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A Concise Review on Sustained Drug Delivery System and Its Opportunities

Manish J. Chauhan*[1], Satish A. Patel[2]

1. Group Leader, Formulation Development, Astron Research Ltd., Ahmedabad

2. S. K. Patel Institute of Pharmaceutical Science & Research, Kharva, Guajarat, India.

ABSTRACT

Presently pharmaceutical industries are focusing on development of sustained release formulations due to its inherent boons. Sustained release dosage forms are designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimum side effects. The basic rationale of sustained release drug delivery system optimises the biopharmaceutical, pharmacokinetic and pharmacodynamic properties of a drug in such a way that its utility is maximized, side-effects are reduced and cure of the disease is achieved. There are several advantages of sustained release drug delivery over conventional dosage forms like improved patient compliance due to less frequent drug administration, reduction of fluctuation in steady-state drug levels, maximum utilisation of the drug, increased safety margin of potent drug, reduction in healthcare costs through improved therapy and shorter treatment period. Sustained release products are designed to bring the blood level of a drug immediately to therapeutic concentrations by means of an initial dose portion called loading dose and then sustain this level for a certain predetermined time with the maintenance portion. The basic goal of sustained release is provide promising way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body and increase patient compliance by reducing frequency of dose.

Key Words: Oral sustained release system, Matrix tablet, Patient compliance, Half-life

*Corresponding Author Email: chauhanmj@rediffmail.com

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INTRODUCTION

The advantage of administering a single dose of a drug that is released over an extended period of time instead of numerous doses is now a days area of interest for formulation scientists in Pharmaceutical industry. 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. Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the formulation. Hydrophilic and hydrophobic polymer matrix is widely used for formulating sustained release dosage form1-4. 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 systems5. Matrix system is widely used to prepare sustained release formulation. It is the release system which prolongs and controls the release of the drug, that is dissolved or dispersed in rate controlling polymer. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. release rate controlling polymer (hydrophilic and hydrophobic) polymers6. By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous sustained release oral dosage forms such as membrane-controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, and intense research has recently focused on the fabrication of sustained release systems for poorly water-soluble drugs7. Various drug delivery techniques have been developed to sustain the release of drugs, including triple-layered tablets (Geomatrix® technology) and osmotic pumps with laser-drilled holes (OROS® technology). These technologies are intricate and relatively expensive to manufacture. Thus, there remains an interest in developing novel formulations that allow for sustained the drug release using readily available, inexpensive excipients by matrix based formulations 8.

Figure 1 indicating release pattern comparison of immediate release formulations with sustained release formulations. From figure 1 it is completely point out that sustained release formulations maintain drug level between therapeutic windows hence minimize adverse effects.

Advantages

Extended-release products offer three potential benefits:

- Sustained blood levels
- Attenuation of adverse effects
- Improved patient compliance.

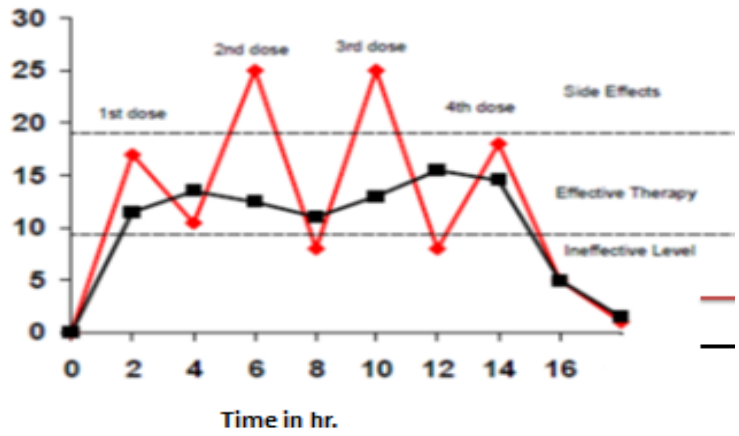

Figure 1: Release profile of immediate release and sustained release dosage form

Sustained Blood Levels

The size and frequency of dosing is determined by the pharmacodynamics and pharmacokinetic properties of the drug. The slower the rate of absorption, the less the blood concentrations fluctuate within a dosing interval. This enables higher doses to be given less frequently. For drugs with relatively short half-lives, the use of extended release products may maintain therapeutic concentrations over prolonged periods.

