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Innovations in Sustained Release Drug Delivery System and Its Market Opportunities

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Abstract

Sustained release dosage forms are designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimum side effects. In the recent years, focus on the development of controlled release drug delivery systems has increased. The basic rationale of controlled release drug delivery system optimises the biopharmaceutical, pharmacokinetic, and pharmacodynamic properties of a drug in such a way that its utility is maximized, side-effects are reduced and cure or control of the condition is achieved, in the shortest possible time by using smallest quantity of drug administered by the most suitable route. There are several advantages of sustained release drug delivery over conventional dosage forms like improved patient compliance due to less frequent drug administration, reduction of fluctuation in steady-state drug levels, maximum utilisation of the drug, increased safety margin of potent drug, reduction in healthcare costs through improved therapy, shorter treatment period and less frequency of dosing. SR products are designed to bring the blood level of a drug immediately to therapeutic concentrations by means of an initial dose portion and then sustain this level for a certain predetermined time with the maintenance portion .SR of drugs in gastro-intestinal tract following oral administration is not affected by the absorption process. SR oral dosage forms have become more important in therapy as a means of reduced dosing frequency, hence potentially improving patient compliance and consequently efficacy. The principal goal of SR dosage forms is the improvement of drug therapy assessed by the relationship between advantages and disadvantages of the use of SR systems.

Key words: SRDS, Controlled drug delivery system, multidosing.

Introduction

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. Improved drug safety could often be achieved by controlling the rate of drug delivery from dosage form. The advantages of sustained release dosage forms are well known. Sustained release dosage forms are prepared by coating the tablets so that the rate of solubility is controlled or individually encapsulating micro particles of varying sizes so that the rate of dissolution can be controlled. With the development of modern synthetic ion exchange resins, pharmaceutical industry adapted the ion exchange technology to achieve sustained release of drug. Keating listed the following advantages of adsorbing basic nitrogen containing drug onto strong acid cation exchange resins and using them in dosage forms: Prolonged release of drug from the complex for 8-12 hours in the gastrointestinal tract .Reduced toxicity by slowing drug absorption ,Improved palatability ,Availability of formulation in liquid and solid sustained release dosage forms ,Increased stability by protecting the drug from hydrolysis or other degradative changes in the gastrointestinal tract .Apart from the effectiveness, safety and purity of the active ingredients embedded in modern dosage forms, the pharmaceutical concept of the latter is becoming increasingly important. Very early on, due consideration has to be given to their pharmacokinetics in order to obtain that specific release profile which guarantees optimum therapeutic efficiency. Controlled release of the actives from oral dosage forms with poly(meth)acrylates can be achieved in many different ways. Enclosing drugs in diffusion-controlled membranes is an important basic principle of controlled time release. Combining neutral, permeable polymers with anionic soluble types permits realization of various release mechanisms, while paying due regard to the physicochemical properties of the drug. The techniques are briefly described and demonstrated. Sustain drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects associated with a sawtooth kinetic pattern. Localize drug action by spatial placement of a controlled release system (usually rate controlled) adjacent to or in the diseased tissue or organ.

Market Opportunities of Sustained Release Dosage Forms

The oral drug delivery market is the largest segment of the drug delivery market, and there’s no sign that it is slowing down. With pharmaceutical companies increasingly turning to drug delivery to extend the revenue-earning lifetime of their biggest products, and seeking to tap into the growing elderly population that requires products with a level of ease-of-use and cost benefit, it’s no surprise that the oral delivery drug market is a $35 billion industry and expected to grow as much as ten percent per year.Oral Delivery provides the definitive break down of the market for oral delivery drug markets. The report covers both the major technologies in oral delivery (controlled-release, delayed release, pulsatile-release, taste-masked and microemulsion formulations) and the products that use these delivery technologies. The global market for advanced drug delivery systems amounted to $134.3 billion in 2008, and was projected to increase to $139 billion in 2009. The estimate for 2014 is $196.4 billion, for a compound annual growth rate (CAGR) of 7.2% in the 5-year period.The largest segment of the market is targeted

drug delivery, which reached $50.9 billion in 2009 and is expected to increase to $80.2 billion in 2014, for a CAGR of 9.5%.Sustained-release products have the second-largest market share, with estimated sales of $36.1 billion in 2009 and $45.8 billion in 2014, for a CAGR of 4.9%. Benefits for short half-life drugs, sustained release can mean less frequent dosing and thus better compliance reduce variations in plasma/blood levels for more consistent result.

