A REVIEW ON: SUSTAINED RELEASE TECHNOLOGY

M.M. GUPTA[1], RAY BRIJESH.*[1]

[1]Department of Pharmaceutics, Faculty of Pharmacy, Jaipur College of Pharmacy, Jaipur, Rajasthan-302022, India.

ABSTRACT

All drug delivery systems, oral drug delivery remain the most preferred option for administration for various drugs. Sustained Release is also 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 rationale of sustained drug delivery system optimizes of the biopharmaceutical, pharmacokinetic and pharmacodynamics properties of a drug in such a way that utility is maximized, side-effects are reduced and cure of the disease is achieved. 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: Sustained release, Mechanism of drug release, Matrix tablet, Drug properties.

INTRODUCTION

All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology, pharmacokinetics, pharmacodynamics and formulation design is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form[1]. Advantages of administering a single dose of a drug that is released over an extended period of time, instead of numerous doses, have been obvious to the Pharmaceutical industry for some time. The desire to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use[2]. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems[3]. Matrix system is widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers[4]. One of the interesting results of pharmaceutical research is the fact that absorption rate of a drug can be decreased by reducing its rate of release from the dosage form.

The product so formulated are designated as sustained action, sustained release, delayed action, prolonged action, depot, respiratory, retarded release and timed release medication.[5,6] Over the past 30 years, as the expense and complication involved in marketing new entities have increased with concomitant recognition of the therapeutics advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled drug delivery system. Sustained release technology is relatively new field and as a consequence, research in the field has been extremely fertile and has produced many discoveries.

With many drugs, the basic goal is to achieve a steady state blood level that is therapeutically effective and non-toxic fir an extended period of time. The design of proper dosage form is an important element to accomplish this goal. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release and depot dosage form are term used to identify drug delivery system that are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. In the case of oral sustained released dosage form, an effect is for several hours depending upon residence time of

*Corresponding author:
Email: raybrijesh@gmail.com

formulation in the GIT. Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges. Some drugs also possess solubility problems. In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels as shown in Figure 1.

Fig. 1. Drug levels in the blood with
a) Traditional drug dose systems and
b) Controlled drug delivery dose systems.
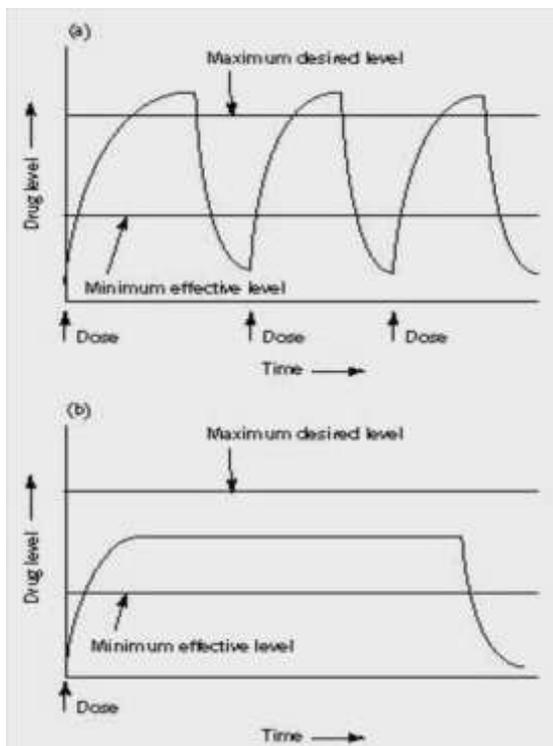
To overcome these problems, controlled drug delivery systems were introduced three decades ago. These delivery systems have a number of advantages over traditional systems such as improved efficiency, reduced toxicity, and improved patient convenience. The main goal of controlled drug delivery systems is to improve the effectiveness of drug therapies.[7-10]

Not all the drugs are the suitable candidates for the sustained release dosage form. Ideal characteristic of the drug for the sustained release dosage form are;
➢ Drug should have a shorter half-life as drug with a longer half-life are inherently long acting drugs.

