Novel Way of Improvement of Drug Therapy By Sustained Release Drug Delivery System: A Review

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Abstract- *All drug delivery systems, oral drug delivery remain the most preferred option for administration for various drugs. Most of the orally administered drugs, targeting is not a primary concern and itis usually intended for drugs to penetrate to the general circulation and perfuse to other body tissues. For this reason, most systems employed are of the sustained release variety. Now days as the expense and complications involved in marketing new drug entities are increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems (DDS). Sustained Release is providing promising way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body. The basic concepts of sustained drug delivery system optimizes of the various parameters like biopharmaceutical, pharmacokinetic and pharmacodynamics properties of a drug in such a way that therapeutic efficacy is maximized, side-effects are reduced and cure of the disease is achieved easily. Sustained release drug delivery is improved patient compliance due to less frequent drug administration, reduction of fluctuation in steady-state drug levels, maximum utilization of the drug, increased safety margin of potent drug, reduction in healthcare costs through improved therapy and shorter treatment period. The principal goal of sustained release forms is the improvement of drug therapy assessed by the relationship between advantages and disadvantages of the use of sustained release system.*

Keywords- Sustain release, drug delivery system, Controlled drug release system, Therapeutic

I. INTRODUCTION

A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body. This process includes the administration of the therapeutic product, the release of the active ingredients by the product, and the subsequent transport of the active ingredients across the biological membranes to the site of action. The term therapeutic substance also applies to an agent such as gene therapy that will induce in vivo production of the active therapeutic agent. Drug delivery system is an interface between the patient and the drug. It may be a formulation of the drug to administer it for a therapeutic purpose or a device used to deliver the drug. This distinction between the drug and the device is important, as it is the criterion for regulatory control of the delivery system by the drug or medicine control agency. There is a wide spectrum between drugs and devices, and the allocation to one or the other category is decided on a case by case basis. Sustained release (SR) preparations are not new but several new modifications are being introduced. They are also referred to as long acting or delayed release when compared to rapid or conventional release preparations. The term sometimes overlaps with controlled release, which implies more sophisticated control of release and not just confined to the time dimension.[1]

Probably the earliest work in the area of sustained drug delivery dosage forms can be traced to the 1938 patent of Israel Lipowski. This work involved coated pallets for prolonged release of drug and was presumably forerunner to the development of the coated particle approach to sustained drug delivery that introduced in the early 1950s. Ideally, a drug should arrive rapidly at the site of action (receptor) in the optimum concentration, remain for the desired time, be excluded from other sites, and be rapidly removed from the site when indicated i.e. the basic goal of the therapy is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time.[2]

Principle of Sustain release drug delivery system

The conventional dosage forms release their active ingredients into an absorption pool immediately. This is illustrated in the following simple kinetic scheme. The absorption pool represents a solution of the drug at the site of absorption, Kr, Ka and Ke - first order rate-constant for drug release, absorption and overall elimination respectively. Immediate drug release from a conventional dosage form implies that Kr>>>>Ka. For non-immediate release dosage forms, Kr<< the release of drug from the dosage form is the

rate limiting step. The drug release from the dosage form should follows zero-order kinetics, as shown by the following equation:

Kr° = Rate In = Rate Out = Ke.Cd.Vd
Where,
Kr°: Zero-order rate constant for drug release-Amount/time
Ke: First-order rate constant for overall drug elimination-time
Cd: Desired drug level in the body – Amount/volume
Vd: Volume space in which the drug is distributed in litter

Ideal properties of drug suitable for sustain release drug delivery system

1. It should be effectively absorbed by oral route and stable in gastro-intestinal (GI) fluid.
2. Drugs that have short half-lives (2-4 hrs) are ideal drug candidate for formulation into SR dosage forms eg. Captopril, Salbutamol sulphate.
3. The dose of drug should not be less than 0.5gm and maximum dose of drug for designing SRDDS is 1.0 gm eg. Metronidazole. IV. The therapeutic range of the drug should be high in SRDDS for drug should have wide therapeutic range enough such that variation in the release does not result in concentration beyond the minimum toxic levels.[3]

Mechanism of drug release

On exposure to aqueous fluid, hydrophilic matrices take up water, and polymer starts hydrating to form a gel layer. An initial burst of soluble drug may occur due to surface leaching when a matrix containing a swellable glassy polymer comes in contact with an aqueous medium, there is an abrupt change from a glassy to a rubbery state which is associated with swelling process with time, water infiltrator deep into the case increasing the thickness by the gel layer. Concomitantly the outer layer becomes fully hydrated and states dissolving or eroding. When water reaches the center of the system and the concentration of drug fells below the solubility value, the release rate of drug begins to reduce. At the same time, an increase in thickness of the barrier layer with time increases the diffusion path length, reducing the rate of drug release. Drug release kinetic associated with these gel layer dynamic, range initially from Fickian to anomalous (Non – Fickian) and subsequently from quasi Constant to constant. In general, two major factors control the drug release from swelling controlled matrix system. They include many processes given below.