Advantages:

i] Patient Compliance:
Lack of compliance is generally observed with long term treatment of chronic disease, as success of drug therapy depends upon the ability of patient to comply with the regimen. Patient compliance is affected by a combination of several factors, like awareness of disease process, patient faith in therapy, his understanding of the need to adhere to a strict treatment schedule. Also the complexity of therapeutic regimens, the cost of therapy and magnitude of local and or systemic side effect of the dosage form.
The problem of lack of patient compliance can be resolved to some extent by administering sustained release drug delivery system.

ii] Reduced 'see- saw' fluctuation:
Administration of a drug in a conventional dosage form [except via intravenous infusion at a constant rate] often results in 'see – saw' pattern of drug concentration in the systemic circulation and tissue compartments. The magnitudes of these fluctuations depend on drug kinetics such as the rate of absorption, distribution, elimination and dosing intervals. The 'see-saw' or 'peak and valley' pattern is more striking in case of drugs with biological half lives of less than four hours, since prescribed dosing intervals are rarely less than four hours. A well-designed sustained release drug delivery system can significantly reduce the frequency of drug dosing and also maintain a more steady drug concentration in blood circulation and target tissue cells.

iii] Reduced total dose:
Sustained release drug delivery systems have repeatedly been shown to use less amount of total drug to treat a diseased condition. By reducing the total amount of drug, decrease in systemic or local side effects are observed. This would also lead to greater economy.

iv] Improved efficiency in treatment:
Optimal therapy of a disease requires an efficient delivery of active drugs to the tissues, organs that need treatment. Very often doses far in excess to those required in the cells have to be administered in order to achieve the necessary therapeutically effective concentration. This unfortunately may lead to undesirable, toxicological and immunological effects in non-target tissue. A sustained release dosage forms leads to better management of the acute or chronic disease condition.

Challenges:
i) Dose dumping:
Dose dumping is a phenomenon where by relatively large quantities of drug in a sustained release formulation is rapidly released, introducing potential toxic quantities of the drug into the systemic circulation. Dose dumping can lead to fatalities in case of potent drug, which have a narrow therapeutic index e.g. Phenobarbital.
ii) limited choise of selecting desired dose in the unit:

In conventional dosage forms, dose adjustments are much simpler e.g. tablet can be divided into two fractions. In case of sustained release dosage forms, this appears to be much more complicated. Sustained release property may get lost, if dosage form is fractured.

iii) Poor In Vitro – In Vivo correlation:

In sustained release dosage form, the rate of drug release is deliberately reduced to achieve drug release possibly over a large region of gastrointestinal tract. Here the so called *'Absorption window'* becomes important and may give rise to unsatisfactory drug absorption in vivo despite excellent in-vitro release characteristics.

iv) Patient variation:

The time period required for absorption of drug released from the dosage form may vary among individuals. Co-administration of other drugs, presence or absence of food and residence time in gastrointestinal tract is different among patients. This also gives rise to variation in clinical response among the patient.

Criteria to be met by drug proposed to be formulated in sustained release dosage forms

a) Desirable half-life:

The half life of a drug is an index of its residence time in the body. If the drug has a short half life (less than 2 hours), the dosage form may contain a prohibitively large quantity of the drug. On the other hand, drug with elimination half life of eight hours or more are sufficiently sustained in the body, when administered in conventional dosage from, and sustained release drug delivery system is generally not necessary in such cases. Ideally, the drug should have half-life of three to four hours.

b) High therapeutic index:

Drugs with low therapeutic index are unsuitable for incorporation in sustained release formulations. If the system fails in the body, dose dumping may occur, leading to fatalities eg. Digitoxin.

c) Small dose:

If the dose of a drug in the conventional dosage form is high, its suitability as a candidate for sustained release is seriously undetermined. This is chiefly because the size of a unit dose sustained release formulation would become too big, to administer without difficulty.

d) Desirable absorption and solubility characteristics:

Absorption of poorly water soluble drug is often dissolution rate limited. Incorporating such compounds into sustained release formulations is therefore unrealistic and may reduce overall absorption efficiency.

e) Desirable absorption window:

Certain drugs when administered orally are absorbed only from a specific part of gastrointestinal tract. This part is referred to as the *'absorption window'*. Drugs exhibiting an absorption window like fluorouracil, thiazide diuretics, if formulated as sustained release dosage form are unsuitable.

f) First pass clearance:

As discussed earlier in disadvantages of sustained delivery system, delivery of the drug to the body in desired concentrations is seriously hampered in case of drugs undergoing extensive hepatic first pass metabolism, when administered in sustained release forms.

