



## Review Article

**TAILORED RELEASE DRUG DELIVERY SYSTEM (TRDDS)**

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**Abstract:** Tailored release dosage forms are developed by changing drug absorption or the site of drug release in order to achieve predetermined clinical objectives. Release of drugs from dosage forms is complemented by the related processes of drug design, of dosage administration, of membrane transport and absorption of drug to the biological site of action. Tailored release formulations have an alteration in the release mechanism. This release drugs have complex formulations that can offer an advantage over standard medication for some patients. The release preparations should only be used where there is a clear clinical advantage over conventional-release preparations. Release technologies have become essential to resolving significant technological, therapeutic, and marketing challenges, such as improving patient compliance, less dosage timings, better safety, better indications, delivering poorly soluble and poorly absorbable drugs, product separation, patent defense, product life-cycle conservatory, and better boundaries. Tailored release formulations design accomplished for oral and non-oral administration routes. This release is also providing hopeful way to decrease the side effect of drug by preventing the variation of the therapeutic concentration of the drug in the body. This article contains the basic information concerning tailored release formulation and also the different types of the same.

**Key words:** Tailored -release, conventional tablet, controlled release systems, matrix systems.

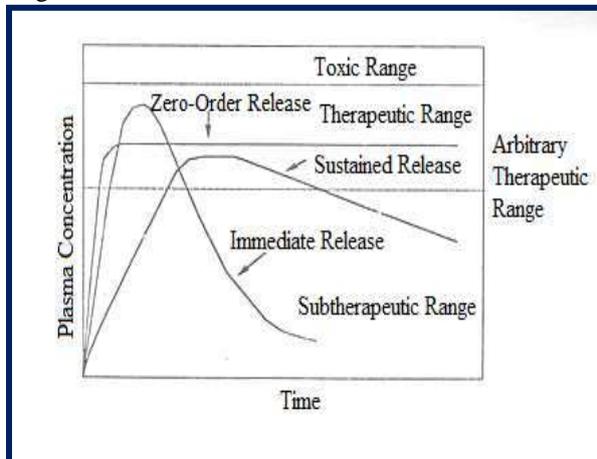
**INTRODUCTION**

The aspiration of any drug delivery system is to offer a therapeutic amount of drug to the proper site in the body to achieve punctually and then maintain the desired drug concentration<sup>1</sup>. 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. In fact the drug delivery system employed plays a fundamental 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 consequently the side-effect profile. Most favorable 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). Figure-1 indicates Plasma Drug Concentration Profiles for Conventional Tablet, a Sustained Release/Tailored Release and a Zero Order

Controlled Release Formulation. 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<sup>2,3</sup>.

Introduction of surrounding substance (matrix) tablet as Tailored release (TR) has given a new advance for novel drug delivery system (NDDS) in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an TR dosage form<sup>4,5</sup>. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems<sup>6</sup>. Matrix system is widely used for the purpose of tailored release. It is the release system which prolongs and controls the release of the drug, that is dissolved or dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers<sup>7</sup>. By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better

compliance of patients. Numerous TR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed; intense research has recently focused on the designation of TR systems for poorly water soluble drugs<sup>8</sup>.



**Figure-1:** Plasma Drug Concentration Profiles for Conventional Tablet, a Sustained Release/Tailored Release and a Zero Order Controlled Release Formulation

#### NEGATIVE ASPECTS OF CONVENTIONAL DOSAGE FORMS:

- Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is obligatory.
- The inescapable fluctuations of drug concentration may lead to under medication or over medication.
- A typical peak-valley plasma concentration time profile is obtained which makes achievement of steady-state condition complicated.
- The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur<sup>9</sup>.