Attenuation of adverse effects

With conventional dosage forms, high peak blood concentrations may be reached soon after administration. With possible adverse effects related to the transiently high concentration. An example is hypotension in patients taking immediate release nifedipine products. The use of an extended-release product avoids the high initial blood concentrations which cause the sudden reduction in blood pressure and other significant hemodynamic changes such as reflex tachycardia[9].

Improved Patient Compliance

Drugs with short half-lives often need to be given at frequent intervals to maintain blood concentrations within the therapeutic range. There is an inverse correlation between the frequency of dosing and patient compliance. A reduction in the number of daily doses offered by extended-release products has the potential to improve compliance. However, this advantage probably only occurs when conventional formulations need to be given three or more times a day.

Disadvantages

- High cost
- Unpredictable and often poor in vitro-in vivo correlations
- Dose dumping
- Reduced potential for dosage adjustment
- Increased potential for first pass clearance and poor systemic availability
- Effective drug release period is influenced and limited by gastrointestinal tract residence time for oral controlled release formulations

For many controlled-release products, the release rate can be altered by various factors including food and the transit through the gut. There may be some differences in the release rate one dose to another, but these have been minimized by modern formulations. Extended-release products contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage forms has potential problems. While some extended-release products can be divided to provide half-doses, others should only be taken whole Modified release products should never be crushed or chewed as the slow release characteristics may be lost and toxicity may result[8].This is particularly important in patients unable to swallow whole tablets, a problem commonly affecting the elderly. The large size of extended-release products may cause difficulties in ingestion or transit through the gut. These problems may results in some drugs causing local tissue damage in patients who have a pathological or drug-induced reduction in gut motility.

Characteristic that makes a drug unsuitable for extended- release formulation*:*

- Short elimination half-life,<2 hr
- Long elimination half-life, >8 hr
- Narrow therapeutic index
- Large doses
- Poor absorption
- Low or slow solubility
- Extensive first-pass clearance

Characteristics That Makes Drugs Suitable For Extended- Release Formulation

Biological Characteristics [10, 11]

- Biological half life
- Absorption
- Metabolism

Biological half life

The usual goal of an oral sustained release product is to maintain therapeutic blood levels over an extended period of time. To achieve 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 ($t_{1/2}$). Each drug has its own characteristic elimination rate, which is the sum of all elimination processes, including metabolism, urinary excretion and all over processes that permanently remove drug from the blood stream. Therapeutic compounds with short half-life (2-8 hr.) are generally are excellent candidate for sustained release formulation, as this can reduce dosing frequency. In general, drugs with half-lives shorter than 2 hours such as furosemide or levodopa are poor candidates for sustained release preparation. Compounds with long half-lives, more than hours are also generally not used in sustaining form, since their effect is already sustained. Digoxin and phenytoin are the examples of drugs having long half life.

Absorption

Since the purpose of forming a sustained release product is to place control on the delivery system, it is necessary that the rate of release is much slower than the rate of absorption. If we assume that the transit time of most drugs in the absorptive areas of the gastrointestinal tract is about 8-12 hours, the maximum half-life for absorption should be approximately 3-4 hours; otherwise, the device will pass out of the potential absorptive regions before drug release is complete. Thus corresponds to a minimum apparent absorption rate constant of 0.17-0.23 h^{-1} to give 80-95% over this time period. Hence, it assumes that the absorption of the drug should occur at a relatively uniform rate over the entire length of small intestine. For many compounds this is not true. If a drug is absorbed by active transport or transport is limited to a specific region of intestine, sustained release preparation may be disadvantageous to absorption. One method to provide sustaining mechanisms of delivery for compounds try to maintain them within the stomach. This allows slow release of the drug, which then travels to the absorptive site. These methods have been developed as a consequence of the observation that co-administration results in sustaining effect. One such attempt is to formulate low density pellet or capsule. Another approach is that of bio-adhesive materials.

Metabolism

Drugs those are significantly metabolised before absorption, either in the lumen or the tissue of the intestine, can show decreased bioavailability from slower-releasing dosage form.

