A Brief Study on Modified Release Dosage Form

*H Nanda, M Majhi, *Research Associate, Rangpo, Sikkim, India

ABSTRACT

The oral route of drug delivery is often thought of the popular and most patient-convenient means of drug administration. A standard solution to increase medication acceptance during this case is to formulate the drug in a exceedingly dosage form that releases the active ingredient steady over an extended period of your time. Such sustained unharvest formulations have gained considerable traction within the pharmaceutical industry, and can still be a significant tool to boost the patients expertise for existing and new medicine. Sustain unharvest system are thought of a wiser approach for the medicine with short half-lives and that need recurrent dosing, the fundamental objective of those indefinite quantity forms is to optimize the delivery of medicines therefore on succeed a live of management on therapeutic result within the face of uncertain fluctuations within the in vivo environment within which drug release takes place. The advances within the formulation technology of modified release dosage type with sustained un-leash oral dosage form has been wide accepted approach as compared to traditional immediate unharvest formulations of a similar drug. It provides a prolong unharvest of the drug over extended amount of your time there by giving the higher patient compliance and increased bioavailability. It leads to blood concentration-time profiles of medication that otherwise suffer from few limitations

Keywords: Oral Route, Stability study, Bioavailability
Introduction

The term Sustained release is known to have existed in the medical and pharmaceutical literature for many decades. It has been constantly used to describe a pharmaceutical dosage form formulated to retard the release of a therapeutic agent.

Oral Controlled Drug Delivery

The design of an oral controlled drug delivery system (DDS) should be primarily aimed at achieving more predictable and increased bioavailability of drug. However, the development process is precluded by several physiological difficulties, such as an inability to restrain and localize the DDS within desired region of gastrointestinal tract and the highly variable nature of gastric emptying process. It can be anticipated that, depending upon the physiological state of the subject and the design of pharmaceutical formulations the emptying process can last from a few minutes to 12 hour. This variability, in turn, may lead to unpredictable bioavailability and time to achieve peak plasma level, since majority of drugs are preferentially absorbed in the upper part of intestine.

Furthermore, the relatively brief intestinal transit time is desirable for complete drug absorption; the residence time depends upon the intestinal motility or concentration. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the intestinal transit time using matrix dosage form. Matrix dosage form can remain the intestinal region for several hours and hence significantly prolong the intestinal residence time of the drugs. Prolonged transit time improve bioavailability, reduce drug wastage, and improve solubility for drugs that are less soluble in a high pH environment. It is also applied for local drug delivery to stomach and proximal intestines. Intestinal transit time helps to provide better availability of drug products with new therapeutic possibility and substantial benefits for patients. All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of mode of delivery (immediate, sustained or controlled release) and the design of dosage form (solid dispersion or liquid) must be developed within intrinsic characteristic of gastrointestinal (GI) physiology.
BASIC ANATOMY AND PHYSIOLOGY OF GIT 3-6

Gastrointestinal Tract

The gastrointestinal tract (GIT) comprises of a number of components, their primary function being secretion, digestion and absorption. The mean length of the entire GIT is 450 cm. The major functional components of the GIT are stomach; small intestine (duodenum, jejunum and ileum) and large intestine (colon) which is grossly different from each other in terms of anatomy, function, secretions and pH.

Stomach

The stomach is an organ with a capacity for storage and mixing. The stomach lining is devoid of villi but consists of considerable number of gastric pits that contribute to the storage capacity of stomach. Under physiological conditions, the gastric absorption of most drugs is insignificant as a result of its limited surface area (0.1-0.2 m²) covered by a thick layer of mucus coating, lack of villi on the mucosal surface, and short residence time of most drugs in the stomach. Its acidic pH (1-3), due to secretion of HCl, favors absorption of acidic drugs if they are soluble in gastric fluid since they are unionized to the large extent in such a pH. The gastric pH aids dissolution of basic drugs due to salt formation and subsequent ionization which are therefore absorbed to a lesser extent from stomach because of the same reason.
Fig 1. Anatomy of Stomach