Design and formulation of oral sustained release drug delivery system

The oral route of administration is the most preferred route due to flexibility in dosage form, design and patient compliance. But here one has to take into consideration, the various pH that the dosage form would encounter during its transit, the gastrointestinal motility, the enzyme system and its influence on the drug and the dosage form. The majority of oral sustained release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the gastrointestinal milieu. Theoretically and desirably a sustained release delivery device, should release the drug by a zero-order process which would result in a blood-level time profile similar to that after intravenous constant rate infusion. Plasma drug concentration-profiles for conventional tablet or capsule formulation, a sustained release formulation, and a zero order sustained release formulation.

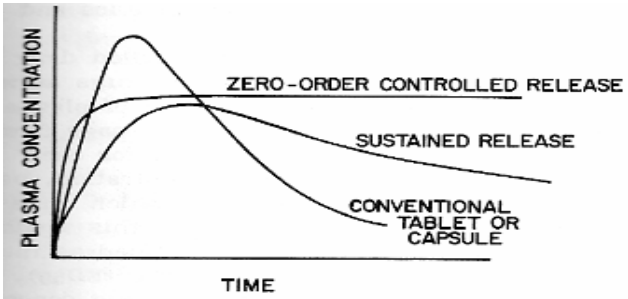


Fig. 1 Plasma drug concentration-profiles for conventional tablet or capsule formulation, a sustained release formulation, and a zero-order controlled release formulation.

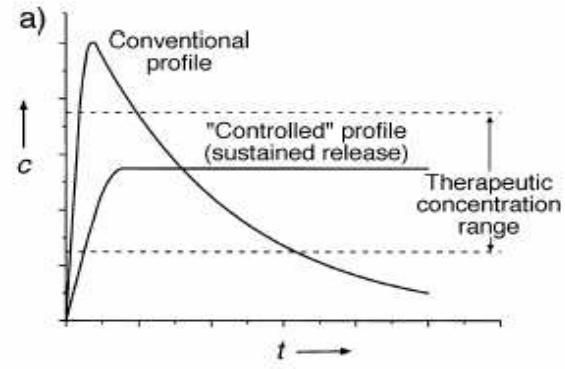


Figure-2 Comparison of Conventional and Controlled Release Profiles

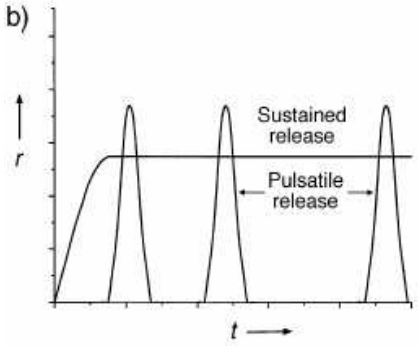


Figure-3 Dosage Regime for Conventional and Controlled Release Systems

Sustained (zero-order) drug release has been attempted to be achieved, by following classes of sustained drug delivery system.

A) Diffusion sustained system.
   i) Reservoir type.
   ii) Matrix type
B) Dissolution sustained system.
   i) Reservoir type.
   ii) Matrix type
C) Methods using Ion-exchange.
D) Methods using osmotic pressure.
E) pH independent formulations.
F) Altered density formulations.

A] 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 dc/dx.

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= ADKΔ C/L

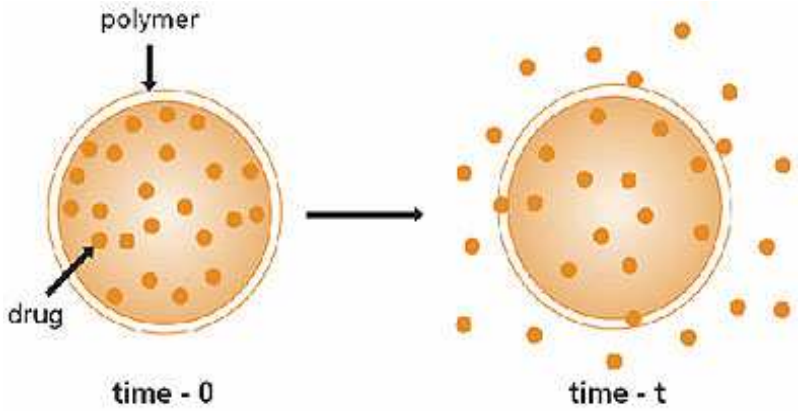
Where A = area

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.

1] Reservoir type:



Schematic representation of diffusion sustained drug release: reservoir system

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.

Characterization

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.
ii] 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.