Physicochemical characteristics[10,11]

- Dose size
- Ionization, pKa and aqueous solubility

- Partition coefficient
- Stability

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 form. Compounds that require large dosing size can sometimes be given in multiple amounts or formulated into liquid systems. Another consideration is the margin of safety involved in administration of large amount of a drug with a narrow therapeutic range.

Ionization, pKa and aqueous solubility

Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the pKa of the compound and the absorptive environment. Presenting the drug in an unchanged form is advantageous for drug permeation. Unfortunately, the situation is made more complex by the fact that the drug's aqueous solubility will generally be decreased by conversion to unchanged form. Delivery systems that are dependent on diffusion or dissolution will likewise be dependent on the solubility of the drug in aqueous media. These dosage forms must function in an environment of changing pH, the stomach being acidic and the small intestine more neutral, the effect of pH on the release process must be defined.

Compounds with very low solubility (<0.01 mg/ml) are inherently sustained, since their release over the time course of a dosage form in the gastrointestinal tract will be limited by dissolution of the drug. On the other hand, drug that is poorly water soluble can be formulated in sustained release dosage form. For the same, the solubility of the drug should be increased by approaches like solid dispersion and inclusion complex and later on that is formulated in the sustained release dosage form. But during this, the crystallization of the drug that is taking place as the drug is entering in the systemic circulation should be prevented and one should be cautious for the prevention of the same.

Partition coefficient

When a drug is administered to the gastrointestinal tract, it must cross a variety of biological membranes to produce a therapeutic effect in another area of the body. It is common to consider that these membranes are lipidic; therefore the partition coefficient of oil-soluble drugs becomes important in determining the effectiveness of membrane barrier penetration. Compounds which are lipophilic in nature having high partition coefficient are poorly aqueous soluble and it retain in the lipophilic tissue for the longer time. In case of compounds with very low partition coefficient, it is

very difficult for them to penetrate the membrane, resulting in poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes. The choice of diffusion-limiting membranes must largely depend on the partitioning characteristics of the drug.

Stability

Orally administered drugs can be subject to both acid-base hydrolysis and enzymatic degradation. Degradation will proceed at a reduced rate for drugs in solid state; therefore, this is the preferred composition of delivery for problem cases. For the dosage form that are unstable in stomach, systems that prolong delivery over entire course of transit in the gastrointestinal tract are beneficial; this is also true for systems that delay release until the dosage form reaches the small intestine. Compounds that are unstable in small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. This is because more drugs is delivered in the small intestine and, hence, is subject to degradation. Propentheline and probanthine are representative example of such drug12.

MOST WIDELY USED APPROACH TO SUSTAINED DRUG RELEASE

Matrix tablet is one of the most widely approach to sustained the drug release. One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Alternatively drug and retardant blend may be granulated prior to compression. The materials most widely used in preparing matrix systems are shown in following table 1, which includes both hydrophilic and hydrophobic polymers. Commonly available hydrophilic polymers include Hydroxypropylmethylcellulose (HPMC), Hydroxypropylcellulose (HPC), Hydroxyethylcellulose (HEC), Xanthan gum, Sodium alginate, Poly (ethylene oxide) and crosslinked homopolymers and copolymers of Acrylic acid. It is usually supplied in micronized forms because small particle size is critical to the rapid formation of gelatinous layer on the tablet surface[13,14]

Table 1: Examples of two classes of retardant material used to formulate matrix tablet.

Sr.No.	Matrix Characteristics	Material
1	Insoluble, inert	Polyethylene, Polyvinyl chloride, Ethyl cellulose
2	Insoluble, erodible	Carnauba wax, Stearic acid, Polyethylene glycol

Matrix Tablets can be classified as,

i) Hydrophilic matrix tablet

Hydrophilic matrix can be utilized as a means to control the drug release rate. Figure 2 indicating sequential steps for drug release from sustained release matrix tablet. The matrix may be tableted by direct compression of the blend of active ingredient and certain hydrophilic carriers or from a wet

granulation containing the drug and hydrophilic matrix materials. The hydrophilic matrix requires water to activate the release mechanism and explore several advantages, including ease of manufacture and excellent uniformity of matrix tablets. Upon immersion in drug release is controlled by a gel diffusion barrier that is formed and tablet erosion. The effect of formulation and processing variables on drug-release behaviour from compressed hydrophilic matrices has been studied by number of investigators.