1. The rate of aqueous medium infiltration into the matrix, followed by a relaxation process (hydration, gelatin or swelling).
2. The rate of matrix erosion As a result of these simultaneous processes, two front are evident, a swelling front, where the polymer get hydrated, and an eroding front. The distance between these two fronts are called diffusion layer thickness.[4]

Diffusion layer thickness depends on the selective rate at which the swelling and eroding fronts move in relation to each other. If the polymer gets slowly, solvent can penetrate deep into the glassy matrix the dissolving the drug; there for gel layer thickness and it stability are council in controlling drug release. Swelling of HPMC matrix tablet was higher for higher a molecular weight. They attributed this to the large hydrodynamic volume occupied by higher molecular weight chain when hydrated. As the polymer chain becomes more hydrated and the gel becomes more dilute, the disentanglement concentration may be reached that is the critical polymer concentration below which the polymer chain disentangle and detached from gelled matrix.[5]

Classification of sustain release drug delivery[6]

1. Diffusion Sustained Release

i. Swellable matrix.
ii. Reservoir/Laminate matrix.

2. Dissolution Sustained Release

i. Matrix/Monolith Dissolution System.
ii. Encapsulation/Coating/Reservoir System.

3. pH Dependent System

4. Altered Density System

i. High Density System.
ii. Low Density System
iii. Muco Adhesive System

5. Osmotic Pump System

6. Ion Exchange System

A. Diffusion systems

Diffusion systems rate release is dependent on the rate at which the drug dissolves through a barrier which is usually a type of polymer. Diffusion systems can be broken into two subcategories, reservoir devices and matrix devices. Diffusion systems are characterized by the release rate of a drug being dependent on its diffusion through an inert

membrane barrier. Basically, diffusion process shows the movement of drug molecules from a region of a higher concentration to one of the 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.[7]

Depending upon the mechanism such system can be classified as

a) Porous membrane controlled system:

In these type of system the rate controlling element is a water insoluble non swellable polymer like ethyl cellulose, poly metha acrylate etc. which controls the drug release through the micro pores present in their membrane or matrix structure

Advantages

- Can provide zero order drug release.

Disadvantages

- High cost per dosage unit.
- In case of dose dumping toxicity can take place.

b) Porous matrix controlled system:

In these type of system the rate controlling element is a water swellable material (hydrophilic polymers and gums) like alginates, xanthan gum, locust bean gum, HPMC etc. or a non swellable water insoluble polymer like ethyl cellulose .

Advantages

- Cost effective.
- Easy to fabricate.
- Drug could be protected from hydrolysis or other changes in GIT, so enhanced stability.
- Compounds with high molecular weight could be formulated.

Disadvantages

- Release rate is affected by presence of food.
- Matrix must be removed after the release of drug.

i. Reservoir Type

Reservoir devices coat the drug with polymers and in order for the reservoir devices to have sustained release effects, the polymer must not dissolve and let the drug be released through diffusion. The rate of reservoir devices can be altered by changing the polymer and is possible be made to have zero-order release; however, drugs with higher molecular weight have difficulty diffusing through the membrane.[8]

ii. Matrix type

Matrix devices forms a matrix (drug mixed with a gelling agent) where the drug is dissolved/dispersed.The drug is usually dispersed within a polymer and then released by undergoing diffusion. However, to make the drug SR in this device, the rate of dissolution of the drug within the matrix needs to be higher than the rate at which it is released.[9]

B. Dissolution sustained system

Dissolution systems must have the system dissolved slowly in order for the drug to have sustained release properties which can be achieved by using appropriate salts and/or derivatives as well as coating the drug with a dissolving material. It is used for drug compounds with high solubility in water. The drugs with slow solubility are suitable candidates for this system and for the drugs having high solubility the dissolution is decreased by conversion into a suitable salt or derivative. The reservoir device coats the drug with an appropriate material which will dissolve slowly. It can also be used to administer beads as a group with varying thickness, making the drug release in multiple times creating a SR.The matrix device has the drug in a matrix and the matrix is dissolved instead of a coating. It can come either as drug impregnated spheres or drug impregnated tablets.[10]

