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A Review on Application of Different Polymers in Controlled Release Matrix Formulations

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ABSTRACT

Controlled release matrix tablet system is a useful tool for controlled and sustained release dosage forms because of its simplicity, increased safety margin of a potent drug, patient compliance,and low cost than traditional drug delivery systems.In recent years, great attention has laid on replacing the drug's conventional administrationwitha controlled rate delivery system. This kind of drug delivery has been at the center of research because of its numerous advantages over traditionaldosage.To prevent the drug release rate from the formulation, polymers are being used as the principal tool. Utilization of polymer is currently stretched out to controlled release drug delivery system. Polymers are derived either from natural source or synthesized chemically. This review aims to discuss different materials used to prepare matrix tablets and various types of matrix systems currently being used, and the matrices' drug release mechanism.

Keywords: Controlled release, matrix system, synthetic polymer, biodegradable polymer.

1.INTRODUCTION

The characteristics of drugs and the form in which they are delivered forms an important criteria for developing a safe, reliable and effective drug delivery system, whichought to beimproved currently[1]. Oral drug administration has been the principal route for drug delivery because the gastrointestinal physiology offers more flexibility in dosage form design when compred to other routes of drug administration[2].During the past 40 years, due to increased costs and complications in promoting efficient drug delivery systems, more critical consideration has been centered ondevelopingmatrix controlled release drug delivery systems[3].

Matrix systems are usually utilized with the final aim of controlled release that extends and regulatess the dissolved or dispersed drug release[4]. The development of matrix tablets eliminates complex processes such as coating and pelletizing dosage manufacturing processes [5]. A controlled release drug delivery system delivers the drug locally or systemically at a fixed rate for a specific period. Controlled release (CR) formulations have been developed for three primary purposes: to reduce the amount of single doses per day, reduce plasma concentration variations, and increase the bioavailability to achieve better therapeutic efficacy and lower toxicity [6].

Polymeric substances are extensively used in a wide range of pharmaceutical products and form crucial concrete oral dosage forms. As a result, there is a need to understand properties of the polymer and methods to characterize the polymer for the rational design and development of solid drug delivery systems orally and about various manufacturing processes [7]. The properties of polymers influence the drug release, and by understanding

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these polymer properties can produce well-characterized and reproducible CR dosage forms [8]. Controlled release systems are affected by various physiological conditions such as pH, ions, motility rate, and enzymes [9].

Numerous matrix systems such as hydrophilic, hydrophobic matrices, and lipid systems have been developed. Intense research is going on to establisha safe and effective polymer for the drug's controlled release.

2.Matrix Systems Types

Depending on the drug release mechanism, matrix system is divided based on the types of polymeric material and retarding agents used as well as on the porosity of matrix

A. Based on a Drug Release Mechanism

1. Reservoir Matrix System

In this system, a membrane is used for the controlled release of the drug from the matrix. The drug will eventually diffuse through the membrane, and the diffusion distance that the drug particles have to cover keeps its release constant.

2. System of Osmotic Pump

On osmotic pressure, osmotic systems operate. They contain a core tablet surrounded by an orifice-coated semipermeable membrane coating. Core tablet is surrounded by two layers , one is active layer which has active ingredient and the other is push layer which has osmotic agent. Tablet absorbs water through the semipermeable membrane, triggering the drug dissolution and suspension. The increase in osmotic pressure allows the dissolved/suspended substance to be pumped out of the delivery orifice. The drug delivery rate can be controlled by adjusting the delivery orifice size and thickeness of thesemipermeable membrane[10].

B. Dependent on Type of Polymer

1.Hydrophobic Matrix System

Waxes are used to prepare hydrophobic matrix systems that are ideal for drugs that have high solubility. In this procedure, the drug is combined with an inert or hydrophobic polymer and then compressed into a tablet that diffuses through a network of channels between compact polymer particles as it dissolves. The water-insoluble fluid that enters the matrix and retains the physical dimension during drug release is the rate-controlling phase in these formulations. In the presence of water and gastrointestinal fluid, such types of matrix tablets are inert [34].Examples of polymers include polyethylene glycol, polyvinyl chloride, polymers of ethylcellulose, and acrylate [11].