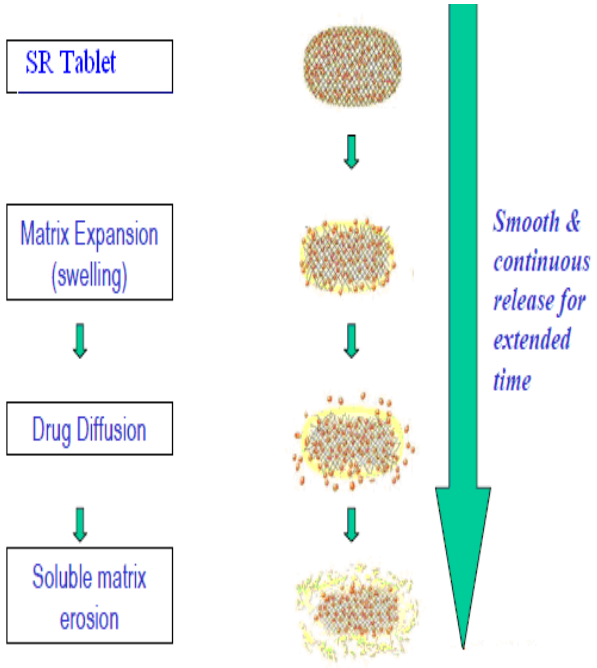

Figure 2: Release mechanism in case of extended release tablet

The matrix building material with fast polymer hydration capability is the best choice to use in a hydrophilic matrix tablet formulation. An inadequate polymer hydration rate may cause premature diffusion of the drug and disintegration of the tablet owing to fast penetration of water. It is particularly true for formulation of water soluble drug. The polymers used in the preparation of hydrophilic matrices are divided into three broad groups as follow,

Cellulose Derivatives: Hydroxyethyl cellulose, Hydroxypropyl methylcellulose (HPMC) 100, 4000 and 15000 cps, Sodium carboxymethyl cellulose and Methylcellulose 400 and 4000 cps.

Non-Cellulose Natural Or Semisynthetic Polymers: Agar-agar, Carob Gum, Alginates, Molasses, Polysaccharides of mannose and galactose, chitosan and modified starches.

Polymers of Acrylic Acid: Polymers which are used in acrylic acid category is Carbopol 934.

Other hydrophilic materials used for preparation of matrix tablet are Alginic acid, Gelatin and Natural gums.

ii) fat-wax matrix tablet

The drug can be incorporated into fat-wax granulations by spray congealing in air, blend congealing in an aqueous media with or without the aid of surfactant and spray-drying techniques. The mixture of active ingredients, waxy materials and fillers also can be converted into granules by compacting with roller compactor, heating in a suitable mixture such as fluidized-bed and steam jacketed blender or granulating with a solution of waxy material or other binders. The drug embedded into a melt of fats and waxes is released by leaching and/or hydrolysis as well as dissolution of fats under the influence of enzymes and pH change in the gastrointestinal tract. The addition of surfactants to the formulation can also influence both the drug release rate and the proportion of total drug that can be incorporated into a matrix.

iii) Plastic matrix tablet (hydrophobic matrices)

The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. Sustained release tablets based upon an inert compressed plastic matrix have been used extensively. Release is usually delayed because the dissolved drug has to diffuse through capillary network between the compacted polymer particles. Plastic matrix tablets, in which the active ingredient is embedded in a tablet with coherent and porous skeletal structure, can be easily prepared by direct compression of drug with plastic materials provided the plastic material can be communicated or granulated to desired particle size to facilitate mixing with the drug particle. In order to granulate for compression into tablets, the embedding process may be accomplished by,

Table: 2 Marketed modified-release oral dosage forms

Type of formulation and dosage form	Manufacturer	Marketed Name	Active moiety	Characteristics
Extended –Release Osmotic tablets	Janssen	Invega	Paliperidone	OROS® (Oral Osmotic System) triple layered push-pull technology
Extended-Release Matrix tablets	Boehringer Ingelheim	Mirapex ER	Pramipexole dihydrochloride	Extended-release with Hyproxypropyl methylcellulose and carbomer homopolymer based matrix tablets
Extended-Release Hydrophilic Matrix	Ranbaxy	Isoptin SR	Verapamil Hydrochloride	Extended-release provided by hydrophilic matrix with sodium alginate that swells and slowly erodes
Extended-Release Hydrophilic Matrix	Roxane	Oramorph SR	Morphine sulphate	Sustained-release hydrophilic matrix system, based on polymer hydroxypropyl methylcellulose
Extended-Release hydrophilic matrix	AstraZeneca	Seroquel XR	Quetiapine fumarate	film coated tablets with hydroxypropyl methylcellulose polymer based matrix tablets

