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MODIFIED RELEASE FORMULATIONS TO ACHIEVE THE QUALITY TARGET PRODUCT PROFILE (QTPP)

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ABSTRACT

Modified Release (MR) Formulations have a modification in the release mechanism. Modified release dosage forms are developed by altering drug absorption or the site of drug release in order to achieve predetermined clinical objectives. Modified drug release from dosage forms is complemented by the allied processes of drug design, of dosage administration, and of membrane transport and absorption of drug to the biological site of action. Modified-release drugs have complex formulations that can offer an advantage over standard medication for some patients. Modified-release preparations should only be used where there is a clear clinical advantage over conventional-release preparations. In general, Modified-release preparations should be reserved for specific patients where there is a problem with compliance, effectiveness or side-effects which these preparations could help overcome. Modified–release technologies have become indispensable to resolving critical technical, therapeutic, and marketing challenges, such as improving patience compliance, less dosage timings, better safety, better indications, delivering poorly soluble and poorly absorbable API's, product differentiation, patent protection, product life-cycle extension, and better margins. Modified-release formulation design can be conducted for oral and non-oral administration routes. Possible therapeutic benefits of an MR product include improved efficacy and reduced adverse events, increased convenience and patient compliance, optimized performance, a greater selectivity of activity, or new indications.

INTRODUCTION: The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration [1].

Advances in molecular biology, and of physiological and disease processes, often identify opportunities for improving the performance of a medication. Performance enhancement might concern providing more options for administration, less frequent administration or simply providing medication that is more acceptable to the user. Possibilities also exist, depending on the kinetics and dynamics of drug action, and its dose– response relationships for improving efficacy or reducing side effects.

Indeed the drug delivery system employed plays a vital role in controlling the pharmacological effect of the drug as it can influence the pharmacokinetic profile of the drug, the rate of drug release, the site and duration of drug action and subsequently the side-effect profile. An optimal drug delivery system ensures that the active drug is available at the site of action for the correct time and duration.

The drug concentration at the appropriate site should be above the minimal effective concentration (MEC) and below the minimal toxic concentration (MTC). This concentration interval is known as the therapeutic range and the concept is illustrated in **Figure 1**, showing the drug plasma levels after oral administration of a drug from an immediate release dosage form. Achieving the desired concentration of a drug is dependent on the frequency of dosing, the drug clearance rates, the route of administration and the drug delivery system employed [2, 3, 4, 5].

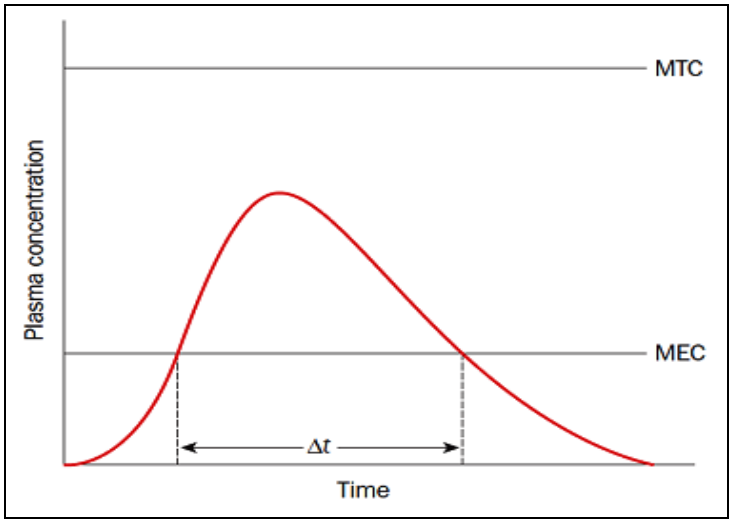

FIGURE 1: DRUG PLASMA LEVELS AFTER ORAL ADMINISTRATION OF A DRUG FROM AN IMMEDIATE-RELEASE DOSAGE FORM

The therapeutic range is the concentration interval between the minimal effective concentration (MEC) and the minimal toxic concentration (MTC). Dt is the time interval the drug is in the therapeutic range.

Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for year. Early modified-release products were often intramuscular injections of suspensions of insoluble drug complexes, e.g. procaine penicillin, protamine zinc suspensions, insulin zinc suspensions or injections of the drug in oil, e.g. fluphenazine decanoate.