2.Hydrophilic Matrix System

The formulation of the hydrophilic matrix grows in size in water due to the solvent passage, which then causes the polymer to extend, creating a barrier to drug release [12]. The matrix building polymer prefers an excellent hydrophilic matrix tablet formulation with fast hydration potential [13].Polymers are the essential rate-limiting components of the hydrophilic matrix[14]. proposed controlling drug release from geometric multilayered capsules and

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observed that a swelling barrier around an active center provides prominent modulation for soluble drugs. Hydroxyl propyl methylcellulose (HPMC), xanthan gum, carbopol 940, and alginates are examples of polymers [15].

3.Lipid Matrix System

Due to the stability and effectiveness of lipid polymers used in formulations, the lipid-based matrix system is an exciting prospect for developing controlled release formulations. Improving the solubility of sparingly soluble drugs is a standard function of the lipid matrix system. Formulations dependent on lipids protect active ingredients from biological degradation or transformation [16]. By using lipid waxes and correlated products, the lipid matrix system is prepared. By spray congealing in the air, mix congealing in an aqueous media, and spray-drying process, the drug may be fused into fat-wax granulations. The addition of surfactants in the mixture influences the drug's release rate and the amount of the overall drug that can be put into a matrix. By pore diffusion and erosion, drug release from such matrices occurs. By pore diffusion and erosion, drug release from such matrices occurs. Rather than an utterly insoluble polymer matrix, the drug release rate is influenced by the digestive fluid's composition. Stearyl alcohol or stearic acid has been used for several controlled-release formulations in blending with carnauba wax for the retardant base [17].

4.Biodegradable Matrix System

The essential criteria for using polymers in the pharmaceutical formulation and controlled release formulation fields are bio-safety and biocompatibility. The biodegradable polymer degrades into biological fluids in regulated forms that release the dissolved or dispersed drugs [18]. These involve polymers containing monomer units that are bound by functional groups to each other. Enzymes biologically degrade them into oligomers or monomers.Examples: polysaccharides, aliphatic poly (esters), and polyanhydrides [19]

5.Mineral Matrix System

These are comprised of polymers that are acquired from different types of seaweeds.For example, Alginic acid is a hydrophilic carbohydrate extracted from brown seaweed species (Phaeophyceae) using dilute alkali method[20].

C.Based on the Porosity of Matrix

1.Macro Porous System

This system releases the compound through the diffusion process into the wider matrix pores with a size ranging from 0.1μm to 1 μm[21].

2.Micro Porous System

Via the larger matrix pores varying from 50 to 200 Å by diffusion route, this system releases the drug.

3.Non-Porous Porous System

As there are no pores, this system releases the drug through the matrix mesh. In this case,

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only the polymer phase occurswithout pore phase [22].

D.Miscellaneous Matrix[23].

1. Multilayered Matrix System

The drug molecules are protected by a semipermeable polymeric material serving as a membrane layer in this matrix system. The matrix center is made up of hydrophilic substances—Swelling, gelling, and control of the drug release is eventually done by dissolving the barrier-layers of the matrix. By modifying the geometry of the barrier-layer in the matrix, different drug release profiles can be obtained.

2. Floating Matrix System[24].

In this matrix system, the matrix's bulk density is low, resulting in stomach buoyancy and drug molecules being released through swelling and erosion processes. For a prolonged period, drug release can occur, prolonging gastric residence time and improving bioavailability.

3. pH Sensitive Matrix System

The enteric coating of the solid dosage form protects the drug from the stomach's indifferent acidic media in this matrix system. Low pH-sensitive drug molecules will, therefore, safely enter the small intestine and colon.

4. Mucoadhesive Matrix System

The drug is released to any mucosal tissue in the body inside the GIT in this matrix system.This system uses swellable hydrophilic polymers that can interact in the mucous layer of the gut with the glycoproteins present [25]

3.Drug Release Kinetics from Sustained Release Matrix System

A. Zero-Order Kinetics

The following equation can predict a zero-order release:

$$Q_t - Q_0 = K_0 t$$

Where, Q_t = Amount of drug release dissolved in time 't'.

Q_0 = Initial amount of drug concentration in solution.

$K_0 t$ = Zero-order rate constant.

When the data are plotted as cumulative percent drug release versus time, if the plot is linear, data obeys zero-order kinetics with slope K0. This model represents an ideal release profile to achieve prolonged pharmacological action[26].

B. First Order Kinetics

The following equation can predict a first-order release:

$$\text{Log } Qt = \frac{\text{Log } Q_o - K_1}{2.303}$$

Where Qt = amount of drug released in time.'

Q_o = Initial amount of drug concentration in solution

K_1 t= First order rate constant.

