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Recent Trends in Sustained Release Drug Delivery System

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Abstract

Now a days as very few drugs are coming out of research and development and already existing drugs are suffering the problem of resistance due to their irrational use specifically in case of drugs like antibiotics. Hence, change in the operation is a suitable and optimized way to make the some drug more effective by slight alteration in the drug delivery.

Keywords: Sustained release system, Matrix system

Introduction

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, parentral, 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.[1] Now a day's most of the pharmaceutical scientists are involved in developing an ideal DDS. Scientists have succeeded to develop a system that can be as near to an ideal system and it encourages the scientists to develop controlled release system.[2] For this reason, most system employed are of the sustained release variety.This ideal system should have advantage of single dose for whole duration of the treatment and it should deliver the drug directly at specific site. Prolonged-release tablets, also known as sustained-release tablets or extended-release tablets are tablets formulated in such a manner as to make the contained active ingredient available over an extended period of time after ingestion.[3] A sustained release (SR) tablet is typically designed to release drug over 12-24 hrs and might contained in an immediate release tablet.[4]

The USP/ NF presently recognize several types of modified release dosage forms.[1]

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

Modified Release dosage form

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]

Delayed Release These 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.[5]

Extended-release A dosage form that allows at least a two fold reduction in dosage frequency as compared to that drug presented as an immediate release form.[6]

A Sustained release dosage form is defined as "Any drug or dosage form modification that prolongs the therapeutic activity of the drug".[7] This delivery system is increasingly being used in the treatment of acute and chronic diseases as they maintain the concentration of drug in plasma above the minimum effective concentration to and below the minimum toxic level for an extended period of time.[8] Sustained release, sustained action, prolonged action controlled release, extended action, timed release, depot and repository dosage forms are terms used to identify drug delivery system that are designed to achieve or prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.[12,16]

Rationale of Developing SR Matrix DDS[14]

1. To extend the duration of action of the drug.
2. To minimize the fluctuations in plasma level.
3. Improved drug utilization.
4. To reduce the frequency of dosing providing the uniform drug delivery.

The basic rationale for sustained drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacological active moieties by using novel drug delivery system or by modifying the molecular structure and physiological parameters inherent in the selected route of administration.[17]

Factors to be consider in designing a Sustained Release Formulation

Biological Factors

- Biological half life

Drugs with short half-lives are usually excellent candidates for sustained release formulation. Drugs with half-life shorter than 2 hours the dosage form may contain a prohibitively large quantity of the drug. Drugs with long half-lives, more than 8 hours are also normally not used in sustaining form, since their drug release pattern is already sustained.[7]

- Absorption

The purpose of designing a sustain release product, it is essential that the rate of release must be slower than the absorption rate. If we assume that the transits time of most drugs and devices in the absorptive areas of the GI tract is about 8-12 hours, the maximum half-life for absorption should be approximately 3-4 hours.[15]

Distribution

High apparent volume of distribution of drug affect the release rate pattern of elimination of the drug, and such drugs are poor candidate for oral sustained release drug delivery system.[7]

Protein Binding

Protein binding plays a significant role in its therapeutic effect regardless the type of dosage form as extensive binding to plasma increase biological half life and thus sometimes SR drug delivery system is not required for this type of drug.[10]

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.[18,15]

Margin of safety

As we know larger the value of therapeutic index safer is the drug.[19]

Plasma Concentration Response Relationship

Generally pharmacological response of drug depends on plasma drug concentration rather than size and dose. But some drugs pharmacological activity is independent of plasma concentrations, which are poor candidate for oral SR drug delivery system. E.g. Reserpine.[2]

Concentration Dependency on Transfer of Drug

Transfer of drug from one compartment to other by zero kinetic process then such drugs are poor candidate for oral SR delivery system, it should be first order kinetics.[11]

Therapeutic Index

It is most widely used to measure the margin of safety of a drug.

$$TI = TD50 / ED50$$

The longer the value of TI, the safer the drug. Drugs with very small value of Therapeutic index are poor candidates for formulation into sustained release products. A drug is considered to be safe if its TI value is greater than 10[15].

