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An Overview of Oral Sustained-Release Tablets, with a Focus on the Matrix Tablet

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***Abstract*: The pharmaceutical industry is currently concentrating on developing oral dosage forms with a prolonged release, which has become a crucial tool in medicine. These formulations for sustained release are intended to release medication at a predetermined rate while maintaining plasma medication levels concentration with little negative effects during the therapeutic window. The main goal of sustained-release medication administration is to modify the drug's biopharmaceutical, pharmacokinetic, and pharmacodynamic properties to lessen adverse effects, improve patient compliance, and ultimately treat the illness. Due to less frequent drug administration, less steady-state drug level fluctuations, maximum drug utilization, the enhanced safety margin of powerful drugs, lower healthcare costs due to better therapy, and shorter treatment times, sustained release drug delivery improves patient compliance. The improvement of medication therapy is the primary objective of sustained release forms, which is determined by the relationship between the benefits and drawbacks of using a sustained release system. Basic information on the matrix-type sustained-release drug delivery system was provided in this review paper.**

***Keywords*: Drug delivery, Matrix, Plasma levels, Sustained release.**

1. Introduction

Regardless of the mode of delivery (immediate, sustained, or controlled release) and the design of dosage forms (either solid dispersion or liquid), all pharmaceutical products designed for systemic delivery via the oral route of administration must be developed within the intrinsic characteristics of GI physiology, pharmacokinetics, pharmacodynamics, and formulation design to achieve a systemic approach to the successful development of an oral pharmaceutical product. Drug administration dosage forms date back to 1938 [1–5].

Israel Lipowski's patent, which focused on coated pellets for prolonged drug release, most likely served as a precursor to the early 1950s introduction of the coated particle method of sustained drug administration [6]. The unique technique of drug delivery provides a way to provide prolonged, regulated delivery and/or target the drug to the desired place, hence boosting the therapeutic effectiveness of contained pharmaceuticals [7].

Any drug delivery system's objective is to quickly and sustainably attain the target drug concentration by making a therapeutic quantity of the drug available to the body's appropriate place [8]. Any drug delivery technique that achieves a delayed release is considered a sustained release system; drug release is spread out over a long length of time. A controlled-release system is one that successfully maintains constant medication levels in the blood or the intended tissue [9].

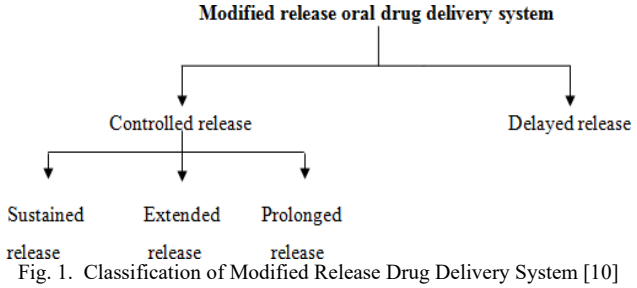

Fig. 1. Classification of Modified Release Drug Delivery System [10]

The oral route is the most common route for drug administration, in part because it is simple to administer and because gastrointestinal physiology allows for more design freedom in dosage forms than most other routes [11]. Drug delivery systems intended to establish or prolong therapeutic impact by continually releasing medication over an extended period following administration of a single dose are referred to as sustained release, prolonged release, modified release, extended-release, or depot formulations. [12]. The benefits of giving a medicine that releases slowly over time in a single dose as opposed to several doses have long been understood by the pharmaceutical industry. Better patient compliance and increased clinical efficacy of the medicine for its intended purpose are frequently associated with that a nearly constant or uniform blood level of a drug [13]. The development of sustained controlled-release drug delivery systems has received more attention due to the increased complexity and expense involved in selling novel pharmacological entities [14]. For sustained release, the matrix system is frequently used. The medicine that is dissolved or distributed is released over a longer period and is period by the release system.

