IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 5, April 2023

A Review on Modified Release Dosage Form

Shejal A. Late[1] and Bipin R. Gandhi[2]
Student, Samarth College of Pharmacy, Belhe, Pune, Maharashtra, India[1]
Assistant Professor, Samarth College of Pharmacy, Belhe, Pune, Maharashtra, India[2]

Abstract: *Among the various routes of drug delivery oral route is most preferred route. But conventional dosage form offers few limitations which could be resolved by modifying the existing dosage form. Sustained and controlled drug delivery system helps in maintaining of constant plasma drug concentration and retards the release rate of drug thereby extending the duration of action. Modified release drug products allow at least a two-fold reduction in dosing when compared to a drug that is presented in a conventional immediate release form. Modified release drug products are designed to release active pharmaceutical ingredient over a longer duration of time; At least, longer than an Immediate release (I.R) formulation. Many Pharmaceutical companies also utilize the proprietary advantages of Modified release formulations to extend the patent life cycle of commercial products thereby bringing in new business.*

Keywords: Modified release, plasma drug concentration, controlled & Sustained release, immediate release

I. INTRODUCTION

The oral course of drug delivery is usually taken into consideration the favored and maximum affected person handy manner of drug administration. The truth is that many compounds are both incompletely or ineffectively absorbed after oral administration (i.e., bioavailability is an issue), or that the specified dosing frequency is simply too brief to permit once- or twice-every day administration (i.e., pharmacokinetic half-existence is an issue).

The principal goals of any drug delivery system are to make certain protection and to enhance efficacy of medicine in addition to affected person compliance. This is carried out through higher manage of plasma drug tiers and much less common dosing. Conventional dosage bureaucracy aren't capable of manage the fee of drug delivery and offer fast drug release, to preserve a healing degree required common drug administration, which results in fluctuated degree of drug in blood and tissues. The attention of medicine can be to begin with high, that could motive toxic, and/or aspect effects. The attention fast falls down under the minimal healing degree with time elapse. In contrast, Modified release dosage bureaucracy aren't best capable of preserve healing tiers of drug with slim fluctuations however they also make it possible to lessen the frequency of drug administration .

1.1 Definition

Modified-release formulations technology provide an powerful method to optimize the bioavailability and ensuring blood concentration-time profiles of medication that in any other case be afflicted by such limitations. The term "modified release" refers to each delayed- and prolonged-launch structures for oral management in addition to oral delivery structures designed in particular to alter the discharge of poorly water-soluble drugs. Also protected are the quick dissolving dosage form for which absorption takes place primarily (however now no longer exclusively) withinside the gastrointestinal (GI) tract. Modified release dosage form are described through the USP as the ones whose drug release traits of time direction and/or area to perform healing or conventional goals now no longer provided through conventional form, while an prolonged release dosage form lets in a twofold discount in dosing frequency or growth in affected person compliance or healing performance. It is thrilling to word that the USP considers that the time period controlled release, extended release and prolonged release are interchangeable with extended release.

Advantages of Modified release Drug Delivery System:

Improved control over the maintenance of therapeutic plasma drug concentration of drugs.

Improved patient compliance, resulting from the reduction in the number and frequency of doses required to maintain the desired therapeutic response, e.g. one per-oral modified release products every 12 hours contributes to the improved control of therapeutic drug concentration achieved with such products

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 5, April 2023

Reduction in overall health care costs: although initial cost of extended release dosage forms may be greater than for conventional forms,. Overallcost of treatment may be greater cause of enhanced therapeutic benefits, fewer side effects , reduction time for health care personal to dispense and administered drugs and monitor patients.
Enhanced of activity duration for short half life drugs.
Improved bioavailability of some drugs.
Minimize drug accumulation with chronic dosing.

