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MODIFIED RELEASE DRUG DELIVERY SYSTEM: CONCEPT AND SYSTEM DESIGN OF RATE-CONTROLLED DRUG DELIVERY SYSTEM

Ankit Singh*[1], Dakshina Gupta[2], Saurabh Singh[3]

[1]*Assistant Professor, Department of Pharmacy, Advance institute of biotech and paramedical sciences, NH 91, Pargahi Bangar, Kalyanpur, Kanpur, Uttar Pradesh 209217*

[2]*Assistant Professor, Department of Pharmacy, Advance institute of biotech and paramedical sciences, Naramau kanpur NH 91, Pargahi Bangar, Kalyanpur, Kanpur, Uttar Pradesh 209217*

[3]*Assistant Professor, Department of Pharmacy, Dayanand Dinanath College Institute of Pharmacy, Ramaipur, Kanpur, Uttar Pradesh 209214*

Corresponding Author*

Ankit Singh:*Assistant Professor, Department of Pharmacy, Advance institute of biotech and paramedical sciences, NH 91, Pargahi Bangar, Kalyanpur, Kanpur, Uttar Pradesh 209217*

ABSTRACT

Purpose*-Among the various routes of drug delivery oral route is most preferred route. But conventional dosage form offers few limitations which could be resolved by modifying the existing dosage form. Sustained and controlled drug delivery system helps in maintaining of constant plasma drug concentration and retards the release rate of drug thereby extending the duration of action. There are various formulation strategies for sustained release tablets among which matrix tablet serves as an important tool. Hence the problem like poor patient compliance, multiple dosing, see-saw fluctuations can be easily minimized. Matrix tablets can be formulated by either direct compression or wet granulation method by using a variety of hydrophilic or hydrophobic polymers. The rate of drug release from the matrix is primarily governed by rate and extent of water penetration, swelling of polymer, dissolution and diffusion of drug.*

Conclusion*- Thus, sustained release matrix tablet can offer better patient compliance and could be quite helpful in treatment of chronic diseases. The present article concentrates on oral sustained release tablets with a special emphasis on matrix tablet.*

KEYWORDS: *Conventional tablet, Sustained release, Controlled release, Polymer, Matrix tablet.*

1. INTRODUCTION

Sustained release, sustained action, controlled release, extended action, timed release dosage forms are the terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after the administration of single dose. The term Controlled release has become associated with those systems from which therapeutic agents maybe automatically delivered at predefined rates over a long period of time. But, there are some confusion in terminology between[3] Controlled release and Sustained release.

Sustained Release: The term sustained release has been constantly used to describe a pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed &/or prolonged & its plasma profile is sustained in duration.

Controlled Release: This term on the other hand, has a meaning that, goes beyond the scope of sustained drug action. It also implies a predictability & reproducibility in the drug release kinetics, which means that the release of drug ingredient from controlled delivery system proceeds at a rate profile that is not only predictable kinetically, but also reproducible from one unit to another.

Advantages of Sustained/Controlled release drug delivery system over the conventional dosage form

- Reduced dosing frequency.
- Dose reduction. Improved patient compliance.
- Constant level of drug concentration in blood plasma.
- Reduced toxicity due to overdose.
- Reduces the fluctuation of peak valley concentration. Night time dosing can be avoided.

