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Sustained Release Oral Dosage Form

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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.***

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1. Introduction

Now a day's conventional dosage forms of drugs are rapidly being replaced by the new and the novel drug delivery systems. Amongst, these the controlled release/sustained release dosage forms have become extremely popular in modern therapeutics. Matrix system is the release system which prolongs and controls the release of the drug, which is dissolved or dispersed. A matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology.

Sustained release constitutes any dosage form that provides medication over an extended time or denotes that the system is able to provide some actual therapeutic control whether this is of a temporal nature, spatial nature or both. Sustained release system generally do not attain zeroorder type release and usually try to mimic zero order release by providing drug in a slow first order. Repeat action tablet are an alternative method of sustained release in which multiple doses of drug are an alternative method of sustained release, in which, multiple doses are contained within a dosage form and each dose is released at a periodic interval. Delayed release system, in contrast, may not be sustaining, since often the function of these dosage forms is to maintain the drug in the dosage for some time before release, for example. Enteric coated tablet. A sustained release dosage form will provide a therapeutic concentration of the drug in the blood that is maintained throughout the dosing interval with a reduction in a peak concentration ratio.

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.The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index whenever over medication occur.

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.

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 counselling.

Various Mechanisms of Medicament Release

1) Diffusion is rate limiting Diffusion is driving force where the movement of drug molecules occurs from high concentration in the tablet to lower concentration in gastro intestinal fluids.
2) This movement depends on surface area exposed to gastric fluid, diffusion pathway, drug concentration gradient and diffusion coefficient of the system.
3) In practice, we can follow either of the two methods,
4) The drug is formulated in an insoluble matrix; the gastric fluid penetrates the dosage form and dissolves the medicament and release the drug through diffusion.
5) The drug particles are coated with polymer of defined thickness so as the portion of drug slowly diffuse through the polymer to maintain constant drug level in blood.

Dissolution is rate limiting the drugs with poor water solubility (BCS class 2 and 4) are inherently sustained release forms. While for water soluble drugs, it's possible to incorporate a water insoluble carrier to reduce dissolution of the drug particles are coated with this type of materials e.g. Polyethylene Glycol. One may skip the use of disintegrating agent to promote delayed release doses form.

Osmotic pressure is rate limiting Osmosis is a phenomenon in which the flow of liquid occurs from lower concentration to higher concentration through a semi permeable membrane which allows transfer of liquid only. The whole drug is coated with a semi permeable membrane with a hole on one end of tablet made by a laser beam.The delivery rate is constant provided that the excess of drug present inside the tablet. But, it declines to zero once the concentration drops below saturation.

Release is controlled by ion exchange Ion exchangers are water insoluble resinous materials containing salt forming anionic or cationic groups. While manufacturing, the drug solution is mixed with resin and dried to form beads which are tableted.

The drug release depends upon high concentration of charged ions in gastro intestinal tract where, the drug molecules are exchanged and diffused out of the resin into the surrounding fluid. This mechanism relies upon the ionic environment of resin and not pH or enzyme on absorption site.

Advantages of Conventional Dosage Forms

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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:

- Continuous release systems
- Delayed transit and continuous release systems
- Delayed release systems

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 dosage form. The various systems under this category are asfollow:

- Diffusion controlled release systems
- Dissolution controlled release systems
- Dissolution and diffusion controlled releasesystems
- Ion exchange resin- drug complexes
- pH-independent formulation

1. 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 dissolutioncontrolled systems, the diffusioncontrolleddevices are manufactured either byencapsulating the drug particle in a polymeric membrane or 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 controlleddevice,the rate of drug released (dm/dt) can be calculated using the following equation:

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

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.

Another configuration of diffusion controlled systems includes matrix 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

2. Dissolution-controlled release systems:-The drug present in such system may be the one:

- Having high aqueous solubility and dissolution rate
- .With inherently slow dissolution rate e.g. Griseofulvin and Digoxin.
- 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 thediffusion 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:

$$dm/dt = ADS$$

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:

- Matrix (or monolith) dissolution controlled systems
- Reservoir dissolution controlled systems
- Dissolution and diffusion controlled release systems

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.

