

Review Article

APPROACHES TO ACHIEVE AN ORAL CONTROLLED RELEASE DRUG DELIVERY SYSTEM USING POLYMERS: A RECENT REVIEW

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ABSTRACT

The present article contains a brief review of various formulation approaches used in controlled release drug delivery systems, the role of polymers in the controlled delivery of many fast release drugs and the mechanism of drug release from these polymeric matrices. The oral controlled release system of many drugs has been known to be an essential part of formulation development in drug delivery systems. It has been the focus of pharmaceutical research for many years due to its various advantages over conventional dosage forms. Administering the drug for release in the blood at a controlled rate, to maintain relatively constant drug levels in plasma over a controlled period of time, can overcome many problems associated with conventional dosage forms. The applicability of these dosage forms is due to reduction in the frequencies of drug dosing, which lead to patient convenience and compliance. In addition, a reduction of wide fluctuations in plasma drug concentration peak can be obtained. As a result, toxicity and poor efficacy can be avoided, especially with drugs of narrow therapeutic indices. Such problems, associated with conventional dosage forms of many drugs, can be overcome by using controlled release drug delivery systems, to deliver the drug for absorption at a controlled rate over an extended period of time. The controlled release dosage form should be tailored so that variations in the components can lead to predictable alterations in the drug release profiles. Various controlled release drug delivery systems have different mechanisms to control the drug release rate, such as the osmotic pump, ion exchange resin and matrix systems which have been widely utilized as controlled release drug delivery approaches. Besides, polymers have often been used in the components of controlled release drug delivery systems. A sustained release profile, without occurring of the dose dumping, and sufficient bioavailability can be achieved when a drug is embedded in some polymeric materials such as gelucires.

Keywords: Controlled release drug delivery system, Matrix system, Polymer, Gelucire.

INTRODUCTION

Oral drug administration is the most preferable and oldest route for drug delivery. This is due to the low cost of medicine preparation and ease of administration, which makes it the most favorable route of drug administration for patients [1, 2]. It has been known as the most popular and successful route for controlled delivery of fast release drugs because of greater flexibility in the designing of dosage forms compared to other routes [3]. Previous reviews reported that more than 50% of the medications which are available in the market were found to be given orally [4, 5].

Research on oral drug delivery with either further development in the delivery system or novelty in the drug formulation is ongoing work for many formulation scientists [6]. The most prominent requirements for a drug delivery system to make it novel are, first to deliver a drug at a controlled rate, and second to pass the active entity to the target site for action. Formulation scientists have been used many possible approaches to achieve this challenging novelty in oral drug formulation, either by unifying drug distribution into a carrier system, or by controlling drug release in the blood to reach the designed plasma drug concentration-time profile [7, 8].

Controlled release drug delivery systems can offer temporal and/or locative control over the release of drugs. Thus, the oral controlled release drug delivery system is the most widely used system for controlling the release of drugs given orally [9]. Many advantages for this system were reported, such as preventing plasma drug level fluctuations, reducing dosing frequency of drug administration, enhancing drug bioavailability, improving patient compliance and minimizing side effects and toxicity of drugs [10]. In comparison, the conventional oral drug dosage form has a number of shortcomings such as, high tendency of plasma drug level fluctuations, increasing the dosing frequency of drug administration, time limitation for drug effectiveness at the target site of action and low oral bioavailability of some drugs due to interaction with food or unsuitable gut environment, for example cefotaxime Na [11].

The drug release profile of the oral controlled release system maintains the drug plasma concentration level within the therapeutic

range, through a specific rate and time frame, resulting in continued therapeutic action [12]. Oral controlled release drug delivery is a system that provides constant oral drug release with expected pharmacokinetic parameters over a predetermined rate and time. It maintains a relatively continuous and effective drug level in the blood. The sustained release formulation of aspirin is one for examples of the oral controlled release drug delivery system. It can be given before bedtime but its effect is prolonged until the next morning for arthritis relief [13]. Many exchangeable terms such as sustained release, prolonged release, modified release, extended release or depot formulations are used to identify controlled release drug delivery systems that are designed to extend the release rate of drugs over an extended period of time from a single given dose [14].