B. Physicochemical Factors

Dose Size

For orally administered drug delivery systems, a solitary dose of 0.5-1.0g is considered maximum for a conventional dosage form. This also holds exact for sustained release dosage form.[20]

Ionization, pka and aqueous solubility

Most drugs are weak acids or bases. The unchanged structure of a drug permeates across membranes of lipids. Presenting the drug in an unchanged form is beneficial for drug permeation. Regrettably, the condition is made additional complex by the fact that the drug's aqueous solubility will generally be decreased by conversion to unchanged form. Compounds with extremely low solubility (<0.01mg/ml) are innately sustained, since their release in the GI tract will be restricted by drug dissolution. Consequently it is understandable that the solubility of the compound will be poor choices for slightly soluble drugs.[32]

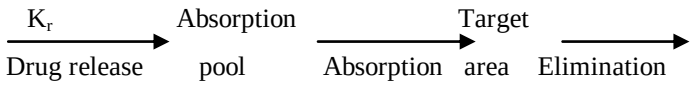
Partition Coefficient

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.[32]

Stability Orally administered drugs can be subject to both enzymatic degradation and acid-base hydrolysis. Degradation will continue at a condensed rate for drugs in solid state. So, this is the favored work of art of delivery for difficulty cases.[32]

Principle of Sustained Release Drug Delivery[9]

The conventional dosage forms release their active ingredients into an absorption pool immediately. This is illustrated in the following simple kinetic scheme.



The absorption pool represents a solution of the drug at the site of absorption,

Kr, Ka and Ke - first order rate-constant for drug release, absorption and overall elimination respectively. Immediate drug release from a conventional dosage form implies that Kr>>>>Ka. For non immediate release dosage forms, Kr<<<Ka i.e. the release of drug from the dosage form is the rate limiting step. The drug release from the dosage form should follows zero-order kinetics, as shown by the following equation:

$Kr° = Rate\ In = Rate\ Out = Ke\ Cd\ Vd$ ……1

Where, Kr°: Zero-order rate constant for drug release-Amount/time, Ke: First-order rate constant for overall drug elimination-time, Cd: Desired drug level in the body – Amount/volume, and Vd: Volume space in which the drug is distributed in liter.

Design of Oral Sustained Release drug Delivery System [23]

The objective in designing a sustained release forms is to deliver drug at a rate necessary to achieve and maintain a constant drug blood level. This is usually accomplished by attempting to obtain zero order release from dosage forms. Generally sustain release system do not attain this type of release and try to mimic zero order release by providing drug in slow first order fashion as shown by following equation.

Rate in = Rate out = K.Cd.Vd

Where,

Cd = Desired drug level, Vd = Volume of distribution, K = elimination rate constant

Classification of Sustained release drug delivery system[23]

Depending upon the manner of drug release, this system has are classified as follows:

A. Continuous Release system

a) Diffusion sustained system

- Reservoir type.
- Matrix type

b) Dissolution sustained system

- Reservoir type.
- Matrix type
- c)Methods using Ion-exchange

d)Methods using osmotic pressure

e)pH independent formulations

B. Delayed Transit and Continuous Release System these systems are designed prolong their residence in the GIT along with their release.

C. Delayed Release System The design of such systems involves release of drug only at specific in the GIT. The drug contained in such a system is those that are

- Destroyed in the stomach or by intestinal enzymes.
- Known to cause gastric distress.
- Absorbed from a specific intestinal site.

A. Continuous release system

a. Diffusion controlled system

- Reservoir devices

This system involves a membrane which controls the release of drugs from the matrix system.[24]

The characteristics of reservoir diffusion system are[35]

- 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.

- Matrix type

A solid drug is distributed into an insoluble matrix and the release rate of drug which generally depend on the rate of drug diffusion and the rate of solid dissolution.

The characterstics of Matrix type[35]

- Zero order release can not be obtained.
- Easy to produce than reservoir devices.
- High molecular weight compounds are delivered through the device.

b. Dissolution controlled Release system

A drug which having a slow dissolution rate this drugs are naturally sustained and for those drugs with high water solubility, decrease their dissolution rate through appropriate salt or derivative formation.

Soluble reservoir system

In this system drug is coated with erodible coat, which is slowly dissolved in the contents of GI tract by alternating layers of drug with the rate controlling coats.[25]

Soluble matrix system (Monolith)

As the drug is homogenously dispersed throughout rate controlling medium, this system is also called monolithic system.[33]

c. Dissolution and Diffusion Controlled Release Systems

In such system, the drug core is encased in a partially soluble membrane. Pores are thus created due to dissolution of parts of membrane which permit entry of aqueous medium in to core and hence rug dissolution, allow diffusion of dissolved drug out of the system.[25]

d. pH-independent formulation

Most of the drug are either weak acid or weak base, the release from sustain release formulation is pH dependent. However, buffer such as salt of citric acid, amino acid, tartaric acid can be added to the formulation, to help to maintain to constant pH their by retarding pH independent drug release.[18]

