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Review Article

SUSTAINED RELEASE DOSAGE FORM: A CONCISE REVIEW

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Abstract

Now days as the expense and complications involved in marketing new drug entities are increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems (DDS). Hence we will change the area of focusing it is suitable to designing sustained drug delivery is to reduce the frequency of dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. The design of oral sustained release DDS depends on various factors such as, physicochemical properties of drug, type of delivery system, disease being treated, and patient condition, and treatment duration, presence of food, gastrointestinal motility, and co-administration of other drugs.

Keywords: Sustained release drug delivery system, Dose frequency, Biological half-life, physicochemical properties of drugs.

Introduction

Sustained release, sustained action, prolonged action controlled release, extended release, depot release these are the various terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over a long period of time after administration of a single dose of drug. The goal in designing sustained release delivery systems is to reduce frequency of dosing or to increase effectiveness of the drug by localization at the site of the action, reducing dose required or providing uniform drug delivery.The ideal drug delivery systems have two things would be required first it would be a single dose the duration of treatment whether it is for days or week, as with infection, or for the life time of the patient, as in hypertension or diabetes. Second it should deliver the active entity directly to the site of the action, thereby minimizing side effects.[1]

DISADVANTAGES 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.

4. The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index whenever over medication occur [1, 6, 7].

ADVANTAGES OF SUSTAIN RELEASE DOSAGE FORMS

1. Reduction in frequency of intakes.

2. Reduce side effects.

3. Uniform release of drug over time.

4. Better patient compliance [1, 5, 8].

DISADVANTAGES OF SUSTAINED RELEASE DRUG DELIVERY

1. Increased cost.

2. Toxicity due to dose dumping.

3. Unpredictable and often poor *in vitro-in vivo* correlation.

4. Risk of side effects or toxicity upon fast release of contained drug (mechanical failure, chewing or masticating, alcohol intake).

5. Increased potential for first- pass clearance.

6. Need for additional patient education and counseling [9-11].

CLASSIFICATION OF ORAL SUSTAINED OR CONTROLLEDRELEASE SYSTEMS

The controlled release systems for oral use are mostly solidsand based on dissolution, diffusion or a combination of bothmechanisms in the control of release rate of drug. Dependingupon the manner of drug release, these systems areclassified as follows:

1. Continuous release systems

2. Delayed transit and continuous release systems

3. Delayed release systems

1. Continuous release systems

Continuous release systems release the drug for aprolonged period of time along the entire length of

gastrointestinal tract with normal transit of the dosageform. The various systems under this category are asfollow:

A. Diffusion controlled release systems

B. Dissolution controlled release systems

C. Dissolution and diffusion controlled releasesystems

D. Ion exchange resin- drug complexes

E. pH-independent formulation

A. Diffusion controlled release systems

In this type of systems, the diffusion of dissolved drugthrough a polymeric barrier is a rate limiting step. Thedrug release rate is never zero-order, since thediffusional path length increases with time as the insolublematrix is gradually depleted of drug. Diffusion of a drugmolecule through a polymeric membrane forms the basisof these controlled drug delivery systems.Similar to the dissolution-controlled systems, the diffusioncontrolleddevices are manufactured either byencapsulating the drug particle in a polymeric membraneor by dispersing the drug in a polymeric matrix. Unlikethe dissolution-controlled systems, the drug is madeavailable as a result of partitioning through the polymer.In the case of a reservoir type diffusion controlled device,the rate of drug released (dm/dt) can be calculatedusing the following equation:

$$Dm/dt=ADK\Delta C/1$$

Where,

A = Area

D = Diffusion coefficient

K = Partition coefficient of the drug between the drug core and the membrane

L = Diffusion path length and

C = Concentration difference across the membrane

In order to achieve a constant release rate, all of theterms on the right side of equation must be held constant.It is very common for diffusion controlled devices toexhibit a non-zero-order release rate due to an increasein diffusional resistance and a decrease in effectivediffusion area as the release proceeds. Anotherconfiguration of diffusion-controlled systems includesmatrix devices, which are very common because of easeof fabrication. Diffusion control involves dispersion ofdrug in either a water-insoluble or a hydrophilic polymer.The release rate is dependent on the rate of drugdiffusion through the matrix but not on the rate of soliddissolution.