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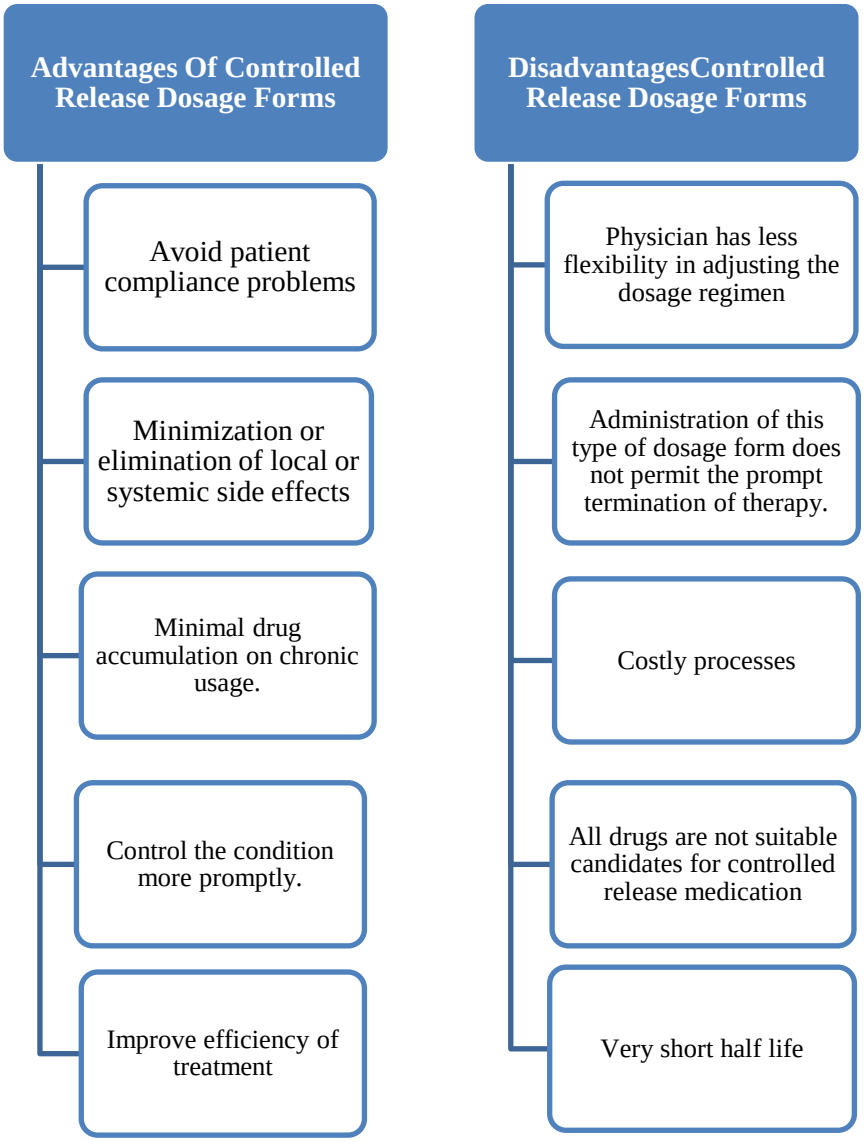

Fig. 1 demonstrate the merits and demerits

Mechanism of Drug Release from Matrix Devices

Dissolution Controlled Release

Sustained release oral products employing dissolution of drug from the solid surface to the bulk solution through an unstirred liquid film, is the rate limiting step. In this case the dissolution process at steady state would be described by Noyes-Whitney equation, As the time limiting step are simplest to prepare. If a drug has a rapid rate of dissolution it is possible to incorporate it into a tablet with a carrier that has a slow rate of dissolution. In the dissolution process if the dissolution process is diffusion layer control, the rate of diffusion.

(Cs -C) ---------- (1)

Where,

dc/dt = Dissolution rate.
KD = Dissolution rate constant.
Cs = Saturation solubility of drug.

Diffusion Controlled Release

These systems are of two types; a. Encapsulation diffusion control In this system water –insoluble polymeric material encases a core of drug. Drug will partition into the polymer membrane and exchange with the fluid surrounding the particle or tablet.

The rate of drug release is given by the equation

dm/dt = AdkΔc---------- (2)

Where,

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A = Area
D = Diffusion coefficient
K = The partition coefficient of the drug between the membrane and the drug core
I = The diffusion path length
Δc = The concentration difference across the membrane. An important parameter

In the above eq. 2 is the partition coefficient, which is defined as the concentration of the drug in the membrane over the concentration if the drug in core

Polymers in Modified Release

Modified release dosage forms are designed by altering drug absorption or the site of drug release in order to accomplish predetermined clinical objectives. Possible therapeutic benefits of a modified release product include improved efficacy and reduced adverse effects, increased convenience and patient compliance, optimized performance, a greater selectivity of activity. Polymers are becoming increasingly important in design and development of modified drug delivery systems to provide modulation of drug release. The pharmaceutical applications of polymers range from their use as binders, solubility modifier, filler, coating agent in tablets to viscosity, flow controlling agents in liquids, suspensions and emulsions. The choice of a specific material and control mechanism for active pharmaceutical has become a critical aspects. The selection of polymeric material mainly is based on drug properties, target site, desired release environment, duration of action and desired release rate.