The primary drawbacks of traditional dosage forms are [16],

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- Poor patient compliance increases the likelihood that a medication with a short half-life that requires frequent administration will be missed.
- Unavoidable drug concentration changes could result in under or over-medication.
- The plasma concentration-time profile is often peak-valley, which makes achieving steady-state conditions challenging.

2. Sustained Release Drug Delivery System

The phrase "sustained release" has frequently been used to refer to a pharmaceutical dosage form designed to delay the release of a therapeutic agent so that its appearance in the systemic circulation is prolonged and its loading dose, drug solubility in polymers, drug diffusivity in a polymer matrix, and duration of the release unit plasma profile are sustained [24–26].

Advantages:

1) A decrease in intake frequency
2) Lessen adverse consequence
3) Consistent medication release over time
4) Increased patient adherence [27]

Disadvantages:

1) A higher price
2) Dose-dumping-related toxicity
3) Poor in vitro-in vivo performance that is frequently unpredictable
4) Correlation When a medicine is released quickly, there is a chance of adverse effects or toxicity (mechanical failure, chewing or masticating, alcohol intake)
5) The Greater possibility of first-pass clearance
6) More counseling and education for patients are required [28]

In the sphere of pharmaceutical technology, the introduction of matrix tablets as the sustained release (SR) has resulted in breakthroughs for novel drug delivery systems (NDDS). During manufacturing, sophisticated production processes like coating and palletization are not included, and the kind and concentration of polymer used in the preparations have the biggest impact on how quickly the medication is released from the dosage form. An SR dosage form is frequently created using a hydrophilic polymer matrix [17–21]. The development of sustained-release or controlled-release drug delivery systems has received more attention as a result of the increased complexity and expense involved in selling novel pharmacological entities [22]. Sustained release is frequently achieved with the aid of matrix systems. The medicine that is dissolved or disseminated is prolonged and controlled by the release system. Time release technology, also known as the sustained release (SR), sustained action (extended-release (ER), timed release, controlled release, modified release continuous-release, is a technique used in pill tablets or capsules to disintegrate slowly and release a drug over a longer period. For sustained release, the matrix system is frequently used. It is the system that delays and regulates a drug's release after it has been dissolved or disseminated.

Biological factors affecting the design of sustained release of dosage forms

- Biological Half-life absorption
- Metabolism
- Therapeutic Index

Physiological factors affecting the design of sustained release of dosage forms

- Molecular size & Diffusivity
- Dosage size
- Aqueous solubility
- Partition coefficient (K) Drug stability [40], [41]

3. Matrix

Active and inactive components are uniformly combined and disseminated in the dosage form to create a matrix system. The popularity of matrix systems can be ascribed to several variables, and it is unquestionably the most widely utilized oral prolonged-release technology. The first law of diffusion by Fick governs the release from matrix-type formulations.

In a matrix system, the medicine is disseminated as solid particles inside a porous matrix made of either a hydrophobic polymer (such as wax, polyethylene, polypropylene, and ethyl cellulose) or a hydrophilic polymer (such as hydroxy propyl cellulose, hydroxy propyl methyl cellulose, methylcellulose, sodium carboxymethylcellulose, alginates, and scleroglucan).

In this context, the term "matrix" refers to the three-dimensional network that holds the medication as well as other components like excipients and solvents needed for the particular preparation. The medicine is continuously released via matrix drug delivery devices. These release the medication using diffusion- and dissolution-controlled processes, respectively. Medication molecules on the surface of the release unit will first disintegrate, causing a fast release of the drug.

Following that, drug particles at progressively greater distances from the release unit's surface will dissolve and diffuse to the outside of the release unit. In this approach, the drug reservoir is created by uniformly dispersing drug particles in a matrix of polymers that controls the rate and is made of either hydrophilic or lipophilic polymers.

By either;

1) Blending a therapeutic dose of finely ground drug particles with a liquid polymer or a highly viscous base polymer, followed by cross-linking of the polymer chain, or
2) Combining drug and polymer at a high temperature, the drug is disseminated in the polymer matrix.