The two types of diffusion-controlled release are:

a. Matrix diffusion controlled systems

b. Reservoir devices

B. Dissolution-controlled release systems[1]

The drug present in such system may be the one:

a. Having high aqueous solubility and dissolution rate

b. With inherently slow dissolution rate e.g. Griseofulvin and Digoxin

c. That produces slow dissolving forms, when it comes in contact with GI fluids

Dissolution-controlled release can be obtained by slowing the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer and coating drug particles or granules with polymeric materials of varying thickness. The rate limiting step for dissolution of a drug is the

diffusion across the aqueous boundary layer. The solubility of the drug provides the source of energy for drug release, which is countered by the stagnant-fluid diffusional boundary layer.

The rate of dissolution (dm/dt) can be approximated by following equation:

dm

dt = ADS

h

Where,

A = Surface area of the dissolving particle

or tablet

D = Diffusivity of the drug

S = Aqueous solubility of the drug

h = Thickness of the boundary layer

The two types of dissolution-controlled release are:

A. Matrix (or monolith) dissolution controlled systems

B. Reservoir dissolution controlled systems

C. Dissolution and diffusion controlled release systems [6]

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

D. Ion exchange resin-drug complexes [8]

It is based on formulation of drug resin complex formed when ionic solution is kept in contact with ionic resins. The drug from this complex gets exchanged in gastrointestinal tract and released with excess of Na+ and Cl- present in gastrointestinal tract. This system generally utilize resin compound of insoluble cross linked polymer. They contain salt forming function group in repeating position on a polymer chain.

E. pH-independent formulation [19]

Most of the drug are either weak acid or weak base, therelease 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 tomaintain to constant pH their by retarding Phindependent drug release. A buffer sustain releaseformulation is prepared by mixing a basic or acidic drugone or more buffering agent, granulating withappropriate excipients and coating with gastrointestinalfluid permeable film forming polymer. Whengastrointestinal fluid permeates through the membrane, the buffering agent adjusts the fluid inside to suitableconstant pH there by rendering a constant rate of drugrelease.

F. Osmotic pressure controlled systems [7]

A semi permeable membrane is placed around thetablet, particle or drug solution that allows transport ofwater into tablet with eventual pumping of drug solutionout of the tablet through the small delivery aperture intablet core. Two type of osmotic pressure controlledsystems are:

a. Type 1 contains an osmotic core with drug

b. Type 2 contains the drug in flexible bag withosmotic core surroundingBy optimizing formulation and processing factor, it ispossible to develop osmotic system to deliver the drug ofdiverse nature at preprogrammed rate.

2. Delayed transit and continuous release systems [1, 4]

These systems are designed to prolong their residence inthe GI tract along with their release. Often the dosageform is fabricated to detain in the stomach and hence thedrug present therein should be stable to gastric pH.Systems included in this category are mucoadhesivesystems and size based systems.

3. Delayed release systems [1]

The design of such systems involves release of drug onlyat specific site in the GIT. The drugs contained in such asystem are those that are:

a. Known to cause gastric distress

b. Destroyed in the stomach or by intestinalenzymes.

c. Meant to extent local effect at a specific GI site

d. Absorbed from a specific intestinal site

The two types of delayed release systems are:

1. Intestinal release systems

2. Colonic release systems

Rationale of controlled drug delivery system

The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery systems or by modifying the molecular structure and/or physiological parameters inherent in a selected route of administration. Thus, optimal design of controlled release systems necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of drug [15].