These systems can further be categorized as

i) Coating dissolution system

In this type of system the drug particles are coated with polymers like cellulose, polymethacrylates, PEGs etc. The resulting pellets are compressed as tablets. The dissolution rate of the coat depends upon thickness and solubility of coat .

ii) Soluble matrix system

These systems are also known as monoliths as the drug is homogenously dispersed in a rate controlling medium. Waxes like bee wax, carnauba wax etc. are used for controlling the dissolution rate.

The rate of dissolution is controlled by either of following mechanisms:

- Altering the rate of fluid penetration into tablet by altering the porosity of tablet.
- Decreasing the wettability of tablet.
- Slow dissolution rate of polymer.[11]

C. Ion exchange resins:

Based upon the principle that GIT has a relatively constant level of ions, this type of system has developed for controlling the rate of delivery of ionizable or ionic drugs. Such a system can be prepared by incubating the drug resin solution or by passing the drug solution through a column containing exchange resin. A cationic drug is complexed with a resin containing SO3 - group and for anionic drug resin containing N(CH3)3 group is used. In the GIT hydronium and chloride ions diffuses into the sustained release tablet and interact with drug resin complex to trigger the release of drug.

Types of ion exchange resins:

a) **Cationic exchange resin:** Contains acidic functional group
b) **Anion exchange resin:** Contains basic functional group.

These systems prevent dose dumping as they have better drug retaining properties. So, chances of toxicity are reduced. Moreover, the polymeric and ionic property of ion exchange resin makes the drug release more uniform than that of simple matrices. [12]

D. Method using osmotic pump:

Osmotic systems are based on the principle of osmosis. Such systems release the drugs at a constant zero order rate. These systems are popularly known as OROS. The system consist of a drug core and an osmotically active substance (osmogen) like mannitol surrounded by a semipermeable membrane coating with an orifice of 0.4 mm made by laser beam to facilitate drug exit. When exposed to GI Fluids, water flows though semipermeable membrane, under the influence of osmotic force of osmogen the drug release is facilitated via orifice. Osmotic controlled-release oral delivery systems (OROS) have the form of a rigid tablet with a semi-permeable outer membrane and one or more small laser drilled holes in it. As the tablet passes through the body, water is absorbed through the semipermeable membrane via osmosis, and the resulting osmotic pressure is used to push the active drug through the opening(s) in the tablet. Osmotic release systems have a number of major advantages over other controlled-release mechanisms.

E. pH-Independent formulation

These systems are designed for acid-labile drugs or drugs irritating GIT mucosa and targeting their delivery to the intestinal tract. It is fabricated by coating the core of tablet with a combination of intestinal fluid insoluble polymer (ethyl cellulose) and intestinal fluid soluble polymer (HPMCP). The coating membrane resists the dissolution of drug in stomach at acidic pH. After gastric emptying the system travels to small intestine. At a pH above 5 the intestine soluble component dissolves; thereby producing a porous membrane that controls the release of drug from the core of the tablet.Since most drugs are either weak acids or weak bases, the release from SR 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. [13]

F. Altered Density Formulations

The transit time of GI contents is usually less than 24 hours. This is major limiting factor in design of sustained release formulation. If the residence time of drug in stomach or intestine is prolonged the frequency of dosing can further be reduced. This could be achieved by altering the density of drug particles, using mucoadhesive polymers or by altering the size of dosage form. It is reasonable to expect that unless a delivery system remains in the vicinity of the absorption site until most, if not all of its drug contents is released, it would have limited utility. To this end, several approaches have been developed to prolong the residence time of DDS in the GI tract.[14]

Altered density formulation can further be classified as:

i) High-density approach:

In this approach, the density of the pellets must exceed that of normal stomach content and should therefore, be at least 1-4 g/cm3.The density of GI fluids is about 1.4 g/ cc so the drug particles having density greater than this value usually 1.6 g/cc can be used for this purpose. These systems have prolonged residence time and not affected by presence of food. Iron oxide and barium sulfate can be used for this purpose.

ii) Low-density approach:

Globular shells which have an apparent density lower than that of gastric fluid can be used as a carrier of the drug for SR purpose. These pellets have density lower than that of