#### TERMINOLOGY:

Controlled and Sustained/Tailored Release, both have been used in incoherent and puzzling manner. Both represent separate delivery process. TR constitutes any dosage form that provides medication over an extended time or denotes that the system is able to provide some actual therapeutic control whether this is of a temporal nature, spatial nature or both. Generally don't attain zero order type release and usually try to mimic zero order release by providing drug in a slow first order. Repeat action tablet are an substitute method of sustained release in which

multiple doses of drug are an alternative method of sustained release, in which, multiple doses are contained within a dosage form and each dose is released at a periodic interval. Delayed release system, in contrast, may not be sustaining, since often the function of these dosage forms is to maintain the drug in the dosage for some time before release, for example. Enteric coated tablet. The ideal way of providing an exact amount of drug at the site of action for a precise time period is usually approximated by most systems. This approximation is achieved by creating a constant concentration in the body or an organ over an extended time; in other words, the amount of drug entering the system is equivalent to the amount of drug removed from the system. All forms of metabolism and excretion are included in the removal process: urinary excretion, enterohepatic recycling, sweat, fecal and so on. Since, for most of the drugs these elimination processes are first order, it can be said that a certain blood level, the drug will have a specific rate of elimination. The idea is to deliver drug at this exact rate for an extended period<sup>10</sup>.

#### BENEFITS OF TAILORED DRUG THERAPY: 11

- Patient compliance due to reduction in the frequency of dosing.
- Employ minimum drug.
- Minimize or eliminates local and systemic side effects.
- Obtain less potentiation or deduction in drug activity with chronic use.
- Minimize drug accumulation with chronic dosing.
- Improves efficacy in treatment.
- Cure or control confirm more promptly.
- Improve control of condition i.e. reduce fluctuation in drug level.
- Improve bioavailability of same drugs.
- Make use of special effects, e.g. sustained release aspect for morning relief of arthritis by dosing before bedtime.

#### DRAWBACKS OF TAILORED RELEASE DOSAGE FORMS: 11

- They are costly.
- Unpredictable and often poor in-vitro in-vivo correlations, dose dumping, reduced potential for dosage adjustment and increased potential first pass clearance.
- Poor systemic availability in general.
- Effective drug release period is influenced and limited by GI residence time.

**DRUGS UNSUITABLE FOR TAILORED 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. Penicillin G.
- 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.

**POLYMERS:**

Various types of polymers are used for tailored release drug delivery system. They may be categorized as-

- Water soluble polymers.
- pH-sensitive enteric polymers.
- Water-insoluble polymers.

**Water soluble polymers:**

These polymers include methyl cellulose, hydroxy propyl methyl cellulose (HPMC), hydroxy ethyl cellulose, methyl hydroxy cellulose, carboxy methyl cellulose sodium, providone, aminoalkyl methacrylate copolymer etc. These are also soluble or sparingly soluble in organic solvent.

**pH-sensitive enteric polymers:**

Some drugs, when administered orally, are decomposed by gastric juice and consequently lead to poor bioavailability for gastrointestinal side effects by direct contact with gastric mucous membrane. Pharmaceuticals (polymers) with an enteric property  $p^H$  sensitivity are beneficial for use with these drugs. They remain in an intact form during passage through the stomach and do not release the drug until they transit to the duodenum, Takahata *et al.*, 1990. pH sensitive polymers dissolve at a certain pH and remain intact at other pH. pH sensitive polymers used in enteric coated preparation dissolve in intestinal fluid and not in gastric fluid i.e., they require alkaline pH for dissolution. These polymers include shellac, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methyl cellulose phthalate, methacrylic acid copolymers etc.

**Water-insoluble polymers:**

These polymers are insoluble in water and gastric juice, but soluble in organic solvents.

These are used in film coating to retard drug release from dosage forms. These may be used in combination with other cellulose polymers as film former. These polymers include ethyl cellulose, methacrylic ester copolymers polyethylene etc.

**DRUGS USED IN TAILORED RELEASE DOSAGE FORMS:**<sup>14</sup>

There are various forms of tailored release dosage forms and various types of drugs are used in each form (Table -1).

**TAILORED RELEASE SYSTEMS:**<sup>11</sup>**Diffusion controlled**

- Reservoir
- Matrix
- Reservoir and monolithic

**Dissolution controlled**

- Encapsulation
- Matrix
- Water penetration controlled
- Osmotically controlled
- Swelling controlled

**Chemically controlled**

- Erodible systems
- Drug covalently linked with polymer

**Hydrogels**

- Chemically controlled
- Swelling controlled
- Diffusion controlled
- Environment responsive

**Ion-exchange resins**

- Cationic exchange
- Anionic exchange

**DISSOLUTION CONTROLLED RELEASE SYSTEMS:**<sup>10</sup>

These types of systems are easiest to design. The drug present in such system may be the one:

- ❖ With inherently slow dissolution rate e.g. Griseofulvin and Digoxin.
- ❖ That produces slow dissolving forms, when it comes in contact with GI fluids.
- ❖ Having high aqueous solubility and dissolution rate.

