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A Review on Sustained Release Drug Delivery System

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ABSTRACT

Sustained release matrix tablets facilitate prolonged and continuous drug release and improve the bioavailability of drugs while avoiding unwanted side effects. The goal in designing sustained or controlled delivery systems is to reduce frequency of dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required, providing uniform drug delivery. Sustained release drug administration means not only prolongation of duration of drug delivery, but the term also implies the predictability and reproducibility of drug release kinetics. The controlled release of drug substances and their effective transport to sites of action can be exploited to maximize the beneficial clinical response and to minimize the incidence of unbeneficial adverse reactions and side effects. Oral ingestion has long been the most convenient and commonly employed route of drug delivery. Indeed, for sustained release systems, oral route of administration has received most of the attention with respect to research on physiological and drug constraints as well as design and testing of products.

INTRODUCTION

Dr. Paul Ehrlich's 'magic bullet' concept though realized late, offers a logical solution to the age-old problem of unrelated and unwanted effects of therapeutic agents and optimizing the drug therapy in its true sense. Although 'sustained/ controlled' drug delivery can be considered as the progenitor of magic bullet concept in practice. The term sustained/controlled has been used with the widest possible meaning[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[2].

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. Generally, the time course of a dosage form (pharmacokinetics) in man is considered to be controlled by the chemical structure of the drug. Decreasing the rate of absorption and/ or changing the dosage form provide a useful adjunct. When it is feasible or desirable to modify the drug compound on a molecular level, often sought is a product that will require less frequent administration to obtain the required biologic activity time profile; for example, a tablet that has the same clinical effect when administered every twelve hours. In another instance, it may be desirable to decrease the absorption rate in order to obtain a more acceptable clinical response[3].

The goal in designing sustained or controlled delivery

Systems are to reduce frequency of dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required, providing uniform drug delivery. If one were to imagine the ideal drug delivery system, two prerequisites would be required. First, it would be a single dose for duration of treatment, whether it is for days of weeks, as with infection, or for lifetime of the patient, as in hypertension or diabetes. Second, it should deliver the drug directly to the site of action, thereby minimizing or eliminating side effects. This may necessitate delivery to specific receptors or to localization to cells or to specific areas of the body.

Oral ingestion has long been the most convenient and commonly employed route of drug delivery. Indeed, for sustained release systems, oral route of administration has received most of the attention with respect to research on physiological and drug constraints as well as design and testing of products. This is because of the fact that there is more feasibility in dosage form design for oral route than for parenteral or any other route. The design of oral sustained release delivery systems is subject to several intercalated variables of considerable importance. Among these are the types of delivery systems, the disease being treated, the patient and the length of therapy and the properties of the drug.

Conventional drug therapy

In conventional drug therapy, it can be seen that the administration of drug by either intravenous injection or an extravascular route e.g. Orally, intramuscularly, or rectally does not maintain drug blood level within the therapeutic range for an extended period of time. The short action is due to the inability of conventional dosage forms to control temporal delivery[4]. Conventional dosage forms are associated with many side effects such as poor patient compliance, the unavoidable fluctuations in the drug concentration which may lead to under medication or overmedication as the steady state concentration values fall or rise beyond the therapeutic range and fluctuation in drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index whenever overmedication occurs[3].

Modified-release drug delivery systems

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of modified release drug delivery systems.

The modified-release delivery systems may be divided conveniently into four categories[4].

Delayed release system

Delayed-release systems are those that use repetitive, intermittent dosing of a drug from one or more immediate- release units incorporated into a single dosage form. Examples of delayed-release systems include repeat-action tablets and capsules, and enteric-coated tablets where timed release is achieved by a barrier coating[4].

Sustained release system

Sustained-release systems include any drug-delivery system that achieves slow release of drug over an extended period of time the systems can provide some control, whether this is of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells, it is considered controlled-release system.

Site-specific targeting

Site-specific and receptor targeting refer to targeting of a drug directly to a certain biological location. In the case of site-specific release, the target is adjacent to or in the diseased organ or tissue.

Receptor targeting

For receptor release, the target is the particular receptor for a drug within an organ or tissue. Both of these systems satisfy the spatial aspect of drug delivery and are also considered to be controlled drug-delivery systems[5].

Sustained release drug delivery systems

During the past few years, conventional dosage forms of drugs are rapidly being replaced by the new and the novel drug delivery systems. Amongst, these the controlled release/sustained release dosage forms have become extremely popular in modern therapeutics.