Table 1: Anatomical and Functional Difference Between the Important Regions of The GIT

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Stomach</th>
<th>Small intestine</th>
<th>Large intestine</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH range</td>
<td>1-3</td>
<td>5-7.5</td>
<td>7.9-8.0</td>
<td>7.5-8.0</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>20</td>
<td>285</td>
<td>110</td>
<td>20</td>
</tr>
<tr>
<td>Diameter (cm)</td>
<td>15</td>
<td>2.5</td>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td>Surface area(sq.M)</td>
<td>0.1-0.2</td>
<td>200</td>
<td>0.15</td>
<td>0.02</td>
</tr>
<tr>
<td>Blood flow(L/min)</td>
<td>0.15</td>
<td>1.0</td>
<td>0.02</td>
<td>-</td>
</tr>
<tr>
<td>Transit time (hrs)</td>
<td>1-5</td>
<td>3-6</td>
<td>6-12</td>
<td>6-12</td>
</tr>
</tbody>
</table>

Small Intestine
It is the major site for absorption of most drugs due to large surface area (200 m²). The fold in the intestinal mucosa, called as the fold of Kerckring, result it three fold increases in the surface area. The surface of these folds possess finger like projection called as villi which increase the surface area 30 times. From the surface of villi protrude several microvilli resulting in 600 times increase in the surface area. The blood flow of the small intestine is 6 to 10 times that of stomach. Moreover, the pH range of 5 to 7.5 is most favorable for most drugs to remain unionized. The peristaltic movement of intestine is slow, transit time is long, and permeability is high. Thus, a contribution of the entire above factors make intestine the best site for absorption of most drugs.

Large Intestine

Its length and mucosal surface area is very small (villi and microvilli are absent) in comparison to small intestine and thus absorption of drugs from this region is insignificant. Its contents are neutral or alkaline. The main role of large intestine is in the absorption of water and electrolytes

Gastric emptying

It is the process of passage from stomach to the small intestine, can also be a rate limiting step in drug absorption because the major site for drug absorption is intestine. Thus, generally speaking, rapid gastric emptying increases bioavailability of drugs.

Intestinal transit

Small intestine is the major site for absorption of most drugs, long intestinal transit time is desirable for complete drug absorption.

Table 2 : Transit time for contents from different region of intestine
<table>
<thead>
<tr>
<th>Intestinal region</th>
<th>Transit time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenum</td>
<td>5 minutes</td>
</tr>
<tr>
<td>Jejunum</td>
<td>2 hours</td>
</tr>
<tr>
<td>Ileum</td>
<td>3 to 6 hours</td>
</tr>
<tr>
<td>Cecum</td>
<td>0.5 to 1 hours</td>
</tr>
<tr>
<td>Colon</td>
<td>6 to 12 hours</td>
</tr>
</tbody>
</table>

The residence time depends upon the intestinal motility or contractions. The mixing movement of the intestine that occurs due to peristaltic contraction promotes drug absorption, by increasing the drug intestinal membrane contact and by enhancing the drug dissolution especially of poorly soluble drugs through induced agitation.

**Controlled drug delivery**

Oral ingestion has long been the most convenient and commonly employed route of drug delivery. Indeed, for sustained-release systems, the oral route of administration has by far received the most attention with respect to research on physiological and drug constraints as well as design and testing of products. This is because there is more flexibility in dosage form design for the oral route than there is for the parenteral route.
**Controlled delivery attempts to¹**

➤ Sustaining drug delivery at predetermined rate by maintaining effective drug level in the body with minimization of undesirable side effects associated with a solution kinetic pattern.

➤ Localize drug action by spatial aspect of controlled release systems adjacent to or in the diseased tissue or organ.

➤ Targeted drug action by using carriers or chemical derivatization to deliver drugs to a particular target cell type.

