SUSTAINED RELEASE TABLETS: A NEWER APPROACH IN CONTROLLED RELEASE DRUG DELIVERY

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INTRODUCTION

Oral route of drug delivery is the most preferred route of the various drug molecules among all other routes of drug delivery because of ease of administration, patient compliance, and flexible design of dosage form. Drug release is the process by which a drug leaves a drug product and is subjected to absorption, distribution, metabolism and excretion, eventually to becoming available for pharmacological action.

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 zero order 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.
- Numerous drug delivery techniques have been developed to sustain the release of drugs, (including triple-layered tablets) and osmotic pumps with laser drilled holes.

These technologies are intricate and relatively expensive to manufacture. Thus, there remains an interest in developing novel formulations that allow for sustained release of drugs using readily available, inexpensive excipients.

**ADVANTAGES OF SUSTAINED RELEASE DOSAGE FORM**\(^{[1,2,3]}\)

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

**DISADVANTAGES OF SUSTAINED RELEASE DRUG DELIVERY**

1. Increased cost.
2. Toxicity due to dose dumping.
4. Risk of side effects or toxicity upon fast release of contained drug (mechanical failure, chewing).
5. Increased potential for first-pass clearance.

**DRUG SELECTION FOR ORAL SUSTAINED RELEASE DRUG DELIVERY SYSTEM**

The biopharmaceutical evaluation of a drug for potential use in controlled release drug delivery system requires knowledge on the absorption mechanism of the drug form the G. I.
tract, the general absorbability, the drug’s molecular weight, solubility at different pH and apparent partition coefficient.

VARIABLE MECHANISMS OF MEDICAMENT RELEASE\[1\]

1. Diffusion is rate limiting
Diffusion is the driving force where the movement of drug molecules occurs from high concentration in the tablet to lower concentration in gastro intestinal fluids. This movement depends on surface area exposed to gastric fluid, diffusion pathway, drug concentration gradient and diffusion coefficient of the system (Fig. 1).

![Diffusion controlled System](image)

In practice, we can follow either of the two methods, a. 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. b. 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.

2. 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.
3. **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 gastric fluid penetrates through the membrane, solubilizes the drug and increases the internal pressure which pumps the drug solution out of the aperture and releases the drug in gastric environment. 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.

4. **Release is controlled by ion exchange**\(^2\)

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.

**Classification of oral sustained or controlled Release systems**\(^3\)

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

**Classification of Modified Release Drug Delivery System**

The IR drug delivery system lacks some features like dose maintenance, sustained release rate & site targeting. The oral Sustained drug delivery has some potential advantage like Sustained release rate & dose maintenance in plasma. The SR formulations have some swelling polymer or waxes or both which controls the release rate. The use of reservoir system is also well known for controlling release rate.
Figure 2: Ideal Plasma Concentration Curves For Immediate Release, Zero Order Release, Sustained Release Drug Delivery System

1. Continuous release systems\(^4\)

Continuous release systems release the drug for a prolonged period of time along the entire length of gastrointestinal tract with normal transit 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

A. Diffusion controlled release systems\(^5\)

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 depleted of drug.

B. Dissolution-controlled release systems

The drug present in such system may be the one:

a. Having high aqueous solubility and dissolution rate with inherently slow dissolution rate e.g. Griseofulvin and Digoxin
b. That produces slow dissolving forms, when it comes in contact with GI fluids
C. Dissolution and diffusion controlled release systems
In such systems, the drug core is encased in a partially soluble membrane.

D. 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.

E. 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.

F. Osmotic pressure controlled systems
A semi permeable membrane is placed around 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 core. Two type of osmotic pressure controlled systems are:
   a. Type 1 contains an osmotic core with drug
   b. Type 2 contains the drug in flexible bag with osmotic core surrounding

2. Delayed transit and continuous release systems
These systems are designed to prolong their residence in the GI tract along with their release.

3. 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:
   c. Intestinal release systems
   d. Colonic release systems

Factors affecting the formulation of oral Sustained release drug delivery system

1. Physicochemical factors
2. Biological factors

1. Physicochemical Factors
a. 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. 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. In case of compounds with very low partition coefficient, it is very difficult for them to penetrate the membrane, resulting in poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes. The choice of diffusion-limiting membranes must largely depend on the partitioning characteristics of the drug.

b. 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 0.5-1.0g is considered maximal for a conventional dosage form. This also holds for sustained release dosage form. Compounds that require large dosing size can sometimes be given in multiple amounts or formulated into liquid systems. Another consideration is the margin of safety involved in administration of large amount of a drug with a narrow therapeutic range.