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When data were plotted as log cumulative percent drug remaining versus time yields a straight line indicating that the release follows first-order kinetics, the constant release rate, K can be obtained by multiplying slope values.

C. Higuchi's Model

Higuchi's equation has described drug release from the matrix device by diffusion:

$$Q = \sqrt{D\delta/\tau}\ (2C-\delta Cs)Cst$$

Where Q = amount of drug released in time't.'
D = Diffusion coefficient of the drug in the matrix
Cs = Solubility of the drug in the matrix
δ = Porosity of matrix
T = Tortuosity
t = Time (h).
The equation may be simplified, then the equation becomes; $Q = K_H \times t^{1/2}$
Where K_H = Higuchi dissolution constant.
According to this equation, when data are plotted, i.e., cumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion-controlled mechanism [27].

4.Types of Polymers Used in Matrix System

Proper selection of the polymer matrix is essentialin developing a successful drug delivery system. A large number of polymersthat are used in sustainedrelease drug delivery are reported in the below table[21].

Table 1: Different types of polymers used in the matrix system[28].

Type of Polymer	Examples
Hydrogels	Poly-hydroxyethyl methacrylate (PHEMA), Crosslinked polyvinyl alcohol (PVA), Crosslinked polyvinylpyrrolidone (PVP), Polyethylene Oxide (PEO), Polyacrylamide (PA).
Biodegradable Polymer	Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyanhydrides, Polyamide, Polyorthoesters, Poly (lactide-co-glycolide) (PLGA), Polyhydroxybutyrate (PHB), Polyglutamic acid, Polyimino carbonates
Non-biodegradable Polymer	Polyethylene vinyl acetate (PVA), Polydimethylsiloxane (PDS), Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethylcellulose (EC).
Mucoadhesive Polymers	Polycarbophil, Sodium Carboxymethylcellulose, Polyacrylic acid, Tragacanth, Methylcellulose, Pectin.
Natural Gums	Xanthan gum, Guar gum, Karaya gum, Gum Arabic, Locust bean gum. Tamarind Gum.
Other	Sodium Alginate, Carrageenan, Chitosan, Hypromellose acetate succinate

A.Hydrogels

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Hydrogels are hydrophilic cross-connected polymer structure consisting of homopolymers or copolymers. Based on the crosslinks' stability, the hydrogel can survive exposure to water [4]. When put in the bloodstream, these dry hydrogels will ingest water or other body fluids and swelland increase in the swelling makes the drug to diffuse across the swollen network into the external world. Many factors like pH, temperature, or ionic quality influence the system either to swell or shrink. For this kind of design, the drug releases only as of the polymer swells.

At high pH values most of the polymers swell and collapse at low pH values, drug delivery occurs upon when pH is increased in the surrounding environment pH. These materials are suitable for oral delivery processes, in which the drug is not released in the stomch due to its low pH values and releases only at high pH values, which exists in the upper small intestine.

B. Biodegradable Polymer

Biodegradable macromolecules degrade to smaller absorbable molecules that are metabolized and eliminated from the body. They are more favored due to their prolonged-release drug formulation, drug stability, and steady release rate over time. These polymers do not require surgical removal and thus are preferred for drug delivery applications [2]. The most commonly used polymers for this application are given below,

1.Polylactic Acid (PLA)

It is a thermoplastic polymer synthesized by the polymerization of monomers of lactic acid. PLA polymer undergoes bio-degradation by bulk erosion. The lactide/glycolide chains of polymer are converted into acids by hydrolysis and are eliminated from the body. Aslow-release drug delivery system was developed for Mitomycin C and Dexamethasone sodium phosphate [29].

2.Polyglycolic Acid (PGA)

PGA is accomplished by ring-opening polymerization of the cyclic diester of glycolic acid &glycolide. PGA is a rigid crystalline polymer that cannot form tablets, capsules, or nanoparticles as these have low solubility and high melting point .

3.Poly (lactide-co-glycolide) (PLGA)

The crystallization of PGA forms PLGA with PLA, which causes a decrease in crystallinity, leading to increased hydration and hydrolysis rates. 29 30 PLGA is used in numerous drug delivery applications. Studies have reported the delivery of low water soluble anticancer agents by PLGA. Diflunisal has been introduced into PLGA microspheres and investigated to treat rheumatoid arthritis

4.Polyhydroxybutyrate (PHB)

PHB is a nontoxic carbon assimilated (starch) biopolymer, produced as an energy source by bacteria in all living organisms. PHB matrix was designed for the controlled delivery method of lithium neutralized polyacrylic acid for bone regeneration in patients.