Designing the drug dosage form is essential for achieving an applicable oral controlled release drug delivery system. The design process includes the characterization of the drug in terms of permeability through the biological membrane and first pass metabolic effect before reaching the blood. The controlled release dosage form of the drug should be tailored so that variations in the components lead to predictable alterations in release profiles. Thus, in this present article, various formulation approaches for the oral controlled release drug delivery system and the role of some prominently used materials such as polymers, are reviewed briefly.

Various systems of oral controlled release dosage forms

Various techniques have been used in the preparation of the controlled release drug delivery system; most of them working under the principle of slowing the dissolution rate of the drug from the dosage form. In general, controlled release formulations can be divided into different categories based on methods of preparation and/or the mechanisms of drug release, which will be shown in the following below.

Matrix system

The matrix system is the most commonly used controlled release delivery system of rapidly released drugs. The drug is uniformly dissolved or dispersed in suitable polymeric materials. Most of these

materials have either hydrophilic or hydrophobic properties, in which the retardant material and drug are homogeneously distributed or dissolved in the polymeric matrix. This is done either by wet granulation or by the direct compression technique in the solid dosage form, where the drug is embedded in the matrix core of the retardant [15]. Therefore, this matrix system is characterized by drug dispersed materials in the polymer blend [15]. Drug release is controlled by gradual dissolution of the matrix or gradual leaching of the drug from the retardant material.

A range of controlled release mechanisms have been explained, including diffusion through matrices or across membranes and erosion. However, knowing the material properties of the matrices is essential to predict the mechanism of drug release. The matrix system of oral controlled release delivery system of drugs is classified according to polymer type, porosity sizes and other miscellaneous ways of matrix preparation.

Classifications of matrix system based on polymer type

Hydrophilic matrix system

This is also known as the swellable controlled release drug delivery system. In this type of matrix system the drug substances are mixed with a hydrophilic gelling agent [16]. Three different groups of polymers are used in the preparation of hydrophilic matrices. These groups are as follows: 1) Cellulose derivatives [15] such as hydroxyethyl cellulose, hydroxypropylmethyl cellulose (HPMC) 25, 100, 4000 and 15000 cps, sodium carboxymethyl cellulose (CMC) and methyl cellulose 400 and 4000 cps. 2) Non-cellulose natural or semi synthetic polymers [17] such as agar-agar, carob gum, alginates, molasses, polysaccharides of mannose and galactose, chitosan and modified starches. 3) Polymers of acrylic acid [17] such as carbopol 934. On the other hand, other hydrophilic materials can also be used such as alginic acid, gelatin and natural gums [15].

Plastic matrix system

In this type of matrix system, a hydrophobic polymer material is granulated with a drug by using latex or pseudo latex as granulating fluid. Examples of materials used in this system are: polyvinyl chloride, ethyl cellulose, cellulose acetate and polystyrene [15, 17, 18].

Fat-wax matrix system

In this type of matrix system, lipid waxes or other related materials are used in the preparation of the matrices. The drug released in this system occurs through both pore diffusion and erosion. The matrices are more sensitive to digestive fluid in the gut as compared to an insoluble polymer matrix [18].

Examples of retardant materials used in the matrix bases of this system are: carnauba wax in combination with stearyl alcohol or stearic acid [18].

Biodegradable matrix system

In this type of matrix system, the polymeric materials used consist of monomers which are linked to each other through functional groups with instable functionality. The degradation of polymeric materials into oligomers and monomers occurs through either biological enzymes produced by surrounding tissues or non-enzymatic processes [19]. Examples of natural polymers used in this matrix base are proteins, polysaccharides, aliphatic polyesters, and polyamides are synthesized polymers [20].

Mineral matrix system

In this type of matrix system, the polymeric material used is hydrophilic carbohydrate and it can be obtained from different species of brown seaweeds by the use of dilute alkali [19].