The *United States Pharmacopoeia* definition of an MR (modified-release) system is that: *"the drug release characteristics of time, course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms..."* This includes technologies that modify the site of drug delivery. The successful formulation of an MR device requires a comprehensive understanding of the mechanisms of drug release from the macroscopic effects of size, shape and structure through to chemistry and molecular interactions. The benefits offered by MR systems include reduced dosing frequency with improved patient compliance, better and more uniform clinical effects with lower incidence of side effects and possible enhanced bioavailability.

'Modified release' means that the escape of the drug from the tablet has been modified in some way. Usually this is to slow the release of the drug so that the medicine doesn't have to be taken too often and therefore improves compliance. The other benefit from modifying release is that the drug release is controlled and there are smaller peaks and troughs in blood levels therefore reducing the chance of peak effects and increasing the likelihood of therapeutic effectiveness for longer periods of time.

The use of a modified-release preparation cannot be justified unless it offers clear clinical advantages over, often less expensive, conventional-release preparations.

Modified-Release preparations may be prescribed to:

- Reduce the dosing frequency and improve patient compliance;
- Reduce fluctuations (peaks and troughs) in drug plasma concentrations, in order to reduce concentration-related side-effects or improve effectiveness;
- Control the site of drug delivery in the gastrointestinal tract.
- There is little good quality evidence to suggest that once daily dosing has a clear clinical advantage over twice daily dosing. Missing a once daily dose can result in long periods of subtherapeutic plasma concentrations. Therefore, twice daily dosing may be preferred in patients known to miss doses.

Chronicle & Modern Development of Modified Release Dosage Forms: The modern era can be marked from WWI (1934-1944) approximately. Pharmaceutical firms developed with a primary mission of consistency in the preparation of dosage forms (drug delivery systems). The first sustained release dosage form was marketed in United Sates in 1952 by Smith Kline & French under the trade name 'Dexadrin Spansule'.

The spansule provided a novel form of drug delivery was a major therapeutic breakthrough. It quickly released the required the initial dose and then slowly and gradually released many extremely small doses to maintain a therapeutic level lasting from 10 to 12 hours, providing all-day or all-night therapy with one dose (GlaxoSmithKline 2002). The global behind the development of oral controlled-release formulations at that time was the achievement of a constant release of the entrapped drug. On the basis of that concept, the zero-order osmotic delivery used in Procardia XL became one of the top 10 best selling medicines in the past century [6].

In 1968, Alejandro Zaffaroni founded ALZA (ALZA Corporation, our Technologies, June 2004), now owned by Johnson and Johnson (Johnson and Johnson 2003), with the aim of creating controlled drug delivery systems whose release rate of drug could be controlled with precision, independent of the release environment. The formation of AlZA marked the beginning of the modern era of drug delivery technology (Robinson). And Elan Corporation was founded in 1969 "with a vision: to approach the challenge of drug delivery from an entirely new angle- that of controlled absorption of a drug to provide longer duration of drug effect".

Two major disease groups that have had an important bearing on the evolving nature of controlled drug delivery are

i) Diabetes – fluctuations in insulin/glucose minimized [sustained drug release] and;

ii) Cancer – target abnormal cells [localized/targeted drug release]

From an economic point of view, the development of novel delivery systems can potentially prove profitable for a modest investment (in terms of acquiring market share). Recently Controlled drug delivery industries have made certain gold standard innovation in drug delivery technology. Ms. Callanan commented, "Definitely a key for large pharma companies is to use novel approaches to extend the patent life of their products or, even if they don't extended the patent life, to add something new to the compound to get marketing advantage. Things like fast-melt technology, extended release compounds, all those areas, those types of technologies; in the next few years they will be exploited to their fullest extent by large Pharma companies".

The popularity and importance of these dosage forms can be appreciated from the fact that for the first time in 1985 the official compendia adopted the use of the term "Modified Release" to identify these dosage forms as being different from the conventional dosage forms (USP XXI). The USP defines modified release dosage forms as "One for which the drug-release characteristics of time-course and/or location are chosen to accomplish therapeutic convenience not offered by conventional dosage forms".