---

**Fig 2.** Plasma concentration time profile
Advantages

Advantages of rate controlled drug delivery systems over conventional dosage forms:

1) **Reduction in drug blood level fluctuations**: By controlling the rate of drug release, “peaks and valleys” of drug-blood or serum levels are eliminated.

2) **Reduction in dosing frequency**: Rate-controlled products deliver more than a single dose of medication and thus are taken less often than conventional forms.

3) **Enhanced patient convenience and compliance**: With less frequency of dose administration, the patient is less at to neglect taking dose. There is also greater patient convenience with daytime and nighttime medication, and control of chronic illness.

4) **Reduction in adverse side effects**: Because there are seldom drug blood level peaks above the drug’s therapeutic range and into the toxic range, and adverse side effects are less frequently encountered.

5) **Reduction in health care costs i.e., economy.**: Although the initial cost of rate-controlled drug delivery systems is usually greater than conventional dosage forms, the average cost of total treatment over an extended time period may be less. With less frequency of dosing, enhanced therapeutic benefit, and reduced side-effects, the time required for health care personnel to dispense, administer and monitor patients is reduced.

Disadvantages

- Increased first pass hepatic clearance so decreased systemic availability.
- Increased variability among dosage units.
- Dose dumping which results toxicity.
- Stability problems (dosage form).
➢ Increased cost than conventional dosage forms.
➢ More rapid development of tolerance.
➢ Need for additional patient education and counselling.
➢ Unpredictable and poor *in vitro-in vivo* correlation.
➢ Difficulty in dose adjustment of drugs normally having different strengths.

**Factors Governing the Design of Controlled Release Dosage Form**

i) **Drug related factors**

Aqueous solubility, Partition coefficient, Molecular size, Drug stability, Protein binding

ii) **Biological factors**

Absorption, Distribution, Elimination, Duration of action, Margin of safety, Side effects, Disease state

**Classification of Oral Controlled Release Systems**

a. **Continuous release systems**

1. Dissolution controlled release systems a. Matrix type b. Reservoir type
2. Diffusion controlled release systems a. Matrix type b. Reservoir type
3. Dissolution and diffusion controlled release systems
4. Ion exchange resin drug complexes
5. Slow dissolving salts and complexes
6. pH dependent formulations
7. Osmotic pressure controlled systems

8. Hydrodynamic pressure controlled systems

b. Delayed transit and continuous release systems

1. Altered density systems: High density, Low density, Floating

2. Mucoadhesive systems

3. Size based systems

c. Delayed release systems

➢ Intestinal release systems

➢ Colonic release systems

Matrix Devices 8, 9, 10, 11

Matrix devices consist of drug dispersed homogeneously throughout a polymer matrix. In the model, drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix.

This process continues with the interface between the bathing solution and the solid drug moving toward the interior. For this system, rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of the dissolved drug leaving the matrix.

Derivation of the mathematical model to describe this system involves the following assumptions:

• A pseudo steady state is maintained during drug release.

• The bathing solution provides sink conditions at all times
• The diameter of the drug particles is less than the average distance of drug diffusion through the matrix.

• The diffusion coefficient of drug in the matrix remains constant i.e. no change occurs in the characteristics of the polymer matrix.

Advantages of Matrix Diffusion System

• Easier to produce than reservoir devices.

• Can deliver high molecular weight compounds.

Disadvantages of Matrix Diffusion System

• Can not obtain zero order release.

• Removal of remaining matrix is necessary for implanted systems

Physicochemical Properties

Aqueous solubility and pKa

A drug to be absorbed it first must dissolve in the aqueous phase surrounding the site of administration and then partition into the absorbing membrane. The physicochemical properties of a drug that influence the absorption are aqueous solubility and pKa. These properties play an influential role in the performance of controlled release systems.

Aqueous solubility of weak acids and bases is governed by the pKa of the compound and pH of the medium.