Sustained release drug administration means not only prolongation of duration of drug delivery, but the term also implies the predictability and reproducibility of drug release kinetics. The controlled release of drug substances and their effective transport to sites of action can be exploited to maximize the beneficial clinical response and to minimize the incidence of unbeneficial adverse reactions and side effects[5].

Advantages of sustained release drug delivery [4, 6, 7]

- Decreased local and systemic side effects.
- Better drug utilization reduction in total amount of drug used.
- Improved efficiency in treatment, optimized therapy, more uniform blood concentration.

- 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.

- Improve bioavailability of some drugs e.g. drugs susceptible to enzymatic inactivation can be protected by encapsulation in polymer systems suitable for sustained release.

Improved patient compliance. The importance of patient compliance in successful drug therapy is well recognized.

Disadvantages of sustained release drug delivery[8]

- Decreased systemic availability in comparison to immediate release conventional dosage forms.

- Poor *in vitro, in vivo* correlation.

- Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.

- Reduced potential for dose adjustment of drugs normally administered in varying strengths.

Classification of oral sustained/controlled release systems

1. Diffusion controlled Systems

(A) Reservoir devices: A core of drug (reservoir) surrounded by a polymeric membrane characterizes them. The nature of the membrane determines the rate of drug release. The characteristics of reservoir diffusion systems are:

✓ Zero order drug release is possible.

✓ The release rate is dependent on the type of polymer.

✓ High molecular weight compounds are difficult to deliver through the device.

(B) Matrix devices: It consists of drug dispersed homogenously in a matrix. The characteristics of matrix diffusion systems are:

- Zero order release cannot be obtained.

- Easy to produce than reservoir devices.
- High molecular weight compounds are delivered through the device[13].

2. Dissolution controlled systems

(a) Matrix dissolution-controlled systems: Aqueous dispersions, congealing, spherical agglomeration, etc. can be used.

(b) Encapsulation dissolution-controlled systems: Particles, seeds, granules can be coated by techniques such as microencapsulation.

3. Diffusion and dissolution-controlled systems: In a bio erodible matrix, the drug is homogenously dispersed in a matrix and it is released either by swelling controlled mechanism or by hydrolysis or by enzymatic attack[14].

Sustained release matrix tablets[8]

One of the least complicated approaches to the manufacture of sustained release dosage forms is the direct compression of drug, release retardant, and additives to form a tablet in which drug is embedded in a matrix core of retardant. Alternatively, drug retardant blend may be granulated prior to compression. Such tablets are called as matrix tablets. Three classes of release retarding materials are used for the formulation of matrix tablets:

- Insoluble or 'skeleton' matrices
- Water insoluble, erodable matrice
- Hydrophilc matrices.

Giunchedi et al (2000) investigated the use of sodium alginate for preparing hydrophilic matrix tablets of ketoprofen. The matrix tablets were prepared by direct compression using sodium alginate, calcium gluconate, and hydroxypropyl methylcellulose (HPMC) in different combinations and ratios. *In vitro* release tests and erosion studies of the matrix tablets were carried out in USP phosphate buffer (P^H7.4). Matrices consisting of sodium alginate alone or in combination with 10% and 20% of HPMC exhibited a prolonged drug release at a fairly constant rate. Incorporation of different ratios of calcium gluconate leads to an enhancement of the release rate from the matrices and to the loss of the constant release rate of the drug.

Only the matrices containing the highest quantity of HPMC (20%) maintained their capacity to release ketoprofen for a prolonged time. (native dextran, hydroxypropyl methylcellulose (HPMC), cetyl alcohol) and binary mixtures of them on PPL release *in vitro* was investigated. A central composite design was applied to the optimization of a sustained-release tablet formulation. The sustained-release matrix tablets with good physical, mechanical and technological properties were obtained with a matrix excipient: PPL ratio of 60:40 (w/w), with a dextran: HPMC ratio of 4:1 (w/w) and with a cetyl alcohol amount of 15% (w/w)[12].

Kranz et al (2006) developed mini matrix tablets to overcome the pH dependent solubility of ZK 811 752, a potent candidate for the treatment of autoimmune diseases, by direct compression of drug, matrix former (polyvinylacetate /polyvinylpyrrolidone: Kollidon® SR) and excipients. To solve the problem of pH-dependent solubility fumaric acid was added to the drug-polymer excipient system. The addition of fumaric acid was found to maintain low pH-values within the mini tablets during release of ZK 811 752 in phosphate buffer pH 6.8. Thus, micro environmental conditions for the dissolution of the weakly basic drug were kept constant and drug release was demonstrated to be pH-independent. Incorporation of water-soluble (lactose) or highly swellable (maize starch) excipients accelerated drug release in a more pronounced manner compared to the water-insoluble excipient calcium phosphate. Stability studies demonstrated no degradation of the drug substance and reproducible drug release patterns for mini matrix tablets stored at 25°C/60% RH and 30°C/70% RH for up to 6 months[22].

