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Recent (Aspects) trend on sustained drug delivery system

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ABSTRACT

Sustained drug delivery system is one of the useful tool as compared with conventional dosage form. By using this dosage form the availability of drug in the body enhanced for longer time and getting prolonged therapeutic activity of the drug. The objective of the most therapeutic regimens is to rapidly raise the plasma concentration to the required level and then to hold it constant for the desired duration of treatment. This article focuses on the potential aspect of the sustained drug delivery system and their application.

Keywords: Sustained release system, Diffusion release system, Reservoir Devices, Monolithic Devices, Matrix System.

1. INTRODUCTION

1.1 Sustained Release Drug Delivery System

For every disease or disorder state of the patient, proper medication is of prime importance to maintain the patient in good health. To achieve this, the medicine or drug is administered conventionally by one or more of several well defined and popular routes of drug administration including oral, parenteral, rectal, alveolar, and Ocular and topical. Among these above mentioned popular routes, oral conventional route of drug administration lies at the top of the hierarchy of the conventional routes. High patient compliance and flexibility in developing dosage forms made the oral drug delivery systems the most convenient mode of drug administration compared to other dosage forms [1]. In conventional oral dosage forms drug dosage must be taken several times which results in fluctuating drug levels in plasma. This drawback of conventional dosage form can be overcome by formulation of sustained release dosage forms which provides drug release in an amount sufficient to maintain the therapeutic drug level over extended period of time, with release profiles sustained by the special technological construction and design of the system. The sustained release dosage form is defined as "any drug or dosage form modification that prolongs the therapeutic activity of the drug", once the maximum level is reached, the amount of drug in the body decrease slowly so it will take longer time to drop below the therapeutic range. The terms sustained or controlled drug release incorporates the element of prolongation of duration of drug action as well as the drug predictability and reproducibility in drug release kinetics [2]. Polymeric sustained drug delivery systems is the one which offer numerous advantages when compared with conventional dosage forms, including improved efficacy, reduced toxicity and improved patient compliance [3,4].

The USP/ NF presently recognize several types of modified release dosage forms.

- Extended released dosage forms (Ex: sustained released dosage forms,

  Controlled release dosage forms).
- Delayed released dosage forms (Ex: enteric coated tablets).

1.1.1. Modified release dosage forms

It is defined as one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, tablets and capsules.

1.1.2. Extended release dosage forms

It is defined as those that allow at least a two fold reduction in frequent dosing compared to the drug presented in a conventional form (Ex: a solution or an immediate release dosage form).

1.1.3. Sustained–release dosage forms

It is defined as any drug or dosage form modification that prolongs the therapeutic activity of the drug. It provides prolonged but not uniform release of drug and reduces the need for repeated

dosing. Once the maximal level is reached, the amount of drug in the body decrease slowly so it will take longer time to drop below the therapeutic range that shown in figure 1.

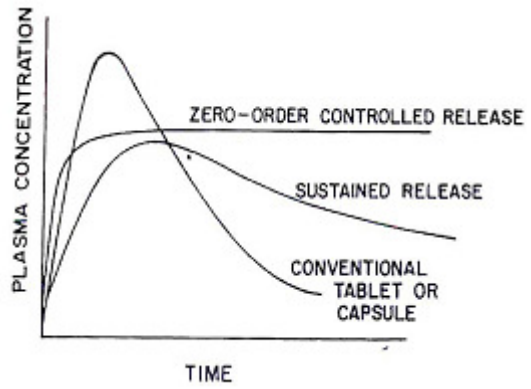

Figure - 1: Typical plasma drug concentration profiles for conventional tablet or capsule formulation, a sustained release and an oral controlled release formulation.