However, when doses are not administered on schedule, the resulting peaks and valleys reflect less

than optimum drug therapy. For example, if doses are administered too frequently, minimum toxic-concentration (MTC) of drug may be reached with toxic side effects resulting. If doses are missed, periods of sub-therapeutic drug blood levels or those below the minimum effective concentration (MEC) may result, with no patient benefit. Extended release tablets and capsules are commonlytaken only once or twice daily compared with counterpart conventional forms that may need to betaken three to four times daily to achieve the same therapeutic effect. Typically, extended release products provide an immediate release of drug which then is followed by the gradual and continual release of additional amounts of drug to maintain this effect over a predetermined period of time (Fig 1)

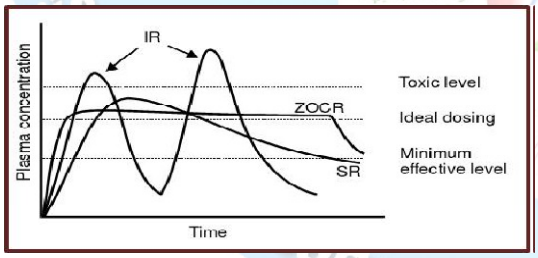

Figure 1.Characteristic representation of plasma concentrations of a conventional immediate release dosageform (IR), a sustained release dosage form (SR) and an idealized zero-order controlled release (ZOCR) dosage form (in combination with a start-up dose).

Drug-candidates suitable for sustained release products

For a successful sustained-release product, the drug must be released from the dosage form at apredetermined rate, dissolve in the gastrointestinal fluids, maintain sufficient gastrointestinal residence time, and be absorbed at a rate that will replace the amount of drug being metabolized and excreted.Zero order oral drug release can be achieved, in principle, by surrounding a core tablet with a membrane that is permeable to both drug and water, as illustrated in Fig 3a. After swallowing, the core becomes hydrated, and drug dissolves until it reaches its saturation concentration or solubility. The core serves as a saturated reservoir of drug. Drug release proceeds by partitioning from the reservoir into the membrane, followed by diffusion across the membrane into the gastrointestinal fluid. So long as saturation is maintained in the core, there will be a stationary concentration gradient across the membrane, and release will proceed at constant rate. Eventually, the dissolved drug's concentration in the core falls below saturation, reducing the concentration gradient andhence the release rate, which decays to zero. If the membrane consists of a water-soluble polymer of high molecular weight, then it will initially swell into a gel,through which drug diffuses. The thickness of the gel layer initially increases with time due to swelling, but ultimately it decreases due to disentanglement and dissolution of polymer chains. At intermediate times, the gel layer may be of approximately constant thickness, and release occurs at a relatively constant rate.

As an alternative to dissolution/partition/diffusion based devices, osmotic pumps have been developed to provide zero order release. An elementary osmotic pump, illustrated in Fig 3, is a tablet or capsule consisting of a core of drug surrounded by a membrane that is permeable to water but not to the drug. A small hole is drilled into the membrane. Upon ingestion, water is osmotically imbibed into the core through the semi permeable membrane, dissolving the drug. A constant osmotic pressure gradient is established between core and the external medium, setting the stage for water influx, which displaces drug through the hole at a constant rate. Eventually, drug concentrationfalls below its solubility, and the rate of osmotic pump-

ing decays. The efficiency of osmotic devices can be improved by enriching the core with excipients such as water soluble polymers. For example, in push-pull osmotic systems, depicted in Fig 3c, the drug formulation is layered between the water soluble polymer and the exit orifice. As water crosses the semi permeable membrane, drug is dissolved. Meanwhile, swelling of the polymer excipients, which is also caused by osmosis, pushes drug through the orifice

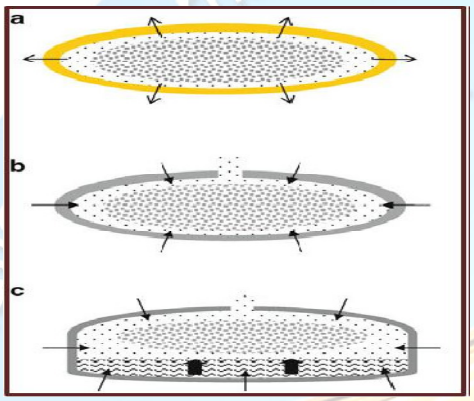

Figure 2.Schematics of devices designed for zero-order drug release.