Sarfraz et al (2006) made an attempt to produce a quick/slow biphasic delivery system for ibuprofen. A dual- component tablet made of a sustained release tableted core and an immediate release tableted coat was prepared by direct compression. Both the core and the coat contained a model drug, ibuprofen. The sustained release effect was achieved with a polymer, hydroxypropyl methylcellulose (HPMC) or ethylcellulose to modulate the release of the drug. The *in vitro* release studies showed the desired biphasic release behavior, depending on the composition of the matrix tablet. And it was concluded that the HPMC core was suitable for providing a constant and controlled release for a long period of time[24].

Shoaib et al (2006) made an attempt to develop a metformin hydrochloride (MH) sustained release formulations based on direct compressed matrix tablets consisting of a combination of MH with the hydrophobic triacetyl-beta-cyclodextrin (TAbetaCD), dispersed in a polymeric material. Different polymers were tested as excipients, i.e. hydroxypropyl methylcellulose,

xanthan gum, chitosan, ethylcellulose, Eudragit(R) L100-55, and Precirol(R). Release studies demonstrated that blends of a hydrophobic swelling polymer (hydroxypropyl methylcellulose or chitosan) with a pH- dependent one Eudragit(R)L100-55) were more useful than single polymers in controlling drug release. In fact, for a given matrix-tablet composition, different sustained-release effects were obtained by varying the relative amounts of MHTAbetaCD as ground or spray dried product[25].

Varshosaz et al (2006) developed a sustained release matrix tablet for highly water oluble tramadol hydrochloride using natural gums (xanthan and guargum) as cost effective, nontoxic, easily available, and suitable hydrophilic matrix systems compared with the extensively investigated hydrophilic matrices (ie,hydroxypropyl methylcellulose (HPMC)/carboxymethyl cellulose (CMC) with respect to *in vitro* drug release rate) and hydration rate of the polymers. Matrix tablets of tramadol were produced by direct compression method. The tablets were evaluated for physical characteristics. The dissolution test was performed in the phosphate buffer media (pH 7.4) upto 8 hours. Tablets with only xanthum gum had the highest mean dissolution time, the least dissolution efficiency (8%), and released the drug following a zero order model via swelling, diffusion, and erosion mechanisms. Guar gum alone could not efficiently control the drug release, while xanthum and all combinations of natural gums with HPMC could retard tramadol HCl release[26].

Yeole et al (2006) made an attempt to increase therapeutic efficacy, reduce frequency of administration, and improve patient compliance, by developing sustained release matrix tablets of diclofenac sodium. Sustained release matrix tablets of diclofenac sodium, was developed by using different drug: polymer ratios, such as F1 (1:0.12), F2 (1:0.16), F3 (1:0.20), F4 (1:0.24) and F5 (1:0.28). Xanthan gum was used as matrix former, and microcrystalline cellulose as diluent. All the lubricated formulations were compressed using 8 mm flat faced punches. Compressed tablets were evaluated for uniformity of weight, content of active ingredient, friability, hardness, thickness, *in vitro* dissolution using basket method, and swelling index. All the formulations showed compliance with pharmacopoeial standards. Among different formulations, F1 showed sustained release of drug for 12 hours with 89.67% release. The effect of other parameters like addition of release modifier (PEG 6000), gum concentration, pH of dissolution medium, rotation speed and dissolution by paddle method, were also studied. Selected formulation (F1) was subjected to stability studies for three months at 0-4°C, room temperature (28°C), and 45°C with RH 75±5%, and showed stability

with respect to release pattern. The kinetic treatment showed that the release of drug follows zero order kinetics (R 2 = 0.9758). Korsmeyer and Peppas equation gave value of n = 0.9409 which was close to one, indicating that the drug was released by zero order kinetic. Thus, Xanthan gum can be used as an effective matrix former, to extend the release of diclofenac sodium[27].