The polymers are inseparable part of our life. The use of polymers and polymer based sustained drug release system has been widely studied by numerous scientists and achieved many fruitful results. The first polymeric devices developed for controlled drug release system was way back in 1960s. The use of hydrogels in drug delivery applications was discovered in the 1960 by Wichterle and Lim. In the mid 70s, hydrogel membranes based on poly methacrylates was used in studies for the design of controlled release systems containing fluorides, for the treatment of dental caries in the patients. Folkman and Long in 1966 first represented a drug delivery system based upon the diffusion of small molecules through the wall of silicone rubber tubing. Polymer based controlled drug release systems are generally classified as either reservoir membrane devices or matrix monolithic devices. In it the release is controlled by a polymeric membrane that surrounds a drug moiety. These polymeric membranes may be subdivided into hydrophobic, nonporous, microporous and water-swollen, hydrophilic substances like hydrogels. Various cellulose materials like cellulose triacetate, polycarbonate and polypropylene, could be used in the formation of membranes with a diameters of the order of 1.5 × 10-3 μm to several microns.

Polymers that are used in pharmaceutical coating are primarily based on cellulosic and acrylic polymers, as they both have good film-forming properties that enable them in the production of tough protective coatings. The process ability of chitosan into film-forms may permit its extensive use in the formulation of film dosage forms or as drug delivery systems. Chitosan could be dissolved in organic acids such as lactic acid and acetic acid, before casted to films. Starch acetate (SA) polymer has been investigated as a novel, multifunctional excipient for the direct compression tableting process. Drug release rate is influenced by factors such as rate of diffusion across the membrane, tablet coating so that neither dissolution nor degradation of the polymer should occur during its active lifetime. Various materials such as fibrinogen, fibrin, and collagen have been tested as carriers for drug delivery systems. Collagen has been shown to have potential as a biomaterial since it is a major constituent of connective tissue. In addition to biocompatibility and non-toxicity to most tissues, collagen has efficient structural, physical, chemical and immunological properties that could be easily altered.

Physiochemical Properties/Parameters

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 0.5-1.0 g is considered maximal for a conventional dosage form. This also holds for sustained-release dosage forms. Those compounds that require large dosing size can sometimes be given in multiple amounts or formulated into liquid system. Another consideration is the margin of safety involved in the administration of large amounts of a drug with narrow therapeutic range.

Ionization and Pka

Drugs existing largely in an ionized form are poor candidates for oral SR DDS. Absorption of the unionized drugs is well whereas permeation of ionized drug is negligible because the absorption rate of the ionized drug is 3-4 times less than that of the unionized drug. The pKa range for an acidic drug whose ionization is pH sensitive is around 3.0-7.5 and pKa range for a basic drug whose ionization is pH sensitive is around 7.0-11.0 are ideal for optimum positive absorption. Drug shall be unionized at the site to an extent 0.1-5.0%.

Partition Coefficient

The partition coefficient is defined as the fraction of drug in an oil phase to that of an adjacent aqueous phase. Partition coefficient influences not only the permeation of the drug across the biological membranes but also diffusion across the rate controlling membrane or matrix between the time when a drug is administered, and when it is eliminated from the body, it must diffuse through a variety of biological membranes that act primarily as lipid-like barriers. A major criterion in evaluation of the ability of a drug to penetrate these lipid membranes (i.e., its membrane permeability) in its apparent oil or water partition coefficient defined as,

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K=CCow

Where,

Co = Equilibrium concentration of all forms of the drug in an organic phase at equilibrium,

Cw = Equilibrium concentration of all forms in an aqueous phase.

Adequate Aqueous Solubility

Most of the drugs are weak acids or weak bases. Drugs with low water solubility will be difficult to incorporate into SR mechanism. For a drug with high solubility and rapid dissolution rate, it is often quite difficult to retard its dissolution rate. A drug of high water solubility can dissolve in water or GI fluid readily and tends to release its dosage form in a burst and thus is absorbed quickly leading to a sharp increase in the blood drug concentration compared to less soluble drug. It is often difficult to incorporate a highly water-soluble drug in the dosage form and retard the drug release, especially when the dose is high. The pH-dependent solubility, particularly in the physiological pH range, would be another problem for SR formulation because of solubilisation obstacles and often compounds with solubility 10 mg/ml present difficulties to solubilisation dosing formulation. In general, highly soluble drugs are undesirable for formulation into an SR product.

Stability

Drugs undergo both acid/base hydrolysis and enzymatic degradation when administered oral route. Drugs that are unstable in gastric pH can be developed as slow release dosage form and drug release can be delayed until the dosage form reaches the intestine. Drugs that undergo gut wall metabolism and show instability in the small intestine are not suitable for SR system. In such case, the drug can be modified chemically to form prodrugs, which may possess different physicochemical properties or a different route of administration should be chosen.