(a) Membrane diffusion controlled release. Drug in core (granulated pattern) dissolves to form saturated solution (dilute dots). Drug then diffuses across membrane (thin tipped arrows).

(b) Elementary osmotic pump. Core is surrounded by a semipermeable membrane, with a small, drilled orifice.

(c) Push–pull osmotic pump.

PREFORMULATION STUDIES

Preformulation testing is an investigation of physical and chemical properties of drug substances alone and when combined with pharmaceutical excipients. It is the first step in the rational development of dosage form.

a) Determination of Melting Point:

Melting point of drug was determined by capillary method. Fine powder of drug was filled in a glass capillary tube (previously sealed at one end). The capillary tube is tied to thermometer and the thermometer was placed in the Thais tube and this tube is placed on fire. The powder at what temperature it will melt was noticed.

b) Solubility:

Solubility of drug was determined in pH 1.2 and pH 6.8 buffers. Solubility Studies wereperformed by taking excess amount of drug in beakers containing the Solvents. The mixtures were shaken for 24 hrs at regular intervals. The solutions were filtered by using whattmann's filter paper grade no. 41. The filtered solutions are analysed spectrophotometrically at 260.5nm as pH 1.2 as blank and 262.4nm as pH 6.8 as blank.

c) Compatibility Studies:

Compatibility study with excipients was carried out by FTIR. The pure drug and its formulations along with excipients were subjected to FTIR studies. In the present study, the potassium bromide disc (pellet) method was employed

d) Identification of Drug:

Weigh accurately about 0.25 gm, dissolve in 50 ml of carbon dioxide-free water and titrate with 0.1 M sodium hydroxide using phenol red solution as indicator. Repeat the operation without the substance under examination. The difference betweenthe titrations represents the amount of sodium hydroxide required.

Methods for Preparation of Controlled Release tablets[19]

1) Wet Granulation Technique

i) Milling and gravitational mixing of drug, polymer and excipients.

ii)Preparation of binder solution

iii) Wet massing by addition of binder solution or granulating solvent

iv) Screening of wet mass.

v) Drying of the wet granules.

vi) Screening of dry granules

vii) Blending with lubricant and disintegrant to produce "running powder"Compression of tablet.

2) Dry Granulation Technique

- Milling and gravitational mixing of drug , polymer and excipients
- Compression into slugs or roll compaction

- Milling and screening of slugs and compacted powder
- Mixing with lubricant and disintegrant
- Compression of tablet.

3) Sintering Technique

- Sintering is defined as the bonding of adjacent particle surfaces in a mass of powder, or in a compact, by the application of heat.
- Conventional sintering involves the heating of a compact at a temperature below the meltingpoint of the solid constituents in a controlled environment under atmospheric pressure.
- The changes in the hardness and disintegration time of tablets stored at elevated temperatureswere described as a result of sintering.
- The sintering process has been used for the fabrication of sustained release matrix tablets for the stabilization of drug release.

Evaluation Parameters

1) Pre Compression Parameters:

A. Bulk density (Db):

It is the ratio of powder tobulk volume. The bulk density depends on particle sizedistribution, shape and cohesiveness of particles.Accurately weighed quantity of powder was carefullypoured into graduated measuring cylinder throughlarge funnel and volume was measured which is calledinitial bulk volume. Bulk density is expressed in gm/ccand is given by,

Db = M / Vo

Where,

Db = Bulk density (gm/cc)

M = mass of powder (g)

Vo= bulk volume of powder (cc)

B. Tapped density (Dt):

Ten grams of powder wasintroduced into a clean, dry 100ml measuring cylinder.The cylinder was then tapped 100 times from aconstant height and tapped volume was read. It isexpressed in gm/cc and is given by,

Dt = M / Vt

Where,

Dt = Tapped density (gm/cc)

M = mass of powder (g)

Vt=tapped volume of powder (cc)

C. Compressibility index:

The compressibility of thepowder was determined by the Carr's compressibilityindex.