Classifications of matrix system based on porosity size [21, 22]

Macro-porous matrix system

In this type of matrix system, drug diffusion occurs through pores with a size range of 0.1 to 1 μm . This system is suitable for drug molecules with molecular sizes less than 1 μm .

Micro-porous matrix system

In this type of matrix system, drug diffusion occurs through pores with a size range of 50 up to 200 \AA . This system is suitable for small drug molecules with molecular sizes less than 200 \AA .

Non-porous matrix system

In this type of matrix system, drug diffusion occurs through the network meshes rather than by diffusion through small pores.

Classifications based on other miscellaneous way of matrix preparations

Multilayered matrix system

In this type of matrix system, the matrix core is made of hydrophilic substances in which the drug molecules are coated with a semi-permeable polymeric material. This semi-permeable polymeric material is utilized as a barrier-layer on both surfaces of the core during preparation [23]. An alteration of the swelling rate of the core can occur due to the presence of barrier-layers, resulting in minimizing the surface area for drug molecules during the release process. Different drug release profiles can be obtained by varying the geometry of the barrier-layer in the matrix [24]. The drug release is controlled by swelling, gelling and finally dissolving the barrier-layers of the matrix.

Floating matrix system

In this type of matrix system, the bulk density of the matrix is lower than the gastric fluid in the stomach. After creating buoyancy in the stomach, the release of drug molecules from the matrix can occur slowly. Drug release can occur over a long period of time, which prolongs gastric residence time and thereby increases the bioavailability of fast release drug molecules [25]. Diltiazem HCl is one of the examples of a fast release drug which was successfully prepared in a controlled release using the floating matrix system [26] and detected on the sensitive HPLC method [27].

The steady release of drug from this hydrophilic matrix system is supported by control of the buoyancy effect and continuous release. HPMC is a widely used polymer in this type of hydrophilic matrix system. It has a pH independent gelling agent property. As a result of this effect, swelling and erosion mechanisms can be obtained together to control and slow down the fast release drug in a steady manner [25].

pH sensitive matrix system

In this type of matrix system, an enteric coating of the solid dosage form can provide protection for the drug from the harsh acidic media of the stomach. Thus, low pH sensitive drug molecules can reach the small intestine and colon safely. This type of matrix system is applicable to protect antigen or protein molecules from the harsh acidic media of the stomach after oral administration. pH sensitive polymers such as HPMC-phthalate or cellulose acetate phthalate can be used in this type of matrix system [28]. These types of polymers are pH-sensitive materials. This matrix system works by releasing the enteric coated drug at a specifically high pH value in the GIT, where drug absorption can occur in the right location [28].

Mucoadhesive matrix system

In this type of matrix system, the drug is released over a controlled period of time. The targeted tissues can be ocular, respiratory, gastrointestinal, buccal, nasal, rectal, urethral and vaginal tissues. [29]. In addition, this type of matrix system can be applied to any mucosal tissue in the body in the GIT. The used materials in this system are swellable hydrophilic polymers which can interact with the glycoproteins being available in the mucous layer of the gut [29].

Osmotic drug delivery system

In this type of drug delivery system, an osmotically active polymer agent is used in the preparation of the system. Thus, the drug is released by osmosis at a predetermined zero-order kinetic rate for an extended and constant period of time until the concentration of the agent in the matrix drops down below the saturation solubility

of the drug in the media [30]. The embedded drug in the system starts releasing through an orifice on the semi-permeable membrane of the system. The drug release gets controlled by a constant osmotic pressure and by hydrostatic pressure differences on both sides of the semi-permeable membrane [31]. No influences on this system can occur by different physiological factors inside the gut lumen. The release characteristics of the drug can thus be easily anticipated from the known properties of the drug and the dosage form [31].

The system is divided into two parts which are packed in the bilayer core. The top layer contains an active drug and the lower layer contains an osmotically active polymeric agent. The bilayer core is coated with a rigid semi-permeable membrane. The drug is compacted in the core and released through an orifice on the membrane.