Extremes in the aqueous solubility of a drug are undesirable for formulation into controlled release product. A drug with very low solubility and a slow dissolution rate will exhibit dissolution-limited absorption and yield an inherently sustained blood level. Formulation of such a drug into a controlled-release system may not provide considerable benefits over conventional dosage forms.
Any system relying upon diffusion of drug through a polymer as the rate-limiting step in release would be unsuitable for a poorly soluble drug, since the driving force for diffusion is the concentration of drug in the polymer or solution, and this concentration would be low. For a drug with very high solubility and a rapid dissolution rate, it often is quite difficult to decrease its dissolution rate and slow its absorption. Preparing a slightly soluble form of a drug with normally high solubility is, however, one possible method for preparing controlled release dosage forms.

Partition Coefficient

A drug to show its action must diffuse through a variety of biological membranes that act primarily as lipid like barriers. Apparent Oil/Water Partition Coefficient (K) explains the penetration of drug through the lipid membranes and can be defined as,

\[ K = \frac{C_0}{C_w} \]

Where,

\( C_0 = \) Equilibrium concentration of all forms of the drug e.g., ionized and unionized in an organic phase at equilibrium.

\( C_w = \) Equilibrium concentration of all forms in aqueous phase.

Drugs with large values of 'K' are very oil soluble and will partition into membrane readily. According to Hansch correlation, the logarithm of the activity of a drug or its ability to be absorbed and the logarithm of its partition coefficient having parabolic relationship.

The explanation for this relationship is that the activity of a drug is a function of its ability to cross membranes and interact with the receptor. The more effectively a drug crosses membranes, the greater its activity.

The Partition Coefficient value should be optimum for effective permeation and better activity. The value of K at which optimum activity is observed is approximately 1000/1. Drugs with K value, which is higher or lower than the optimum, are poorer candidates for formulation into controlled-release dosage forms.
Drug stability

One important factor for oral dosage forms is the loss of drug through acid hydrolysis and/or metabolism in the GI tract. Since a drug in the solid state undergoes degradation at a much slower rate than a drug in suspension or solution, it is possible to improve the relative bioavailability of a drug that is unstable in GI tract by placing it in a slowly available controlled release form. Extensive binding to plasma proteins will be evidenced by a long half-life of elimination for the drug and such drugs generally do not require a controlled–release dosage form. Drugs sometimes may bind to biopolymers in the GI tract, which could have an influence on controlled-drug delivery.

Molecular size and diffusivity

Drugs in many controlled-release systems must diffuse through a rate controlling membrane or matrix. The ability of a drug to diffuse through membranes, it is so called diffusivity, (diffusion coefficient), is a function of its molecular size (or molecular weight). It is possible to relate log D empirically to some function of molecular size as,

\[ \log D = - S_v \log V + K_v = - S_m \log M + K_m \]

Where,

\[ V = \text{molecular volume.} \]
\[ M = \text{molecular weight.} \]
\[ S_v, S_m, K_v, K_m = \text{constant.} \]

The value of 'D' thus is related to the size and shape of the cavities as well as size and shape of drugs. ‘D’ value for drugs with intermediate molecular weight (150 to 400), through flexible polymers range from $10^{-6}$ to $10^{-9}$ cm$^2$/sec, with values on the order of $10^{-8}$ being most common.

Biological Properties

Absorption
The rate, extent and uniformity of absorption of a drug are important factors when considering formulating into a controlled-release system. For a drug with a very rapid rate of absorption (i.e. Ka >> 0.23 hr\(^{-1}\)), the above discussion implies that a first order release rate constant Kr < 0.17 hr\(^{-1}\) is likely to result in unacceptably poor bioavailability in many patients.

**Distribution**

The distribution of a drug into vascular and extra vascular spaces in the body is an important factor in its overall elimination kinetics. Two parameters that are used to describe the distribution characteristics of a drug are its Apparent Volume of Distribution and the ratio of drug concentration in the tissue to that in plasma at the steady state, the so called T/P ratio.

**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. Formulation of these enzymatically susceptible compounds as prodrug is another viable solution.

