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A REVIEW ON SUSTAINED RELEASE DRUG DELIVERY SYSTEM

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ABSTRACT

Most of the orally administered drugs, targeting is not a primary concern and it is usually intended for drugs to penetrate to the general circulation and perfuse to other body tissues. For this reason, most systems employed are of the sustained release variety. It is assumed that increasing concentration at the absorption site will increase circulating blood levels, which in turn, promotes greater concentration of drug at the site of action. If toxicity is not an issue, therapeutic levels can thus be extended. In essence, drug delivery by these systems usually depends on release from some type of dosage form, permeation through biological milieu and absorption through an epithelial membrane to the blood. In this review we discussed about the sustained drug delivery system.

KEYWORDS

Targeting, Blood levels, Epithelial membrane, Sustained release and Absorption.

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INTRODUCTION

Sustained release is defined as the delivery of drug as an initial (loading) dose immediately and the loading dose is followed by a slow constant release. It is the drug delivery system that is designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. 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[1-6].

Drawbacks of Conventional Dosage Forms

1. Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
2. The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
3. A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.

The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur. Figure No.1 shows different types of drug release mechanisms.

Advantages

1. Reduction in drug plasma level fluctuations.
2. Maintenance of a steady plasma concentration of the drug over a prolonged time period, simulating an intravenous infusion of a drug.
3. Drug plasma levels are maintained within a narrow window with no sharp peaks and with AUC* of plasma concentration versus time curve comparable with total AUC from multiple dosing with immediate release.
4. Dosage forms, greatly reducing the possibility of side effects, which increases as we approach the MSC.
5. Oral drug delivery is the most common and convenient for patients, and a reduction in dosing frequency enhances compliance.

Disadvantages

Increased variability among dosage units

1. Stability problem
2. Toxicity due to dose dumping
3. Increased cost
4. More rapid development of tolerance
5. Need for additional patient education and counseling
6. Reduced potential for dosage adjustment of drugs normally administered in varying strength.

Classification of Sustained Release Dosage Forms[7-15]

Sustained dosage forms are classified in to the following

1. Monolithic systems
a. Hydrophilic matrix
b. Lipid matrix
c. Insoluble polymer matrix
2. Reservoir/ Membrane controlled systems
3. Osmotic pump systems
4. Coated beads/granules
5. Microencapsulation

Monolithic or matrix systems

These systems can be divided into two groups:

1. Those with drug particles dispersed in a soluble matrix, with drug becoming available as the matrix dissolves or swells and dissolves (*hydrophilic colloid matrices*); and
2. Those with drug particles dispersed in an insoluble matrix, with drug becoming available as a solvent enters the matrix and dissolves the particles (*lipid matrices and insoluble polymer matrices*).

Drugs dispersed in a soluble matrix rely on slow dissolution of the matrix to provide sustained release. Excipients used to provide a soluble matrix often are those used to make soluble film coatings.

Drug particles may be incorporated into an insoluble polymer matrix. Drug release from these matrices follows penetration of fluid into the formulation, followed by dissolution of the drug particles and diffusion of the solute through fluid-filled pores. This type of delivery system would not be suitable for the release of compounds that are insoluble or those compounds that have low aqueous solubility. Excipients used in the preparation of insoluble polymers include hydrophobic polymers such as polyvinyl acetate, ethyl cellulose and some waxes. At this point each of the three main types of monolithic/matrix systems will be discussed.

Lipid matrix systems

Wax matrices prepared by direct compression; hot-melt granulation or roller compression; have their active agent contained in a hydrophobic substance that remains intact during drug release. The release of the drug depends on an aqueous medium dissolving the channeling agent, which leaches out of the matrix forming capillary pores. The active ingredient then dissolves in the aqueous medium and

diffuses out of the matrix, by way of the water-filled capillaries. A typical formulation consists of an active drug, a wax matrix former (hydrophobic material that are solids at room temperature and do not melt at body temperature, e.g., hydrogenated vegetable oils, cottonseed oils, Soya oils, microcrystalline wax and carnauba wax), a channeling agent (soluble in the gastrointestinal tract (GIT), in water and leaches out of the formulation leaving tortuous capillaries through which the dissolved drug may diffuse in order to be released, (e.g., Sodium chloride and sugars), a solubiliser and pH modifier, an anti-adherent/glidant and a lubricant.