Disadvantages (limitations) of Modified release Drug Delivery System:
Variables physiological factors such as, Gastrointestinal PH, enzyme activities, gastric and intestinal transit rates, food and severity of disease, which often influence drug bioavailability from conventional per-oral dosages forms, may also interfere with precision of control of release and absorption of drugs from per-oral modified release dosages forms.
Slow release of drug may produce a localized concentration that causes local irritation to gastrointestinal mucosa.
Drugs having biological half lives of 1 hour or less are difficult to formulate modified release. The high rates of elimination of such drugs from the body mean that an extremely large maintenance dose would be required to provide 8-10 hours continuous therapy.
In modified release products there is possibility of unsafe over dose due to improper formulation of dosage form.
Administration of sustained Release medication doesn't permit the prompt termination of therapy.
The physician has less flexibility in adjusting dosages regimens. This is fixed by the dosage form design.
Retrieval of drug is difficult in case of toxicity, poising or hypersensitivity reactions.
Higher cost of formulation.

Types of Modified Release Dosage Form

Type of MRDF	• Dissolution Granules • Diffusion Granules • Enteric Coated Granules • Reservoir • Matrix • 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	• Dissolution • Erodible • Matrix (Some) • Hydrodynamically Balanced System • Ion Exchange Resins
Dissolution Granules	• Spansule 1956 • Compazine (Antiemetic) • Capsule system with particles having coatings of specific,

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 5, April 2023

	different thicknesses, producing a steady drug release • Polymeric Materials like Ethylcellulose,cellulose Acetate Phthalate • Formulation of small particles can be difficult
Diffusion Granules	• Non-eroding, semi-permeable copolymer membrane • Allows water to penetrate and drug to diffuse out • See SODAS
SODAS	• 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	• Allow SODAS, normally used in capsules, to be compressed into tablets by • Adhering to SODAS • Expanding and contracting when compressed to prevent damage to the SODAS • Actually cheaper than normal tableting, due to conserved drug materials • Sodium Starch Glycollate • Naprelan (Naproxen Sodium)
HardCapsules with Enteric Coated Granules	• Immediate release beads • Delayed release beads • Prilosec
Reservoir System	• aka Membrane System • What the % & % ToDo
Matrix Systems	• Monolithic Systems • Diffusion coefficient of the drug in the matrix controls the rate • Can be cut • Types • Erodible • Hydrophilic • Inert/Swellable
Wax Erodible Matrix	• Drug suspended in fats or waxes, which must be broken down to absorb drug • pH dependent • Enzyme dependent • Meal dependent • Examples • Procan Arrhythmia • Imdur Isosorbite Mononitrate • Slo-Fe • Difficult to prepare

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 5, April 2023

Erodible Matrix with Bioadhesive	• Stuck under the lip • Example Actiq (Fentanyl)
Geomatrix	• 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	• 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 • Hydrophillic Drug required • Tablet will be passed in feces • Matrix materials • Polyethylene • Polyvinyl Acetate • Polymethacrylate • Two Mix techniques • Mix drug into polymerized matrix material • Mix drug and monomers in dry form, then perform polymerization reaction
Inert Matrix with Reservoir	• Film Coat • Outer Hydrophillic Matrix drug • Inner fast form tablet acts as a reservoir • Cannot Split • Adalat CC (Nifedipine) • Plendil (Felodipine) • o Hydrophillic matrix surrounding another matrix reservoir
Hydrophilic Matrix	• Non-digestable material (Polymeric Materials), but matrix breaks apart (due to disintegrant properties) into small particles • Carboxymethylcellulose • Hydroxypropyl Methylcellulose • Sodium Alginate • Examples • Calan SR (Verapamil) • Can Split • Ispotin SR (Verapamil) • Can Split • Seldane D • Immediate Release Terfenadine & Pseudoephedrine • Hydrophilic matrix of Pseudoephedrine • Splittable • Tylenol ER • Immediate and sustained release bilayer system