Carr's index (%) = = b=(v/b) X100

Table 1.Grading of powders for their flow propertiesaccording to carr's index

Sr. No	Carr's Index	Flow Properties
1	5-15	Excellent
2	12-15	Good
3	18-21	Fair to Passable
4	23-30	Poor
5	33-38	Very Poor
6	>40	Very Very Poor

D. Hausner ratio:

Hausner ratio = tapped density/bulk density

Values of Hausner ratio; < 1.25: good flow

>1.25: poor flow

If Hausner ratio is between 1.25-1.5, flow can beimproved by addition of glidants.

E. Angle of repose (θ):

It is defined as the maximumangle possible between the surface of pile of thepowder and the horizontal plane. Fixed funnel methodwas used. A funnel was fixed with its tip at a givenheight (h), above a flat horizontal surface on which agraph paper was placed. Powder was carefully poured

through a funnel till the apex of the conical pile justtouches the tip of funnel. The angle of repose was thencalculated using the formula,

Tanθ =h/r

θ = tan-1(h/r)

where, θ = angle of repose,

h = height of pile,

r = radius of the base of the pile.

Table 2.Comparison between angles of reposes and flowproperty

Sr. No.	Angle of repose	Flow properties
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	>40	Very Poor

F. Total Porosity: Total porosity was determined bymeasuring the volume occupied by a selected weight ofa powder (Vbulk) and the true volume of the powderblend (The space occupied by the powder exclusive ofspaces greater than the intermolecular spaces, V).

Porosity (%) =Vbulk-V/Vbulkx 100

G. Flow rate:

Flow rate of granules influences thefilling of die cavity and directly affects the weight of thetablets produced.

2. Post Compression Parameters

A. Thickness and diameter:

Control of physical dimension of the tablet such asthickness and diameter is essential for consumeracceptance and tablet uniformity. The thickness anddiameter of the tablet was measured using Verniercalipers. It is measured in mm.

B. Hardness:

The Mansanto hardness tester was used to determinethe tablet hardness. The tablet was held between afixed and moving jaw. Scale was adjusted to zero; loadwas gradually increased until the tablet fractured. The value of the load at that point gives a measure ofhardness of the tablet. Hardness was expressed inKg/cm2.

C. Friability (F):

Tablet strength was tested by Friabilator USP EF-2. Preweighed tablets were allowed for 100 revolutions(4min), taken out and were dedusted. The percentageweight loss was calculated by rewriting the tablets. The% friability was then calculated by,

D. Weight variation test :

The weight of the tablet being made in routinely-measured to ensure that a tablet contains the properamount of drug. The USP weight variation test wasdone by weighing 20 tablets individually, calculatingthe average weight and comparing the individualweights to the average. The tablet meet the USP test ifnot more than 2 tablets are outside the percentagelimits and if no tablets differs by more than 2 times thepercentage limit. USP official limits of percentagedeviation of tablet are presented in the following table,

Table 3.Weight variation limits

Sr. No.	Average weight of tablet (mg)	Maximum % of difference allowed
1	130 or less	10
2	130-324	7.5
3	324 or more	5

$$PD = \frac{(W_{avg}) - (W_{initial})}{(W_{avg})} \times 100$$

Where, PD = Percentage deviation,

W avg = Average weight of tablet,

W initial =individual weight of tablet.

E. Uniformity of drug content:

Five tablets of various formulations were weighedindividually and powdered. The powder equivalent toaverage weight of tablets was weighed and drug wasextracted in Phosphate buffer pH 6.8, the drug contentwas determined measuring the absorbance at 262.4 nmafter suitable dilution using a UV/VisibleSpectrophotometer (UV-1800).

CONCLUSION

Oral Sustained release (S.R) / Controlled release (C.R) products provide an advantage over conventional dosage forms by optimizing biopharmaceutics, pharmacokinetic and pharmacodynamics properties of drugs in such a way that it reduces dosing frequency to an extent that once daily dose is sufficient for therapeutic management through uniform plasma concentration providing maximum utility of drug with reduction in local and systemic side effects and cure or control condi-

tion in shortest possible time by smallest quantity of drug to assure greater patient compliance. This review describes the various factors influencing the design and performance of sustained/controlled release products along with suitable illustrations.

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