

MODIFIED RELEASE DOSAGE FORMS¹Nalla Chandana, ¹Harish Gopinath, ¹Debjit Bhowmik, ²I Williamkeri, ²Thirupathi Reddy A

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Corresponding author: E.Mail:chandanana@gmail.com**ABSTRACT**

Modified-release dosage forms have been developed to deliver drug to the part of the body where it will be absorbed, to simplify dosing schedules, and to assure that concentration of drug is maintained over an appropriate time interval. Drugs that are not inherently long lasting require multiple daily dosing to achieve the desired therapeutic effects. Multiple daily dosing is often inconvenient and can result in missed doses, made-up doses and patient non-compliance with therapeutic regimen. Blood levels of drugs from conventional immediate-release dosage forms taken more than once daily following definite schedule usually demonstrate sequential peaks and troughs (valleys) associated with each dose. Designed to release their medication in controlled manner, at pre-determined rate, duration and location in the body to achieve and maintain optimum therapeutic blood levels of drug.

KEY WORDS: Modified-release, therapeutic regimen, Multiple daily dosing, bioavailability.

1. INTRODUCTION

The Oral Solid Dosage forms are the preferred route of administration for many drugs and most widely used formulations for new and existing modified release products. As they provides several advantages compared to single-unit dosage forms (e.g.: Pellets, capsules or tablets) and have risks such as spontaneous drug release from a single-unit tablet due to damage coating or its attachment in the stomach or intestine causing an irritation of the gastric or intestinal mucosa, are reduced by the use of multiunit forms. Moreover, such small single units enable a more reproducible dispersion throughout the gastrointestinal tract leading to a reduction of drug release variations and an improved bioavailability. Thus it reduce in drug dose and side effects. One that allows a reduction in dosing frequency to that presented by a conventional dosage form such as a solution or an immediate release dosage forms. The term "immediate release" pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation and/or the absorption of drug, is neither appreciably, nor intentionally, retarded by galenic manipulations. In the present case, immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption (Brahmankar, 2000).

Variables to consider for modified release dosage form:

1. Low dose
2. Short half life
3. Long half life drugs already have the desired kinetics
4. Wide Therapeutic Window
5. Absorbed through the entire GI
6. Modest to rapid absorption
7. Highly stable in the GI
8. Chronic treatment
 - o Hormone Replacement
 - o Hypertension
 - o Chronic Pain, Allergies

Advantages:

1. Increased time within the Therapeutic Window due to lower peak plasma concentration and shallower slope
2. Has kinetics similar to IV infusion, with the ease of a tablet
3. Reduce dosing frequency
4. Improve patient compliance
5. Reduce gastric irritation and side effects
6. Possible to enhance the bioavailability
7. Alleviate the risk of dose dumping
8. Reduce fluctuation in circulation drug level
9. Avoidance of night time dosing
10. More uniform effect

Disadvantages:

1. If a toxic dose is given, it will stay toxic for a long time
2. Takes a long time to titrate patient
3. Strong first pass effect by staying below the metabolizing enzymes saturation point
4. Risk of Dose Dumping (failed delivery device) a large immediate dose
5. Inflexible dosing schedule
6. Can't usually split tablets

Types of modified release dosage form:

Type of MRDF	<ul style="list-style-type: none"> • Dissolution Granules • Diffusion Granules • Enteric Coated Granules • Reservoir • Matrix <ul style="list-style-type: none"> ○ Inert ○ Erodible ○ Swellable ○ Hydrophilic • Osmotic Pump • Repeat Action • Altered Density • Hydrodynamically Balanced • SODAS • Microparticles • Meter Release • Ion Exchange Resins
Which MRDF Systems can be split	<ul style="list-style-type: none"> • Dissolution • Erodible • Matrix (Some) • Hydrodynamically Balanced System • Ion Exchange Resins
Dissolution Granules	<ul style="list-style-type: none"> • Spansule 1956 • Compazine (Antiemetic) • Capsule system with particles having coatings of specific, different thicknesses, producing a steady drug release • Polymeric Materials like Ethylcellulose, Cellulose Acetate Phthalate • Formulation of small particles can be difficult
Diffusion Granules	<ul style="list-style-type: none"> • Non-eroding, semi-permeable copolymer membrane • Allows water to penetrate and drug to diffuse out • See SODAS
SODAS	<ul style="list-style-type: none"> • Spheroidal Oral Drug Absorption System • Semipermeable, non-erodable Membrane of Acrylic Acid • Elan's Page on SODAS • Can open and sprinkle, according to Elan's Website • Cardizem CD (Diltiazem) uses two different types of beads with membranes of different thicknesses to control when drug begins diffusing • Verelan (Verapamil)
Hydrodynamic Cushion System	<ul style="list-style-type: none"> • Allow SODAS, normally used in capsules, to be compressed into tablets by <ol style="list-style-type: none"> 1. Adhering to SODAS 2. Expanding and contracting when compressed to prevent damage to the SODAS • Actually cheaper than normal tableting, due to conserved drug materials • Sodium Starch Glycollate

	<ul style="list-style-type: none"> • Naprelan (Naproxen Sodium)
Hard Capsules with Enteric Coated Granules	<ul style="list-style-type: none"> • Immediate release beads • Delayed release beads • Prilosec
Reservoir System	<ul style="list-style-type: none"> • aka Membrane System • What the % & % ToDo
Matrix Systems	<ul style="list-style-type: none"> • Monolithic Systems • Diffusion coefficient of the drug in the matrix controls the rate • Can be cut • Types <ul style="list-style-type: none"> ○ Erodible ○ Hydrophilic ○ Inert/Swellable
Wax Erodible Matrix	<ul style="list-style-type: none"> • Drug suspended in fats or waxes, which must be broken down to absorb drug <ul style="list-style-type: none"> ○ pH dependent ○ Enzyme dependent ○ Meal dependent • Examples <ul style="list-style-type: none"> ○ Procan Arrhythmia ○ Imdur Isosorbite Mononitrate ○ Slo-Fe • Difficult to prepare
Erodible Matrix with Bioadhesive	<ul style="list-style-type: none"> • Stuck under the lip • Example Actiq (Fentanyl)
Geomatrix	<ul style="list-style-type: none"> • Outer coating does not erode • Inner erodible matrix • eg Dilacor (Diltiazem) is a capsule of 3-4 geomatrix tablets with 60 mg each • Outer coats will be passed in feces
Inert Matrix	<ul style="list-style-type: none"> • Hydrophilic Matrix • Gradumet Ferro-Folic 500 has an immediate release layer and an inert matrix layer • pH Independent • Enzyme Independent • Dependent on solubility in GI fluids • Hydrophilic Drug required • Tablet will be passed in feces • Matrix materials <ul style="list-style-type: none"> ○ Polyethylene ○ Polyvinyl Acetate ○ Polymethacrylate • Two Mix techniques <ul style="list-style-type: none"> ○ Mix drug into polymerized matrix material ○ Mix drug and monomers in dry form, then perform polymerization reaction
Inert Matrix with Reservoir	<ul style="list-style-type: none"> • Film Coat • Outer Hydrophilic Matrix drug • Inner fast form tablet acts as a reservoir • Cannot Split • Adalat CC (Nifedipine) • Plendil (Felodipine) <ul style="list-style-type: none"> ○ Hydrophilic matrix surrounding another matrix reservoir
Hydrophilic Matrix	<ul style="list-style-type: none"> • Non-digestible material (Polymeric Materials), but matrix breaks apart (due to disintegrant properties) into small particles