GI fluids. So, such tablets tend to float on gastric juice for an extended time period thereby slowing down the drug release. Such system can be formulated by granulating a drug with 20-80% of hydrogel like HPMC, HPC and HEC. On contact with GI fluids, tablets swells and form a diffusible gel barrier that lowers the density of the system lower than 1; thereby allowing it to float.[15]

Advantages of sustained release drug delivery:

Following are the potential advantages of sustained release products

1. Decreased local and systemic side effects reduced gastrointestinal irritation.
2. Better drug utilization reduction in total amount of drug used.
3. Improved efficiency in treatment, optimized therapy, more uniform blood concentration.
4. Reduction in fluctuation in drug level and hence more uniform pharmacological response, cure of control of condition more promptly, less reduction in drug activity with chronic use.
5. Method by which sustained release is achieved can improve the bioavailability of some drugs e.g. drugs susceptible to enzymatic inactivation can be protected by encapsulation in polymer systems suitable for sustained release.
6. Improved patient compliance, less frequent dosing, reduced night-time dosing, reduced patient care time. The importance of patient compliance in successful drug therapy is well recognized. It has been found that there is an inverse relationship between the number of dosages per day and the compliance rate.
7. Although the initial unit cost of sustained release products is usually greater than that of conventional dosage forms because of the special nature of these products, the average cost of treatment over an extended time period may be less. Economy may also result from a decrease in nursing time and hospitalization time.[16]

Disadvantages of sustained release drug delivery

The disadvantages of sustained release drug delivery system are

1. Decreased systemic availability in comparison to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time complete release, site specific absorption, pH dependent stability, etc.
2. Poor in vitro – in vivo correlation.
3. Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
4. Reduced potential for dose adjustment of drugs normally administered in varying strengths.[17]

There are certain considerations for the formation of sustained release formulation;

1) If the active compounds has a long half-life (over 6 hours), it is sustained on its own.
2) If the pharmacological activity of the active compound is not related to its blood levels, time releasing has no purpose.
3) If the absorption of the active compound involves an active transport, the development of a time release product may be problematic.
4) Finally, if the active compound 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 unwarranted and another mode of administration would be recommended[18]

Evaluation of Oral Sustained Release Tablets

1. Thickness of tablet:

Thickness of tablet is evaluated by using micrometer screw gauge. Test is carried out randomly on twenty tablets and average values are calculated.

2. Hardness of tablet:

Hardness of tablet of each batch is evaluated by Monsanto hardness tester and average values are calculated.

3. Uniformity of weight:

20 tablets are selected randomly and weighed individually and collectively; average weight is calculated.

% of weight variation=(Individual Weight Average weight/Average Weight) × 100

4. Uniformity of content:

This test is done to make sure that every tablet should contain the same amount of active ingredient with little or no variation within a batch. For content uniformity test 30 tablets

are selected and 10 are assayed individually. At least 9 must assay between ±15% of the declared potency and should not exceed ±25%

5. Friability:

20 tablets are weighed and placed in friabilator. The chamber is rotated for 4 minutes at a speed of 25 r.p.m. the tablets are removed from the chamber and weighed again. Loss in weight indicates friability. The tablets to be considered of good quality if loss in weight is less than 0.8%

6. In vitro dissolution studies

The test is carried out to measure the amount of time required for certain percentage of drug to go into the solution under the specific test conditions. Rotating paddle type and rotating basket type apparatus can be used as per pharmacopoeial standards or as mentioned in monograph of particular drug. The test is passed if for each of the five tablets, the amount of active ingredient in solution is not less than 70% of the stated amount or as specified in the monograph of the API in pharmacopoeia. [19]

Factors Influencing the Design and Performance of Sustained Release Products

The type of delivery system and route of administration of the drug presented in sustained drug delivery system may depend upon two properties. They are

I. Physicochemical Properties of drugs
II. Biological Factors.

I. Physicochemical Properties of Drugs

1) Dose size

For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general a single dose of 0.5 to 1gm is considered maximum.

2) Ionization, PKa and Aqueous Solubility

The pH Partition hypothesis simply states that the unchanged form of a drug species will be preferentially absorbed through many body tissues. Therefore it is important to note the relationship between the P Ka of the compound and its absorptive environment. For many compounds, the site of maximum absorption will also be the area in which the drug is least soluble. For conventional dosage forms the drug can generally fully dissolve in the stomach and then be absorbed in the alkaline pH of the intestine.