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 5, April 2023

	• Can be split
Osmotic Pump	• 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 • Volmax (Albuterol) Elementary, no push • Procardia XL (Nifedipine) • Covera HS (Verapamil) • Ditropan XL (Oxybutynin)
Repeat Action	• Tablet-within-a-Tablet system • Outer sugar coat • Immediate release drug layer • Enteric Coated Tablet • Inner layer usually released 4-6 hours after ingestion • Cannot be split • Examples • Proventil Repetabs (Albuterol) • Claratin D Loratadine outside, pseudoephedrine inside
Altered Density	• Sinker • Designed to stay in the stomach for up to 12 hours • Semipermeable capsule is weighted down with • 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	• 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 • Valrelease (Diazepam)
Microparticles	• Microparticles are embedded in a matrix, as particles, which are put into a capsule • Examples • K-Dur • Tablets containing Microparticles coated in an insoluble membrane, controlling release • Cannot be split or sprinkled

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 5, April 2023

	• Theo-Dur Sprinkle (Theophylline) • 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) • Three Layers • Slow-eroding, semipermeable Polymeric • Materials membrane • Starch/sugar core • Drug layer • As water penetrates the membrane, drug is force out
Dual Dosage Forms in a Hard Capsules	• An immediate released and a MRDF • Macrobid (Nitrofurantoin) • Two Tablets within the Capsule • Cardene SR (Calcium Channel Blocker) • Immediate Powder and Modified Release Granules • Data Sheet
It's Gotta be the Glues	• Another tablet from pellets • The membrane controlling drug release may crack during compression, but a layer of "Glue" reseals the coating • Inactive ingredients • Silicon Dioxide • cellulose compounds • sodium stearyl fumarate • Polyethylene Glycol • Titanium Dioxide • paraffin • Can be split • Erodes completely • Toprol XL (Metoprolol) • o United States Patent US6797283
Ion Exchange Resins	• Drug is released by exposure to HCl • Stable & palatable • Requires an ionizable drug • Examples • Ionamin (Phentermine) • o Tussinonex (Chlorpheniramine) combines an ion exchange system with a semipermeable membrane (Pennkinetic system)

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 5, April 2023

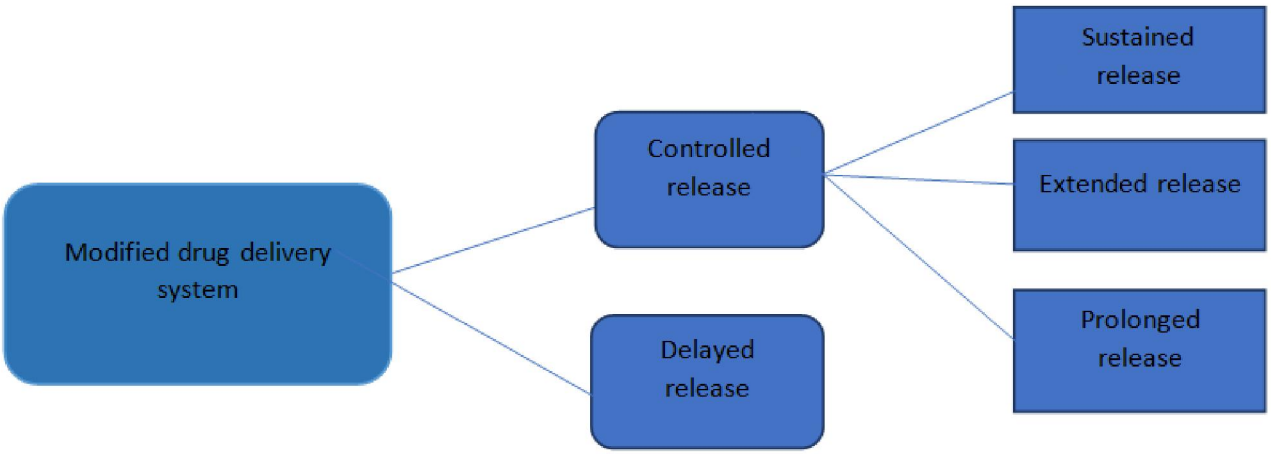

Fig 1- Categories of modified release delivery system

Categories of Modified Release Dosage Form

Controlled-release :- the drug is released at a constant rate and plasma concentrations after administration do not vary with time.