1.2. Factors to be considered in designing a Sustained Release Formulation

It is a reasonable assumption that drug concentration at the site of action is related to drug plasma level and that, in the great majority of cases, the intensity of effect is some function of drug concentration at the target site. The objective of the most therapeutic regimens is to rapidly raise the plasma concentration to the required level and then to hold it constant for the desired duration of treatment. The extent to which this situation can be achieved depends on many factors, including the minimum effective concentration of the drug, the level at which side effects occur, the dose administered, the rate of drug release from the dosage form, the rate of elimination and the frequency of dosing. The major purpose for developing prolonged release formulations of the drug is generally to maintain the blood concentration of the active ingredient at therapeutically effective levels. Therefore, it is desirable that average minimum effective concentration and optimal therapeutic concentrations be clarified for each drug by evaluating blood concentrations of the active ingredient or therapeutic moiety(s) including active metabolite(s) in relation to drug efficacy. Information on the biopharmaceutical properties of the active ingredient for a prolonged release dosage form is essential in rationalize formulation design. Particular attention should be given to the following factors [5,6]:

- Location of major absorption sites or specificity in the site of absorption.
- Absorption rate.
- The elimination half-life of the drug
- Absorption is non-linear due to the saturated drug absorption, first pass effects, or other reasons.
- Elimination is non-linear due to drug metabolism saturation or other factors.
- Inactivation or metabolism of the drug in the body, including the gastrointestinal tract.
- Dose and molecular size.
- GIT transit and emptying time.
- Partition coefficient, solubility and stability of drug.
- Environmental condition.

1.3. Types of Oral Sustained Drug Delivery System [7- 9]

1.3.1. Diffusion release system

In these types of systems, the rate controlling step is not the dissolution rate but the diffusion of dissolved drug through a polymeric barrier. The drug release rate is never zero-order since the diffusion path length increases with time as the insoluble matrix gradually depleted of drug [9].

13.1.1. Reservoir Devices

A characteristic approach to sustained release is to encapsulate or contain the drug entirely as a core, within a polymer film or coat. A lot of various factors that can affect the diffusion process may readily be applied to reservoir devices (*e.g.*, polymer functionality, the effects of additives, porosity, film casting conditions, etc.) and, hence, the choice of polymer must be an vital consideration in the development of reservoir devices. Modeling the release characteristics of reservoir devices in which the transport of the drug is by a solution-diffusion mechanism therefore typically involves a solution to unsteady-state conditions (concentration dependent flux) for the relevant boundary conditions. When the device contains dissolved active agent, the rate of release decreases exponentially with time as the concentration (activity) of the agent within the device decreases (*i.e.*, first order release). If, however, the active agent is in a saturated suspension, then the driving force for release is kept constant (zero order) until the device is no longer saturated. Alternatively the release-rate kinetics may be desorption controlled, and a function of the square root of time [10].

1.3.1.2. Monolithic Devices (Matrix Devices)

Monolithic (matrix) devices are possibly the most common of the devices for sustaining or controlling the release of drugs. This is probably because they are relatively easy to fabricate, compared to reservoir devices and there is not the danger of an accidental high dosage that could result from the rupture of the membrane of a reservoir device. In such a device the active agent is present as dispersion within the polymer matrix, and they are typically formed by the compression of a polymer/drug mixture or by dissolution or melting. The dosage release properties of monolithic devices may be dependent upon the solubility of the drug in the polymer matrix or in the case of porous matrixes, the solubility in the sink solution within the particle's pore network, and also the tortuosity of the network (to a greater extent than the permeability of the film) [11].

1.3.1.3. Dissolution release system

Dissolution controlled system are designed to decrease their rate of dissolution drugs for sustain release preparations. These systems can be made in numerous different ways.

- By altering layers of drug with the rate controlling coats.
- By altering the thickness of the coating.

The dissolution process can be considered to be diffusion-layered controlled. The rate determining step is the rate of diffusion from the solid surface to the bulk solution. This dissolution process at steady state described by the Noyes –Whitney equation as [11],

dc/dt = KDA (CS-C) = DA/h (CS-C)

Where,

dc/dt = dissolution rate

KD = dissolution rate constant

A = surface area

CS = saturation solubility of the solid

C = concentration of solute in the bulk solution

D = diffusion coefficient

h = thickness of the membrane.