2. Ion exchange resin-drug complexes:-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.

3. pH-independent formulation:-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 formulate on, to help tomaintain to constant pH their by retarding PH independent drug release.

4. Osmotic pressure controlled systems:-A semi permeable membrane is placed around thetablet, particle or drug solution that allows transport ofwater into tablet with eventual pumping of drug solution out 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 surrounding

By optimizing formulation and processing factor, it ispossible to develop osmotic system to deliver the drug ofdiverse nature at pre-programmed rate.

5. Delayed transit and continuous release systems:-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 muco-adhesive systems and size based systems.

Delayed release systems:-The design of such systems involves release of drug only at specific site in the GIT. The drugs contained in such a system 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:

- Intestinal release systems
- Colonic release systems

6. 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. 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 toxicconcentration (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.

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.

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.

Preformulation Studies: Pre-formulation 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.

- **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.

- **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.
- **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
- **Identification of Drug:** Weigh accurately about 0.25gm, 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

1. Wet Granulation Technique

a) Milling and gravitational mixing of drug, polymer and excipients.
b) Preparation of binder solution
c) Wet massing by addition of binder solution or granulating solvent
d) Screening of wet mass.
e) Drying of the wet granules.
f) Screening of dry granules
g) 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

3. Sintering Technique

a) Sintering is defined as the bonding of adjacent particle surfaces in a mass of powder, or in a compact, by the application of heat.
b) 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.
c) The changes in the hardness and disintegration time of tablets stored at elevated temperatureswere described as a result of sintering.
d) The sintering process has been used for the fabrication of sustained release matrix tablets for the stabilization of drug release.

Evaluation Parameters

Pre Compression Parameters

1. Bulk density (Bd): It is the ratio of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured into graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume. Bulk density is expressed in gm/cc and is given by,

$$Db = M / Vo$$

Where, Db = Bulk density (gm/cc)
M = mass of powder (g)
Vo= bulk volume of powder (cc)

2. Tapped density (Dt):- Ten grams of powder was introduced into a clean, dry 100ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and tapped volume was read.

It is expressed 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)

3. Compressibility index:- The compressibility of the powder was determined by the Carr's compressibility index.

Sr.no.	Carrs index	Flow properties
1.	5-15	Excellent
2.	12-15	Good
3.	18-21	Fair to possible
4.	23-30	Poor
5.	33-38	Very poor
6.	≥40	Very very poor

4. 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 be improved by addition of glidants.

5. 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 a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of funnel. The angle of repose was thencalculated using the formula,

$$Tan\theta = h/r \ \theta = tan\text{-}1(h/r)$$

where, θ = angle of repose,
h = height of pile,
r = radius of the base of the pile.

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

$$Porosity\ (\%) = Vbulk\text{-}V/Vbulk x\ 100$$

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

Post Compression Parameters

1. Thickness and diameter: Control of physical dimension of the tablet such as thickness and diameter is essential for consumeracceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Vernier calipers. It is measured in mm.

2. Hardness: The Mansanto hardness tester was used to determine the 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.

3. 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 was done by weighing 20 tablets individually, calculatingthe average weight and comparing the individual weights to the average. The tablet meet the USP test ifnot more than 2 tablets are outside the percentage limits and if no tablets differs by more than 2 times thepercentage limit.

$$PD = W_{avg}XW_{initial}/W_{aveg}\ X100$$

Where, PD = Percentage deviation,
W avg = Average weight of tablet,
W initial =individual weight of tablet.

4. Uniformity of drug content:- Five tablets of various formulations were weight individually 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 nm after suitable dilution using a UV/Visible Spectrophotometer (UV-1800).

2. Conclusion

Oral Sustained release (S.R) / Controlled release (C.R) products provide an advantage over conventional dosage forms by optimizing bio-pharmaceutics, 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 condition in shortest possible time by smallest quantity of drug toassure greater patient compliance. This review describes the various factors influencing the designs.

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