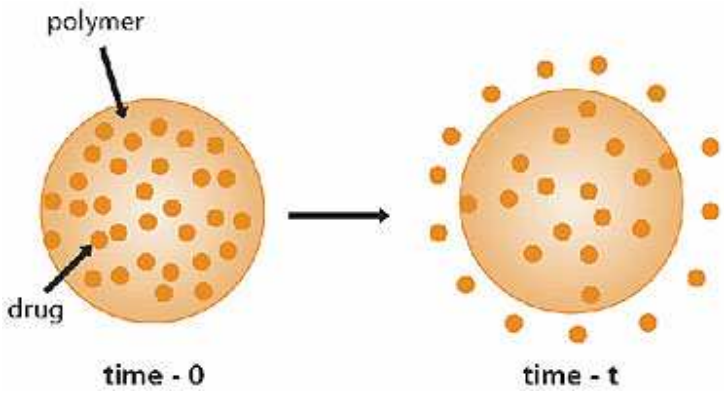
Higuchi has derived the appropriate equation for drug release for this system,

$$Q = D\varepsilon / T [2 A - \varepsilon Cs] Cst^{½}$$

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

Characterization
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.



Schematic representation of diffusion sustained drug release: matrix system

A third possible 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:-

$$\text{Release rate} = AD / L = [C_1 - C_2]$$

Where A = Area, D = diffusion coefficient, C_1 = Drug concentration in the core, C_2 = Drug concentration in the surrounding medium, L = diffusional path length

Thus diffusion sustained 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.

B] Dissolution sustained systems:

A drug with a slow dissolution rate is inherently sustained 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. The same approach can be employed for compounds that are degraded by the harsh conditions found in the gastric region.

i) 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 shown in figure, 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 sustained 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. This is shown in figure. Since the beads have different coating thickness, their release occurs in a progressive manner.

Those with the thinnest layers will provide the initial dose. The maintenance of drug levels at late times will be achieved from those with thicker coating. This is the principle of the spansule capsule. Cellulose nitrate phthalate was synthesized and used as an enteric coating agent for acetyl salicylic acid tablets.

ii) Matrix type:

The more common type of dissolution sustained dosage form as shown in figure. It can be either a drug impregnated sphere or a drug impregnated tablet, which will be subjected to slow erosion.

Two types of dissolution- sustained 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.

C] Methods using lon Exchange:

It is based on the formation of drug resin complex formed when a ionic solution is kept in contact with ionic resins. The drug from these complex gets exchanged in gastrointestinal tract and released with excess of Na^+ and Cl^- present in gastrointestinal tract

Resin + - Drug - + Cl^- goes to resin $\pm$ Cl^- + Drug-

Where x^- is cl^- conversely

Resin $^-$ - $drug^+$ + Na $^+$goes resin $^-$ Na^+ + Drug

These systems generally utilize resin compounds of water insoluble cross – linked polymer. They contain salt – forming functional group in repeating positions on the polymer chain. The rate of drug diffusion out of the resin is sustained by the area of diffusion, diffusional path length and

rigidity of the resin which is function of the amount of cross linking agent used to prepare resins. The release rate can be further sustained by coating the drug resin complex by microencapsulation process.[15]

D] 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 sustained systems are:-

Type A contains an osmotic core with drug

Type B contains the drug in flexible bag with osmotic core surrounding.

E] 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, phthalic 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 thereby rendering a constant rate of drug release e.g. propoxyphene in a buffered sustained release formulation, which significantly increase reproducibility.

F] 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 it it would have limited utility. To this end, several approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract.

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/cm^3.

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 sustained release purpose.

Factors Influencing Design of sustained Release Dosage Forms:

The therapeutic efficacy of drug under clinical conditions is not simply a function of its intrinsic pharmacological activity but also depends upon the path of the drug molecule from the site of administration to the target site. Different conditions encountered by the drug molecule while traversing the path of distribution may alter either the effectiveness of the drug or affect the amount of the drug reaching the receptor site.

A] Pharmaceutics:

This refers to the development/manufacturing of an efficient delivery system in which the drug has maximum physiological stability and optimum bioavailability.

B] Biopharmaceutics / pharmacokinetics:

This involves the study of absorption, distribution, metabolism and excretion of the drug, before and after reaching the target site and evaluation of the relationship between delivery system and therapeutic response.

C] Pharmacodynamics/ Clinical Pharmacology:

It is the study of the mechanism of action and clinical efficacy of a drug administered in dosage form in terms of onset, intensity and duration of pharmacological activity.

Drug properties influencing the design of sustained or sustained release drug delivery system are classified as:

1] Physicochemical properties of the drug

These include dose size, aqueous solubility, protein binding, molecular size, drug stability and partition coefficients.

2] Biological factors

These include absorption, distribution, metabolism, duration of action, margin of safety, side effects of drug, disease state and circadian rhythm.