1.3.1.3.1. Encapsulation/coating dissolution system:

The particles are encapsulated by one of the several microencapsulation techniques with gradually break up materials.

1.3.1.3.2. Matrix dissolution release system

Matrix systems or monoliths since the drug is consistently dispersed throughout a rate-controlling medium.

1.3.1.3.3. Diffusion and diffusion release system

In this system, the drug core is covered in a partially soluble membrane. Pores are thus created due to dissolution of parts of the membrane as such and allow entry of aqueous medium into the core and hence drug dissolution and allow diffusion of dissolved drug out of the system [12].

1.3.1.3.4 Ion – Exchange resin-drug complexes

Sustained drug delivery is achived by exchanging ionizable acidic and basic drugs complexing with insoluble nontoxic resins like anionic and cationic exchanger respectively. The drug is released slowly by diffusion through the resin particle structure [12].

1.3.1.3.5. pH independent formulation

This systems are considered to remove the influence of changing GIT pH on dissolution and absorption of drugs by formulating them with enough amount of buffering agents that adjust the pH to desired value as the dosage form passes along the GIT and allow drug dissolution and release at a constant rate independent of GIT pH [12].

1.4 Advantages of Sustained Release Dosage Forms

Improved patient compliance and convenience due to less frequent administration [13, 14].

- Reduction in fluctuations in steady state levels
- Better control of disease condition and reduced intensity of local or systematic side effects.
- Better control of plasma levels of high potency drugs increased safety margin.
- Reduction in total amount of dose administered.
- Reduction in health care costs through shorter treatment period, reduction in personal time to dispense administers, monitors patients improved therapy and less frequency of dosing,.

1.5 Disadvantages of Sustained Release Dosage Forms [13, 14]

- Poor *In-vitro-in vivo* correlation.
- Decreased systemic availability in comparison to immediate release

- Possibility of dose dumping to food or chewing physiologic or formulation variables or grinding of oral formulation by the patient and thus increased risk of toxicity.
- Reduced possible dosage alteration of drugs normally administered in varying strengths.
- Recovery of drug is difficult in case of toxicity, poisoning or hypersensitive reactions.
- High cost of formulation.

1.6. Matrix System

The matrix system are generally used for manufacturing dosage forms because it makes manufacturing easy. This system is based on the use of a blend of hydrophilic and hydrophobic polymer to sustain the drug release. In sustained release tablets are formulated so that the active ingredient is surrounded in the matrix insoluble substances that explain in figure 2 [15].

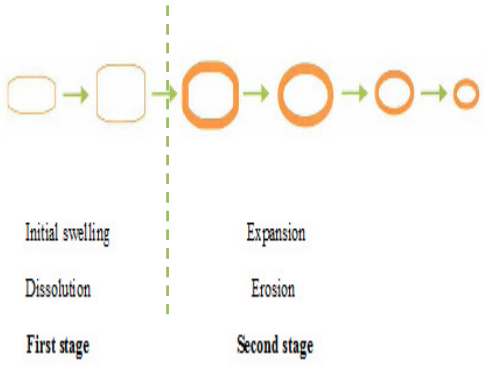

Figure – 2: Schematic release profile of the matrix tablet.

Preparation of drug embedded matrix tablet involve the direct compression of a combine of drugs, retardant materials and additives. A wide range of polymers has been employed as drug delay agents each of which presents a different approach to the matrix system. Polymers forming insoluble matrices areb of three types like first category of retarding materials, also given as plastic matrix systems, the second class represents hydrophobic materials, which are potentially erodible and third group includes polymers those form hydrophilic matrices [16]. Plastic matrix systems, widely used for sustaining the release of drug due to their chemical inertness and drug embedding ability. Channeling agents are used in Liquid penetration into the matrix is the rate-limiting step. The waxy materials and hydrophobic are potentially erodable and control the release of drug through pore diffusion and erosion. Polymers belonging to hydrophilic matrix systems, when exposed to an aqueous medium, does not disintegrate, but after hydration immediately develops a highly viscous gelatinous surface barrier which controls the drug release from and the liquid penetration into the centre of the matrix system. In some sustained release formulation the matrix swell up to form gel, so that the drug has first dissolve in matrix, then exit through the outer surface.