Insoluble polymer matrix systems

Drugs are embedded in an inert polymer, which is not soluble in the gastrointestinal fluid. Drug release has been compared to the leaching from a sponge. The release rate depends on drug molecules in aqueous solution diffusing through a network of capillaries formed between compact polymer particles. The factors influencing drug release rate from insoluble polymer matrix systems are:

1. Pore structure – pore forming salts and compression force,
2. Excipients – wet ability changed by the soluble and insoluble components,
3. Particle size of polymer component – influences the surface area exposed to the medium.

There are three primary mechanisms by which active agents can be released from a matrix delivery system, which involve diffusion, degradation, and swelling followed by diffusion. (Figure No.2 shows the mechanism of drug release).

Hydrophilic colloid matrix systems

These swell able-soluble matrices are hydro gels that swell on hydration. The systems are capable of swelling followed by gel formation, erosion and dissolution in aqueous media. Their behavior is in contrast to a true hydro gel, which swells on hydration but does not dissolve. Drug particles are dispersed in an insoluble matrix and the drug becomes available as the solvent enters the matrix and dissolves the drug particles. This is enhanced by the swelling, which is followed by gel formation, erosion of the matrix system and the dissolution of the drug. Hydrophilic polymer matrix systems comprise a mixture of the drug, the hydrophilic colloid, release modifiers and lubricant/glidant. Diffusion of the drug through the hydrated matrix is the rate limiting step in drug release. Two common types of hydrophilic matrix systems are the true gels which are cross-linked polymeric structures formed. Drug diffusion with increasing time of exposure to dissolution media by chemical bonds (covalent) or physical bonds (helix formation based on hydrogen bonds or ionic interactions), for which chitosan is an excellent polymeric example, and the viscous matrices which are simple entanglements of adjacent polymer chains.

Reservoir or membrane-controlled systems

The rate controlling part of the system is a membrane through which the drug must diffuse as shown in Figure No.2. To allow diffusion out, the membrane has to become permeable, e.g. through hydration by water normally present in the gastrointestinal tract, or by the drug being soluble in a membrane component, such as a plasticizer. Unlike hydrophilic matrix systems, the membrane polymer does not swell on hydration to form a hydrocolloid matrix and does not erode. Two diffusion processes occur namely ‘water in’ followed by ‘drug out'. The membrane system has a polymer membrane at the surface and the matrix system has polymer throughout the whole system. The drug reservoir is coated with a membrane. The system is composed of the core (the drug, filler/substrate, lubricant/glidant, solubiliser), the coating (the membrane polymer, plasticizer/membrane modifier, colorant). Typical polymers used for the membrane are ethyl cellulose, acrylic copolymers, shellac and zein. The release-controlling polymer is film-coated onto the system. The membrane system may be formulated as a single-unit system or as a multiple-unit system. The single unit is essentially a tablet, which differs from conventional tablets in that its core does not disintegrate but dissolves and the formulation requires water to penetrate for the drug to dissolve so that diffusion can occur. The multiple-unit system

comprises more than one discrete unit as coated spheroids (pellets, 1 mm in diameter) compressed in a tablet or filled into a hard gelatin capsule.

Osmotic pumps

A semi-permeable membrane surrounds a mixture of drug and an osmotically active constituent as in Figure No.3. Water is taken up by osmotic action and the dissolved drug is discharged through a small orifice. The rate of drug release is controlled by the rate at which water enters through the membrane and the rate at which drug passes out of the hole/orifice and the swelling of the polymer push layer (Osmotic pumps are shown in Figure No.4).

Coated beads or granules

A solution of the drug substance in a non-aqueous solvent (e.g. alcohol) is coated onto small, inert beads or granules made of a combination of sugar and starch. When the drug dose is large, the starting granules may be composed of the drug itself. Some of the granules are left uncoated to provide immediate release of the drug. Coats of a lipid material (e.g. beeswax) or cellulose material (e.g. ethyl cellulose) are applied to the remaining granules. Some granules receive few coats, and some receive many. The various coating thicknesses produce sustained-release effect.