➢ Drug should be absorbed from large portion of gastrointestinal tract, since absorption must occur through the gut.
➢ Drug should be having a good solubility profile to be a good candidate for sustained release dosage form.
➢ Dose of the drug should not be too large, as a larger dose is to be incorporated into sustained release dosage form.

Potential advantage of sustained release dosage form
➢ Avoid patient's compliance problem due to reduced frequency of dosing.
➢ Blood level oscillation characteristics of multiple dosing of conventional dosage form is reduced because a more even blood level is maintained.
➢ Employ a less total drug.
➢ Minimize or eliminate local or systemic side effects.
➢ Minimize drug accumulation with chronic dosing.
➢ Obtained less potential of reduction in drug activity with chronic use.
➢ Improved efficiency in treatment.
   • Cure or control condition more promptly.
   • Improved control of condition i.e. reduced fluctuation in drug level.
   • Improved bioavailability of some drugs.
➢ Make a use of special effects, e.g. sustained release aspect for relief of arthritis by dosing before bedtime.
➢ Economy.
➢ Overall, administrations of sustained release form enable increased reliability of therapy.

MECHANISM OF DRUG RELEASE FROM MATRIX DEVICES[9]
(1) Dissolution controlled release
Sustained release oral products employing dissolution 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 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,

$$d_c/d_t = K_D A (C_s - C) \text{----------------- (1)}$$

Where,
   d_c/d_t = Dissolution rate.
   K_D = Dissolution rate constant.
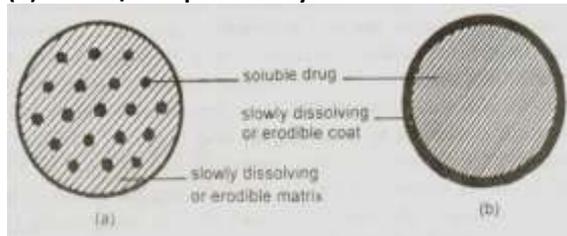 C_s = Saturation solubility of drug.

C   = The concentration of drug in bulk of the solution.

Dissolution control formulations are categories as

➢ Encapsulation dissolution control
➢ Matrix dissolution control

Fig. 2. Schematic representation of dissolution controlled release systems
(a) matrix system, and
(b) coated/encapsulated system

a. Encapsulation dissolution control

This method involves coating individual particles or granules of drug with slowly dissolving material. The coated particles can be compressed directly into tablet as in spacetabs or placed in capsule as in spansule products.

b. Matrix dissolution control

This method involves compression of the drug with a slowly dissolving carrier in a tablet form. Here the rate of drug availability is controlled by the rate of penetration of the dissolution fluid into the matrix. This in turn, can be controlled by porosity of the tablet matrix, the presence of hydrophilic and the wettability of the tablet and particle surface.

(2) 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.

Fig. 3. Drug release of diffusion across the insoluble membrane of reservoir device.
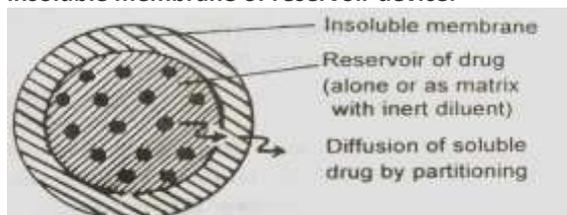
The rate of drug release is given by the equation.

$$d_m/d_t = Adk\Delta c \text{-------------------- (2)}$$

Where,

A = Area
D = Diffusion coefficient

K = The partition coefficient of the drug between the membrane and the
   drug core
I = The diffusional 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.

b. Matrix diffusion control

Fig. 4. Diffusion controlled devices
(a) rigid matrix, and (b) swellable matrix.
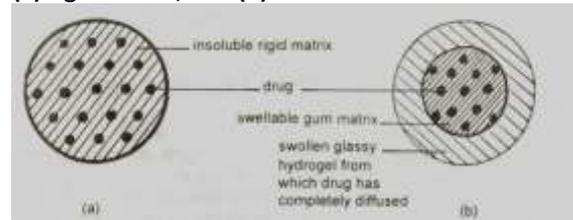
In this system, a solid drug is dispersed in lipophillic or a hydrophilic polymer matrix and the rate of release of drug depends on the rate of drug diffusion and not on the rate of solid dissolution.