Drugs having high aqueous solubility and dissolution rate, shows challenge in controlling

their dissolution rate. Dissolution-controlled release can be obtained by slowing the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer and coating drug particles or granules with polymeric materials of varying thickness. The rate limiting step for dissolution of a drug is the diffusion across the aqueous boundary layer. The solubility of the drug provides the source of energy for drug release, which is countered by the stagnant-fluid diffusional boundary layer. The rate of dissolution ( $dm/dt$ ) can be approximated by Equation 1.

$$\frac{dm}{dt} = \frac{ADS}{h} \dots\dots 1$$

Where,

S = Aqueous solubility of the drug.

A = Surface area of the dissolving particle or tablet.

D = Diffusivity of the drug and

h = Thickness of the boundary layer.

#### **DIFFUSION-CONTROLLED SYSTEMS:**

The basic mechanism of drug release from these two systems is fundamentally different besides these simple systems, combination of reservoir and monolithic systems also exist in practice. Diffusion systems are characterized by release rate of drug is reliant on its diffusion through inert water insoluble membrane barrier.

There are basically two types of diffusion devices.

1. Reservoir devices
2. Matrix devices

#### **RESERVOIR DEVICES:**

Reservoir devices are characterized by a core of drug, the reservoir, encircled by a polymeric membrane. The nature of the membrane determines the rate of release of drug from the system. The process of diffusion is generally described by a series of equations that were first detailed by Fick (Fick, 1885). The first of these states that the amount of drug passing across a unit area is proportional to the concentration difference across that plane. The equation is given as-

$$J = \frac{-D \cdot dC}{dX} \dots (2)$$

Where, the flux J, given in units of amount/area—time; D, is the diffusion coefficient of the drug in the membrane in units of area/time. This is a reflection of the drug molecule's ability to

diffuse through the solvent and is dependent on such factors as molecular size and charge. This coefficient may be dependent on concentration (Barrier, 1956); hence, its designation as a coefficient and not a constant, although for the purpose of designing a pharmaceutical system it is usually considered a constant  $dC/dX$  represents the rate of change in concentration C relative to a distance X in the membrane. It is useful to make the supposition that a drug on either side of the membrane is in equilibrium with its particular membrane surface. There is, then, equilibrium between the membrane surfaces and their bathing solutions. Another vital point to consider is that, in general, the amount of drug contained in the reservoir is far greater than the usual dose required, since the dosage form is designed to sustain delivery over many dosing intervals. Any error in production or any accidental damage to the dosage form that would directly depict the reservoir core could depict the patient to a potentially toxic dose of drug. This becomes significant when designing these dosage forms for drugs with narrow therapeutic ranges or high toxicity.

#### **MONOLITHIC DEVICES (MATRIX DEVICES) :**

The term matrix tablet describes a tablet in which the drug is applied in a skeleton of nondissolving material. In this case, the drug is dispersed or embedded in a matrix of retardant material, which may be encapsulated in particulate form or compressed into tablets. The drug may be insoluble (network model) or soluble (Dispersion model) in the retardant material. It needs simply direct compression of blended drugs and retarding additives to form tablets. It is one of the least complicated approaches to the manufacture of sustained/tailored release dosage forms, which consists of a drug dispersed in a polymer, the polymer playing the role of a matrix<sup>15, 16, 17, 18</sup>. On the other hand, retardant-drug blends may be granulated prior to compression. It was found that the choice of matrix material, amount of drug incorporated in the matrix additives, the hardness of the tablet, density variation and tablet shape could markedly affect the release rate of drug<sup>19</sup>.