Benefits of Matrix system [16]

- Economic.
- Flexibility.
- Easy to manufacturing.
- Effective to obtained dissolution profile.

1.6.1 Materials used as retardants in matrix tablets formulations

Polymers used as retardant material in matrix tablet formulation. An ideal polymer for a sustained drug delivery system should have the following characteristics:

- Polymer as well as its degradation products should be nontoxic and non absorbable from the gastrointestinal tract.
- It should adhere quickly to moist tissue and should possess some site specificity.
- The polymer should not decompose on storage or during shelf life of the dosage form.
- It should be nonirritant to the mucous membrane.
- The polymer should be inexpensive.
- It should preferably form a strong non covalent bond with the mucin epithelial cell.
- It should allow easy incorporation of the drug and offer no hindrance to its release.

1.6.2. Release from matrix device

Matrix delivery system are of two types namely diffusion/swelleble system, and dissolution In diffusion systems, drug release is mainly governed by the hydration of matrices, followed by diffusion of drug molecules from the hydrated layer to the surrounding bulk solution and sometimes partially by erosion/dissolution. Examples include Eudragits and cellulose ethers. With dissolution systems, drug release is mainly due to dissolution/erosion of the matrix and hence achievement of constant drug delivery rate is easier by these systems. Sodium carboxymethylcellulose and natural gums are

examples of polymers that are gaining popularity in matrix drug delivery systems. Drug release from matrix may be diffusion, erosion and swelling which may depend on molecular size of polymer, nature of polymer, polymer ratio, compounds of polymer etc.

Table -1: Different types of polymer used in sustained release formulations.

Polymers	Drugs
Carbopol 934	Ambroxol hydrochloride
Carboxymethyl cellulose	Diclofenac sodium
Chitosan	Trimetazidine dihydrochloride
Gaur gum	Diltizem
Gum karaya	Verapamil
Hydroxy ethyl cellulose	Metformin hydrochloride
Hydroxy propyl cellulose	Losartan potassium
Hydroxy propyl methyl cellulose	Theophyllin
Pectin	Dimenhydrinate
Polyethylene glycol	Tramadol hydrochloride
Polyvinyl pyrrolidon	Metronidazole
Sodium alginate	Naproxen
Tragacanth	Acetaminophen

1.6.3. Methods of preparation

Developing oral controlled release tablets for highly water-soluble drugs with controlled release rate has been a challeng step to the pharmaceutical technologist. Oral administration of most of the highly water-soluble drugs, if not formulated properly, may causes release the drug at faster rate than desired and are likely to produce toxic concentrations.

1.6.3.1. Direct Compression

In this process powdered materials are compressed directly without changing the o properties of the drug like physical and chemical [17].

1.6.3.2. Wet Granulation

In this method weighed quantities of drug and polymer are mixed with sufficient volume of granulating agent. After enough cohesiveness was obtained, the mass is sieved through 22/44 mesh. The granules are dried at 40°C and thereafter kept in a desiccator at room temperature. Once dried the granules retained on 44 meshes were mixed with 15% of fines. Glidant and lubricants are added and the tablets are compressed using a single-punch tablet compression machine [17].

1.6.3.3. Melt Granulation

In this process use of a substance, which melts at relatively low temperature. This substance can be added in the molten form over the substrate, which is then heated above its melting point. In melt granulation substance act as liquid binding agent and hence does not require use of organic solvents. Different lipophilic binders such as Glyceryl Palmitostearate were tried by using melt granulation technique [18].