	<ul style="list-style-type: none"> ○ Carboxymethylcellulose ○ Hydroxypropyl Methylcellulose ○ Sodium Alginate • Examples <ul style="list-style-type: none"> ○ Calan SR (Verapamil) <ul style="list-style-type: none"> ▪ Can Split ○ Ispodin SR (Verapamil) <ul style="list-style-type: none"> ▪ Can Split ○ Seldane D <ul style="list-style-type: none"> ▪ Immediate Release Terfenadine & Pseudoephedrine ▪ Hydrophilic matrix of Pseudoephedrine ▪ Splittable ○ Tylenol ER <ul style="list-style-type: none"> ▪ Immediate and sustained release bilayer system ▪ Can be split
Osmotic Pump	<ul style="list-style-type: none"> • Semipermeable membrane allows only water into the device • The increased pressure forces drug out the delivery orifice • Often coupled with a Push pump • True zero order delivery • Cannot be split • Will pass in feces • Examples <ul style="list-style-type: none"> ○ Volmax (Albuterol) Elementary, no push ○ Procardia XL (Nifedipine) ○ Covera HS (Verapamil) ○ Ditropan XL (Oxybutynin)
Repeat Action	<ul style="list-style-type: none"> • Tablet-within-a-Tablet system <ul style="list-style-type: none"> ○ Outer sugar coat ○ Immediate release drug layer ○ Enteric Coated Tablet • Inner layer usually released 4-6 hours after ingestion • Cannot be split • Examples <ul style="list-style-type: none"> ○ Proventil Repetabs (Albuterol) ○ Claratin D Loratadine outside, pseudoephedrine inside
Altered Density	<ul style="list-style-type: none"> • Sinkers • Designed to stay in the stomach for up to 12 hours • Semipermeable capsule is weighted down with <ul style="list-style-type: none"> ○ Barium Sulfate ○ Titanium Oxide ○ Zinc Oxide ○ Ferric Powder (non-absorbable) • Drug is mixed into spheres of matrix of ethylcellulose, hydroxypropylcellulose or cornstarch to control • Example Inderal LA (Propranolol) in microcrystalline cellulose beadlettes
Hydrodynamically Balanced System	<ul style="list-style-type: none"> • Floaters • Designed to float in the stomach, but don't really work well • Combined with a Hydrophilic Colloids like acacia • Erodes • Can be split • Example <ul style="list-style-type: none"> ○ Valrelease (Diazepam)

<p>Microparticles</p>	<ul style="list-style-type: none"> • Microparticles are embedded in a matrix, as particles, which are put into a capsule • Examples <ul style="list-style-type: none"> ○ K-Dur <ul style="list-style-type: none"> ▪ Tablets containing Microparticles coated in an insoluble membrane, controlling release ▪ Cannot be split or sprinkled ○ Theo-Dur Sprinkle (Theophylline) <ul style="list-style-type: none"> ▪ Hard Capsules containing Microparticles coated (soluble?) for extended release ▪ Can be sprinkled on food, but should not be divided for multiple doses ○ Theo-24 (Theophylline) <ul style="list-style-type: none"> ▪ Three Layers <ol style="list-style-type: none"> 1. Slow-eroding, semipermeable Polymeric Materials membrane 2. Starch/sugar core 3. Drug layer ▪ As water penetrates the membrane, drug is force out
<p>Dual Dosage Forms in a Hard Capsules</p>	<ul style="list-style-type: none"> • An immediate released and a MRDF • Macrobid (Nitrofurantoin) <ul style="list-style-type: none"> ○ Two Tablets within the Capsule • Cardene SR (Calcium Channel Blocker) <ul style="list-style-type: none"> ○ Immediate Powder and Modified Release Granules ○ Data Sheet
<p>It's Gotta be the Glues</p>	<ul style="list-style-type: none"> • Another tablet from pellets • The membrane controlling drug release may crack during compression, but a layer of "Glue" reseals the coating • Inactive ingredients <ul style="list-style-type: none"> ○ Silicon Dioxide ○ cellulose compounds ○ sodium stearyl fumarate ○ Polyethylene Glycol ○ Titanium Dioxide ○ paraffin • Can be split • Erodes completely • Toprol XL (Metoprolol) <ul style="list-style-type: none"> ○ United States Patent US6797283
<p>Ion Exchange Resins</p>	<ul style="list-style-type: none"> • Drug is released by exposure to HCl • Stable & palatable • Requires an ionizable drug • Examples <ul style="list-style-type: none"> ○ Ionamin (Phentermine) ○ Tussinonex (Chlorpheniramine) combines an ion exchange system with a semipermeable membrane (Pennkinetic system)