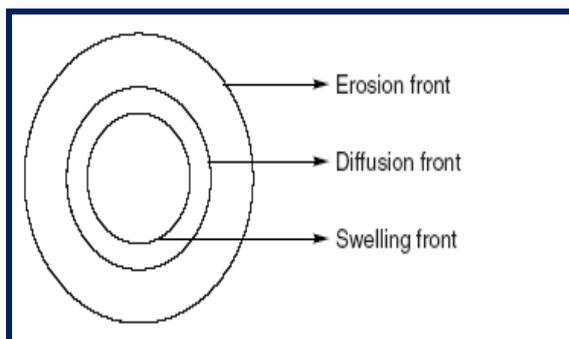
Monolithic (matrix) devices are possibly the most common of the devices for controlling the release of drugs. This is possibly because they are relatively easy to fabricate, compared to reservoir devices, and there is not the danger of an accidental high dosage that could result from the rupture of the membrane of a reservoir device. In such a device the active agent is present as dispersion within the polymer matrix, and they are typically formed by the compression of a polymer/drug mixture or by dissolution or melting. The dosage release properties of monolithic devices may be dependent upon the solubility of the drug in the

polymer matrix or, in the case of porous matrices, the solubility in the sink solution within the particle's pore network, and also the tortuosity of the network (to a greater extent than the permeability of the film), dependent on whether the drug is dispersed in the polymer or dissolved in the polymer. For low loadings of drug, (0 to 5% W/V) the drug will be released by a solution-diffusion mechanism (in the absence of pores). At higher loadings (5 to 10% W/V), the release mechanism will be complicated by the presence of cavities formed near the surface of the device, as the drug is lost. Matrix type drug delivery systems are an interesting and promising option when developing

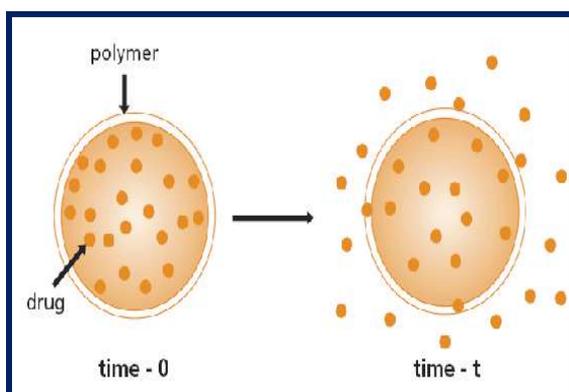
an oral controlled release system. Matrix tablets are easy to manufacture by direct compression. The kinetics often follows the laws described by Higuchi. Diffusion is the dominant mechanism controlling the dissolution of water-soluble drugs and erosion of the matrix is the dominant mechanism controlling the release of water insoluble drugs. However, generally the release of drugs will occur by a mixture of these two mechanisms. The swelling behavior of swellable matrices is mechanistically described by front positions. Front indicates the position in the matrix where the physical conditions sharply change<sup>20</sup>.

**Table -1: Drugs used in tailored release dosage form**

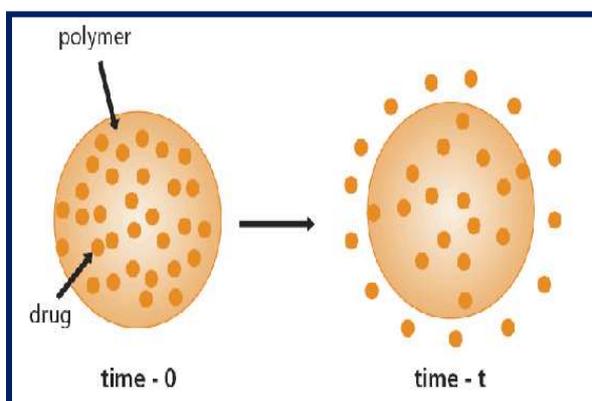
Types	Examples
Reservoir Diffusion Products	Nicotinic acid, nitroglycerine, papaverine hydrochloride, chlorpheniramine maleate, acetyl salicylic acid, theophylline etc.
Matrix Diffusion Products	Methamphetamine hydrochloride, ferrous sulfate, triplennamine hydrochloride, procainamide hydrochloride, oxytriphyline etc.
Encapsulated Diffusion Products	Dextroamphetamine hydrochloride, acetazolamide, trihexyphenidyl hydrochloride, chlorpromazine hydrochloride, diphenyl pyraline hydrochloride etc.
Matrix Dissolution Products	Bromopheniramine maleate, quinidine sulfate, diethyl propion hydrochloride, chlorpheniramine maleate, nicotinic acid etc.
Ion-exchange Resin Long Acting Products	D-and dl-amphetamine on cation exchange resin, phenyl-tert-butyl amine on cation exchange resin, p-amino salicylic acid on anion exchange resin, phenyl toloxamine and hydrocodone on cation exchange resin etc.
Aqueous Suspensions	Penicillin G procaine, penicillin G benzathine, medroxy progesterone acetate, methyl prednisolone acetate etc.
Oil Solution Products	Fluphenazine enanthate in sesame oil, testosterone cypionate in cotton-seed oil etc.
Oil Suspension Products	Methamphetamine hydrochloride, ferrous sulfate, procainamide hydrochloride, oxytriphyline HCl etc.