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5. Poly Caprolactone (PCL)

PCL is obtained by ring-opening polymerization of the lactone & e-caprolactone e-CL) (e-CL). Enzymatically catalyzed polymerization of e-CL has also been reported. PCL crystallizes readily and is degraded by hydrolysis into 6-hydroxycaproic acid faster at basic pH. PCL is a capable candidate for controlled release applications. Controlled drug delivery system has been reported in the literature.

6.Polyanhydrides

Poly anhydride is characterized by anhydride bonds and is prepared by melt-condensation polymerization. Polyanhydrides undergo hydrolytic degradation and become water-soluble materials, resulting in polymer erosion.

7. Polyamide

Polyamides are commonly referred as Nylons, which form an essential group of polycondensation polymers. They are aliphatic and thermoplastic. In 2012, US patent was published on 'Polyamide rate-modulated monolithic drug delivery system.

8. Polyrthoesters (POE) (POE)

POE is suitable for orthopedic uses. The lactic segment will reach a time of deterioration which is 15 to hundreds of days. Carboxylic acid results fromthe degradation of the lactide segments, which further catalyze the orthoester's degradation. Studies showed that POE-based norethindrone and stabilising factor [Mg (OH) 2] implants results in controlled delivery of levonorgestrel.

9. Polyglutamic Acid

Polyglutamic acids can be modified chemically due to its high water solubility and several carboxyl groups, which provide low immunogenicity and low toxicity. Nanoscaled Poly (l-glutamic acid)/Doxorubicin controlled drug delivery has been reported to successfully treat lung cancer.

10. Polyiminocarbonates

These are obtained from the polymerization of desaminotyrosyl tyrosine alkyl esters. They maintain the development and attachment of cells and provide a high degree of tissue compatibility. These undergo hydrolysis degradation by cleavage of ester bonds, and the imino-carbonate bonds are presently being studied for use as bone screws and pins for bone fixation in fractures [30]

C. Non-Biodegradable Polymer

The non-biodegradable polymer particles are useful as carriers of growth factors or antimicrobials mixed with restorative materials. A significant drawback of non-degradable polymers is that a procedure is needed to dig these polymers out of the body after the drug vanishes. Thus, non-degradable polymers can be used only if the removal of these polymers is simple [31]

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D. Mucoadhesive Polymers

1. Sodium Carboxymethyl Cellulose (NaCMC)

This is an ionic cellulose dependent polymer that is susceptible to changes in pH. On hydration, NaCMC forms a viscous gel coating on the surface. This polymer releases drug through the process of erosion. Various studies have reported the influence of NaCMC on drug release.

2. Pectin

Pectins are ionic polysaccharides present in plant cell walls. They release drug particles by diffusion-controlled inert porous matrix system. It has been documented that pectins form water-soluble complexes with some NSAIDs. The dissolution rate of benzydamine hydrochloride/pectin coprecipitate and a physical mixture of benzydamine hydrochloride and pectin was very low compared to intact benzydamine hydrochloride and a physical mixture of benzydamine hydrochloride and galacturonic acid. This proposed the use of pectin as an ingredient for controlled-release formulations.

E. Natural Gums

Natural gums are nontoxic, readily hydrate, and swell in aqueous media.

1.Guar Gum

Guar gum is derived from the field endosperms of Cyamopsis tetragonolobus (Leguminosae family) It is composed of galactan and mannan units bounded across glycosidic linkages. We can prepare hydrophilic matrix tablets from Guargumbecause of its high water absorptivity, low toxicity, and low cost. The release rate of the drug from guar gum tablets slows down over time. In-vitro drug release was carried out by Toti&Aminabhavi in simulated gastric and intestinal conditions. The drug release persisted for polyacrylamide-grafted-guar gum and hydrolyzed polyacrylamide-grafted-guar gum copolymers up to 8 and 12 hours, respectively.

2. Arabic Gum

Gum arabic is an exudate of the Acacia Senegal stem and branches and the other acacia species (Leguminosae family). The gum contains d-galactose, l-arabinox, d-glucuronic acid and l-rhamnose. Acacia is commonly used in oral and topical drug formulations as a suspending and emulsifying agent. The polymers have a major impact on the drug release up to 2 and 8 hours as studied by [32].