1.6.3.4. Hot-Melt Extrusion Process

Hot-melt extrusion equipment consists of downstream auxiliary equipment,an extruder, and other monitoring tools used for performance and product quality evaluation. In the hot-melt extrusion process, a mixture of the active ingredients, the thermoplastic polymers and other processing aids is fed into the barrel of the extruder through the hopper. The materials are transferred inside the heated barrel by a rotating screw. Temperatures at different zones are controlled by several thermocouples in the barrel. The materials melt at elevated temperatures and the molten mass is continuously pumped through the die attached at the end of the barrel. Materials are subject to only a few minutes in the extruder. Depending upon the dimensions of the die cylinders, films can also be produced from the extruder. Sustained release technology is widely used in different category of drugs like Antidiabetic, Diuretics, Antihypertensive, Antianginal drugs NSAID etc. in order to maintain the concentration of drug within the therapeautic range over a extended period of time with enhanced efficacy and safety profile minimizing of frequency of dosing and improved patient compliance [19].

1.7. Recent Trends In Sustained Release Drug Delivery Systems

Zahirul Khan has clasified the sustained release dosage form on the basis of its structural and physical appearance as, single unit dosage form, and multiple unit dosage form and mucoadhesive delivery systems [20].

1.7.1. Single Unit Dosage Forms

This refers to diffusion controlled system where the therapeutic agent is evenly distributed (dispersed /dissolved) throughout the solid matrix. This system can be classified as follows.

1.7.1.1. Complex reservoir system or coated tablets or multilayered system

The core material which typically, the drug alone or blended with hydrophobic or hydrophilic inert material and it is compressed into tablets.

1.7.1.2. Hydrophobic/Swellable tablets

Optimum alkaloid such as morphine salts homogenized with its salt and fatty acid or any ethylene vinyl acetate copolymer (hydrophobic filler) and then compressed into tablets was reported to give constant release pattern of the drug during in-vitro studies.

1.7.1.3. Semisolid matrix systems

In this system drug is incorporated in an oily "semisolid" hydrophobic carrier, and finally mass is typically filled into a gelatin capsule to prepare dosage form.

1.7.2 Multiple Unit Dosage Forms

It represents a mixture of the dosage form, the source of which may either be homogenous or heterogeneous. It offers the advantage of combining two or more drugs, in a single dosage form where the patient requires combination therapy. Another advantage is to release one of the drugs or part of the same can be sustained released. These are also useful where drug excipients and drug interactions are inevitable in a single unit dosage form. Multiple unit dosage forms are also known to have less variance in transit time through the G.I. tract than single unit dosage forms. The various forms which are available are [22],

1.7.2.1. Microgranules/spheroids

Drugs wet granulated alone or incorporated into inert granules, and then coated to control the release pattern.

1.7.2.2. Beads

Beads are prepared from various polymers and other inert materials have been used as carrier to deliver the water soluble drugs orally in the form of sustained release preparation.

1.7.2.3. Pellets

Pellets prepared by coating inert drug pellet with film forming polymers. The drug release depends upon coating composition of polymers and amount of coatings.

1.7.2.4. Microcapsules

Microcapsules are prepared by applying relatively thin coating to small particles of solids, droplets of liquid and dispersion. Its uniqueness lies in smallness of particles and their use and adaptation to a wide variety of dosage forms.

1.7.3. Mucoadhesive Delivery System

It utilizes principle of bioadhesion for optimum delivery of the drug from the device. Bioadhesion is defined as the occurrence in which one biological substance is adhered to another substance which may either be of biological or non biological origin. If the substance is mucosal membrane, the phenomenon is known as "muco adhesion". Conventional controlled release dosage forms described above are unable to restrain and localize in selected region of tract. Mucoadhesive system is suitable to increase the contact time of drug with absorbing membrane and localization of delivery of drug at targeted sites.

1.8. Factors Affecting Release of Drug From Matrix

The following factors affect the release of drug from matrix systems[23, 24].

- Viscosity of polymer
- Mixture of polymer
- Ratio of polymer to drug
- Particle size of drug
- Tablet thickness
- Compression pressure
- Added diluents
- Microenvironment pH of matrix
- Tablet surface area
- Entrapped air in tablet
- Drug solubility

2. 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.