It can alternatively be made by combining the drug and polymer in a common solvent, then allowing the solvent to evaporate at a high temperature or under a vacuum. This polymer matrix diffusion-controlled drug delivery system has a time-dependent drug release rate, defined as a steady state.

$$Q/t1/2 = (2AC_RD_p)1/2$$

A stand for the initial loading dose of the drug in the polymer matrix,

CR for the system's drug reservoir concentration, and

D_p for the drug molecules' diffusivity therein.

Controlling the loading dose, the drug's solubility in polymers, its diffusivity in the polymer matrix, and the porosity of the release unit all help to regulate drug release. [23]

Classification of matrix tablets:

Inert monolithic matrix tablets:

Incorporating a drug in an inert matrix is probably the easiest way to provide continuous release of medication from an oral dose form. Inert here refers to something that doesn't interact with bodily fluids. Its primary selling point is that drug release from plastic matrix tablets is independent of the health and condition of the digestive juices, which can exhibit significant inter- Intra -variability (pH, viscosity).

The porous matrix tablet does not break down like ordinary tablets do after passage through the gastrointestinal tract; instead, it stays whole, allowing for the recovery of the skeleton in the faeces. (Insoluble) polymers and lipophilic chemicals make up the majority of the ingredients employed in the creation of these inert matrices. The earliest synthetic (semi) polymers to be employed in the production of matrix tablets included polyethylene, polyvinyl chloride, polymethyl methacrylate, polystyrene, polyvinyl acetate, cellulose acetate, and ethyl cellulose. Carnauba wax, hydrogenated castor oil, and tristearin were some of the fat substances utilized.

The main flaws of the majority of inert polymeric matrix tablets were their poor direct compression qualities, intrinsic first-order drug release issues, and difficult cleaning of the agglomeration machinery used to provide the necessary compression characteristics in agglomerates.

Mechanism of the release of inert monolithic matrix tablets:

Leaching is a process used to release material from tablets of the inert matrix. Drug particles dispersed in the polymer matrix dissolve in the penetrating gastrointestinal fluids and are released from the tablet by diffusion through the porous network of both already existing pores and pores that were produced by the drug particles dissolving. An ongoing structure connecting all drug particles is present at drug loadings of more than 10-15 volume% (percolating drug network).

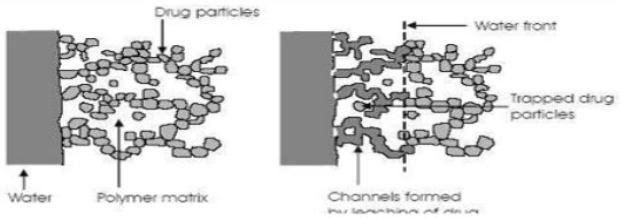

Fig. 2. Schematic presentation of leaching-based release mechanism

Solvent-activated matrix tablets:

Using solvent-activated matrix tablets to achieve zero order Hoffenberg's initial proposed release, or constant release rates over a long period A system that achieves controlled release through the interaction of a polymer and water is referred to as a solvent-activated drug delivery system.

The polymer may become plasticized, swell, dissolve, erode, or degrade as a result of the interaction with water. Gel-forming hydrophilic matrix tablets and erodible (hydrophobic) matrix tablets are the two most significant varieties of solvent-activated matrix tablets.

Gel-forming hydrophilic matrix tablets:

The medication is disseminated in a swellable hydrophilic polymer in homogeneous or heterogeneous systems known as gel-forming hydrophilic or swellable matrix systems. Since these systems provide the opportunity to establish a consistent medication delivery over an extended period, researchers have extensively investigated them. The properties of the polymer affect drug release.

