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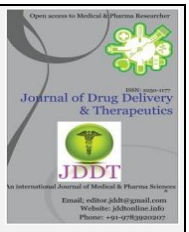

Open Access Review Article

AN UPDATED REVIEW ON MODIFIED RELEASE TABLETS

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ABSTRACT

For some time now modified drug release has been studied and used extensively during the development of pharmaceutical drug products because of its advantages over immediate release formulations. As per the forecasting by Global Business Intelligence (GBI) research, the growth in oral drug delivery market will uplift in the coming years. 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: Immediate release (I.R), Modified release (M.R), Novel drug delivery systems (NDDS), Loading doze (LD), Maintenance doze (MD), New Drug Application (NDA)

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INTRODUCTION

Years ago in 1895, a very well reputed British Pharmaceutical Journal predicted "Tablets have had their day and will pass away to make room for something else." Now, with almost more than 100 years after this statement, today, oral solid dosage forms are the leading drug delivery systems in the market, and they are not going to perish in coming 30 years. The oral route was and is still the preferred route of drug administration due to its prominent advantages compared to the other routes. Conventional oral drug delivery systems are known to provide an immediate release of drug, in which one cannot control the release of the drug and effective concentration at the target site, therefore alteration of drug release is required [1].

However, the sophisticated instrumentation, modern mathematical models and computational power have revolutionized the entire process of all the aspects of formulation and development of drug delivery systems in last few decades. Novel drug delivery systems have emerged and advanced the concept of drug delivery from a simple pill to a programmable, time controlled smart system[2].

Rationale for development of modified release system:

The main objectives of any drug delivery system are to ensure safety and to improve efficacy of drugs as well as patient compliance. This is achieved by better control of plasma drug levels and less frequent dosing. Conventional dosage forms are not able to control the rate of drug delivery and provide rapid drug release, to maintain a therapeutic level required frequent drug administration, which leads to fluctuated level of drug in blood and tissues. The concentration of drugs may be initially high, that can cause toxic, and/or side effects. The concentration quickly falls down below the minimum therapeutic level with time elapse. In contrast, Modified release dosage forms are not only able to maintain therapeutic levels of drug with narrow fluctuations but they also make it possible to reduce the

frequency of drug administration. The concentration of a drug released from controlled release dosage forms fluctuates within the therapeutic range over a long period of time.

A given formulation exhibits pharmacological response only for the time period when the drug blood levels are within the therapeutic window or the therapeutic range. On administrating the drug by either IV or an oral route (Immediate release dosage form), the drug blood levels are not achieved within the therapeutic range for an extended period of time. On the contrary, to overcome this, therapeutic efficacy and safety of drugs can be improved by more precise spatial and temporal placement within the body, thereby reducing both the size as well as the number of doses. A modified-release dosage form is defined "as one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosages forms.[3]

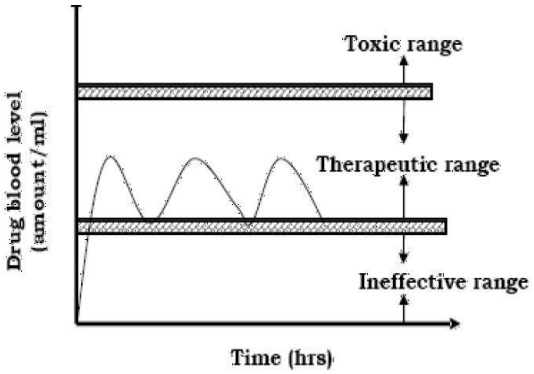

Figure 1 Typical drug blood levels versus time profile for intravenous and oral route of administration

Classification:

The modified release system, i.e. non-immediate release systems, may be divided conveniently in three categories:

Table 1

1.	Delayed release	
2.	Sustained release	Controlled release, Prolong release
3.	Site specific and receptor release	Organ targeting, Cellular targeting, Sub cellular targeting

1) Delayed release: Delayed release systems are those systems that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Repeat action tablets and capsules are the classical examples. A delayed release dosage form does not produce or maintain uniform drug blood levels within the therapeutic range. The drug release pattern is shown in Figure 2.