It is further classified into-

Sustained release

Sustained release tablet owing a twofold or more reduction in frequency of management of a drug in comparison With the frequency required through a conventional dosage form. It is designed to preserve steady degrees of a drug in thePatient's bloodstream through releasing the drug over an extended Period. Maintaining steady blood degrees of the drug in the bloodstream will increase the therapeutic effectiveness of thedrug..

Extended release

A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release, and long-acting drug products

Prolonged Release

They are designed to release the drug slowly and to provide a continuous supply of the drug over an extended period. They prevent very rapid absorption of the drug, which could result in extremely high peak plasma drug concentration.

Delayed-Release

The release of the active substance from such modified release dosage forms is delayed for a certain period after administration or application of the dosage. The subsequent release is similar to that of an immediate release dosage form. Examples of delayed-release systems include repeat-action tablets and capsules, and enteric-coated tablets where timed release is achieved by a barrier coating. Examples of delayed-release systems include repeat-action tablets and capsules, and enteric-coated tablets where timed release is achieved by a barrier coating .

Fig.2 Marketed preparation of Modified Release Dosage form

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 5, April 2023

Factors considering for selection of drugs for the development of Modified release dosage forms:

Molecular size and diffusivity:

Diffusion may be defined as a mass transfer of individual molecules of a drug substance and mainly by random molecular motion associated with concentration gradient. During time course of the drug it must diffuse through various biological membranes in the body. The drugs in the form of modified release dosage form must diffuse through a matrix or polymeric membrane. The ability of drug diffuse through polymers is called as diffusivity and is a function of its molecular weight or molecular size. The drugs or polymer which are having high molecular weight show very slow release kinetics in sustained release device by diffusion through polymeric membrane.

PKa-Ionization constant:

Ionization constant is one of the important properties used to measure the strength of an acid or base and determine the charge on the drug molecule at any given PH. The ionized forms of drugs are poor candidates for sustained or controlled dosage format the absorption site. The drug molecules are active only at unionized state and cross rapidly through lipoidal membranes than ionized molecules.

Partition coefficient:

The partition coefficient is used to measure of how hydrophilic or hydrophobic a drug substance is or it's a measure of Hydrophilicity-Lipophilicity balance. Partition coefficient impacts each permeation of drug throughout the biological membrane and diffusion throughout the rate controlling membrane or matrix. The drug with excessive partition coefficient are very oil soluble and will partition hastily into numerous membranes withinside the body and show more activity .

Drug Stability:

The drug balance is more essential parameter withinside the dosage form design. When the drug administered orally, it losses through hydrolysis or degradation withinside the GIT. So it is important to enhance the relative bioavailability of drug that is unstable in gastric region and such drugs ought to appropriate for delayed release dosage form so as to launch the drug withinside the intestine. The drugs that are having stability issue withinside the gastric region are much less appropriate for modified release dosage form and design the drug to deliver uniformly throughout the gastric region.

Aqueous solubility:

Solubility may define as the maximum amount of drug substance that goes into the solution form in a specific amount of solvent. The solubility of drug substance mainly depends on concentration, pressure and solvent used. High solubility may define as highest dose strength is soluble in 250mL or less of aqueous media over the pH range of 1-7.5.The drugs with aqueoussolubility influences drug dissolution rate and it establishes the concentration in solution. The dissolution rate is related to aqueous solubility and explained by Noyes-Whitney equation. The drug with high solubility and a rapid dissolution rate is difficult to control or decrease the dissolution rate and slow its absorption. The drugwith low solubility difficult to sequester ahighly soluble dosage form and retard the drug release in case of high drug dose. The drug with very low solubility and slow dissolution rate will exhibit very limited absorption and not provide a considerably much benefits than immediate release dosage form.