MATERIAL USE AS RETARDANTS IN MATRIX TABLET FORMULATION[11]

These classes of retardant materials are used to prepare matrix tablet formulations.

a. Water insoluble inert materials

e.g. polyethylene, polyvinyl chloride, methyl acrylate, methacrylate copolymer, ethyl cellulose.

b. Insoluble, erodable materials

e.g. Steryl alcohol, stearic acid, polyethylene glycol, carnauba wax, caster wax, polyethylene glycol monosterate, triglycerides.

c. Hydrophillic materials

e.g. Hydroxy propyl methylcellulose, sodium CMC, methylcellulose, hydroxy ethyl cellulose.

Natural gums: Galactomannose (guargum), chitosan, gum acacia, locust bean gum, sodium alginate, karaya gum, pectins, xanthan gum.

d. Natural polymers

eg. Ispaghula husk, tamarind seed polymer.

DRUG PROPERTIES RELEVANT TO SUSTAINED RELEASE FORMULATION[12-14]

The design of sustained - release delivery systems is subject to several variables of considerable importance. Among these are the route of drug delivery, the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug. Each of these variables are interrelated and this imposes certain constrains upon choices for the route of delivery, the design of the delivery system and the

length of therapy. Properties of drugs are very important for designing a sustained release dosage form mainly physicochemical and biological properties of the drug are most important.

Physicochemical properties
a) Aqueous solubility and pKa
A drug to be absorbed it must be dissolved in the aqueous phase surrounding the site of administration and then partition into the absorbing membrane. Two of the most important physicochemical properties of a drug that influence its absorptive behavior are its aqueous solubility and if it is a weak acid or base its pKa. These properties pay an influential role in the performance of controlled release systems. The aqueous solubility of a drug influences its dissolution rate, which in turn establishes its concentration solution and hence the driving force for diffusion across membrane. The dissolution rate is constant only if surface area 'A' remain constant, but the important point to note is that the initial rare is directly proportional to aqueous solubility Cs. Therefore, aqueous solubility of a drug can be used as a first approximation of its dissolution rate. Drugs with low aqueous solubility have low dissolution rates and usually suffer oral bioavailability problems. Formulation of such a drug into a sustained release system may not provide considerable benefits over conventional dosage forms. Any system upon diffusion of drug through a polymer as the rate - limiting step in release would be unsuitable for a poorly soluble drug, since the driving force for diffusion is the concentration of drug in the polymer or solution, and this concentration would be low. For a drug with very high solubility and a rapid dissolution rate, it is often quite difficult to decrease its dissolution rate to slow its absorption. Preparing a slightly soluble form of a drug with normally high solubility is, however, one possible method for preparing controlled release dosage forms.

b) Partition Coefficient
Between time that a drug is administered and the time is eliminated from the body, it must diffuse through a variety of biological membranes that act primarily as lipid like barriers. A major criteria in evaluation of the ability of a drug to penetrate these lipid membranes is its apparent oil/water partition coefficient defined as

$$K = C_0/C_W \text{---------------------- (3)}$$

Where;

C_o = Equilibrium concentration of all forms of the drug e.g. ionized and

unionized in an organic phase at equilibrium.

C_w = Equilibrium concentration of all forms in aqueous phase.

In general, drugs with extremely large values of 'K' are very oil soluble and will partition into membrane quite readily. According to Haunch correlation, the logarithm of the activity of a drug or its ability to be absorbed and the logarithm of its partition coefficient having parabolic relationship. The explanation for this relationship is that the activity of a drug is a function of its ability to cross membranes and interact with the receptor. The more effectively a drug crosses membranes, the greater its activity. The optimum partition coefficient value of a drug in which it most effectively permeates membranes and thus shows the greatest activity. The value of K at which optimum activity is observed is approximately 1000/1. Drugs with a partition coefficient that is higher or lower than the optimum is, in general, poorer candidates for formulation into controlled-release dosage forms.