For sustained release formulations much of the drug will arrive in the small intestine in solid form. This means that the solubility of the drug is likely to change several orders of magnitude during its release. Compounds with very low solubility are inherently controlled, since their release over the time course of a dosage form in the GIT will be limited by dissolution of the drug. The lower limit for the solubility of a drug to be formulated in a sustained release system has been reported to be 0.1mg/mL Thus for slightly soluble drugs, diffusional systems will be poor choice, since the concentration in solution will be low. For example Tetracycline has maximum solubility in the stomach and least solubility in the intestine where it is maximally absorbed. Other examples of drugs whose incorporation into sustained release systems are limited because of their poor aqueous solubility and slow dissolution rate are digoxin, warfarrin, griseofulvin and salicylamide. Very soluble drugs are also good candidates for the sustained release dosage forms. [20]

3) Partition coefficient

The compounds with a relatively high partition coefficient are predominantly lipid soluble and easily penetrate membranes resulting high bioavailability. Compounds with very low partition coefficient will have difficulty in penetrating membranes resulting poor bioavailability. Furthermore partitioning effects apply equally to diffusion through polymer membranes. [21]

4) Drug Stability

The drugs, which are unstable in stomach, can be placed in a slowly soluble form and their release delayed until they reach the small intestine. However, such a strategy would be detrimental for drugs that either are unstable in the small intestine (or) undergo extensive gut wall metabolism, as pointed out in the decrease bioavailability of some anticholinergic drugs from controlled /sustained release formulation. In general the drugs, which are unstable in GIT environment poor candidates for oral sustained release forms. [22]

1. Protein Binding

It is well known that many drugs bind to plasma proteins with a concomitant influence on the duration of drug action. Since blood proteins are mostly recirculated and not eliminated. Drug protein binding can serve as depot for drug producing a prolonged release profile, especially if a high degree of drug binding occurs.[23]

II. Biological Factors

1. Biological Half-Life

Therapeutic compounds with half-life less than 8 hrs are excellent candidates for sustained release preparations. Drugs with very short half-life (less than 2 hrs) will require excessively large amounts of drug in each dosage unit to maintain controlled effects. Thus forcing the dosage form itself to become too large to be administered .Compounds with relatively long half-lives, generally greater than 8 hrs are not used in the sustained release dosage forms, since their effect is already sustained and also GI transit time is 8-12 hrs. So the drugs, which have long -half life and short half- life, are poor candidates for sustained release dosage forms. Some examples of drug with half-lives of less than 2 hours are ampicillin, cephalexin, cloxacillin, furosemide, levodopa, penicillin G and propylthiouracil. Examples of those with half-lives of greater than 8 hours are dicumarol, diazepam, digitoxin, digoxin, guanethidine, phenytoin and warfarin.[24]

2. Absorption

The characteristics of absorption of a drug can greatly affect its suitability as a sustained release product. Drugs which are absorbed by specialized transport process (carrier mediated) and drug absorption at special sites of the gastrointestinal tract (Absorption Window) are poor candidates for sustained release products.[25]

3. Metabolism

The metabolic conversion of a drug to another chemical form usually can be considered in the design of a sustained-release system for that drug. As long as the location, rate and extent of metabolism are known and the rate constant for the process are not too large, successful sustained-release products can be developed. There are two factors associated with the metabolism of some drugs; however that present problems of their use in sustained-release systems. One is the ability of the drug to induce or inhibit enzyme synthesis; this may result in a fluctuating drug blood level with chronic dosing. The other is a fluctuating drug blood level due to intestinal metabolism or through a hepatic first-pass effect. Examples of drugs that are subject to intestinal metabolism upon oral dosing are Hydralazine, salicylamide, nitroglycerine, isoproterenol, chlorpromazine and levodopa. Examples of drugs that undergo extensive first-pass hepatic metabolism are propoxyphene, nortriptyline, phenacetine, propranolol and lidocaine.[26]

Rationale of sustained release drug delivery system

The basic rationale for sustained drug delivery is to alter the pharmacokinetic and pharmacodynamics of pharmacologically active moieties by using novel drug delivery systems or by modifying the molecular structure and/or physiological parameters inherent in a selected route of administration. It is desirable that the duration of drug action become more to design properly. Rate controlled dosage form, and less, or not at all, a property of the drug molecules inherent kinetic properties. As mentioned earlier, primary objectives of controlled drug delivery are to ensure safety and to improve efficiency of drugs as well as patient compliance. This achieved by better control of plasma drug levels and frequent dosing. For conventional dosage forms, only the dose and dosing interval can vary and, for each drug, there exists a therapeutic window of plasma concentration, below which therapeutic effect is insufficient, and above which toxic side effects are elicited. This is often defined as the ratio of median lethal dose (LD 50) to median effective dose (ED50).[27]