II. 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.

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.301
Volume 3, Issue 5, April 2023

III. ACKNOWLEDGMENT

We excess my thanks and gratitude to Trustee of Samarth Rural Educational Institute's and Samarth college of Pharmacy, Belhe with their valuable guidance and support.

CONFLICT OF INTEREST: The author declared no conflict of interest.

REFERENCES

[1]. Charman Susan. A, Charman, William. N. Oral modified release delivery system In: Rathone, Michael. J., (Eds.),modified release drug delivery technology, 10thed. Marcel Dekker, New York, 2003; 1-10.
[2]. Narasimharao R, Anusha Reddy M, SwethaReddy N, Divyasagar P and Keerthana K. Design and Evaluation of Metformin Hydrochloride Extended Release Tablets by Direct Compression. International Journal of Research in Pharmaceutical and Biomedical Sciences.2011; 2(3):1118-33
[3]. Collette, J.H., Moreton, R.C.,. Modified release peroral dosage forms In: Michael,E.Aulton's pharmaceutics the design & manufacture of medicines, 3rdchurchill livingstone Elsevier, china, 2007; 483-498.
[4]. Umamaheshwari, R.B., Jain, N.K. Controlled & novel drugdelivery system In: Pharmaceutical product development. 1st,CBS publisher & distributors, New Delhi, India, 2005; 419-454.
[5]. Ding, Xuan., Alani, W.G. Adam., Robinson, R. Joseph. In:Extended release & targeted drug delivery system", the science & practice of pharmacy 21st,Lippincott Williams &wilking, new Delhi, India, 2007; 939-961.
[6]. Apollo pharmacy https://www.apollopharmacy.in/medicine/pregeb-m-150mg-tablet
[7]. Jantzen GM, Robinson JR. Modern Pharmaceutics, 3rd ed., New York, Marcell Dekker, 1995, 575- 609.
[8]. Kamboj S, Gupta GD. Matrix Tablets: An Important Tool for Oral Controlled-Release Dosage Forms, Pharmainfo.net, 7(6), 2009
[9]. Jayanthi B, Manna PK, Madhusudhan S, Mohanta GP, Manavalan R. Per oral extended release products- An overview. J Appl Pharm Sci 2011; 1(2): 50-5.
[10]. https://m.indiamart.com/proddetail/metformin-hydrochloride-sustained-release-tablets-ip-500mg-20545908148.html
[11]. Kawashima Y, Ohno H, Takenaka H. Preparation of spherical Matrixes of prolonged-release drugs from liquid suspension. J Pharm Sci 1981; 70(8): 913-6. [http://dx.doi.org/10.1002/jps.2600700821] [PMID: 7310663]
[12]. Mamidala RK, Ramana V, Sandeep G. et al. Factors influencing the design and performance of oral sustained/controlled release dosage forms. Int J Pharm Sci Nanotech 2009; 1: 583-94.
[13]. Harnish patel, Dhrupesh R. Panchal, Upendra Patel, Tushar Brahmbhatt, Mayur Suthar. Matrix Type Drug Delivery System:A Review. Journal of Pharmaceutical Science andBioscientificResearch. 2011; 1(3):143-51.
[14]. Manish Shivadas Wani, M.H.Dehghan, et al., Controlled Released System – A Review, 2008; 6(1), 197 http://www.pharmainfo.net/reviews/controlled-releasedsystem-review, accessed on 11-09-2010
[15]. Jones D, FASTtrack: Pharmaceutics: Dosage Form and Design. London: Pharmaceutical Press; 2008.
[16]. Tozer T N, Rowland M, Introduction of Pharmacokinetics and Pharmacodynamics: The Quantitative Basis of Drug Therapy. Baltimore, MD: Lippincott Williams & Wilkins; 2006.