Advantages of Sustained release drug delivery[35, 25]

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

Disadvantages of Sustained Release Drug Delivery System[26, 39]

- Increased cost.
- Toxicity due to dose dumping.
- Unpredictable and often poor in vitro-in vivo correlation.
- Risk of side effects or toxicity upon fast release of contained drug (mechanical Failure, chewing or masticating, alcohol intake).[11]
- Increased potential for first- pass clearance.
- Less flexibility in acute dose adjustment

MATRIX SYSTEM

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.[10] In such systems, the drug in the form of powder is mixed with matrix forming component and the mixture is shaped in the required mold.[11] These are the type of controlled drug delivery systems, which release the drug in continuous manner. These release the drug by both dissolution controlled as well as diffusion controlled mechanisms.[12, 13] .To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid nonswellable hydrophobic materials or plastic materials[13]

Materials used as retardant in Matrix tablets formulation[37]

1. Insoluble,Inert- e.g polyethyiene, PVC,EC, Methyl acrylate-methacrylate polymer
2. Insoluble erodible-Carnauba wax, Stearyl alcohol, steric acid,Castor wax, polyethylene glycol monosterate triglycrides
3. Hydrophillic- Methylcellulose(400cps, 4000cps) HPMC, HPMC (60 HG,90 HG, 25 cps 15000cps), CMC

Methods of preparation[34]

Direct Compression

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

Wet Granulation

In this method weighed quantities of drug and polymer are mixed with sufficient volume of granulating agent. After enough cohesiveness was obtained, then screening of wet mass. The granules are dried and screening of dry granules, then blending with lubricant and disintegrant to produce "running powder"tablets are compressed using a single-punch tablet compression machine.[34]

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.Different lipophilic binders were tried by using melt granulation technique.

Hot-Melt Extrusion Process

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.

The materials melt at elevated temperatures and the molten mass is continuously pumped through the die attached at the end of the barrel. Depending upon the dimensions of the die cylinders, films can also be produced from the extruder.

Effect of Release limiting factor on drug release[35]

- Polymer hydration:
- Drug solubility
- Solution solubility
- Polymer diffusivity
- Thickness of polymer diffusional path
- Thickness of hydrodynamic diffusion layer
- Drug loading dose
- Surface area and volume
- Diluent's effect
- Additives

Recent trends in Sustained release drug delivery system[28, 16,]

For orally administered dosage forms, sustained drug action is achieved by affecting the rate at which the drug is released from the dosage form and or by slowing the transit time of dosage form through the gastrointestinal tract. 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.

- **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.

- 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.

- 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.

- 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.
- Ion exchange resins

A drug–resin complex is formed by prolonged exposure of drug to the resin. The drug from these complexes gets exchanged in gastrointestinal tract and later they are released with excess of Na+ and Cl- present in gastrointestinal tract.[29]

Osmotic pump

The system is composed of a core tablet surrounded by a semipermeable membrane coating having a 0.4mm diameter hole produced by laser beam [16]. The tablet, particle or drug solution that allows transport of water into tablet with eventual pumping of drug solution out of the tablet through the small delivery aperture in tablet coating.[30]. E.g. Glucotrol XL (glipizide) tablets (Pfizer), Covera – HS ® (verapamil HCl) tabs. (Searle)[38]

- **Multiple Unit Dosage Forms**

It represents a mixture of the dosage form, the source of which may either be homogenous or heterogeneous. The various forms which are available are

Multitablet system[31]

Small spheroids compressed tablets 3 to 4 mm in diameter may be prepared to have varying drug release characterstics. They them may be placed in gelatin capsule shells to provide the desired pattern of drug release

Coated Beads, granules& Microsphere

In these systems, the drug is distributed on to beads, pellets, granules, or other particulate systems. Using conventional pan coating or air suspension coating, a solution of the drug substance is placed on small inert nonpareil seeds or beads made of suger and starch or on microcrystalline cellulose spheres.

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.

Microencapsulated drug

Microencapsulation is a process by which solids, liquids, or even gases may be enclosed in microscopic particles by formation of thin coatings of wall material around the substance.

Mucoadhesive Delivery System

It utilizes principle of bioadhesion for optimum delivery of the drug from the device. Mucoadhesive system is suitable to increase the contact time of drug with absorbing membrane and localization of delivery of drug at targeted sites.

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. 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.

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FIGURE1.