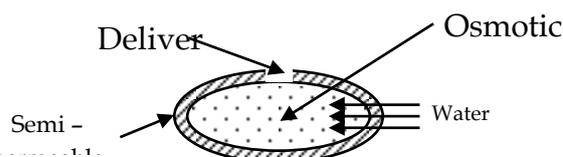
**Figure-2:** Different front positions in a swellable matrix



**Figure-3:** Reservoir diffusion controlled drug delivery device



**Figure-4:** Monolithic (matrix) diffusion controlled drug delivery device.



**Figure-5:** OROS Osmotic System

Drug bioavailability, which is initially depending on the drug – polymer ratio, may be modified by inclusion of diluents such as lactose in place of polymer in the formulations. High drug polymer ratios result in formulation from which drug release is controlled by attrition HPMC is a dominant vehicle used for the preparation of oral controlled drug delivery systems. The adjustment of the polymer concentration, the viscosity grade and the addition of different types and levels of excipients to the HPMC matrix can modify the drug release rate.

#### Plastic Matrix:

Insoluble, inert polymers are used to appropriate tablets that are designed to be egested intact and do not rupture separately in the GI tract. Tablets may be directly compressed from mixtures of drug and matrix former, if ethyl cellulose is used as the matrix former, a wet granulation procedure using ethanol can be carried out. Capsules/tablets are so designed that the inner core contains the tailored release portion of the drug and the outer shell/coat enclosing the core contains drug for immediate release (loading dose).

#### Release mechanism:

The release of drugs from insoluble matrices has been investigated and the possible following four mechanisms may consider.

- Drug molecularly dissolved in the matrix and drug diffusion occurs by a solution – diffusion mechanism.
- Drug dispersed in the matrix and then after dissolution of the drug, diffusion occurs via a solution – diffusion mechanism.
- Drug dissolved in the matrix and diffusion occurs through water – filled pores in the matrix.
- Drug dispersed in the matrix and then, after dissolution, diffusion occurs through water – filled pores.

#### Factors affecting release:

- More identical release pattern can be attained by adding wetting agents which promote the penetration of water into the matrix polymer, allowing drug dissolution and diffusion from the pores or channels created in the matrix.
- Release of water soluble drugs is independent on the physical properties of GI tract fluids, unless the drug is in a salt form that precipitates within the matrix pores on dissolution when penetrated by acid or basic media.
- The particle size of the insoluble matrix components influences release rate, larger particles leading to an increase in release rate.

**Erodable Matrix:**

A homogeneous dispersion of drug in the retardant base can be obtained by the fusion method, in which the wax is melted and drug and additives are blended with the molten wax matrix at temperatures slightly above the melting point. Then the molten material may be spray congealed, solidified and milled, solidified and flaked or poured on the cold rotating drum to form sheets, which are then milled and screened to form a granulation. Drugs using erodable matrices may be compressed into tablets or granulated into capsules. The processes used to prepare formulations for compression depends on the polymer and drug: polymer ratio. With high drug polymer ratios a wet granulation process is required. Low milligram potency formulations may be directly compressed or granulated using alcohol if the polymer is not in a form amenable to direct compression. As a loading dose, the outer coat of a matrix tablet contains drug for immediate release, and the remainder is released in a sustained fashion. Complete release of drug from wax lipid matrices is not possible as a certain portion of the dose remains coated with impermeable wax films.