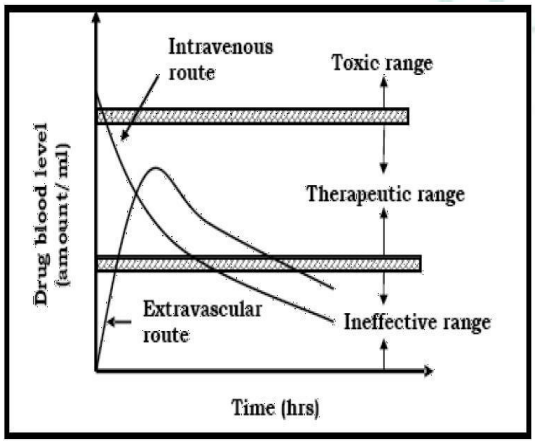

Figure 2 Typical drug blood levels versus time profiles for delayed release

2) Sustained release: It includes all drug delivery systems that achieve slow release of drug over an extended period of time. Ideally, a sustained release oral dosage form is designed to rapidly release pre-determined fraction of the total dose (loading dose) into gastrointestinal tract, which will produce the desired pharmacological response as promptly as possible and the remaining fraction of the total dose (maintenance dose) is then released at a controlled rate

Controlled release: Drug product is designed so that the release rate of maintenance dose is equal to the elimination rate. The constant blood levels can be achieved from controlled release system.

Prolonged release: Prolonged release dosage forms reduce fluctuation in plasma drug levels by slowing down the absorption rate due to slower drug release rate. It extends the period of time the drug concentration is in the therapeutic range but does not maintain constant blood levels as controlled release systems.

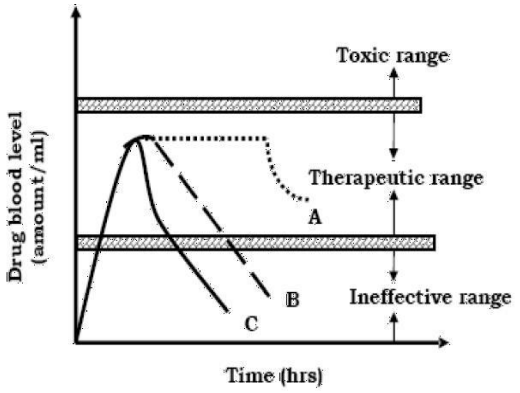

Figure 3: Drug blood level versus time profile showing the relationship between controlled release (A), Prolonged release (B), & conventional release (C)

3) Site specific and receptor release: In the case of site specific release, the target is a certain organ or tissue (e.g. in the treatment of arthritis or gout). While for receptor release, the target is the particular receptor for a drug within an organ or tissue (e.g. H1 and H2 antagonists located in tumor cells). Both these systems satisfy the spatial aspect of drug delivery. This type of drug release is difficult to achieve.

Advantages of modified release dosage form (Robinson and Longer 1676)[4-5]

1. Avoid patient compliance problems
2. Better drug utilization and employed less total drug

a. Minimize or eliminate local side effects and systemic side effects

b. Obtain less potentiation or reduction in drug activity with chronic use

c. Minimize drug accumulation with chronic dosing

3. Improve efficiency in treatment
4. Cure or control condition more promptly
5. Improve control of condition i.e. reduce fluctuation in drug level
6. Improve bioavailability of some drugs
7. Make use of special effects e.g. Sustained release aspirin for morning relief of arthritis by dosing before bedtime
8. Economical

Limitations of modified release system (Robinson and Longer 1676)[6]

1. Drug with following characteristics cannot be given by modified release dosage form.

a. Drugs with very narrow therapeutic index.

