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SUSTAINED RELEASE DRUG DELIVERY SYSTEM: A REVIEW

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Abstract

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that has been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage form. Nowadays most of the pharmaceutical scientists are involved in developing an ideal DDS. 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. 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. [1]

Keyword: Sustained Released Drug Delivery System,Oral dosage form ,Tablet

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]

Advantages of Sustain Release Dosage Forms

1. Decrease in frequency of intakes.
2. Reduce side effects.
3. Uniform release of drug over time.
4. Enhanced patient compliance.[11]

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 rapid release of contained drug (mechanical failure, chewing or masticating, alcohol intake).
5. Increased potential for first- pass clearance.
6. Need for adNNUFditional patient education and counseling.[12]

Objectives of oral sustained released dosage form

1. To maintain the concentration of drug at constant level for a preferred period of time.
2. To reduce the frequency of doses administrated as compared to conservative dosage form
3. It should deliver active entity directly to site of action, minimizing or eliminating side effects.[13]
4. This may necessitate delivery to specific receptors or to localization to cells or to definite areas of the body.
5. The safety margin of potent drugs can be improved.
6. Incidence of both local and systemic adverse side effects can be reduced in sensitive patient. [14]

Classification of Oral Sustained or Controlled Release Systems

The controlled release systems for oral use are mostly solids and based on dissolution, diffusion or a combination of both mechanisms in the control of release rate of drug. Depending upon the manner of drug release, these systems are classified as follows:

1. Continuous release systems
2. Delayed transit and continuous release systems
3. Delayed release systems. [17]

1. Continuous release systems

Continuous release systems release the drug for a extended period of time along the entire length of gastrointestinal tract with normal transportation of the dosage form. The various systems under this category are as follow:

A. Diffusion controlled release systems
B. Dissolution controlled release systems
C. Dissolution and diffusion controlled release systems
D. Ion exchange resin- drug complexes
E. pH-independent formulation
F. Osmotic pressure controlled systems. [18]

A. Diffusion controlled release systems [19] In this type of systems, the diffusion of dissolved drug through a polymeric barrier is a rate limiting step. The drug release rate is never zero-order, since the diffusional path length increases with time as the insoluble matrix is gradually exhausted of drug. Diffusion of a drug molecule through a polymeric membrane forms the basis of these controlled drug delivery systems.

B. Dissolution-controlled release systems [20] The drug present in such system may be the one Having elevated aqueous solubility and dissolution rate 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.[24] The rate limiting step for dissolution of a drug is the diffusion across the aqueous boundary layer.

C. Dissolution and diffusion controlled release systems [21] In such systems, the drug core is encased in a partly 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.

Physicochemical factors influencing oral sustainedrelease dosage form design [2,3]

1. **Dose Size:** In general, single dose of 0.5 – 1.0 g is considered maximal for a conventional dosage form. This also holds true for sustained-release dosage forms. Another Consideration is the margin of safety involved in administration of large amounts of drug with a narrow therapeutic range.

2. **Ionization**, **pKa and aqueous solubility:** Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the pKa of the compound and the absorptive environment. Delivery systems that are dependent on diffusion or dissolution will likewise be dependent on the solubility of drug in the aqueous media. For dissolution or diffusion sustaining forms, much of the drug will arrive in the small intestine in solid form meaning that the solubility of the drug may change several orders of magnitude during its release. The lower limit for the solubility of a drug to be formulated in a sustained release system has been reported to be 0.1 mg/ml.

3. Partition coefficient: Compounds with a relatively high partition coefficient are predominantly lipid-soluble and, consequently, have very low aqueous solubility. Furthermore these compounds can usually persist in the body for long periods, because they can localize in the lipid membranes of cells. Meaning that the solubility of the drug may changes several orders of magnitude during its releases. The lower limit for the solubility of a drug to be formulated in a sustained release system has been reported to be 0.1 mg/ml.

4. **Stability:** Orally administered drugs can be subjected to both acid-base hydrolysis and enzymatic degradation. For drugs that are unstable in the stomach, systems that prolong delivery over the entire course of transit in the GI tract are beneficial.

Compounds that are unstable in the small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form.