At the present time USP/NF recognizes several types of modified release dosage form – 'Extended-release', 'Delayed-release' and 'Targeted-release'. According to Ballard (1978), Sustained release, sustained action, prolonged action, controlled release, extended action, time release, depot and respiratory dosage forms are terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. In the case of injectable dosage forms, this period may vary from days to months. In the case of orally administered forms, however, this period is assured in hours and critically depends on the residence time of the dosage from in the gastrointestinal tract.

The majority of oral drug delivery systems are matrix-based. In such systems, the tablet is in the form of a compressed compact that contains an active ingredient, a lubricant, an excipient and a filler or binder. Erosion, diffusion and swelling of the matrix are the various methods through which the systems control drug delivery. The polymer properties invariably play an important role in the release pattern of the drug. If the polymer is predominantly hydrophilic, the swelling process chiefly controls the drug release. The swellable- matrices are monolithic systems prepared by compressing a powdered mixture of a hydrophilic polymer and a drug. The success of these drug delivery systems is attributed to the established table manufacturing technology (J.E. Hogan, 1989).

Thus hydrophilic matrices are an interesting option when developing an oral sustained-release formulation. They can be used for controlled release of both water-soluble and water-insoluble drugs. Release of drugs from such matrices can be controlled through their physical properties, the correct choice of gelling agent and setting up the conditions for fabrication [7].

The development of controlled release formulation continues to be a big success for the pharmaceutical industry. The success of any technology relies on the ease of its manufacturing process and its reproducibility of desirable biopharmaceutical properties. The market for oral controlled drug delivery alone is expected to grow at 9% or more every year through 2007 [6]. The future of controlled-release products is promising especially in the areas of Chromopharmacokinetic systems and Mucoadhesive delivery [8].

Terminology used to describe Modified Release Dosage Form: The term modified release [9] drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. The term modified-release defines preparations that have been designed in such a way that the rate or place at which the active ingredients are released has been modified [10].

This is an all encompassing term that the BNF now uses to cover preparations such as sustained-release, controlled-release and delayed release.

The sole use of the term modified-release is helpful to simplify the confusing terminology. However, its use conceals the differences between the drug delivery systems, which may be defined as:

- **Sustained-release** - the drug is released slowly at a rate governed by the delivery system [11].
- **Controlled-release** - the drug is released at a constant rate and plasma concentrations after administration do not vary with time.
- **Delayed-release** - the drug is released at a time other than immediately after administration3 i.e. the site of release is controlled.

The terminology used to describe modified release dosage form has not been harmonized. The following terminology equivalency table makes them easy to understand (copied from the Pharmacopoeial Discussion Group Sign-Off Document dated June 10, 2010).

USP	EP	JP
Immediate-Release DF	Immediate-Release DF	Not Described
Modified-Release DF	Modified-Release DF	Not Described
-Extended-Release DF	Prolonged-Release DF	Not Described
-Delayed-Release DF	Gastro-Resistant DF	Enteric-Coated Preparations

One of the problems that have occurred during this technology explosion is the tremendous variation in terminologies that has been used to describe these complex product formulations. Examples of terms that have been applied include:

Types of Modified Release Drug System

1. Extended release dosage forms
2. Sustained release
3. Controlled release
4. Delayed release dosage forms
5. Targeted release dosage forms
6. Repeat action dosage forms
7. Prolonged action dosage forms

In more elaborated form the Modified Release Dosage Forms can be classified as

- Dissolution Granules
- Diffusion Granules
- Enteric Coated Granules
- Reservoir

- Matrix
    a. Inert
    b. Erodible
    c. Swellable
    d. Hydrophilic
- Osmotic Pump
- Repeat Action
- Altered Density
- Hydrodynamically Balanced
- SODAS
- Microparticles
- Meter Release
- Ion Exchange Resins

Extended Release Dosage Forms: Extended release products are formulated to make the drug available over an extended period after administration. This allows a reduction in dosing frequency compared to a drug presented as a conventional dosage form (e.g. as a solution or an immediate-release dosage form). No definition for controlled release or targeted release is provided by the FDA or pharmacopoeias. Extended-release products offer 3 potential benefits: sustained blood levels, attenuation of adverse effects, improved patient compliance. Extended-release products contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form has potential problems. Extended release can be achieved using sustained- or controlled-release dosage forms.