1. The solid drug and the plastic powder can be mixed and kneaded with a solution of the same plastic material or other binding agent in an organic solvent and then granulated.

2. The drug can be dissolved in the plastic by using an organic solvent and granulated upon evaporation of the solvent.

3. Using latex or pseudo latex as granulating fluid to granulate the drug and plastic masses.

Examples of excipients used to form hydrophobic matrices are Polyvinyl chloride, Ethyl cellulose, Cellulose acetate and Polystyrene.

Following table indicating some of the marketed extended oral dosage form with details of type of formulation and its characteristics.

TYPES OF SUSTAINED ELEASE PRODUCTS BASED ON MECHANISM OF DRUG RELEASE

Diffusion-controlled products

In these systems, there is a water-insoluble polymer which controls the flow of water and the subsequent egress of dissolved drug from the dosage from. Both diffusion and dissolution processes are involved. In`reservoir´ devices , a core of drug is coated with the polymer and in`matrix´ systems ; the drug is dispensed throughout the matrix. Cellulose derivatives are commonly used in the reservoir types, while the matrix material may be plastics, e.g. Methylacrylate-methyl methacrylate, polyvinyl chloride, hydrophilic polymers such as cellulose derivatives or fatty compounds including carnauba wax.

Dissolution-controlled products

In these products, the rate dissolution of the drug (and thereby availability for absorption) is controlled by slowly soluble polymer or by microencapsulation. Once the coating is dissolved, the drug becomes available for dissolution. By varying the thicknesses of the coat and its composition, the rate drug release can be controlled[15].Some preparations contain a fraction of the total dose as an immediate-release component to provide a pulse dose soon after administration. The pellets dosage forms of diffusion-or dissolution controlled products can be encapsulated or prepared as a tablet. These products should not be chewed as the coating may be damaged. One of advantages of encapsulated pelleted products is that the onset of absorption is less sensitive to stomach empting. The entrance of the pellets into the small intestine (where the majority of drug absorption occurs) is usually more uniform than with non-disintegrating extended-release tablet formulations.

Erosion products

The release of drug from these products is controlled by the erosion rate of a carrier matrix. The rate of drug from these products is controlled by the erosion. An example of this formulation is Sinemet CR, with this product; some patients may experience a later onset of effect after the morning dose, compared to conventional levodopa tablets, because of the delayed release of the drug.

Osmotic pump systems

The rate release of drug in these products is determined by the constant inflow of water across a semi permeable membrane into a reservoir which contains an osmotic agent. The rate release is constant and can be controlled within tight limits yielding relatively constant blood concentration[16]. The advantage of this type of product is that the constant release is unaltered by the environment of the gastrointestinal tract and relies simply on the passage of water into the dosage form. The rate of release can be modified by altering the osmotic agent and the size of the hole.

Ion exchange resins

Some drugs can be bound to ion exchange resins and, when ingested, the release of drug is determined by the ionic environment within the gastrointestinal tract[17].

CONCLUSION

Wide range of drugs is formulated now in a variety of different per oral extended-release dosage forms. However, only those which result in a significant reduction in dose frequency and/or a reduction in toxicity resulting from high concentration in the blood or gastrointestinal tract are likely to improve therapeutic outcomes. To be a successful extended-release product, the drug must be released from the dosage form at a predetermined rate, dissolve in the gastrointestinal fluids, maintain sufficient gastrointestinal residence time, and may be absorbed at a rate and will replace the amount of drug being metabolized and excreted. In a nut shell, sustained-release formulations are a promising way to improve the patient's compliance by reducing dosing intervals and minimizing adverse effects. Out of many approaches to sustained drug release, matrix based approach is widely used due to its simplicity, scalability and from stability point of view.

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