**Release mechanism:**

Erodable matrices control release through both pore diffusion and erosion. The rate limiting step in this case is the permeation of water into the matrix.

**Factors affecting release:**

In the absence of additives, drug release is prolonged and non uniform. As a result, surfactants (Sterile alcohol, Polyethylene glycol monostearate) and wicking (Finely divided powders of methyl cellulose, Alginate acid, Carboxy methylcellulose) agents in the form of hydrophilic polymers are added which promote water penetration and subsequent matrix erosion.

**Hydrophilic Matrix:**

These delivery systems are also called swellable-soluble matrices. In general they include a compressed mixture of drug and water-swellable hydrophilic polymer. The systems are capable of swelling, followed by gel formation erosion and dissolution in aqueous media. High milligram potency formulations may require wet granulation. Whereas, low milligram potency formulations may be directly compressed or granulated using alcohol, if the polymer cannot be directly compressed.

**Factors affecting release:**

Drug release depends on the polymer selected for the formulation as well as on the drug polymer ratio. The best matrix former belonging to this group is hydroxymethylcellulose because-

- It is inert.

- It does not harmfully interact with either acidic or basic drugs and on contact with water it slowly forms a gel which is more resistant to attrition.

**OSMOTIC PUMPS / OSMOTIC SYSTEMS:**

In these systems, release of drug depends on osmotic pressure gradient. Osmotic pressure is used as the driving force to generate a constant release of drug, provided a constant osmotic pressure is maintained.

**Oral Osmotic Systems (OROS):**

The system is composed of a core tablet encircled by a semi permeable membrane coating having a 0.4mm diameter hole produced by laser beam. This device can be used as a drug delivery system for any water soluble drug and can be designed to release significant fractions of the total dose at zero order rates (unaffected by in vivo conditions).

**Parameters that can be regulated to manage release rate:**

The release route of drug from the system may be controlled by changing:

- The surface area,
- The thickness
- The nature of the membrane,
- The diameter of the delivery orifice and
- The osmotic gradient.

The diameter of the orifice must be smaller than a maximum size to minimize drug delivery by diffusion through the orifice and larger than a minimum size to minimize the hydrostatic pressure in the system which acts in opposition to the osmotic pressure. For devices containing KCl, orifices can range from 75 to 275  $\mu\text{m}$  in diameter. The release rate of the drug from the device is independent of GI pH (because ions do not diffuse into the device), or movement of the GI tract. In other words, release rate is independent of the environment. Materials used as semi permeable membrane include polyvinyl, alcohol, polyurethane, cellulose acetate, ethylcellulose and polyvinyl chloride.

**SOME PATENTED TECHNOLOGIES:**<sup>12</sup>

- 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

#### **ADVANTAGES OVER IMMEDIATE RELEASE FORMULATIONS:** <sup>13</sup>

- 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

#### **CHANGEABLE TO CONSIDER FOR FORMULATIONS:** <sup>13</sup>

- 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

#### **FACTORS AFFECTING TAILORED RELEASE DOSAGE FORMS :** <sup>11</sup>

##### **Physicochemical properties of drug-**

##### *Dose Size:*

If an oral product has a dose size greater than 0.5gm it is a poor candidate for tailored release system, Since addition of sustaining dose and possibly the sustaining mechanism will, in most

cases generates a substantial volume product that unacceptably large.

##### ***Aqueous Solubility:***

Most of drugs are weak acids or bases, since the unchanged form of a drug preferentially permeates across lipid membranes drugs aqueous solubility will generally be decreased by conversion to an unchanged form for drugs with low water solubility will be difficult to incorporate into sustained release mechanism. The lower limit on solubility for such product has been reported 0.1mg/ml. drugs with great water solubility are equally difficult to incorporate in to sustained release system. pH dependent solubility, particularly in the physiological pH range, would be another problem because of the variation in pH throughout the GI tract and hence variation in dissolution rate

##### ***Partition Coefficient:***

Partition coefficient is generally defined as the fraction of drug in an oil phase to that of an adjacent aqueous phase. Consequently compounds with relatively high partition coefficient are predominantly lipid soluble and as a result have very low aqueous solubility. Compounds with very low partition coefficients will have complexity in penetrating membranes resulting poor bioavailability. Typical relationship between drug activity and partition coefficient K, generally known as Hansch Correlation.