Sustained release: Sustained release dosage forms are those dosage forms which are designed to release drug continuously at sufficiently slow / controlled rate over an extended period of time, thus maintaining a minimum effective concentration (MEC) of the drug in the blood at a constant level throughout the treatment period and provide prolonged therapeutic effect after administration of a single dose.

Difference between Sustained Release and Extended Release Medications: There is no major difference between sustained release and extended release medications; they both refer to a group of medicines that have been designed to be absorbed in the body and take effect within a specific frame of time, such as 12 or 24 hours. They both make use of time-release technology, as compared to the instant-release technology employed in the manufacture of other drugs.

There are some advantages of using sustained release drugs, and its most popular benefit is the ability to keep stable amounts of the medication in the bloodstream. They also don't have to be taken as frequent as instant-release drugs. However, the rate that at which the drug is released depends on a number of important factors. In most cases, the release is quite slow that it applies for several hours until effect is felt, but it is also possible to modify the drug's coating in order to control the time and location of release.

When it comes to formulating these types of medications, there are certain things to consider. One is that if the active compound has a half-life of over 6 hours, the release can be sustained on its own. On the other hand, if it has a short half-life, a larger amount of the active compound is required in order to produce a sustainable and effective dosage. Care will also have to be taken to ensure that toxicity does not occur. Another thing is that if the active compound has no pharmacological relation to the blood levels, there is no use for time-release. Also, if the active compound requires transport for absorption to occur, there may be significant problems in the time-release process. Not all drugs created through time release technology can be treated the same, especially in dosage as some capsule forms will work when swallowed whole while others do not work when cut up or split.

Controlled release: It is a system that delivers an agent (active pharmaceutical ingredient) at a controlled rate for an extended time that might localize drug action by spatial placement near where it is needed and target drug action by using techniques to deliver drug to a particular cell type. It is the medication, which due to its special technological construction provides for drug release having predefined kinetics (zero order, *t*1/2,

1st order, etc.) at a sufficient rate to maintain the desired therapeutic level over an extended period of time. It is also the term used to denote *sustained-release* products with zero-order release kinetics. Controlled release pharmaceuticals are designed to release drugs *in vivo* according to a predictable, therapeutically rational programmed rate to achieve the optimal serum-drug concentration in the minimal time.

Controlled release dosage forms enhance the safety, efficacy, reliability, and convenience of drug therapy by controlling the rate and duration of drug release to control drug actions and to reduce the frequency of drug administration, thus encouraging patient compliance. Increasingly important applications of controlled release technology include patterned, targeted, triggered, and closed-loop delivery [12].

Advantages of Controlled Release:

- Reproducible rate, prolonged delivery
- Less frequent administration
- Better patient compliance
- Increased convenience
- Reduced side effects because effective C is maintained
- Targeting can eliminate damage to non-target organs
- Less drug used
- n Re-patenting without new drug development

Challenges to Controlled Release:

- Cost of formulation – preparation and processing
- Fate of controlled release system if not biodegradable
- Biocompatibility
- Fate of polymer additives, e.g., plasticizers, stabilizers, antioxidants, fillers

Difference between Sustained Release and Controlled-release Medications: Controlled-release systems also offer a sustained-release profile but, in contrast to sustained-release forms, controlled-release systems are designed to lead to predictably constant plasma concentrations, independently of the biological environment of the application site. This means that they are actually controlling the drug concentration in the body, not just the release of the drug from the dosage form, as is the case in a sustained-release system. Another difference between sustained- and controlled-release dosage forms is that the former are basically restricted to oral dosage forms whilst controlled-release systems are used in a variety of administration routes, including transdermal, oral and vaginal administration.

Controlled release of drugs from a dosage form may be achieved by the use of so-called therapeutic systems. These are drug delivery systems in which the drug is released in a predetermined pattern over a fixed period of time. The release kinetics is usually zero-order. In contrast to sustained-release systems, the dose in the therapeutic systems is of less importance than the release rate from the therapeutic system. Ideally the release rate from the dosage form should be the rate-determining step for the absorption of the drug and in fact for the drug concentration in the plasma and target site. However, controlled-release systems are not necessarily target-specific, which means that they do not 'exclusively' deliver the drug to the target organ. This may be achieved by so-called targeted delivery systems which aim to exploit the characteristics of the drug carrier and the drug target to control the biodistribution of the drug [2-5].