Classification of SR Formulation:

The most common methods used to achieve sustained release of orally administered drugs are as follows: (12)

a. Diffusion System
i. Reservoir Device
ii. Matrix Device
b. Dissolution System
c. Osmotic System
d. Ion-exchange Resin
e. Swelling and Expansion System
f. Floating System
g. Bioadhesive or Mucoadhesive system

Design of Oral Sustained Release Drug Delivery System

The oral route administration is mostly adopted route because of its comfortable dosage form, design and patient care. Several parameters should be kept in mind before formulating sustain release dosage form which includes various pH in GIT, the gastrointestinal motility, the enzyme system and its effect on the dosage form and the drug. Most of sustained release dosage form follows the mechanism of diffusion, dissolution or combination of both, to produce slow release of drug at predetermined rate. Hypothetically, a sustained release dosage form should release the drug by a zero-order mechanism which maintains drug plasma level time similar to intravenous infusion. Plasma drug concentration-profiles for conventional tablet or capsule formulation, a sustained release formulation, and a zero order sustained release formulation are as follow in given figure

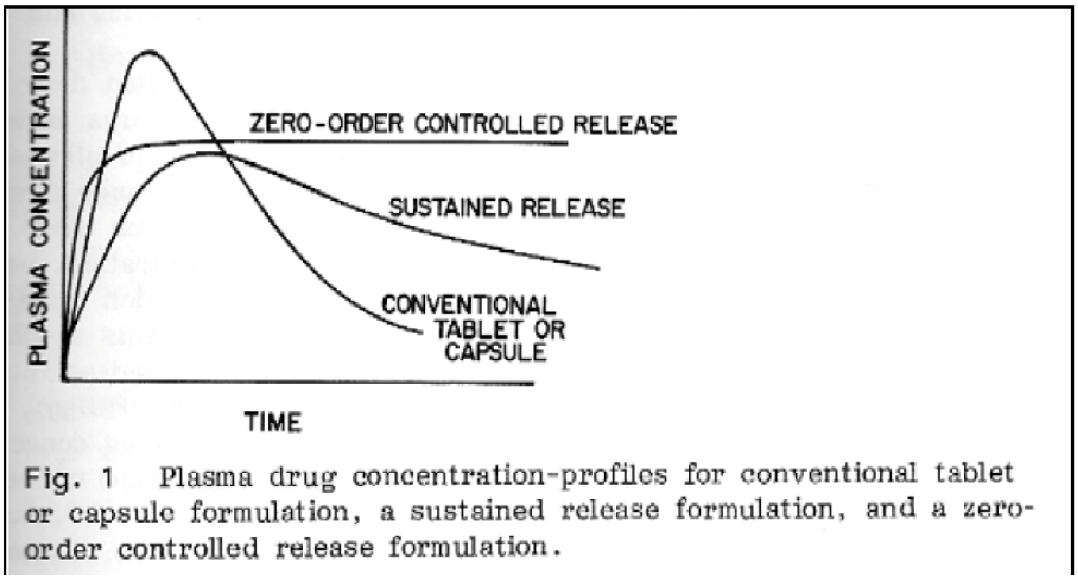

Fig. 1 Plasma drug concentration-profiles for conventional tablet or capsule formulation, a sustained release formulation, and a zero-order controlled release formulation.

Fig No.01:Plasma Drug Concentration for Tablet or capsule

Biological Factors Influencing Oral Sustained-Release Dosage Form Design[3, 7]

The usual goal of an oral sustained-release product is to maintain therapeutic blood levels over an extended period. The elimination rate is quantitatively described by the half-life. Each drug has its own characteristic elimination rate, which is the sum of all elimination process, including metabolism, urinary excretion, and all other processes that permanently remove drug from the bloodstream.

Therapeutic compound with short half-lives are excellent candidates for sustained release preparations, since this can reduce dosing frequency. However, this is limited, in that drug with very short half-lives may require excessively large amounts of drug in each dosage unit to maintain sustained effect, forcing the dosage form itself to become limitingly large. In general, drugs with half-lives shorter than 2 hours are poor candidates for sustained-release preparations. Compounds with long half-lives, more than 8 hours, are also generally not used in sustaining forms, since there effect is already sustained.

Absorption

The characteristics of absorption of a drug can greatly affect its suitability as a sustained-release product. Since the purpose of forming a sustained-release product is to place control on the delivery system, it is necessary that the rate of release much slower than the rate of absorption. 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; otherwise, the device will pass out of the potential absorptive regions before drug release is complete. This corresponds to a minimum apparent absorption rate constant of 0.17-0.23 $hours^{-1}$ to give 80-95% over this time period. The absorption rate constant is an apparent rate constant, and should, in actuality, be the release rate constant of the drug from the dosage form. Compounds that demonstrate true lower absorption rate constants will probably be poor candidates for sustaining system.

Distribution

The distribution of drugs into tissue can be an important factor in the overall drug elimination kinetics since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibration with blood and extracellular fluid. One aspect of this distribution is binding of drug to tissue and proteins in blood. The apparent volume of distribution of a drug is frequently used to describe the magnitude of distribution, including binding, within the body. For design of sustained/controlled release products one would like to have as much information on drug disposition as possible but, in reality, decisions are usually based on only a few pharmacokinetic parameter, one of which is the apparent volume of distribution.