Gel-forming hydrophilic matrix tablets are plasticized by the aqueous gastrointestinal system after being swallowed, causing the hydrophilic polymer to experience macromolecular chain relaxation and volume expansion. A distinct front may be seen, which divides a dry, glassy core from a moist and rubbery gel layer, as a result of the gastrointestinal fluids penetrating the tablet. The release is controlled by leaching and lesion of drug particles that were present at the surface before the creation of the release-controlling gel, which causes a burst effect in most cases.

The relative position of the rubber-glass interface, the rate at which it penetrates the tablet, the drug's diffusion coefficient, and the rate at which the gel is erosive all affect how the drug is released from swellable devices. When the rate of drug diffusion through the swelling gel layer is higher than the rate of drug penetration, the drug's diffusion rate through the gel layer controls release, and the diffusion-regulated (Fickian) release mechanism is shown.

Release of the integrated drug is controlled by the interface penetration rate and zero-order drug release with a constant release rate may be accomplished if drug diffusion through the gel layer is rapid relative to the water penetration rate. Several dimensionless criteria have been proposed to describe drug release from swelling-controlled dosage forms. The Deborah number (D_e) is a measure of the relationship between the typical relaxation time of the swelling polymer (t) and the typical diffusion time of water into the polymer (q) [29], [30]. The relationship between the front velocity of solvent penetration and the rate of drug diffusion through the swollen polymer is represented by the swelling interface number (S_w):

$$D_e = q / t$$
$$S_w = n.d(t) / ID$$

d(t) is the thickness of the swelling layer, and

ID is the drug's diffusion coefficient in it.

D_e and S_w must be determined because neither of these variables is adequate in and of themselves to characterize release behavior. Peppas and colleagues [8] have looked into diffusion and solvent-controlled drug release from swellable polymeric devices with different geometries in great detail. The simple equation below can be used to quickly examine release from swellable tablets:

$$M_t / M = kt^n$$

Where K is a constant that represents a device's structural and geometrical characteristics, Mt/M is the fractional drug release, and n indicates the kind of release mechanism.

A Fickian diffusion-controlled release mechanism with n » 0.5 is observed when the pace at which the penetration front travels inward into the glassy core is high compared to the rate at which dissolved drug molecules diffuse through the swelling gel layer.

The release of the integrated drug is controlled by the interface penetration rate if the drug diffuses through the gel layer more quickly than the solvent does. This results in zero-order release (n=1), also known as solvent penetration regulated release or case II for dosage forms with slab geometry. Anomaly-classified release profiles are those with intermediate n-values (0.5<n<1).

Guar gums, poly (ethylene oxide), poly (vinyl alcohol), ethylene vinyl alcohol copolymers (EVA), and dextran's are other swellable polymers that have been utilized in swelling-controlled oral drug delivery systems that exhibit solvent-controlled release.

Erodible matrix tablets:

Another intriguing material platform for zero-order drug release is erodible polymers, such as polyanhydrides. Polyanhydrides generate a gel layer that erodes at a predetermined rate after water penetration, similar to certain HPMC grades.

By selecting the proper polymer composition, the gel layer's thickness may stay constant throughout time, resulting in a consistent release rate up until the drug's depletion [31].

Bilayer tablet:

Today, oral ingestion accounts for almost 90% of formulations produced. This demonstrates that this category of formulations is the most widely accepted, and the researcher's attention is mostly focused on this direction. Reduced dose frequency is the primary goal of sustained medication delivery. By delivering the drug slowly and continuously during a partial dose interval, modified-release drug products aim to optimize a therapeutic regimen while also improving patient compliance and convenience. The successful expansion of controlled-release formulation has entered a new age with the bilayer tablet [32].

Bi-layer tablets can be used to segregate two incompatible substances, release two medications sequentially in combination, and create sustained-release tablets where the first layer is an instantaneous release as the first dose and the second layer is a maintenance dose. The bi-layer tablets can be used for a variety of purposes because they are made of monolithic, partially coated, or multilayered matrices. Generally, predictable dosage forms result in undesirable toxicity, subpar efficacy, and broad variations in drug concentration in the blood and tissues.