c. 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 solid state; therefore, this is the preferred composition of delivery for problem cases. For the dosage form that are unstable in stomach, systems that prolong delivery over entire course of transit in the GI tract are beneficial; this is also true for systems that delay release until the dosage form reaches the small intestine. Compounds that are unstable in 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. Propentheline and probanthine are representative example of such drug.

d. 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. Presenting the drug in an unchanged form is
advantageous for drug permeation. Unfortunately, the situation is made more complex by the fact that the drug’s aqueous solubility will generally be decreased by conversion to unchanged form. Delivery systems that are dependent on diffusion or dissolution will likewise be dependent on the solubility of the drug in aqueous media. These dosage forms must function in an environment of changing pH, the stomach being acidic and the small intestine more neutral, the effect of pH on the release process must be defined. Compounds with very low solubility (<0.01 mg/ml) are inherently sustained, since their release over the time course of a dosage form in the GI tract will be limited by dissolution of the drug. So it is obvious that the solubility of the compound 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.

2. Biological Factors\[7,8\]
   a. Biological half life
   The usual goal of an oral SR product is to maintain therapeutic blood levels over an extended period of time. To achieve this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life (t1/2). Each drug has its own characteristic elimination rate, which is the sum of all elimination processes, including metabolism, urinary excretion and all over processes that permanently remove drug from the blood stream. Therapeutic compounds with short half-life are generally are excellent candidate for SR formulation, as this can reduce dosing frequency. In general, drugs with half-lives shorter than 2 hours such as furosemide or levodopa are poor candidates for SR preparation. Compounds with long half-lives, more than 8 hours are also generally not used in sustaining form, since their effect is already sustained. Digoxin and phenytoin are the examples.

   b. Absorption
   Since the purpose of forming a SR product is to place control on the delivery system, it is necessary that the rate of release is much slower than the rate of absorption. If we assume that the transit time of most drugs in the absorptive areas of the GI tract is about 812 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. Thus corresponds to a minimum apparent absorption rate constant of 0.17-0.23 h⁻¹ to give 80-95% over this time period. Hence, it assumes that the absorption of the drug should occur at a
relatively uniform rate over the entire length of small intestine. For many compounds this is
not true. If a drug is absorbed by active transport or transport is limited to a specific region of
intestine, SR preparation may be disadvantageous to absorption. One method to provide
sustaining mechanisms of delivery for compounds tries to maintain them within the stomach.
This allows slow release of the drug, which then travels to the absorptive site. These methods
have been developed as a consequence of the observation that co-administration results in
sustaining effect. One such attempt is to formulate low density pellet or capsule. Another
approach is that of bioadhesive materials.[9]

c. Metabolism
Drugs those are significantly metabolized before absorption, either in the lumen or the tissue
of the intestine, can show decreased bioavailability from slower-releasing dosage form. Even
a drug that is poorly water soluble can be formulated in SR dosage form. For the same, the
solubility of the drug should be increased by the suitable system and later on that is
formulated in the SR dosage form. But during this the crystallization of the drug, that is
taking place as the drug is entering in the systemic circulation, should be prevented and one
should be cautious for the prevention of the same.

Formulation of SRDDS
There are no. of formulation are considered in-

Drug complexes
The principal advantage of preparing drug derivatives for sustained release is those materials
can be formulated into diverse dosage forms. This approach has proven effective in the
development of injectable depot forms, in which release profiles are not subject to the
variability characteristics of gastrointestinal tract. Sensitivity to in vivo variables is a definite
disadvantage of per orally administered forms; in vivo studies may not consistently support
sustained release claims.

Encapsulated slow release granules[10]
The first significant marketed sustained release dosage forms were encapsulated mixed slow
release beads, to which was applied the barrier principles of controlling drug release, based
on model D. For low milligram potency formulations, nonpareil seeds are initially coated
with an adhesive followed by powdered drug and the pellets are dried. This step is repeated
until the desired amount of drug has been applied. The resultant granules are subsequently
coated with a mixture of solid hydroxylated lipids such as hydrogenated castor oil or glycercytrihydroxystearate mixed with modified celluloses. The thickness of the barrier was regulated by the no. of applied coatings to obtain the desired release characteristics. The original formulation utilised glycerol monostearate bees wax compositions, which tended to be physically unstable, showing altered release pattern on aging.

**Tableted slow release granulation**

Compression of time release granulations into tablets is an alternate to encapsulation. Such tablets should be designed to disintegrate in to stomach so as to stimulate the administration of a capsule form having the advantage associated with sustained release encapsulations, while retaining the advantage of the tablet dosage forms. Three examples, each utilizing a different process, illustrate this type of formulation. The first is a tabletted mixed release granulation in which binders with different retardant properties are used to prepare three different granulations, which are colour coated for identification, blended & tabletted. This first is a conventional non sustained release granulation prepared using gelatin as a binder, the uses vinyl acetate and the third uses shellac as binders. Drug release is controlled by erosion of the granulation in intestinal fluid the vinyl acetate granulation disintegrates at a faster rate than the shella granulation.