Lopes et al (2007) developed a once in daily sustained release matrix tablet of ibuprofen using hydroxypropyl methylcellulose as release controlling factor and to evaluate drug release parameters as per various release kinetic models. In order to achieve required sustained release profile, tablets were directly compressed using Avicel pH 101 and magnesium stearate. The formulated tablets were also characterized for physical and chemical parameters and results were found in acceptable limits. Different dissolution models were applied to drug release data in order to evaluate release mechanisms and kinetics. Criteria for selecting the most appropriate model were based on linearity (coefficient of correlation). The drug release data fit well to the Higuchi expression. Drug release mechanism was found as a complex mixture of diffusion, swelling and erosion[29].

Mandal et al (2007) developed sustained release matrix tablets containing 450 mg lithium carbonate (LC) using different types and ratios of polymers including carbopol (CP), sodium carboxymethylcellulose (Na CMC) and hydroxypropyl methylcellulose (HPMC). The tablets were prepared by either direct compression or wet granulation. *In vitro* and *in vivo*, newly formulated sustained-release LC tablets were compared with sustained release commercial tablet (Eskalith CR). *In vivo* studies were conducted in nine healthy subjects in a cross over design. The matrix tablets containing 15% CP exhibited suitable release kinetics and uniform absorption characteristics comparable to that of Eskalith CR. *In vivo*, this formulation produced a smooth and extended absorption phase very much similar to that of Eskalith CR with the identical elimination half-life and extent of absorption[30].

Cao et al (2007) prepared two types of carnauba wax-based lipophilic matrix tablets using spray-dried granules (SDT) or directly compressible powdered mixtures (DCT) for sustained release. The model drug was a highly water-soluble potassium citrate and loaded about 74% of the total tablet weight. The SDT slowly eroded and disintegrated during the release study without showing sustained release when the hydrophilic excipients were added. In contrast, the DCT was more efficient for ustained release. The release rate decreased with increasing carnauba wa concentration. In particular, the sustained release rate was markedly pronounced

when the lipophilic stearyl alcohol and stearic acid were combined with the carnauba wax. The surface of the intact DCT appeared to be smooth and rusty. The DCT rose to the surface from the bottom of the vessel during the release test, and numerous pores and cracks with no signs of disintegration were also observed after the release test. The release profile was dependent on the formulation composition and preparation method of the matrix tablet. Diffusion- controlled leaching through the channels of the pores and cracks of the lipophilic matrix tablet (DCT) is a key to the sustained release[31].

Cui et al (2008) examined the possibility of preparing sustained release pellets of ciprofloxacin. The pellets were subjected to a coating process with methacrylic acid copolymers to produce sustained release characteristics. The pellets with different coatings were investigated by release tests *in vitro*. Finally, pellets with the best coating suspension were subjected to a multiple doses pharmacokinetic study. The *in vitro* release profiles showed that pellets coated with Eudragit NE30D and Eudragit L30D55, at a ratio of 1:8 (w/w) and a coating level of 8% with diethyl phthalate plasticizer equivalent to 10% of solid material in the coating suspension were suitable for sustained release. In the bioavailability study, the principal pharmacokinetic parameters showed there were differences between the sustained release pellets and the conventional ciprofloxacin capsules. The relative bioavailability of ciprofloxacin sustained release pellets compared with conventional ciprofloxacin capsules was 116.35 ± 33.31%. All the statistics indicated that the preparation has a sustained release effect with many advantages over conventional preparations[32].

CONCLUSION

By the above discussion, it can be easily concluded that sustained release formulations are helpful in increasing the efficiency of the dose and also improving the patient compatibility.

Development of oral sustained release dosage form, which will prolong the drug release leading to minimize the peak in plasma and provide patient convenience. The advantages of sustained release tablets/capsules are that they can be taken less frequently than their conventional form and they maintain the steady level of drug in plasma.

By several techniques the residence time of drug delivery system in the GIT can be prolonged. Difference between controlled releases is zero order release that is the drug releases with time irrespective of concentration. But sustained release dosage forms release drug over a prolong period of time. Nowadays, the oral route of administration for Sustained

release drug delivery system has received more attention due to its more flexibility, reduced dosing frequency and better patient compliance. The design of oral Sustained release drug delivery system depends on various factors like, physic-chemical properties of drug, type of delivery system, disease being treated, patient condition, treatment duration, presence of food, gastrointestinal motility and co- administration of other drugs. From the above discussion, we can conclude that Moreover; the reasonable cost of oral Sustained release drug delivery system has lead ease of market penetration as replacement of oral conventional drug delivery systems.

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