3. Gum Karaya

The sterculia tree is a karaya gum that is made up of galactose, rhamna and glucuronic acid. Reddy et al., have reported that diltiazem drug release from tablets formulated with unmodified karaja gum was 99.9% in the end of 10 h, and 68.2% at the end of 12 h for karaya gum tablets.

4. Bean Gum Locust

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Locust bean gum is a β-d-mannopyranosyl linear strand. Harikrishnan et al. has been observed that 50 percent locust bean gum formulation is more mucoadhesive than any other formulation. The improvement in concentration of locust bean gum increases the strength and swelling ratio of the bioadhesive.

5. Gum Xanthum

Xanthan gum is formed by the fermentation of Xanthomonas campestris gram-negative bacterium. It consists of the following: d-glucose, d-manose and glucuronic acid. Xanthan gum can be used in formulations mentioned for sustained release [33].

F. Other

1. Sodium Alginate

Alginates are present in brown aquatic algae and used in drug formulations as binders and tablet disintegrants. They are also used in controlled release formulations because of their ability to hydrate a gel [21]. Chan and. Al. they have assessed 17 different grades of sodium alginate with other particles, viscosities and chemical compositions. They stated that sodium alginate could form a gel in both acidic and neutral media.

2. Carragineans

Carrageenan is a marine hydrocolloid originating primarily from Chondrus crispus and Gigartina stellata, used mainly for gelling and thickening purposes. They are d-galactose sulfated esters and 3, 6-anhydrod-galactose [1]. Gupta et al., definedcarrageenic-containing matrices were considered useful for 8–12 hours for modifying the release of three model drugs.

3. Chitosan Chitosan

Chitosan is a polyelectrolyte from shells of crab and shrimp. Chitosan can be used as a vehicle for preparations for sustained release. One essential aspect of the chitosan granules was that they float with pH 1.2 in an acidic medium after swelling.This floating property can be useful for designing controlled drug preparations [1]. In vitro furosemide release study was conducted by Sahu et al. It found that it follows Zero Order Equation and followed the proper non-Fickian diffusion procedure were better explained in all formulations.

Extremely biocompatible and less immunogenic substances are natural polymers. Among them most importantand of particular interest are natural polymers, chitosan, alginate, and cellulose derivatives. The combination of natural polymers with synthetic polymers provides additional advantages as a controlled release for drugs by complementing each other's properties.

In contrast to PLGA, polylactides are hydrophobic and take a longer duration to degrade. PLGA polymers degrade more rapidly than PLGA carboxylic end. Copolymerization can also lead to a better regulated method of drug delivery. Several new polymers are currently being studied in controlled drug delivery applications.

4.Mathematical Model for Matrix Tablet Drug Release Mechanism.

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Drugs on the external layer of the matrix system exposed to the external fluid environment are first dissolved and distributed out of the matrix. This process takes place at the interface between the external fluid environment and the drug moving inside. The dissolution rate of drug particles in the matrix must be much faster than the rate of diffusion of the dissolved drug leaving the matrix for this mechanism to be controlled by diffusion.

5. Methods Of Preparation Of Matrix Tablet

1. **Direct Compression**

   This process involves direct compression of powdered materials without changing thephysical and chemical properties of the drug.

2. **Wet Granulation**

   In this method, drug andpolymer of appropriate weight are mixed with a suitableamount ofgranulating agent. After a constant blending, the wet mass was passed through a mesh. The granulesare then dried and blended with lubricant and disintegrating agents. The formed granules are compressed using acompression machine.

3. **Melt Granulation**

   In this process, a substance meltingat low temperature is used, which in molten form spread over the substrateand heated above its melting point. Differentlipophilic binders were tried by using the meltgranulation technique[34].

CONCLUSION

This review article concluded that matrix type controlled-release formulations support increasing the dose's efficiencyand these arecompatible to patient's health.This controlled-release formulation isbeneficial in patients who need continuous drug delivery for anextended period. Polymers acquired anexclusivepotency in their function towards drug delivery systems,enabling the new advancement in the formulation of new drug delivery systems. These polymers can prepare matrix type controlled-release formulations,releasing the drug in a controlled manner. Moreover, all of these are cost effective.Preparatoryprocedures with no trouble allow theadjustment of releasekinetics of delivery requirements. This suitability of matrix-forming polymers confirms their importance in pharmaceuticalapplication. They represent the alternative solution formany oral delivery problems like fluctuating drugplasma levels, low bioavailability, frequentdose administration etc. Hence,a matrix type controlled drug delivery system canprevail over the above troubles of conventional oraldrug delivery.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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