Methods to achieve oral sustained drug delivery:

There are various methods employed for the fabrication of oral sustained release delivery systems. *Ritschel* has given a detailed report of these techniques. These are as follows.

a. Hydrophilic matrix
b. Plastic matrix
c. Barrier resin beads
d. Fat embedment
e. Repeat action
f. Ion exchange resin
g. Soft gelatin depot capsules
h. Drug complexes

Matrix devices:

Historically, the most popular drug delivery system has been the matrix because of its low cost and ease of fabrication. Methods of altering the kinetics of drug release from the inherent first order behavior especially to achieve a constant rate of drug release from matrix devices have involved several factors.

Requirements of matrix materials:

The matrix materials must comply with the following conditions,

1. They must be completely inert and non- reactive with the drug and additives in the tablet.
2. They must be able to form a stable and strong matrices when compressed either directly or more often as granules prepared by the addition of a binding agent.
3. They must be non-toxic.

Hydrophilic matrix system:

Carboxymethylcellulose sodium, hydroxymethyl cellulose, polyethylene oxide, polyvinyl-107, molidones and natural gums can be used as matrix materials. The matrix may be tableted by direct compression of the blend of active ingredient and certain hydrophilic carriers or from a wet granulation containing the drug and hydrophilic matrix material. Upon immersion in water the hydrophilic matrix quickly forms a gel layer around the tablet. Drug release is sustained by a gel diffusional barrier and /or tablet erosion.

Injectable Products

The parenteral administration route is still the most effective and common form of delivery for macromolecules (such as peptides and proteins), for active drug substances with metabolic liabilities (i.e. drugs for which the bioavailability is limited by high first pass metabolism effect or other physico-chemical limitations) and for drugs with a narrow therapeutic index (i.e. several anticancer drugs - where slow infusion is the best way to control the exact pharmacokinetic into the blood).Moreover, at the same time, this administration route is the least preferred by patients because of the discomfort and inconvenience that it causes. For this reason, whatever drug delivery technology that can reduce the total number of injections throughout the drug therapy period is truly advantageous not only in terms of compliance, but also for the potential to improve the quality of the therapy. Such reduction in frequency of drug dosing is achieved, in practice, by the use of specific formulation technologies that guarantee that the release of the active drug substance happens in a slow and predictable manner.For several drugs, depending on the dose, it may be possible to reduce the injection frequency from daily to once or twice monthly or even less frequently. In addition to improving patient comfort, less frequent injections of drugs in the form of depot formulations smoothes out the plasma concentration-time profiles by eliminating the hills and valleys. Such smoothing out of the plasma profiles has the potential to not only boost the therapeutic benefit, but also to reduce unwanted events and side effects. While for a series of sparingly soluble active drug substances, such as steroids, sterile aqueous , oleaginous suspensions or oily solutions are formulation approaches that allow an extended duration of action , (in these cases the release of the active from the injected formulations is governed quite exclusively by the dissolution kinetic of the active drug substance, which can last up to several months according to the administered dose and the physico-chemical properties of the drug). For the majority of the drug substances, such as peptides and macromolecules , it is mandatory to utilize specific drug delivery technologies that can tailor and govern the release profile of the active drug substance from the formulation itself.

Conclusion

Development of sustained release oral dosage forms is beneficial for optimal therapy regarding efficacy, safety and patient compliance. In case of sustained release (SR) dosage forms the release of the active agent, although, is lower than in the conventional formulations, however, it is still substantially affected by the external environments into which it is going to be released. The advantages of sustained-release tablets or capsules are that they can often be taken less frequently than instant formulations of the same drug, and that they keep steadier levels of the drug in the bloodstream. Sustained-release tablets are formulated so that the active ingredient is embedded in a matrix of insoluble substance (various: some acrylics, even chitin, these are often patented) so that the dissolving drug has to find its way out through the holes in the matrix. In some SR formulations the matrix physically swells up to form a gel, so that the drug has first to dissolve in matrix, then exit through the outer surface. There are certain considerations for the formation of sustained release formulation:If the active compound has a long half-life (over six hours), it is sustained on its own. If the pharmacological activity of the active is not related to its blood levels, time releasing then has no purpose. If the absorption of the active involves an active transport, the development of a time-release product may beproblematic.Finally, if the active has a short half-life, it would require a large amount to maintain a prolonged effective dose. in this

case, a broad therapeutic window is necessary to avoid toxicity; otherwise, the risk is unworthy to take and another mode of administration would be recommended.Difference between controlled release and sustain release or sustained release is that controlled release is perfectly zero order release that is, the drug releases with time irrespective of concentration.On the other hand,sustain release or sustained release implies slow release of the drug over a time period.It may or may not be controlled release.

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