Modified release drug delivery system:

The drug delivery systems can be divided into the following categories:

- Delayed released
- Controlled released

- Sustained released
- Extended released
- Site specific targeting
- Receptor targeting
- **Delayed Released Drug Delivery system** :These systems are based on pH dependent drug release mechanism of similar to conventional enteric-coated formulations, but they differ in target site for delivery and therefore type of enteric polymers. Most commonly used polymers are derivatives of acrylic acid and cellulose. These polymers have ability to withstand from low pH end several hours (Jantzen, 1995).

Example: Enteric coated tablets and capsules which includes repeat action tablets, where time released is achieved by a barrier coating.

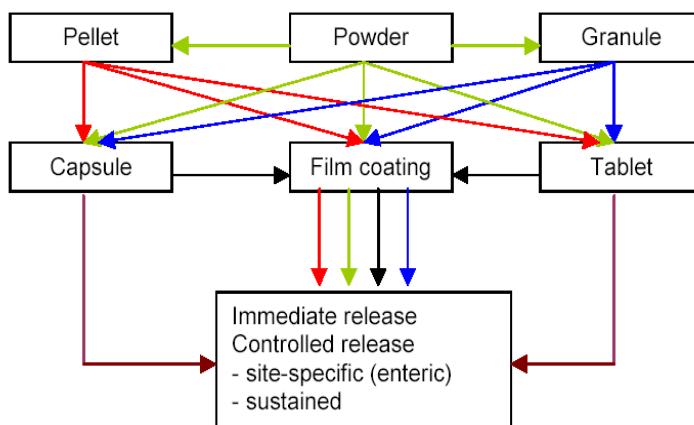


Figure.1. Relationship of pharmaceutical Delayed Release dosage forms

Controlled released (Time control delivery system): The systems are useful for synchronous delivery of a drug either at pre selected times such that patient receives the drug when needed or at a pre selected site of the GI Tract. These systems are particularly useful in the therapy of diseases, which depends on circadian rhythms.

Sustained released: These systems include any drug delivery system that achieves slow release of drug over an extended period of time.

Extended released: Pharmaceutical dosage forms that release the drug slower than the normal at predetermined rate and necessarily reduce the dosage frequency.

Site specific targeting: These systems refer to targeting of a drug directly to an certain biological system. In this case the target is adjacent to or in the diseased organ or tissue.

Receptor targeting : Site specific targeting and receptor targeting systems satisfy the aspect of drug delivery and are also considered to be controlled drug delivery systems.

Rationale for extended release pharmaceuticals: These are some drugs which have long half life and hence are long lasting and they are required to be given one a day to system adequate blood levels and the desired therapeutic effects. There are on the other hand many drugs which are not long lasting and require multiple daily dosing to achieve the desired therapeutic levels. Multiple daily dosing is after is inconvenient for the patient and can result in missed doses, made up doses and patient non compliance with the therapeutic regimen. Another drawback of multiple dosing is that when doses are not administered on schedule, the resulting peaks and valleys reflect less than optimum drug therapy and if the doses are administered too frequently minimum toxic concentrations may be recalled with toxic side effects resulting. If doses are missed, periods of sub therapeutic blood levels or those below the minimum effective concentration may result, with no patient benefit (Selly, 1999).