C) Drug stability
One important factor for oral dosage forms is the loss of drug through acid hydrolysis and/or metabolism in the GI tract. Since a drug in the solid state undergoes degradation a much slower rate than a drug in suspension or solution. It is possible to improve significantly the relative bioavailability of a drug that is unstable in the stomach; the most appropriate controlling unit would be one that release its content only in the intestine. The reverse in the case for those drugs that are unstable in the environment of the intestine, the most appropriate controlling unit in this case would be one that releases its contents only in the stomach, so, drugs with significant stability problems in any particular area of the GI tract are less suitable for formulation into controlled release systems that deliver their content uniformity over the length of the GI tract. Controlled drug delivery systems may provide benefits for highly unstable drugs because the drug may be protected from enzymatic degradation by incorporation into a polymeric matrix.

d) Protein Binding
There are some drugs which having tendency to bind with plasma proteins (eg. Albumin) and causes retention of the drug in the vascular space. The main force of attraction responsible for binding is wanderwals forces, hydrogen bonding and electrostatic forces. In general, charged compounds, because of electrostatic effects. If a drug with protein then

the distribution of the drug into the extravascular space is governed by the equilibrium process of dissociation of the drug from the protein. The drug-protein complex can serve therefore as a reservoir in the vascular space for controlled drug release to extravascular tissues, but only for those drugs that exhibit a high degree of binding. Thus, the protein binding characteristics of a drug can play a significant role in its therapeutic effect, regardless of the type of dosage form. Extensive binding to plasma proteins will be evidenced by a long half-life of elimination for the drug and such drugs generally does not required a controlled-release dosage form, however, drugs that exhibit a high degree of binding to plasma protein also might bind to biopolymers in the GI tract, which could have an influence on controlled-drug delivery.

e) Molecular size and diffusivity

Drugs in many sustained - release systems must diffuse through a rate controlling membranes or matrix. The ability of a drug to diffuse through membranes, it's so called diffusivity (diffusion coefficient), is a function of its molecular size (or molecular weight). An important influence upon the value of the diffusivity. 'D', in polymers is the molecular size for molecular weight of the diffusing species.

Biological Properties
a) Absorption

The rate, extent and uniformity of absorption of a drug are important factors when considering it's formulation into a sustained - release system. Since the rate limiting step in drug delivery from a sustained - release system is its release from a dosage form, rather than absorption, a rapid rate of absorption of drug relative to its release is essential if the 'system is to be successful. In case of controlled release dosage form $K_r <<< K_a$ this becomes most critical in the case of oral administration. Assuming that the transit time of a drug through the absorption half-life should be to 4 hrs. This corresponds to a minimum absorption rate constant K_a of 0.17 to 0.23 hr necessary for about 80 to 95 % absorption over a 9 to 12 hr transit time. For a drug with a very rapid rate of absorption, (ie., $K_a >> 0.23$ hr^{-1}), the above discussion implies that a first order release rate constant $K_r < 0.17$ hr-^{1} is likely to result in unacceptable poor bioavailability in many patients. Therefore, slowly absorbed drugs will be difficult to formulate into controlled release systems where the criteria that $K_r <<< K_a$ must be met.

b) Distribution

The distribution of a drug into vascular and extravascular spaces in the body is an important factor in its overall elimination kinetics. Two parameters that are used to describe the distribution characteristics of a drug are its apparent volume of distribution and the ratio of drug concentration in the tissue is that in plasma at the steady state called T/P ratio. The magnitude of the apparent volume of distribution can be used as a guide for additional studies and as a predictor for a drug dosing regimen and hence there is a need to employ a controlled-system.

c) Metabolism

Drugs that are significantly metabolized before absorption, either in the lumen or tissue of the intestine can show decreased bioavailability from slower-releasing dosage forms. Most intestinal wall enzyme systems are saturable. As the drug is released at a slower rate to these regions, less total drug is presented to the enzymatic process during a specific period allowing more complete conversion of drug to its metabolite. Formulation of these enzymatically susceptible compounds as prodrug is another viable solution.