**Biological Half Life**

The goal of an oral sustained release product is to maintain therapeutic blood levels over an extended period. To 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. Each drug has its own characteristic elimination rate, which is the sum of all elimination processes including metabolism, urinary excretion and all other processes that permanently remove drug from blood stream.

Drugs with half-life less than 2 hrs are poor candidates for sustained release preparations. Drugs with long half-life, more than 8 hrs, are also generally not used in sustaining forms, since their effect is already sustained but small dose size of drug can prepare sustained form for reducing there side effect and give prolong action.

**Side Effects and Safety Considerations**
There are very few drugs whose specific therapeutic concentrations are known. Instead, a therapeutic concentration range is listed, with increasing toxic effects expected above this range and a fall off in desired therapeutic response observed below the range.

\[
TI = \frac{TD50}{ED50}
\]

Where,

\[
TD50 = \text{median toxic dose}
\]

\[
ED50 = \text{median effective dose}
\]

For potent drugs, the value of TI is small. Larger the value of TI, safer the drug. Drugs with very small value of TI are poor candidates for formulation into controlled-release product. A drug is considered to be relatively safe if its TI value exceeds 10.

**Dose Size**

Generally, controlled-release systems will contain greater amount of drug than a corresponding conventional dosage form. For those drugs requiring large conventional doses, the volume of the sustained dose may be so large as to be impractical or unacceptable. The same may be true for drugs that require a large release rate from the controlled-release system, e.g. drugs with shorter half-life and small dose size like 0.5 -10 mg.

**Matrix Tablet** 10-11, 12-16

One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blends of drug, retardant material, and additives to form a tablet in which drug is embedded in a matrix core of retardant.

**Materials Used As Retardants In Matrix Tablet Formulations**

There are three classes of materials used as release retardants in matrix tablet formulations viz:
1) **Insoluble inert polymers**

   Tablets prepared from these materials are designed to be ingested intact and not break apart in GI tract. Ingested tablets contain unreleased drug in the core.

   e.g. Polyethylene

   Poly vinyl chloride, Ethyl cellulose

   Methyl acrylate – methacrylate copolymer

2) **Insoluble, erodable polymers**

   These form matrices that control release through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to the totally insoluble polymer matrix. Total release of drug from wax-lipid matrices is not possible, since a certain fraction of the dose is coated with impermeable wax films.

   e.g. Carnuba wax in combination with stearic acid, stearyl alcohol,

   Castor wax & Triglycerides

3) **Hydrophilic polymers**

   This group represents non-digestable materials that form gels in situ. Drug release is controlled by penetration of water through a gel layer produced by hydration of the polymer and diffusion of drug through the swollen, hydrated matrix, in addition to erosion of the gelled layer. The extent to which diffusion or erosion controls release depends on the polymer selected for formulation as well as on drug: polymer ratio.

   e.g. Methyl cellulose

   Hydroxy ethyl cellulose

   Hydroxypropylmethylcellulose,

   Sodium alginate.
Types of Matrix Tablets

There are three Types of Matrix Tablets

1) Hydrophilic matrices

2) Fat wax matrices

3) Plastic matrices

1) Hydrophilic Matrix Tablet

e.g. Sodium Carboxy-methylcellulose, Methylcellulose, HPMC Hydroxylethylcellulose, Polyethylene Oxide, Poly Vinyl Pyrrolidine, Poly Vinyl Acetate, Gelatin, Natural Gums etc.

Several commercial patented hydrophilic matrix systems are currently in use, such as synchron technology and hydrodynamically balanced system.

Advantages

➢ Ease of manufacture.

➢ Excellent uniformity of matrix tablet.

2) Fat wax matrix tablet

The drug can be incorporated into fat wax granulations by spray congealing in air, blend congealing in an aqueous media with or without the aid of surfactants and spray drying techniques.

e.g. Polyethylene, Ethyl Cellulose, Glyceryl Esters of Hydrogenated Resins has been added to modify the drug release pattern.

