Efficacy in treatment will be increased by this and side effects are reduced. The efficacy of interaction of drug at the target site will be less unless the delivery of drug to the site of action is done at the required concentration and also the rate at which minimum side effects are seen with therapeutic effects being maximum. The same thing will be achieved by target drug delivery system.

Pharmacological properties of a drug will affect the biological effect of a drug. These biological effects arise when a drug interacts with the receptors at the target [20-25].

For a successful targeted drug delivery system, four principles are required: evade, retain, target and release, that is, drug needs to be properly loaded to the

respective drug delivery vehicle, it must have the ability to escape the secretions of the body which might degrade it, leading to a increase in residence time in circulation and so reaching the site of target and, the drug should be released at the site of target within the time period that is effective for functioning of the drug.

VIII. IMMEDIATE RELEASE DRUG DELIVERY SYSTEM:

Lot of the dosage forms are designed in a way that the drug is released as soon as possible after administration, for therapeutic reasons if the fastest onset action is required then this dosage form is very helpful. An example of this type of dosage form is pain killer tablet, it should be released in the gastrointestinal tract and into the body, as soon as its taken. Pharmacological effect may be seen within seconds for intravenous injections, and the reason for this is:

- The solution already contains the drug, and it does not have to be specifically released from the dosage form.
- As we are administering drug directly into the body, during the phase where the drug is penetrating through skin or mucosal membranes, before the drug can reach target organs no time is wasted.

In oral drug release systems, the drug is released get mix up with gastro intestinal fluids. If the drug is released in the form of powders or granules, it needs to dissolve first before released as drug. If the oral drug is given as tablet it needs to disintegrate first, if compressed granules are used to form this, it has to start form the level of granules, which has to further disintegrate into powder and from the powder drug dissolution and delivery happens. If the drug is given in the form of capsule, the shell material used for the capsule needs to disintegrate first. After that the drug is released from the solid powder or granule in the situation of hard gelatin, or in the case of soft capsule of gelatin drug is released in the form of liquid. This type of immediate release drugs onset the action within minutes or hours[26-30].

In the immediate release dosage forms drugs are released in a single action. This means the release of drug is very immediate, which then passes through mucosal membrane and then to into the body. The drug then, within a short period of time reaches highest plasma level. Due to passive diffusion the drug is passed through mucosal membranes.

For treating the cancer, combination therapy using multiple therapeutic combination therapy is widely used. The drug delivery systems which can release two or more drugs are useful in this purpose. New techniques can be developed to design new materials, and new structure carriers for multi agent delivery systems. Machine learning has been used to develop several techniques that will help in drug design and discovery. In the combination therapy, to release the therapeutic agents, chemical structure of drug is important. Along with biological evaluation, it is important to translate resulting delivery systems into clinical applications. In this paper author did a research on diabetes in rabbits using eugenol. There was significant improved bioavailability of gliclazide on multidose treatment with eugenol followed by gliclazide in diabetic rabbits. Other pharmacokinetic parameters are also significantly altered as shown in the results. Pharmacodynamic studies also clearly revealed that there is an improved reduction in the blood glucose levels with combined multidose treatment of eugenol and gliclazide compared with treatment of gliclazide alone. Hence, it can be concluded that there is a pharmacokinetic and pharmacodynamic advantage of administering gliclazide along with multidose eugenol [30-34].

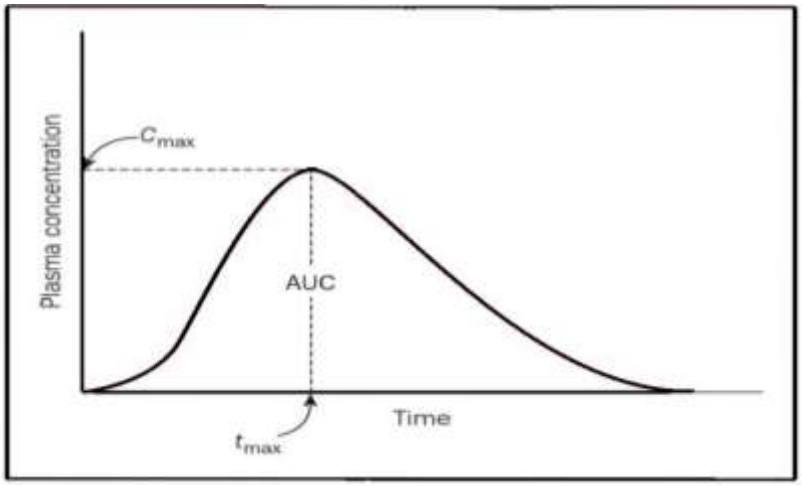

Figure 5: ideal concentrations of plasma for immediate release oral dosage forms vs time. At high levels the drug plasma concentration is called Cmax. The time at which Cmax is reached is called Tmax. The area under concentration of plasma vs time profile is called AUC, and it reflects the total absorbed drug amount.

The effort that is required to produce new drug carrier system is high. These carriers can give hope to treat and diagnose, multiple diseases. Several technologies that are developed progressed into clinical studies and products have been released which shows favorable results. In this review it was shown that these new drug carriers are promising enough that can treat diseases like cancer, and also have strong future growth in terms of capability. But, there are some issues involved which needs to be understood in order to ensure the effectiveness and safety of drugs. Nevertheless, in the future, new entities will become available and responsive and "clever" polymers will offer new perspectives for the treatment of diseases.

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