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. Most intestinal wall enzyme systems are saturable. As the drug is released at a slower rate to these regions, less total drug is presented to the enzymatic process during specific period, allowing more complete conversion of the drug to its metabolites. Formulation of these enzymatically susceptible compounds as prodrugs is another viable solution.

Rational for development of SRDDS (Sustained Released Drug Delivery System)

1. Formulations of SRDDS minimize dosing frequency and sustained release provides availability of a drug at action site throughout the treatment to improve clinical efficiency of a drug molecule.
2. To reduce cost of treatment by reducing number of dosage requirement.
3. To minimize toxicity due to overdose which is often conventional dosage form.
4. To enhance the activity duration of a drug possessing short half-life

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 were performed 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 between the 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 melting point of the solid constituents in a controlled environment under atmospheric pressure.
- The changes in the hardness and disintegration time of tablets stored at elevated temperatures were 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.

Physicochemical Factors Influencing Oral Sustained-Release Dosage Form Design[3, 7]

Dose Size

For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5-1.0 gm is considered maximal for a conventional dosage form. This also holds for sustained-release dosage forms. Those compounds that require large dosing size can sometimes be given in multiple amounts or formulated into liquid system. Another consideration is the margin of safety involved in administration of large amounts of a drug with narrow therapeutic range.

Aqueous Solubility

Compounds with very low solubility (less than 0.01mg/ml) are inherently sustained, since there release over the time course of a dosage form in the GI tract will be limited by dissolution of the drug. The lower limit for the solubility of a drug to be formulated in a sustained-release system has been reported to be 0.1mg/ml, so it is obvious that the solubility of the compound will limit the choice of mechanism to be employed in sustained delivery system. Diffusional systems will be poor choices for slightly soluble drugs, since the driving force for diffusion, which is the drug's concentration in solution, will be low.

Partition Coefficient

When a drug is administered to the GI tract it must cross a variety of biological membranes to produce a therapeutic effect in another area of the body. It is common to consider that these membranes are lipidic; therefore, the partition coefficient of oil-soluble drugs becomes important in determining the effectiveness of membrane barrier penetration. Partition coefficient is generally defined as the ratio of the fraction of drug in an oil phase to that of an adjacent aqueous phase. Accordingly, compounds with a relatively high partition coefficient are predominantly lipid-soluble and, consequently, have very low aqueous solubility.

Stability

Orally administered drugs can be subject to both acid-base hydrolysis and enzymatic degradation. Degradation will proceed at a reduced rate for drugs in the solid state; therefore, this is the preferred composition of delivery for problem cases. For drugs that are unstable in the stomach, systems that prolong delivery over the entire course of transits in the GI tract are beneficial; likewise, for systems that delay release until the dosage form reaches the small intestine. Compound that is unstable in the small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. This is because more drugs is delivered in the small intestine and, hence, is subject to degradation.

Protein Binding

It is well known that many drugs bind to plasma proteins with concomitant influence on the duration of drug action. Since blood proteins are four the most part re-circulated and not eliminated, drug protein binding can serve as the depot for drug producing a prolonged release profile, especially if high degree of drug binding occurs. There are, however, other drug – protein interaction that have bearing on drug performance.

Evaluation Parameters

1) Pre Compression Parameters:

A. Bulk density (Db): 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)

B. 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)

C. Compressibility index: The compressibility of the powder was determined by the Carr's compressibility index.
Carr's index (%) = b=(v/b) X100

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 be improved by addition of glidants.

E. Angle of repose (θ): It is defined as the maximum angle possible between the surface of pile of the powder and the horizontal plane. Fixed funnel method was used.
A funnel was fixed with its tip at a given height (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 then calculated 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.

F. Total Porosity: Total porosity was determined by measuring the volume occupied by a selected weight ofa powder (Vbulk) and the true volume of the powderblend (The space occupied by the powder exclusive of spaces greater than the intermolecular spaces,
V). Porosity (%) =Vbulk-V/Vbulkx 100

G. Flow rate: Flow rate of granules influences the filling of die cavity and directly affects the weight of the tablets produced.

2. Post Compression Parameters

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

B. Hardness: The Mansanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in Kg/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 percentage weight loss was calculated by rewriting the tablets.

D. Weight variation test : The weight of the tablet being made in routinelymeasured to ensure that a tablet contains the proper amount of drug. The USP weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablet meet the USP test if not more than 2 tablets are outside the percentage limits and if no tablets differs by more than 2 times the percentage limit.

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