3) Plastic matrix tablets
e.g. Polyvinyl chloride, Polyethylene, Vinyl Acetate, Vinyl Chloride copolymer, Vinyllidine chloride, Acrylate (or) Methyl methacrylate polymer, Ethyl cellulose, Cellulose acetate, Polystyrene.

With plastic material(s) tablets can be easily prepared by direct compression of drug provided the plastic material can be comminuted or granulated to desired particle size to facilitate mixing with drug particles.

**Method of Manufacturing** 10.

There are a few crystalline substances, such as sodium chloride, potassium chloride, that may be compressed directly. The vast majority of the drugs are rarely easy to tablet due to poor compressibility and/or flowability. The use of compressible diluents and flow modulators makes this process the most streamlined method of tablet manufacture.

A directly compressible diluent is an inert substance that may be compacted with little difficulty and may compress even when quantities of drugs mixed with it.

Compression capacity is still maintained when other tablet materials necessary for flow, disintegration, and so forth are blended in.

**Tablet Evaluation** 17

**I. Tablet dimensions**

Tablet dimension include thickness and diameter of tablets. Ten tablets each formulation was measured using a calibrated Vernier caliper.

**II. Hardness**

Hardness of tablets has been defined as the force required breaking a tablet in diametric compression test. The resistance of the tablets to chipping, abrasion or breakage under condition of storage, transportation and handling before usage depends in its hardness. The Schleuniger tablet hardness tester was used to evaluate hardness of tablet. The Schleuniger tester operates in a
horizontal position. An anvil driven by an electric motor presses the tablet at a constant load rate against a stationary anvil until the tablet breaks. A pointer moving along a scale indicator provides the breaking strength value. The instruments read in both kilograms and strong Cobb units.

Hardness of 10 tablets of each formulation were evaluated by Pfizer tablet hardness tester.

III. Friability

It is a measure of mechanical strength of tablets. Friability was determined by the subjecting a sample of twenty preweighed matrix tablets equivalent 6.9 gm to abrasion in automated USP friabilator. The dedusted tablets were weighed and percentage friability was calculated from the difference in the weight of matrix tablets before and after the friability.

Formula:

\[ F = 100 \left(1 - \frac{W_o}{W}\right) \]

Where, \( F \) = percentage friability

\( W_o \) = initial weight of 20 tablets

\( W \) = weight after friability testing.

IV. Weight Variation

The USP weight variation test was carried out by weighing 20 tablets individually; average weight was calculated, comparing the individual weight to average weight. The tablets meet USP test if no tablets differs by more than two times of percentage deviation. The weight tolerance for matrix tablets depends upon an average tablet weight. Standard deviations were compared with the U.S.P. limits.

Table 4 Weight variation Test
### Average weight of Tablets vs Maximum percentage deviation

<table>
<thead>
<tr>
<th>Average weight of Tablets</th>
<th>Maximum percentage deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>130 or less</td>
<td>10</td>
</tr>
<tr>
<td>130 – 324</td>
<td>7.5</td>
</tr>
<tr>
<td>324 mg or more</td>
<td>5</td>
</tr>
</tbody>
</table>

Not more than two of the individual weights deviate from the average weight by more than the percentage shown in above table and none deviates by more than twice that percentage.

**Conclusion**

Modified release (Matrix) tablets have emerged as an efficient mean of enhancing the bioavailability and controlled delivery of many drugs. Hence the above study demonstrated that combination of various viscosities of hydrophilic polymers and direct compression vehicle ratios could be successfully employed for formulating extended release matrix tablets.

**References**


13. Panic Disorder, 2008 American Psychological Association, Answers Questions about

14. The National Institute of Mental Health (NIMH), Panic Disorder, reviewed, 2008

15. Brahmankar, D.M. and Jaiswal, S.B., In; Biopharmaceutics and Pharmacokinetics A
Treatise, 1st Edn., Vallabh Prakashan publications, Delhi, 1995, 342.