Advantages of extended release dosage form:

1. This decreases the need for multiple dosing and hence improves patient compliance and chances of toxicity.
2. It provides an immediate release of drug which promptly produces the desired therapeutic effect which then is followed by the gradual and continual release of additional amounts of drug to maintain this effect over a pre-determined period of time.

3. The sustained release drug levels provided by extended release drug products often eliminate the need for night dosing which is beneficial for the patient and the caregiver.
4. Reduction in drug blood level fluctuations by controlling the rate of drug release, "Peak and Valley" of drug blood levels are eliminated.
5. Reduction in adverse side effects
6. Reduction in overall health care costs. Although the initial cost may be greater than that for conventional the overall cost of treatment may be less due to enhanced therapeutic benefit, fewer side effects and reduced time required of health care personnel to dispense and administer drugs and monitor patients.

Disadvantages of extended release dosage form: The loss of flexibility in adjusting the drug dose and / or dosage regimen and an increased risk of sudden and total drug release or "dose dumping" due to failure of the technology of the dosage unit.

Ideal characteristics of the drug candidate for extended release formulation:

A. Physiochemical Properties of the drug:

a) Aqueous solubility: Lower limit solubility for such product is reported to be 0.1 mg/ml. As the drug must be in solution form before absorption, drug having low aqueous solubility usually suffers oral bioavailability problem due to limited GI transit time of undissolved drug and limited solubility at absorption site. So these types of drug are undesirable. Drug having extreme aqueous solubility are undesirable for ER because, it is too difficult to control release of drug from the dosage form. Physiological pH dependent solubility i.e. variation in solubility at different GI pH are undesirable (e.g. Aspirin, which is less soluble in stomach, but more soluble in intestine) as it will yield variation in dissolution rate. A drug with good aqueous solubility, pH independent solubility is desirable for oral new drug delivery system

b) Partition Co-efficient: As biological membrane is lipophilic in nature through which the drug has to pass through, so partition co-efficient of drug influence the bioavailability of drug very much. Drug having lower partition co-efficient values less than the optimum activity are undesirable for oral ER drug delivery system, as it will have very less lipid solubility and the drug will be localized at the first aqueous phase it come in contact e.g. Barbituric acid. Drug having higher partition co-efficient value greater than the optimum activity are undesirable for oral ER drug delivery system because more lipid soluble drug will not partition out of the lipid membrane once it gets in the membrane. The value of partition co-efficient at which optimum activity is observed is approximately 1000:1 in 1-octano/water system.

c) Drug stability *in-vivo*: As most of ER Drug delivery system is designing to release drug over the length of the GIT, hence drug should be stable in GI environment. So drug, which is unstable, can't be formulated as oral ER drug delivery system, because of bioavailability problem.

E.g. - Nitroglycerine.

d) Protein binding: The Pharmacological response of drug depends on unbound drug concentration drug rather than total concentration and all drug bound to some extent to plasma and or tissue proteins. Proteins binding of drug play a significant role in its therapeutic effect regardless the type of dosage form as extensive binding to plasmaincrease biological half life and thus sometimes ER drug delivery system is not required for this type of drug.

e) Drug pKa & Ionization at physiological pH: As we know only unionized drug are absorbed and permeation of ionized drug is negligible, since its rate of absorption is 3 to 4 times less than that of the unionized drug. pKa range for acidic drug where ionization is pH sensitive is around 3.0 – 7.5 and pKa range for basic drug whose ionization is pH sensitive is around 7.0-11.0 are ideal for optimum positive absorption. Drug shall be non-ionized at the site to an extent 0.1 – 5.0%. Drugs existing largely in ionized form are poor candidates for oral ER drug delivery system. e.g.:- Hexamethonium.

f) Mechanisms and sites of absorption: Drug absorption by carrier mediated transport and those absorbed through a window are poor candidate for oral ER drug delivery system e.g. – several B vitamins. Drugs absorbed by passive diffusion, pore transport and through over the entire length of GIT are suitable candidates for oral ER drug delivery system.

