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SUSTAINED RELEASE DOSAGE FORM: A Review

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Abstract: Oral drug delivery is the most preferred system for administration of various drugs. For oral administration there are several dosage forms which have several advantages. In case of the Sustained release drug delivery the main advantages are ; betterment of patient compliance due to reduction in dose frequency, reduction of fluctuation in steady-state drug levels, maximum utilization of the drug, increased safety margin of potent drug, reduction in healthcare cost through improved therapy and shorter treatment period. Sustained Release is also suitable to overcome the side effect of drug and also increase therapeutic efficacy of drug. The design of oral sustained release DDS depends on several 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. The main objective of this review is to provide complete knowledge of sustained release dosage along with its advantages, disadvantages , classification and to also describe the various criteria for selection of drug for the drug delivery system.

Keywords: Sustain release drug delivery, Diffusion System, patient compliance, gastrointestinal residence time

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 that administration of a single dose of drug. 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 minimising side effects.

ADVANTAGES OF SUSTAIN RELEASE DO- SAGE FORMS

1. Reduction in frequency of intakes.
2. Uniform release of drug over time.
3. Reduce side effects
4. Better patient compliance

DISADVANTAGES OF SUSTAINED RELEASE DRUG DELIVERY

1. Increased cost.
2. Unpredictable and often poor in vitro-in vivo correlation.
3. Risk of side effects or toxicity upon fast release of contained drug
4. Toxicity due to dose dumping.
5. Need for additional patient education and counselling
6. Increased potential for first- pass clearance.

Classification of SR Formulation:

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

1. Diffusion System

i. Reservoir Device

ii. Matrix Device

2. Dissolution System
3. Osmotic System
4. Ion-exchange Resin
5. Swelling and Expansion System
6. Floating System
7. Bioadhesive or Mucoadhesive system

Biological Factors Influencing Oral Sustained- Release Dosage Form Design

1. Biological half-life:
   Therapeutic compounds with short half-lives are excellent candidates for sustained-release preparations, since this can reduce dosing frequency.

2. Absorption :
   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. If a drug is absorbed by active transport, or transport is limited to a specific region of the intestine, sustained-release preparations may be disadvantageous to absorptions

3. 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. As the drug is released at a slower rate to these regions, less total drug is presented to the enzymatic process during a specific period, allowing more complete conversion of the drug to its metabolite

Physicochemical factors influencing oral sustained- release dosage form design

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. 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.

3. 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.

4. 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. 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.

Drug-candidates suitable for sustained release products

For a successful sustained-release product, the drug must be released from the dosage form at a predetermined rate, dissolve in the gastrointestinal fluids, maintain sufficient gastrointestinal residence time, and be absorbed at a rate that will re- place the amount of drug being metabolised 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. 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 and hence 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 dis-entanglement 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.

Evaluation Parameters

A. **Pre-Compression Parameters**:

1. 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)

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.

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

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 maximum angle possible be- tween 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,

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

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

B. Post Compression Parameters

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

2. Hardness:
The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held be- tween a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tab- let fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed inKg/cm2.

3. 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.

4. Weight variation test:
The weight of the tablet being made in routinely- measured to ensure that a tablet contains the per 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 meets 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.

5. Uniformity of drug content:
Five tablets of various formulations were weighed- individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in Phosphate buffer pH 6.8, the drug content was determined measuring the absorbance at 262.4 nm after suitable dilution using a UV/ Visible Spectrophotometer (UV-1800).

6. In Vitro Dissolution Study:

Drug release study is generally determined in Rotating Paddles apparatus. Mainly buffer is used as a dissolution medium. The temperature of the bath maintained at 37 ^{o}C and required sample of the dissolution medium in which drug is release is taken at a regular interval and the same quantity of the medium is replaced. The amount of the drug released is determined using an UV spectrophotometer.

7. Stability Studies:

Short Term Stability Study: To determine change in vitro release profile on storage, a short term stability study of the optimal batch.

Conclusion:

By the above discussion, it can be 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. On the other hand, sustained release implies slow release of drug over a time period. Sustain released formulation may or may not be controlled release. From the above discussion, we can conclude that development of SRDDS depend upon a variety of factors such as Biopharmaceutics, Pharmacokinetic and Pharmacodynamic characteristics of drug. Sustained release drug delivery system has leaded no difficulty of market penetration as replacement of oral predictable drug delivery system.

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