3. REFERENCES

1. Martins O and Emeje Olobayo Ofoefule O. The effect of the molecular size of Carboxymethyl cellulose and some polymers on the sustained release of theophylline from a hydrophilic matrix. **Acta Pharm.,** 2006. 56, 325-335.
2. Amaral MH, Sousa Lobo JM, and Ferreira DC. Formulation and evaluation of sustained

release matrix tablet. **Drug development and industrial pharmacy,** 2001; 13: 123-133.

3. Kumar MNVR, and Kumar N. Formulation and evaluation of sustained release matrix tablet. **Drug Dev. Ind. Pharm.,** 2001; 27(1):1-30.
4. Kim CJ and Technomic Pub. Formualtion and evaluation of floating drug delivery system **Acta Poloniae,** 2000, 63, 1.
5. Robinson JR and Vincent HL. Controlled drug delivery fundamentals and application, 2nd Edition, **Marcel Dekker,** INC, New York, 1987; 36.
6. Peter G, Welling R and Michael Dobrinska, Robinson JR and Lee VHL. Controlled Drug Delivery, 2nd Edition, **Marcel Dekker,** INC, New York, 1987; 255-259.
7. www.wikipedia.org sustained release tablets.
8. Robert Langer S and Donald Wise L. Medical Applications of Controlled Release, Inc, vol. I, **CRC Press,** 1984; 159.
9. Brahmankar DM and Jaiswal SB. Bio pharmaceutics and pharmacokinetics a treatise, 2nd Edition, Vallabh Prakashan, 2001; 348-35.
10. www.inintium.demon.co.uk.
11. www.inintium.demon.co.uk.
12. Brahmankar DM and Jaiswal SB. Bio pharmaceutics and pharmacokinetics a treatise, 2nd edition, **Vallabh Prakashan,** 2001, 348-354.
13. Welling PG, Dobrinska MR, Robinson JR and Lee VHL. Controlled Drug Delivery Fundamentals and Applications, **Marcel Dekker,** Inc., New York, 1987, 2nd Edn, (29) 255-259.
14. Williams L and Wilkins, T. Wai- Yip Lee and Robinson JR, Formulation and Characterization of Sustain Release Matrix tablet, **The Science and Practice of Pharmacy,** Maryland, 20th ed., 2000; 903-914.
15. Gennaro AR and Remington. The science and practice of pharmacy, **Maryland,** 20th Edition, 2000; 910-911.
16. www.wikipedia.org.
17. Lachman L, Liberman HA and Kanig JL. The Theory and practice of industrial pharmacy Lea and Febiger, Philadelphia, 3rd edition, 1987; 318- 320.
18. Sandip BT, Krishna Murthy I, Ravendra Pai M, Pavak RM and Chowdary PW. **AAPS Pharm Sci Tech.,** 2003; 4: (3) 31.
19. Gruenhagen HH. Polymer/drug-melt extrusion therapeutic and technological appeal. **Pharmaceutical Technology Europe,** 1996; 11: 22-27.
20. Lapidus J and Lordi NG. Formulation variables affecting drug release from xanthan gum, **J. Pharm. Sci.,** 1968; 57:1292-1301.
21. Colomba P, Bettini RM. Rheological behaviour of hydrophilic polymers, **J. Pharm. Sci.,** 1991; 86:(1-8)-19.
22. Higuchi T. Polymer Permeability, **J. Pharm. Sci.,** 1962; 52: 1145.
23. Lachman L, Liberman HA and Kanig JL. The Theory and practice of industrial pharmacy, **Lea and Febiger, Philadelphia,** 3rd Edition, 1987; 430-456.
24. Miyazaki S, Kubo W and Attwood D. Oral sustained delivery of Paracetamol from in situ-gelling gellan and sodium alginate It. **J. Pharm.,** 2005; 1-2: 38- 49.