##### ***Pka:***

The relationship between Pka of compound and absorptive environment. Presenting drug in an unchanged form is adventitious for drug permeation but solubility decrease as the drug is in unchanged form.

##### ***Drug Stability:***

Orally administered drugs can be subject to both acid base hydrolysis and enzymatic degradation. Degradation will proceed at the reduced rate for drugs in the solid state, for drugs that are unstable in stomach; systems that prolong delivery over the entire course of transit in GI tract are beneficial. Compounds that are unstable in the small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. This is because more drug is delivered in small intestine and hence subject to degradation

##### ***Molecular size and diffusivity:***

The ability of drug to diffuse through membranes it's so called diffusivity & diffusion

coefficient is function of molecular size (or molecular weight). Generally, values of diffusion coefficient for intermediate molecular weight drugs, through flexible polymer range from 10-8 to 10-9 cm<sup>2</sup> / sec. with values on the order of 10-8 being most common for drugs with molecular weight greater than 500, the diffusion coefficient in many polymers frequently are so small that they are difficult to quantify i.e. less than 16-12 cm<sup>2</sup>/sec. Thus high molecular weight drugs and / or polymeric drugs should be expected to display very slow release kinetics in sustained release device using diffusion through polymer membrane.

#### **Protein binding:**

It is well known that many drugs bind to plasma proteins with a concomitant influence on the duration of drug action. Since blood proteins are for the most part re-circulated and not eliminated, drug Protein binding can serve as a depot for drug producing a prolonged release profile, especially if a high degree of drug binding occurs. Extensive binding to plasma proteins will be evidenced by a long half life of elimination for drugs and such drugs generally most require a sustained release dosage form. However drugs that exhibit high degree of binding to plasma proteins also might bind to bio-polymers in GI tract which could have influence on sustained drug delivery. The presence of hydrophobic moiety on drug molecule also increases the binding potential.

#### **BIOLOGICAL FACTORS:**<sup>11</sup>

##### **Biological Half Life:**

The common objective of an oral tailored release product is to maintain therapeutic blood levels over an extended period. To action this, drug must enter in the circulation of approximately the same rate of which it is eliminated. The elimination rate is quantitatively described by half-life (t<sub>1/2</sub>). Therapeutic compounds with short half lives are outstanding candidates for sustained release preparations. Since this can reduce dosing frequency. In general drugs with half-lives shorter than 3hrs are poor candidates of sustained release dosage forms of dose size will increase as well as compounds with long half lives, more than 8 hrs are also not used in sustained release forms because their effect is already sustained.

##### **Absorption:**

The rate, extent and uniformity of absorption of a drug are important factors when considered its formulation into a tailored release system. As the rate limiting step in drug delivery from a sustained-release/TR system is its release from a dosage form, rather than absorption. Rapid

rate of absorption of drug, relative to its release is essential if the system is to be successful. It we assume that transit time of drug must in the absorptive areas of the GI tract is about 8-12 hrs. The maximum half life for absorption should be approximately 3-4 hrs. Otherwise device will pass out of potential absorption regions before drug release is complete.

##### **Distribution:**

The distribution of drugs into tissues can be important factor in the overall drug elimination kinetics. Since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibrium with blood and extra vascular tissue, consequently apparent volume of distribution assumes different values depending on time course of drug disposition. For design of sustained/controlled release products, one must have information of disposition of drug.

##### **Metabolism:**

Drugs that are significantly metabolized before absorption, either in lumen or the tissue of the intestine, can show decreased bioavailability from slower-releasing dosage forms. Most intestinal wall enzymes systems are saturable. As drug is released at a slower rate to these regions less total drug is presented to the enzymatic. Process device a specific period, allowing more complete conversion of the drug to its metabolite.

#### **CONCLUSION:**

By the above discussion, it can be easily concluded that tailored-release formulations are helpful in increasing the efficiency of the dose as well as they are also improving the patient's compatibility. Generally 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 tailored release tablets and multiparticulates such as drug-loaded pellets and granules, mini-tablets and drug crystals. More over all these comes with logical price.

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