Design of sustained release drug delivery system

Practically there are two modern methods are mostly used by pharmaceutical manufacturing scientist in the designing of dosage form for sustained release tablet. In that the first approach method are mainly involved to modifying of properties like physical and chemical nature of the drug and the second method is how to modify the release of drug from the prepared dosage form. Physical and chemical characteristic of the active component can be developed by formatting complex type, drug and adsorbates formulation, or prodrug synthesis. The conversion of inactive form to active nature process is mostly attempted and investigated. The second method is used in the formulation development of sustained release system. This is popular method because it's inherent advantage. The advantage of this method in the design of dosage form is independent. The final formulation form could be in a liquid suspension form, a capsule or a tablet. Generally some important criteria could be considering in the formulation of a sustained release dosage form. Not all the drug ideal characteristic. Drugs which shown neither very slow or nor very fast rate of absorption and excretion. Drugs with very short half life that is less than 2 hours are poor candidates for sustained release because large quantities of drug required for such a formulation. The drug should be absorbed in the gastro intestinal region. Drug manufacturing in sustained release tablet it have been good solubility in the intestinal and gastric fluid. They are administered in relatively small doses, drug with large single doses frequently are not suitable for sustained release. Sustained release dosage form mainly used in case of chronic condition than the acute condition. If the medicine need for acute condition at that we have to change the dose adjustment by physician alike that is

given in sustained release form. Drug should have solubility and permeability properties. Drug with less protein binding properties. Drug should not produce local irritation.[28]

MASR x AND COSR x Sustained Release Technology

A. MASR x Technology

The objective is to assess factors affecting drug release from guar-gum-based once-daily matrix sustained-release formulations (MASR x). The tablets were designed to hydrate completely into the tablet core. In the process, the tablet core expanded and released the drug in a sustained-release manner.

B. COSRxTechnology

Formulations base on constant sustained-release matrix (COSRx) technology can also be developed using guar gum as a major rate-controlling polymeric material. Depending on the solubility of the drug, low- or high-viscosity guar gum can be use. The formulation involves a guar-gum-base tablet and a combination of water-soluble and water-insoluble polymeric tablet coat. When the tablet is placed in a dissolution medium, there is slow diffusion of water through the polymeric wall leading to swelling and gelatins of the guar gum/drug core. As the hydration a progress, the tablet continues to swell until the wall breaks, forming a sandwich-like structure. The release of drug proceeds primarily out of the sides of the tablet as it passes through the intestinal tract. The tablets provide a nearly zero-order drug release following a programmed period of delayed drug release.[29]

Pharmacokinetic Simulation of Sustained Release Products

The plasma drug concentration profiles of many sustained release products fits an oral one compartment model assuming first order absorption and elimination. Compared to an immediate release product, the sustained release product typically shows a smaller absorption rate constant, because of the slower absorption of the sustained release product. The time for peak concentration (t_{max}) is usually longer , and the peak drug concentration (C_{max}) is reduced. If the drug is properly formulated, the area under the plasma drug concentration curve should be the same, parameters such as C_{max}, t_{max} and AUC conveniently show how successfully the extended release product performs in-vivo. For example, a product with t_{max} of 3 hours would not be very satisfactory if the product is intended to last 12 hours. Similarly, an excessively high C_{max} is a sign of dose dumping due to inadequate formulation. The Pharmacokinetic analysis of single and multiple-dose plasma data has been used by regulatory agencies to evaluate many sustained release products. The analysis is practical because many products can be fitted to this model even though the drug is not released in a first order manner. The limitation of this type of analysis is that the absorption rate constant may not release to the rate of drug dissolution in vivo.[30]

II. CONCLUSION

Now a day's pharmaceutical industry focusing for development of sustained release oral dosage forms as it become an important tool in medical practice. These sustained release formulations are designed to release drug in predetermined rate and able to maintained plasma drug concentration in therapeutic window with minimum side effects. The basic rational behind sustained release drug delivery is to alter biopharmaceutical, pharmacokinetic and pharmacodynamic of drug to reduce side effect, give patient compliance and cure the disease.

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