d) Biological Half Life

The usual goal of an oral sustained release product is to maintain therapeutic blood levels over an extended period. To this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life. Each drug has its own characteristics elimination rate, which is the sum of all elimination processes including metabolism, urinary excretion and all other processes that permanently remove drug from blood stream. Therapeutic compounds with short half-life are excellent candidates for sustained-release preparations, since this can reduce dosage frequency. However, this is limited, in that drugs with very short biological half-life as it may require excessively large amounts of drug in each dosage unit to maintain sustained effect, forcing the dosage form itself to become limiting large. In general, drugs with half-life shorter than two hrs. are poor candidates for sustained release preparations. Drugs with long half-life, more than 8 hrs., are also generally does not be used in sustaining forms, since their effect is already sustained.

e) Side Effects and Safety Considerations

There are very few drugs whose specific therapeutic concentrations are known. Instead, a

therapeutic concentration range is listed, with increasing toxic effects expected above this range and a falloff in desired therapeutic response observed below the range. The most widely used measure of the margin of safety of a drug is its therapeutic index, (TI). For very potent drugs, whose therapeutic concentration range is narrow, the value TI is small. In general, larger the value of TI, Usually are poor candidates for formulation into controlled-release product. A drug is considered to be relatively safe if its TI value exceeds 10.

f) Dose Size

Since a controlled-release system is designed to alleviate repetitive dosing, it is naturally contain greater amount of drug that a corresponding conventional dosage form. For lose drugs requiring large conventional doses, the volume of sustained dose may be so large so to be impractical or unacceptable, depending on the route of administration. The same may be true for drugs that require a large release rate from the controlled-release system, e.g., drugs with shorter half-life. For oral route, the volume of the product is limited by patient acceptance.

CONCLUSION

By the above discussion, it can be easily concluded that sustained-release formulation are helpful in increasing the efficiency of the dose as well as they are also improving the patient's compatibility. More over all these comes with reasonable cost. The dosage form is easy to optimize and very helpful in case of the antibiotics in which irrational use of the same may result in resistance.

REFERENCES
1) Chien Y. W. Novel Drug Delivery System 1992; 2: 139 – 140.
2) Altaf AS, Friend DR, MASRx and COSRx Sustained-Release Technology in Rathbone MJ, Hadgraft J, Robert MS, Modified Release Drug Delivery Technology, Marcell Dekker Inc., New York, 2003.
3) Gwen MJ and Joseph RR, In Banker GS and Rhodes CT, Eds., Modern Pharmaceutics, 3rd Edn , Vol. 72, Marcel Dekker Inc. New York, 1996, 575.
4) Salsa T, Veiga F And Pina M.E, Drug Develop. Ind. Pharm., 1997, 23, 931.
5) Jantez GM, Robinson JR. Sustained and controlled release drug delivery systems. In: Banker GS, Rhodes CT, editors. Modern pharmaceutics. 3rd edition. New York: marcel dekker inc; 1996.
6) Popli H, shrma SN. Trends in oral sustained – release formulations-I The eastern pharmacist 1989; 32: p. 99-103.
7) Remington. The Science and Practice of pharmacy, 20th Edition, vol. I: 903-913
8) Brahmankar D. M. and Jaiswal S .B. in "Biopharmaceutics and Pharmacokinetics", "A Treatise," Vallabh Prakashan, 1st Edition, 1995: 347- 352.
9) Lee V. H., Robinson J. R. Sustained and Controlled Release Drug Delivery System, Marcel Dekker, New York: 71-121,138-171.
10) Brannon-Peppas, L. Med. Plast. & Biomater, Volume 199, Issue 6: 34-46
11) Liberman H. A. Pharmaceutical Dosage Form: Tablets, Vol. I, 2nd Edition: 136.
12) Aulton M.E. Hand Book of pharmaceutics Edition. 2001: 291-295.
13) Howard C. Ansel. Pharmaceutical Dosage Form and Drug Delivery Systems; 7th Edition: 229-243.
14) Jain N.K. Controlled and Novel Drug Delivery. CBS Publiser, new Delhi, 1-2, 2002: 676-698.