g) Molecular size and diffusivity: With large molecular size are poor candidate for oral ER drug delivery system because it the ability of the drug to diffuse polymeric membrane is a function of its diffusivity (or diffusion co-efficient). Diffusivity depends on size shape of the cavities of the membrane. The diffusion co-efficient of intermediate molecular weight drug i.e.-100 to 400 Dalton, through flexible polymer range from 10⁻⁶ to 10⁻⁹ cm²/sec. For drugs having molecular weight > 500 Daltons the diffusion co-efficient in many polymers are very

less i.e. less than 10-12 cm²/sec. Drugs is very difficult to control release rate of medicament from dosage form e.g. proteins and peptides.

h) Dose size: If a product has dose size >0.5gm it is a poor candidate for oral ER drug delivery system, because increase in bulk of the drug, thus increases the volume of the product.

B. Biological Properties of Drug:

a) Absorption: For oral ER drug delivery system the rate of drug absorption (k_a) should be more -API than that of the rate of drug release (k_r) from the dosage form i.e. $k_r \ll k_a$. Drug that are slowly absorbed or absorbed with a variable absorption rate of elimination of drug are poor candidate for oral ER drug delivery system. Some possible reasons for a low extent of absorption are poor water solubility, small partition co-efficient, acid hydrolysis, and metabolism or its site of absorption.

b) Distribution: Drugs with high apparent volume of distribution, which influence the rate of elimination of the drug, are poor candidate for oral ER drug delivery system e.g. Chloroquine.

c) Metabolism: Drug, which extensively metabolized is not suitable for ER drug delivery system. A drug capable of inducing metabolism, inhibiting metabolism, metabolized at the site of absorption of first-pass effect is poor candidate for ER delivery, since it could be difficult to maintain constant blood level e.g. levodopa, nitroglycerine.

d) Half-life of drug: A drug having biological half-life between 2 to 8 hours is best suited for oral ER drug delivery system. As if biological half-life < 2hrs the system will require unacceptably large rate and large dose and biological half-life >8hours formulation of such drug into oral ER drug delivery system is unnecessary.

e) Margin of safety: As we know larger the value of therapeutic index safer is the drug. Drugs with less therapeutic index usually poor candidate for formulation of oral ER drug delivery system due to technological limitation of control over release rates.

f) Plasma concentration response relationship: Generally pharmacological response of drug depends on plasma drug concentration rather than size and dose. But some drugs pharmacological activity is independent of plasma concentrations, which are poor candidate for oral ER drug delivery system. E.g. Reserpine.

g) Concentration dependency on transfer of drug: Transfer of drug from one compartment to other by zero kinetic process then such drugs are poor candidate for oral ER delivery system, it should be first order kinetics.

Techniques for producing an extended release product: The technology is mainly based on

1. Modifying drug dissolution by controlling access of biologic fluids to the drug through the use of barrier coatings.
2. Controlling drug diffusion sets from dosage forms.
3. Chemically reacting or interacting between the drug substance or its pharmaceutical barrier and site specific biologic fluids.

Some of extended release oral dosage forms are available as:

- Coated beads, Granules or Micro sphere
- Multi tablet System
- Microencapsulated Drug
- Embedding drug in slowly eroding or hydrophilic matrix system.
- Embedding drug in inert plastic metrics.
- Complex formation
- Ion exchange resins
- Osmotic pump
- Floating tablets

2. CONCLUSION

Modified release dosage forms are drug delivery systems which, by virtue of formulation and product design, provide drug release in a modified form distinct from that of the conventional dosage forms. Drug release can either be delayed or extended in nature. So modified release dosage forms are ideal dosage forms and it has several applications in pharmacy like reduction in drug blood level fluctuations, reduction in frequency of dosing, enhanced patient compliance reduction in incidence of adverse side effects, reduction in overall healthcare costs also.

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