Micro encapsulation

This is a process by which solids, liquids or gases are encased in microscopic capsules. Thin coatings of a "wall" material are formed around the substance to be encapsulated. An example is Bayer timed-release aspirin.

Coacervation

Coacervation is the most common method of microencapsulating. This occurs when a hydrophilic substance is added to colloidal drug dispersion and causes layering and formation of microcapsules. According to Bakan coacervation is carried out in three steps under continuous agitation, namely formation of three immiscible chemical phases, deposition of the coating and rigidisation of the coating.

Polymers of Materials Used as Retardants in SRDD System Formulations

The following polymers used in SDDS System Formulations (Table No.1).

Table No.1: Shows different types of polymers used in SRDDS

S.No	Matrix characteristics	Examples of polymeric materials
1	Insoluble	Polyethylene, Polyvinyl chloride, Methyl acrylate – methacrylate copolymer, Ethylcellulose
2	Insoluble, erodable	Carnauba wax (stearyl alcohol, stearic acid, polyethylene glycol) Castor wax (polyethylene glycol monostearate) Triglycerides
3	Hydrophilic	Methylcellulose, Hydroxymethylcellulose, Hydroxypropylmethylcellulose, Sodium carboxymethylcellulose, Carboxypropylmethylene, Galactomannose and Sodium alginate