Delayed Release Dosage Forms: Pharmaceutical preparation that releases the drug(s) at a time other than promptly after administration [13]. Typically, this is related to enteric coated tablets. Enteric coating is used on tablets, granules, pellets, and capsules to make them resistant to gastric fluids but designed to disintegrate, disrupt, or dissolve when the preparation enters the duodenum. Enteric coating is used for one of the following reasons: to protect the drug from degradation by the acid in the stomach (e.g., erythromycin), to protect the stomach from the irritant effect of the drug (e.g., aspirin), to facilitate absorption of a drug distally to the stomach.

Targeted Release Dosage Forms: Targeted drug delivery, sometimes called smart drug delivery [14] is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others. The goal of a targeted drug delivery system is to prolong, localize, target and have a protected drug interaction with the diseased tissue. It is the dosage form that releases drug at /near the intended physiological site of action. Targeted release dosage forms may have extended release characteristics. By doing so, it is possible to enhance the activity and specificity of the drug and to reduce its toxicity and side-effects.

Drug targeting can be achieved by designing systems that passively target sites by exploiting the natural conditions of the target organ or tissue to direct the drug to the target site. Alternatively drugs and certain delivery systems can be actively targeted using targeting groups such as antibodies to bind to specific receptors on cells.

Repeat Action Dosage Forms: It is a dosage form distinguished from a sustained-release dosage form, by the fact that it releases the medicinal agent, or part of it, at any time other than promptly after administration as opposed to a slow, controlled manner. A repeat action tablet contains usually two doses of the drug, the first being released immediately following per-oral administration. The second dose is released later, when the layer of enteric coating is dissolved.

Prolonged Action Dosage Forms: A product in which the rate of release of active substance from the formulation after administration has been reduced, in order to maintain therapeutic activity, to reduce toxic effects, or for some other therapeutic purpose.

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.
- 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 and Drug layer. As water penetrates the membrane, drug is force out

SODAS: SODAS (Spheroidal Oral Drug Absorption System) is Elan Drug Technologies' multiparticulate drug delivery system. Based on the production of controlled release beads, the SODAS technology is characterised by its inherent flexibility, enabling the production of customised dosage forms that respond directly to individual drug candidate needs. Benefits offered by the SODAS technology include:

1. controlled absorption with resultant reduction in peak to trough ratios
2. targeted release of the drug to specific areas within the gastrointestinal tract
3. absorption independent of the feeding state
4. suitability for use with one or more active drug candidate
5. facility to produce combination dosage forms
6. sprinkle dosing by administrating the capsule contents with soft food
7. once or twice daily dose resembling multiple daily dose profiles

Matrix System: The matrix system is defined as uniform dispersion of drug in a solid which is less soluble than the drug in the depot fluid and which as the continuous external phase of dispersion, effectively inhibits the passage of drug from the matrix to the depot fluid. Release is controlled by a combination of several physical factors which include permeation of the matrix by water, leaching and erosion of matrix materials.

Repeat Action Tablet: Repeat action tablets contain fractions of drug that dissolve or release at different times. Such tablets represent an older class of products. They usually contain an immediate-release fraction & other fractions that periodically release the drug.

Mixed-Release Granules: This method uses granules as used in the preparation of compressed tablets. Two sets of granules are used. One set, which carries the immediate-release component of the drug, is prepared in the usual manner. The second set contains drug that is either coated with slowly digestible or poorly soluble materials or mixed with dissolution retarding additives. Hydrogenated vegetable oils, a number of waxes, fatty acids, glyceryl monostearate, glyceryl distearate, glyceryl monopalmitate, mixtures of some of these glyceryl esters and bees wax or higher fatty alcohol & higher fatty acids used either singly or as mixtures, have all been used in the preparation of such granules.

The Osmotic Tablet: The oral osmotic tablet is also a relatively recent addition to sustained-release tablet technology. This device consists of a core tablet & a semi permeable coating with a hole, produced by a laser beam, through which the drug exists. The product operates on the principle of osmotic pressure, which develops as gastrointestinal fluids permeate the semi permeable membrane & reach the core. These fluids dissolve the drug contained in the core & the osmotic pressure forces (or pumps) the drug solution out of the delivery orifice.