Biological Properties

Half Life

The usual goal of an oral sustained-release product is to maintain therapeutic blood levels over an extended period. The duration of action significantly influences the design of oral SR delivery system and it is dependent on the biological half-life. Factors influencing the biological half-life of a drug include its elimination, metabolism and distribution patterns. Drugs with short half-lives required frequent dosing to minimize fluctuations in the blood levels. SR dosage forms would appear very desirable for such drugs. For a given steady state drug concentration, the zero-order rate of release of a drug from its dosage form is directly proportional to its rate of elimination. Thus drug with very short half-lives require faster rate of release, for a modest duration of time while dosage form requires large dosage. In general, drugs with half-lives shorter than 2 hrs are poor candidates for sustained-release preparations. Compounds with long half-lives, more than 8 hrs, are also generally not used in sustaining forms, since there effect is already sustained.

Absorption

Absorption is the transfer of a drug from its site of administration to the bloodstream. The rate and efficiency of absorption depend on the route of administration. For IV delivery, absorption is complete; that is, the total dose of drug reaches the systemic circulation. Drug delivery by other routes may result in only partial absorption and, thus, lower bioavailability. For example, the oral route requires that a drug dissolves in the GI fluid and then penetrates the epithelial cells of the intestinal mucosa, yet disease states or the presence of food may affect this process.

The constant blood or tissue concentration of drug can be obtained from the oral SR systems through uniform and consistent release as well as absorption of the drug. The desirable quality of the sustaining system is that it should release completely absorbed. Apparently the release of the drug from the system is the rate limiting step, where rapid absorption relative to the drug release is always expected, i.e., Kr << Ka.

If we assume the transit time of dosage forms in the absorptive areas of GI tract is about 8-12 hrs, the maximum half-life for absorption should be approximately 3-4 hrs. Otherwise, the dosage form will pass out of absorptive regions before drug release is complete. Therefore, the compounds with lower absorption rate constants are poor candidates. Some possible reasons for the low extent of absorption are poor water solubility, small partition co-efficient, protein binding, acid hydrolysis and metabolism or site specific or dose-dependent absorption. Drugs with the high apparent volume of distribution, which influence the rate of elimination of the drugs, are a poor candidate for oral SR DDS. A drug which extensively metabolizes is not suitable for SR DDS. A drug capable of inducing metabolism, inhibiting metabolism, metabolized at the site of absorption or first-pass effect is the poor candidate for SR delivery, as it could be difficult to maintain constant blood level. Drugs that are metabolized before absorption, either in the lumen or the tissues of the intestine, can show decreased bioavailability from the sustained releasing systems.

Approaches for SR/CR oral formulation

Sustained release drug delivery system. It includes any drug delivery system achieves release of drug over an extended period of time, which not depend on time. Hydrophilic polymer matrix is widely used for formulating an Sustained dosage form. The role of ideal drug delivery system is to provide proper amount of drug at regular time interval & at right site of action to maintain therapeutic range of drug in blood plasma. Controlled release It includes any drug delivery system which releases the drug pre determined rate over an extended period time.

Additional measures to assess bioequivalence

It is generally agreed that the present regulatory criteria are adequate in the assessment of bioequivalence for many MR

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formulations with conventional drug release profiles in vivo. However, for MR products designed to achieve a rapid rise in drug plasma concentrations (and thus a rapid onset of therapeutic effect) following administration or newer MR products with different drug release mechanisms (such as pulsatile- or chrono-release), other measures in addition to the current pharmacokinetic parameters (i.e., AUC and Cmax) may be needed for assuring bioequivalence. The use of pharmacokinetic/Pharmacodynamics (PK/PD) modeling and simulations allows for linking drug concentrations to their effects (safety or efficacy) and thus can be used to assess the impact of a difference in input rate on therapeutic equivalence.

CONCLUSION

Drug delivery is the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals. For the treatment of human diseases, nasal and pulmonary routes of drug delivery are gaining increasing importance. These routes provide promising alternatives to parenteral drug delivery particularly for peptide and protein therapeutics. For this purpose, several drug delivery systems have been formulated and are being investigated for nasal and pulmonary delivery. These include liposomes, proliposomes, microspheres, gels, prodrugs, cyclodextrins, among others. Nanoparticles composed of biodegradable polymers show assurance in fulfilling the stringent requirements placed on these delivery systems, such as ability to be transferred into an aerosol, stability against forces generated during aerosolization, biocompatibility, targeting of specific sites or cell populations in the lung, release of the drug in a predetermined manner, and degradation within an acceptable period of time.

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