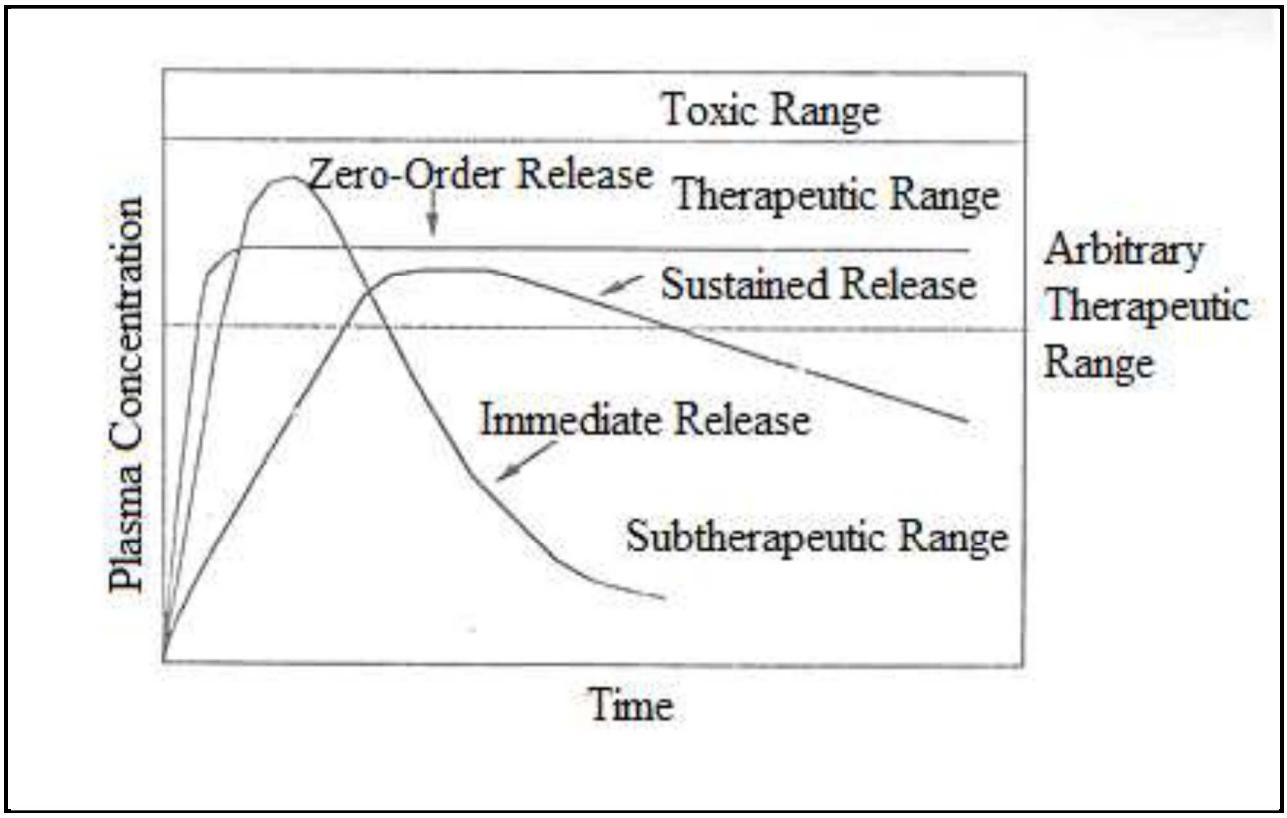

Figure No.1: Plasma Drug Concentration Profiles for Conventional Tablet Formulation, a Sustained Release Formulation and a Zero Order Controlled Release Formulation