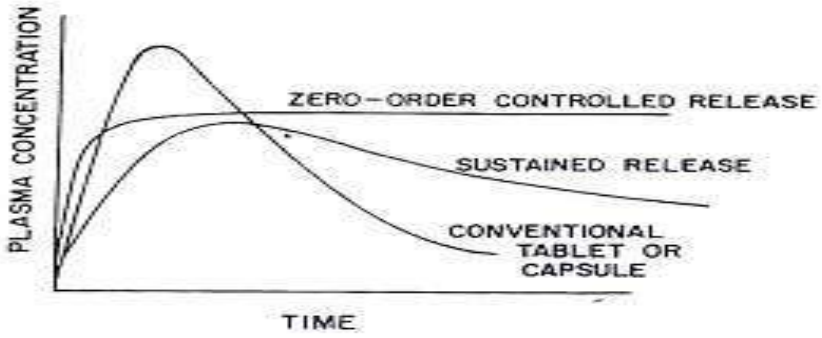

Figure2: Plasma drug concentration profile for conventional release, a sustained release and zero order controlled release formulation[1]

Characterstics that make drugs unsuitable for sustained release formulation[36]

[1] Characterstices	Drugs
[2] Short elimination half-life (< 2 hours)	Penicillin G, furosamide
[3] Long elimination half-life (> 8 hours)	Diazepam, phenytoin
[4] Poor absorption	Riboflavin, ferrous salts
[5] Large doses required	Sulfonamides
[6] Cumulative action and undesirable side effect; [7] drugs with low therapeutic indices	phenobarbitol, digitoxin
[8] No clear advantages for sustained release [9] Formulation	Griseofulvin
[10] Precise dosage titrated to individual [11] is required.	Anticoagulants, cardiac gylcosides

Proprietary Modified-Release oral dosage form[28]

[12] Drug product and Manufacturer	Dosage form characterstics
[13] Delayed release	
[14] E-Mycin(erythromycin) delayed release tablets (knoll) [15] [16] [17]	Tablets entric coated with cellulose Acetate phthalate, carnauba wax, and Cellulose polymer:use: antibiotic
[18] Erythromycin delayed release capsule(Abbott) [19] [20]	Capsules contain entric coated pellets Of erythromycin base.Use:antibiotic
[21] Extended-release coated particles and beads	
[22] Toprol-XL (metoprolol succinate) tablets [23] (AstraZeneca) [24]	Drug pellets coated with cellulose polymer compressed in to tablets. Use: treatment of Hypertension
[25] Indocin SR(Indomethacin) capsules (Merck) [26] [27] [28] [29]	Coated pellets for SR. Formulation Includes PVA-Crotonic acid Copolymer and HPMC. Use: analgesic nd antiinflammatory
[30] Extended- release inert matrix	
[31] Desoxyn(methamphetamine HCL) gradumet	Drug impregnated in an inert ,porous,

[32] Tablets(Abbott) [33] [34]	plastic matrix.use:attention deficit Disorder
[35] Extended release hydrophilic/ eroding matrix [36] Depakote ER (divalproex sodium) extended release [37] Tablets (Abbott) [38] [39]	Drug is dispersed and compressed in a hypromellose and microcrystalline cel Cellulose matrix. Use:antiepileptic
[40] Extended-release microencapsulated [41] K-Dur microburst release system [42] (Potassium chloride) tablets(Key) [43] [44] [45]	Immediately dispersing drug microencapsulated with EC and hydroxyl Propyl cellulose. Use: potassium Depletion.
[46] Extended-release osmotic [47] Glucotrol XL (glipizide) tablets(Pfizer) [48] [49] [50] [51]	Controlled release GITS osmotic system. Ingredients include polyethylene oxide, Hydroxypropyl cellulose, cellulose Acetate.use: antihyperglycemic

Controlled/Sustained &Modified release formulations currently available in market[40]

[52] Product [53] (Tradename)	[54] Drug	[55] Type
[56] Entocost	[57] Budenoside capsule(9mg)	[58] CR capsule for colon specific [59] Drug delivery
[60] Cifran OD	[61] Ciprofloxacin tablets (500mg/g)	[62] Effervesent Matrix type floating tablets
[63] Roliten OD	[64] Tolterodine tartrate extended release capsule(2/4 mg)	[65] Reservoir type CR beads encapsulated in empty gelatin shells
[66] Co- amoxyclav ER tablets	[67] Amoxycillin & potassium clavulanate tablets	[68] Matrix type CR bilayer tablets
[69] Desval ER tablets	[70] Divalproex Soddium extended release tablets(250/500 mg/g)	[71] Matrix type diffusion controlled ER tablets
[72] Contifluo	[73] Tamsolusin CR beads	[74] Diffusion and dissolution controlled beads