The idea of a controlled drug delivery system was born out of the necessity for frequent dosage and variable absorption. Increasing therapeutic efficacy and ensuring safety are the fundamental goals of sustained-release drug delivery [33].

Advantages of bilayer tablet:

1) Better chemical and microbiological stability than other oral dose forms, according to this.
2) By separating incompatible components, physical and chemical incompatibilities are reduced.
3) Coating technology can be used to hide offensive tastes and odors.
4) It can be made to have a modified discharge, keeping one layer's release as extensive and the other as instantaneous.
5) It is less expensive than other dose types.
6) Well suited for industrial production.
7) It is simple to swallow and has a low tendency to hang up [34].

Disadvantages of bilayer tablet:

1) Because they are amorphous and low-density, some drugs resist compression into impenetrable compacts.
2) Rotary presses for bilayers are pricey.
3) Astringent testing substances, offensive-smelling medications, or oxygen-sensitive drugs
4) Might need to be coated or encapsulated.
5) Poor individual layer weight control.
6) Low yield due to layer separation and insufficient hardness. [35]

Types:

Homogenous type:

When the medication release patterns are dissimilar from one another, bilayer tablets are chosen. Designing and adjusting the properties of release and dissolution is possible using a bilayer. Bilayer tablets are made with a layer of medication intended for immediate release and a second layer with a second dose or an extensive release method for the medication.

Heterogeneous type:

The sequential release of two medications in combination and the separation of two incompatible compounds are both viable uses for bilayer tablets [36].

Need of bilayer tablet:

1) Create novel drug delivery systems, such as chewing devices and floating tablets, for the administration of fixed-dose combinations of various active pharmaceutical ingredients.
2) Regulating the rate of administration of a single active pharmaceutical ingredient [37].

Table 1
Marketed formulations of bilayer tablets [39]

S. No.	Product Name	Chemical Name	Developer
1	ALPRAX PLUS	Sertraline, Alprazolam	Torrent Pharmaceuticals Ltd.
2	DIAMICRON®XRMEX500	Gliclazide, Metformin Hcl	Sedia® Pharmace -Uticals Pvt. Ltd
3	DIUCONTIN-K®20/250	Furosemide, Potassium Chloride	T.C. Health Care Pvt. Ltd.
4	Glycomet®-GP2Forte	Metformin Hydrochloride, Glimepiride	USV Limited
5	New Cold Plus	Levocetirizine Hcl, Phenylpropanolamine Paracetamol	Piramol Healthcare Ltd.
6	Revelol®-Am 25/5	Metoprolol Succinate, Amlodipine Besilate	Ipca Laboratories Ltd.
7	TRIOMUNE 30	Nevirapine, Lamivudine	Cipla Ltd.

General properties of bilayer tablet dosage forms:

The bilayer tablet should:

1) Have a beautiful product identification
2) Be free of pollution and discoloration
3) Be without chips or cracks
4) It needs to be strong enough to endure mechanical shock during production, shipment, and application.
5) To preserve its physical properties over time, it should be chemically and physically stable [38].

Various approaches used in the bilayer tablet

1) Floating drug delivery system
2) Polymeric Bio-adhesive system
3) Swelling system/unfolding system

Types of bilayer tablet press

1) Single-side added tablet press
2) Double-side added tablet press
3) Bilayer tablet press with displacement monitoring

4. Conclusion

The main objective of this review article was to guide the formulation of sustained-release matrix tablets, as well as information on factors affecting dosage form, criteria for choosing a drug for sustained-release delivery with benefits and drawbacks, and different polymers used in such systems. The conclusion from the foregoing discussion is that matrix tablets are useful in boosting dosage efficiency in evoking appropriate therapeutic responses while overcoming patient compliance issues with conventional dosage forms. Cost-effectiveness and a once-daily dose are other plus factors. All of these are reasonably priced as well. As a result, the design of the dosage form is becoming more effective and optimized with sustained-release matrix tablets.

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