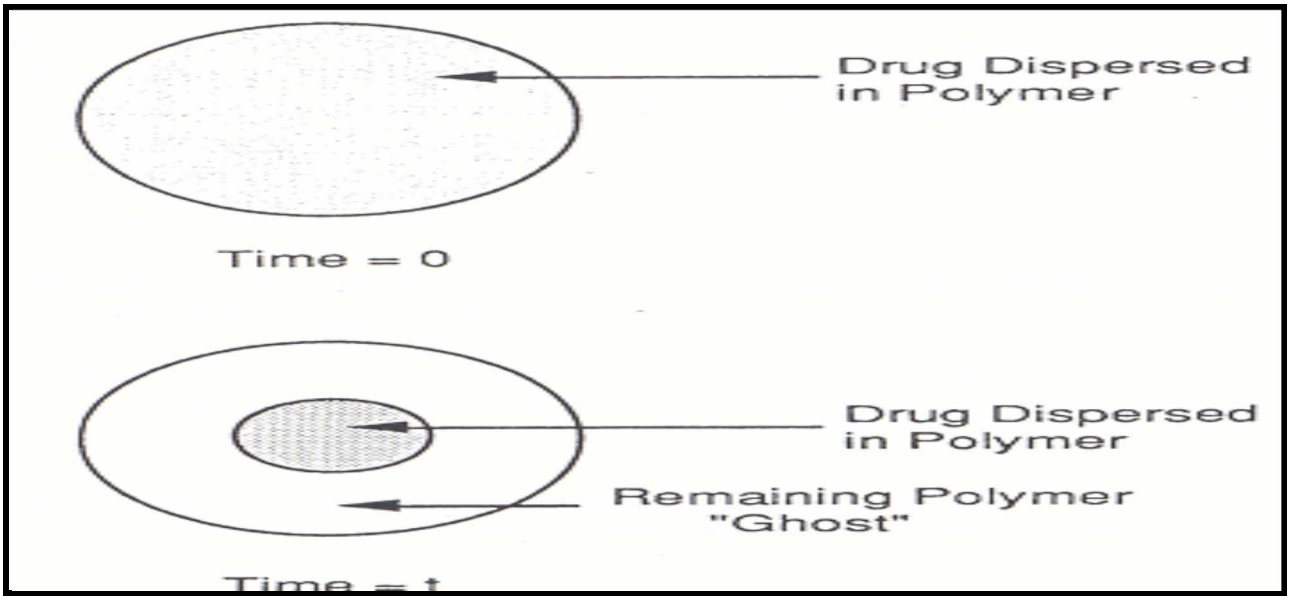

Figure No.2: Drug delivery from an insoluble polymer matrix diffusion system

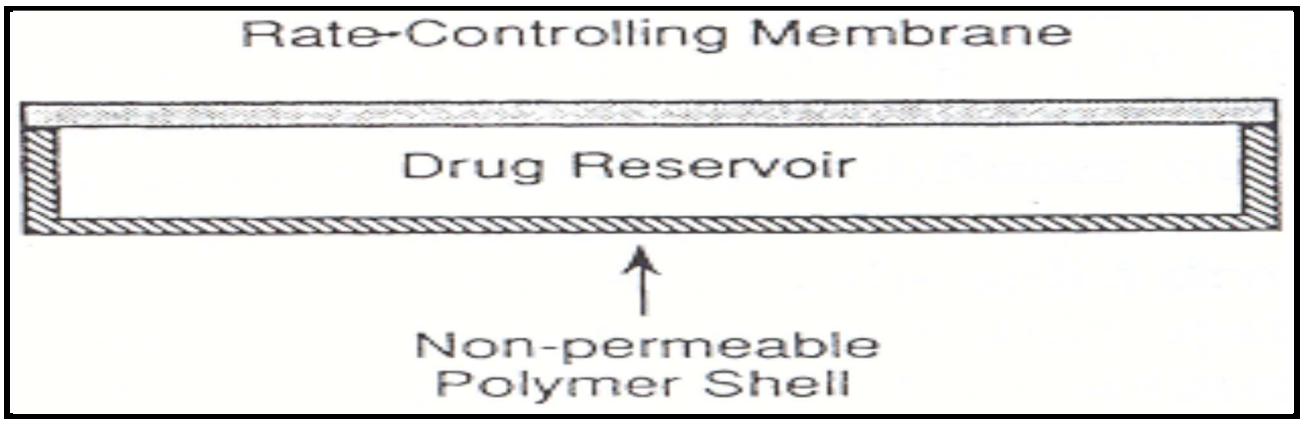

Figure No.3: Diagrammatic representation of a slab configuration of a reservoir diffusion system

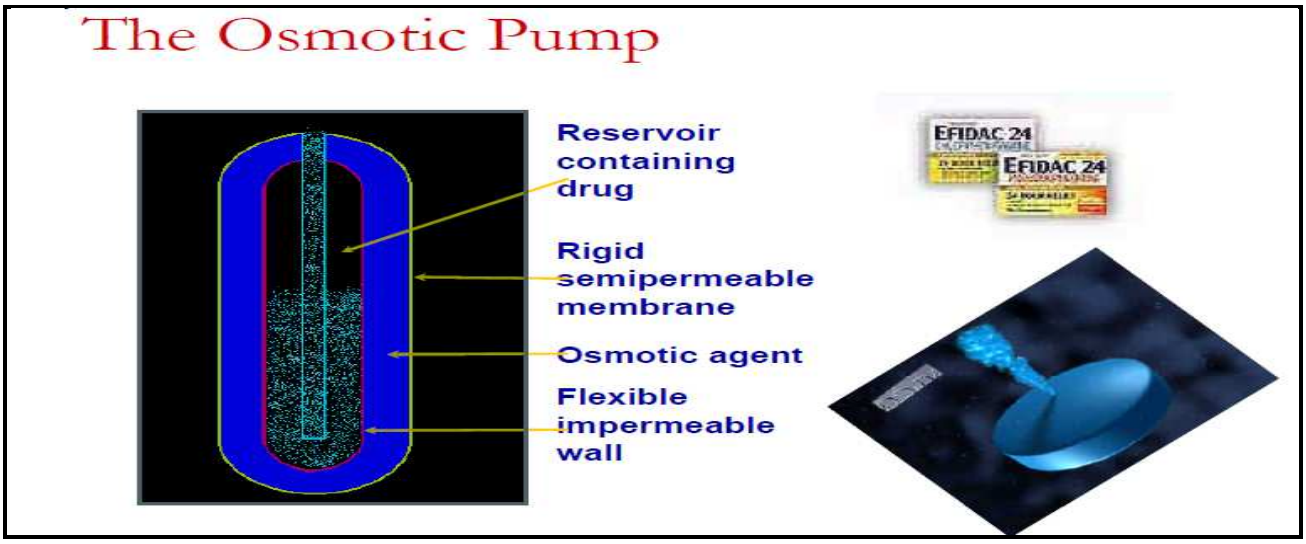

Figure No.4: Osmotic Pumps

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CONCLUSION

Sustained release formulation is more advantageous than conventional dosage form. Those are reduction in dose frequency, patient compliance and dose missing. The sustained release formulations are mostly used in the treatment of diseases like Diabetes, cancer etc.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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