b. Drugs with erratic absorption from gastrointestinal track

c. Drugs with long biological half life

d. Drugs which needs to adjust dose regime

e. Drugs with very high dose

2. The dose cannot be subdivided as in conventional dosage form
3. Difficult to provide antidote for sustained release formulations

Factors considering for selection of drugs for the development of Modified release dosage forms: [8-9]

i. 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 polymers which are having high molecular weight show very slow release kinetics in sustained release device by diffusion through polymeric membrane

ii. 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 form at the absorption site. The drug molecules are active only at unionized state and cross rapidly through lipoidal membranes than ionized molecules.

iii. 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 influences both permeation of drug across the biological membrane and diffusion across the rate controlling membrane or matrix. The drugs with high partition coefficient are very oil soluble and will partition rapidly into various membranes in the body and show greater activity.

iv. Drug Stability: The drug stability is most important parameter in the dosage form design. When the drug administered orally, it losses through hydrolysis or degradation in the GIT. So it is necessary to improve the relative bioavailability of drug that is unstable in gastric region and such drugs should suitable for delayed release dosage form in order to release the drug in the intestine. The drugs which are having stability problems in the gastric region are less suitable for modified release dosage form and design the drug to deliver uniformly throughout the gastric region.

v. Aqueous solubility: [10-11] 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 aqueous solubility 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 drug with low solubility difficult to sequester a highly 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 forms.

Selection of Polymers: [12-14] Development of modified release dosage forms for highly soluble drugs is becomes challenge to the formulation scientist. These drugs will release the drug readily at a faster rate and produces untoward effects on oral administration. So, considerable attention was needed for the selection of polymers to retard the drug release for highly soluble drugs. Based on flexibility, desirable drug release and cost effective, hydrophilic polymers are most suitable to

retard the drug release and various water swellable or water soluble with high molecular weight polymers were used in hydrophilic matrices such as Hydroxy propyl methyl cellulose and Polyethylene oxide. HPMC is most commonly used polymer in matrix formulations because of their features like pH independent performance, excellent stability, suitable for direct compression and granulation techniques. Polyethylene oxide also commonly used polymer in matrix formulations because of their versatile application for direct compression, granulation technique, fast hydration and gel formation.

Why the need to convert IR to MR?

Attention in the development of Modified release dosage forms in Pharmaceutical industry is increasing day-by-day as there are more advantages than immediate release dosage forms. This is particularly more important to innovator companies for the development of modified release dosage forms to get additional market exclusivity for newly developed modified release dosage forms as well as additional Intellectual Property to the company by protecting these complex modified release forms with Patents and thus delaying the entry of generic products to the market. This strategy generally used by Innovator companies to shift the market from immediate release dosage forms to Modified release dosage forms, once after Data exclusivity/Patent is expired for immediate release dosage forms and capture all the market, thus delaying generic companies to enter the market. Below is list of few of the examples of drugs where modified release dosage forms are approved after long time of immediate release dosage forms are approved, and captured the most of the market and become block busters

Table 2: Approval dates of Immediate and Modified release dosage forms in USA[7]

S. No	Drug name (Brand name)	Company name	Approval date of IR	Approval date of MR	MR patent No & Expiry
1	Bupropion(Wellbutrin SR)	GSK	Dec 30,1985	Oct 4, 1996	5358970& 2013
2	Metformin(Glucophage XR)	BMS	Mar 3,1995	Oct 13,2000	6475521& 2018
3	Zolpidem(Ambien CR)	SANOFI	Dec 16,1992	Sep 2, 2005	6514531& 2020
4	Nifedipine(Adalat CC)	BAYER	Nov27,1985	Apr 21,1993	5264446& 2010
5	Carbamazepine(Carbatrol)	SHIRE	Mar11,1968	Sep 30,1997	5912013& 2016

Regulatory approval of Modified release products in New Drug Application (NDA) [15]:

In principle, FDA approval of MR products in new drug applications (NDAs) submitted by innovator firms is based on evidence of an adequate drug exposure–response framework. Exposure can be expressed by blood levels or dose, and response by validated clinical endpoint(s) or surrogate endpoint(s). The exposure–response framework should include knowledge of the impact that drug input rate and its delivery course have on response or established therapeutic range for the MR product under consideration. Preferably, a quantitative and predictive exposure–response relationship exists, and tolerance does not develop over time. In general, there are three types of NDAs for MR drug products: (a) IR to MR switch, (b) MR to MR switch with unequal dosing intervals, and (c) MR to MR switch with equal dosing intervals. Regulatory requirements vary with the type of NDA submitted to FDA. For example, in the case of switching from an IR to an MR product, the key question is whether there is an adequate exposure–response framework established by the previously approved IR product. If the answer is yes, no clinical efficacy trial may be needed, and the only requirement is to conduct three clinical pharmacology studies under single-dose (fasting and fed) and steady-state conditions. The main goal is to ensure that the new MR product has similar exposure course of the drug compared with the previously approved product with proven efficacy. If the answer is no, one efficacy and/or safety trial may be necessary in addition to the three clinical pharmacology studies. In the clinical efficacy trial for the MR product, a head-to head comparison between the MR and IR products is not considered a requirement, and thus NDA sponsors opt to do placebo-controlled studies without an IR formulation in the trial., NDA sponsors may also be asked to perform animal studies with the appropriate regimen in addition to the clinical efficacy trial in patients.

Pharmaceutical Equivalence of Modified Release Products[15]:

In the USA, pharmaceutical equivalents are referred to drug products in identical dosage forms that contain identical amounts of the identical active drug ingredient and meet the identical or compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

IR drug products: pharmaceutical equivalence may provide a presumption of therapeutic equivalence, which can be further verified by appropriate in vivo bioequivalence studies. In fact, these in vivo studies may be waived under certain circumstances, e.g., BCS class I drugs formulated in rapidly dissolving products.

MR drug products: In MR drug products, however, traditional appraisal of pharmaceutical equivalence may not provide a presumption of therapeutic equivalence. This is partly because in vitro and in vivo correlations (or relationships) might not have been carried out in the development of many MR products. In addition, excipients used for control of drug release are critical to the performance of MR products. To ensure therapeutic equivalence of MR products, a scrutiny of pharmaceutical equivalence is essential, which may include careful characterization of physicochemical

properties of the dosage form, purity of the drug substance and excipients, solubility, dissolution, and stability of the drug/product.

Additional measures to assess bioequivalence:

It is generally agreed that the present regulatory criteria are adequate in the assessment of bioequivalence for many MR formulations with conventional drug release profiles in vivo. However, for MR products designed to achieve a rapid rise in drug plasma concentrations (and thus a rapid onset of therapeutic effect) following administration or newer MR products with different drug release mechanisms (such as pulsatile- or chrono-release), other measures in addition to the current pharmacokinetic parameters (i.e., AUC and Cmax) may be needed for assuring bioequivalence. The use of pharmacokinetic/Pharmacodynamic (PK/PD) modeling and simulations allows for linking drug concentrations to their effects (safety or efficacy) and thus can be used to assess the impact of a difference in input rate on therapeutic equivalence.

CONCLUSION

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. Modified drug delivery system helps in maintaince of constant plasma drug concentration and retards the release rate of drug thereby extending the duration of action. Geographically, the global modified -release drug delivery technology market is classified into regions viz. North America, Latin America, Western Europe, Eastern Europe, Asia-Pacific, Japan, Middle East and Africa. North America will continue to hold the largest share in the global controlled-release drug delivery technology market due to rising number of NDA and ANDA applications being filed by the key players. Europe is expected to hold second largest share in the global market for modified -release drug delivery technology market. As a result of this, the future of the modified release tablets seems to be very promising especially with the coming up of new molecules which will definitely be explored further for better therapeutic effect and most importantly for the patient compliance.

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