Ion-Exchange Resin: The phenomenon of ion exchange presents a useful method of sustaining action control. Ion-exchange resins are water-insoluble crosslinked polymers containing salt forming groups in repeating positions on the polymer chain. Drug molecules are attached to the anionic or cationic group of ion-exchange resin and due to attachment drugs release is retarded. The ion-exchange method involves the administration of a dosage form containing salts of drugs complexes with an ion-exchange resin that exchanges the drug for ions as it passes through the gastrointestinal tract. Examples of this type of product are Duromine containing the basic drug Phentermine complexed onto an anionic resin, and MS Containing suspension which uses a polystyrene sulphonate resin.

Drugs Unsuitable For Modified Release Dosage Forms:

- Drugs whose precision of dosage is important; e.g. anticoagulant and cardiac glycosides.
- Drugs that are not effectively absorbed from GIT. e.g. Riboflavin
- Drugs that are absorbed and excreted rapidly (having biological half life < 1hr.) e.g. PenicillinG.
- Drugs having long biological half life (>12 hrs.) e.g. Diazepam, Phenytoin.
- Drugs having low therapeutic indices e.g. Phenobarbital, Digitoxin.
- Drugs having no clear advantage for sustained release formulation e.g.Griseofulvin
- Drugs whose large dose is required e.g. sulfonamides.

Potential advantages of Modified Drug Therapy: Potential advantages of modified drug therapy include avoidance of patient compliance problems include minimization of local and systemic side effects and drug accumulation, improved efficiency in treatment by curing the condition more promptly, reduction of fluctuations in drug levels, improved bioavailability of certain drugs [15].

The major benefits of modified drug delivery system can be enlisted as [16]:

Decreased in Dosing Frequency:

- Reduced peak to trough ratio of drug in systemic circulation
- Reduced rate of rise of drug concentration in blood
- Sustained & Consistent blood level with in the therapeutic window
- Enhanced bioavailability
- Customized delivery profiles
- Reduced side effects
- Improved patient compliance

There are also some patented technologies of modified release drug delivery system [16]:

- Port technology
- Flamel technology
- Elan drug technology
- Microchip technology for delivery of insulin
- OROS Push pull technology
- L – Oros technology
- En Sotrol technology
- DUROS Technology

Comparing Modified Release Dosage Forms with other Dosage Forms: Modified release dosage forms are formulations where the rate and/or site of release of the active ingredient(s) is different from that of the conventional (immediate release) dosage form administered by the same route. This deliberate modification is achieved by special formulation design and/or manufacturing method.

Prolonged Release Dosage Forms:

Advantages over immediate release formulations:

- Reduced fluctuations in drug plasma concentrations which possibly may result in a more continuous effect and by avoiding high peak concentrations, a reduction of the incidence and/or intensity of adverse drug reactions
- A dosage regimen with lower frequency of administration and thereby potentially improvement of patient compliance

Delayed release dosage form: Advantages over immediate release formulations:

- To protect the active substance from the acid environment of the stomach,
- Or to protect the stomach from the active substance.
- To enable an active substance to be released in a defined segment of the intestine in order to decrease drug absorption and/or yield local action.

Variables to consider for MRDF formulations:

- Low Dose
- Short half life
    - Long half life drugs already have the desired kinetics
- Wide Therapeutic Window
- Absorbed through the entire GI
- Modest to rapid absorption
- Highly stable in the GI
- Chronic treatment
    - Hormone Replacement
    - Hypertension
    - Chronic Pain
    - Allergies

Disadvantages of MRDF:

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

From a technological viewpoint, the dosage forms featuring a modified release of the active ingredient can be distinguished between:

1. Monolithic systems
2. Multiparticulate systems

Monolithic systems: This is essentially a tablet formulation, but with differences from conventional dosage forms in that modified-release tablet cores should not disintegrate but dissolve/swell or erode so that diffusion can occur. They either pass the gastrointestinal tract as a whole or gradually become smaller due to degradation or only release the active ingredient in the intestines.