**Controlled release technology[10]**

Controlled release dosage forms are designed to release drug in vivo according to predictable rates that can be verified by a vitro measurements. Of the many approaches to formulation of sustained release medication, those fabricated as insoluble matrix tablets come closest to realization of this objective, since release of water soluble drug from this forms should be independent of in vivo variables. Controlled release technology implies a quantitative understanding of the physicochemical mechanism of drug availability to the extent that the dosage forms release rate can be specified. Potential developments & new approaches to oral controlled release drug delivery include hydrodynamic pressure controlled systems, intragastric floating tablets, transmucosal tablets, and micro porous membrane coated tablets.

**Evaluation Parameters[11,12,13]**

**Precompression parameters**

- Bulk density
- Tapped density
- Carr’s index (%)
- Hausner ratio
- Angle of repose.

**a). Bulk density:** A simple test has been developed to evaluate the flow ability of a powder by comparing the poured density ($\rho_{B\text{min}}$) and tapped density ($\rho_{B\text{max}}$) of a powder and the rate at which it packs down. Tapped density was determined by taking 20 g of the granules in 50 ml measuring cylinder and tapping it to a constant volume in a bulk density apparatus.

**b). Tapped density:** The measuring cylinder containing a known mass of blend was tapped for a fix time. The minimum volume ($V_t$) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density ($\rho_t$) was calculated.

**c). Carr’s index:** Based on the poured density and tapped density, the % compressibility of the granules was computed using the Carr’s compressibility index:

$$\text{Carr’s index} (\%) = \frac{\text{Tapped density} - \text{poured density}}{\text{Tapped density}} \times 100$$

**d). Hausner ratio:** Hausner ratio was calculated using the formula

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Poured density}}$$

**e). Angle of repose:** Angle of repose of the granules was determined by height and cone method. A funnel was fixed to a desired height and granules were filled in it. They were allowed to flow down on a graph paper fixed on a horizontal surface. The angle of repose was calculated using the formula:

$$\tan \Theta = \frac{h}{r}$$

Where h and D are height and diameter of the pile respectively.

**Postcompression parameters**

The prepared tablets were evaluated for,

- Thickness
- Hardness
- Friability
- Weight variation
- Drug content
- *In-vitro* dissolution studies
a). **Thickness:**- Six tablets were randomly selected and the thickness of each was measured by digital Vernier caliper. Mean and standard deviation were computed and reported.

b). **Hardness:**-The hardness of ten tablets was measured using Monsanto Hardness tester. Mean and standard deviation were computed and reported. It is expressed in kg/cm².

c). **Friability:**-The friability of the tablets was determined using Roche friabilator. Ten tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25rpm for four minutes. After four minutes the tablets were weighed again. The % friability was then calculated using the formula:

\[
\% \text{ Friability} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100
\]

d). **Weight variation:**-Twenty tablets were individually weighed and average weight was calculated. The individual weight was compared to the average weight. The tablets pass the test if not more than two tablets are outside the percentage limit and if no tablet differs by more than two times the percentage the percentage limit.

e). **Drug content uniformity:**-Uniformity of drug content test as described in the IP was followed. One tablet was powdered and transferred to a 25 ml volumetric flask. 15 ml of pH 6.8 phosphate buffer was added and the mixture shaken for 10 minutes. The volume was made up and filtered. The first 5 ml of the filtrate was rejected, and after suitable dilution (here 10 times) the sample was analyzed spectrophotometrically at 296.0 nm, and the drug was determined. This test was carried out individually for five tablets from each batch of formulations and the drug content range of five from minimum to maximum was recorded.

f). **In-vitro Dissolution Studies:**-In-vitro dissolution study was performed by using USP Type II Apparatus (Paddle type) [Electrolab (TDT-06T) Tablet Dissolution Tester] at 100 rpm. Distilled water 900 ml was used as dissolution medium, and the temperature of which maintained at 37 ± 0.5°C. Aliquots of dissolution medium (10 ml) was withdrawn at specific time intervals (1 hr) and was filtered and the first 5 ml of the filtrate was rejected. The amount of drug dissolved was determined by UV spectrophotometer by measuring the absorbance of the sample at 296.0 nm. Three trials for each batch were performed and average percentage drug release with standard deviation was calculated and recorded.
REFERENCES