Matrix tablets are only example of a monolithic system with modified release of the active ingredient. Initially, the gastrointestinal fluid is permeating into the structural matrix thereby gradually dissolving the active ingredient. Subsequently the active ingredient diffuses following the concentration gradient into the surrounding medium from where it can be absorbed by the organism. During the entire process the matrix essentially retains its geometrical shape. In this technological principle, the duration and the rate of release of the active ingredient are determined by the formulation components.

Water-insoluble materials that compact by brittle fracture are not suitable if used alone. The following fillers are employed: lactose, microcrystalline cellulose, dextrose, sucrose and polyols. If these are to be suitable for use as fillers they should not have osmotic effects. The choice of solubiliser will be governed by the solubility characteristics of the drug. The other materials to be used Monolithic systems include buffers, surfactants, polyols and polyethylene glycol. The fact that single-unit cores are compressed into tablets, lubricant system will have to be included [17].

The swelling matrix follows another principle. In this system, a polymer matrix swells slowly due to the presence of gastrointestinal fluid and significantly increases in volume. The result is a highly viscous polymer structure which continuously releases the embedded active ingredient by diffusion. Duration and release rate of the active ingredient can be controlled via the type of polymer matrix used. The controlled erosion is another principle using a different type of matrix. The gastrointestinal fluid continuously erodes the surface of the system and thereby releases the active ingredient. In contrast to the other previously discussed types, this system uses partially or completely soluble polymers.

Multiparticulate systems: These are comprised of more than one discrete unit within one dosage unit. Ingredients include coated spheroids filled into hard gelatine capsule shell or, less commonly, compressed into a tablet. Monolithic systems form a single discrete functional unit. In contrast, the functional principle of Multiparticulate systems is divided into numerous functional units. Pellets are typically belonging to the Multiparticulate drug delivery forms.

As per definition, pellets are small, free flowing, spherical particles which can be obtained through aggregation of fine powders or granulates of active ingredients and excipients using the appropriate technical equipment.

A distinction is drawn between coated pellets and matrix pellets. Coated pellets are manufactured by coating a starter particle by means of suspension/ solution layering in a fluidized bed. Matrix pellets are produced by extrusion/spheronisation, direct pelleting or melt extrusion. The drug release from this dosage form can be defined by the formulation of the tablet and the pellets. Approaches in manufacturing of drug containing multiple units systems include: The use of inert sugar spheres (nonpereils) coated first with drug and then with the release-controlling membrane and the formulation of small spheroids containing the drug using an extrusion/spheronisation process.

A typical formulation for a wet mass for extrusion/ spheronisation might comprise the following ingredients with their individual parts by weight in the brackets next to each: Active drug (1-20), lactose (60), microcrystalline cellulose (40), binder (2-4) and water (40). After spheronisation the material is dried prior to coating. Multiparticulate systems possess some advantages. With multiple-unit systems the gastro-intestinal transit is more consistent and allows the release mechanism to be optimised for individual drugs in a system delivering two or more active components [17].

CONCLUSION: 'Modified release' formulations are with the modification to have advantageous influence on the escape/release of the drug from the dosage form in some way. Modified release drug products have been successfully marketed for many years. The concept of Modified Release Formulations emerged

with an objective to improve patient's compliance. Usually this is to slow the release of the drug and keep steadier levels of the drug in the bloodstream so that the medicine doesn't have to be taken too often and therefore improves compliance. Technologies are available for the formulation, development and production of MR tablets and multiparticulates such as drug-loaded pellets and granules, mini-tablets and drug crystals.

Over the last decade, the approach to Modified release drug delivery systems has changed from a line extension strategy to a clinically superior approach for marketed drugs as well as for new chemical entities. The benefits offered by MR systems include reduced dosing frequency with improved patient compliance, better and more uniform clinical effects with lower incidence of side effects and possible enhanced bioavailability. The rational design of MR systems, where biological, physicochemical and physico-mechanical considerations have been taken into account during formulation of MR dosage form has alleviated the risk of 'dose dumping' *in vivo*.

Modified release dosage forms are often designed to maximize a therapeutic effect or minimize side effects to achieve the Quality Target Product Profile (QTPP). Design and development of these dosage forms is focused on meeting the target product performance in the patient, and therefore they are well-suited to the science and risk-based approaches under Quality by Design paradigm.

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