When the matrix is exposed to an aqueous environment, the soluble drug draws water through the semi-permeable coating membrane. Subsequently, a saturated aqueous drug solution occurs in the device as a result of drug water exposure. Then, an increase in the volume due to the influx of water increases the inner hydrostatic pressure leading to an efflux of saturated drug solution from the membrane orifice [32, 33].

This type of drug delivery system is unique, dynamic and widely used in clinical practice [34, 35]. A number of drugs have been incorporated and used in this system such as nifedipine [36-38], metoprolol [39], oxprenolol [40], ibuprofen [41], naproxen sodium [42] and diltiazem HCl [33].

Components of osmotic drug delivery system

A number of components are used for the osmotically controlled release drug delivery system. These components are: drug, osmotic agent, semi-permeable membrane, plasticizer, wicking agent, pore forming agent and coating agent [36]. The first four components are reviewed briefly below:

Drug

Ideally, the model drug should have a short biological half-life and be used for prolonged treatment. A number of model drugs have been reported such as Diltiazem HCl, Carbamazepine, Metoprolol, Oxprenolol, Nifedipine and Glipizide [43].

Osmotic agents

They are usually ionic compounds of either inorganic salts or hydrophilic polymers [44]. The drug is released continuously in the hydrated formulation by the uptake of water through a driving force created by the osmotic agent until the concentration gradient across the membrane becomes finally maintained.

Many salts can be used as osmotic agents such as sodium chloride, potassium chloride, or sulfates of sodium, potassium and lithium. In addition, sugars such as glucose, sorbitol, sucrose or inorganic salts of carbohydrates can also be used for the same purpose. On the other hand, some polymers can be used such as poly (cellulose), osmotic solutes, or colorants such as ferric oxide [44, 45]. Polymers such as poly (alkylene oxide), poly (ethylene oxide), and poly (alkali carboxy methylcellulose) are included in the push layer of certain osmotic drug delivery systems. Furthermore, hydrogels such as carbopol (acidic carboxy polymer), cyanamer (polyacrylamides) and aqua-keeps can also be used [44].

Semi-permeable membrane

Cellulose acetate is one of the components which is applicable for this purpose and it is available in different acetyl content such as agaracetate, betaglucan acetate, polyether copolymer, olyacetals, polyglycolic acid and poly lactic acid [46].

Plasticizers

They have an influence on the permeability of the polymeric coating film of the system, as it can alter the viscous properties of the used polymer. Many plasticizers can be used such as polyethylene glycols, ethylene glycol monoacetate, ethylene glycol diacetate, tri ethyl citrate, diethyl tartarate and diacetin [47].

Ion exchange resins (IER) drug delivery system

In this type of drug delivery system, the resins used are water insoluble cross-linked polymers carrying ionizable functional groups and consist of a salt-forming group at specific positions on the polymer chain [48, 49]. The used resins are usually polymers with integrated ionic moieties which have a tendency to form reversible exchangeable counter-ions between the liquid and the solid phase. Upon administration of the drug resin complex, the drug release occurs in the presence of a high concentration of the polyelectrolyte's counter ions in the gut media. The drug molecules are exchanged, diffused out and finally passed into gastrointestinal fluids [50]. The ability of the resin to exchange ions is determined by the ionizable group. Therefore, IER are classified according to the ionizable group. The different types of classes are strong acid cation exchange resins, weak acid cation exchange resins, strong base anion exchange resins and weak base anion exchange resins [51]. These reacting groups of ion-exchange resins can be used to bind drugs.

In addition to the oral controlled drug delivery system application of IER, this system can also be used for many ways of drug administration such as transdermal, nasal and topical drug delivery systems [52]. Several studies have reported the use of IER for drug delivery in clinical medicine such as sulfonated and carboxylic resins with a polystyrene backbone [53]. In addition, polystyrene and polymethacrylate cross-linked polymers are considered the most common resins used in pharmaceutical formulations. Another reported study showed that the rate of drug availability can be controlled by manipulating the polymer coating in the ion exchange system with hydrophobic polymers such as ethyl cellulose or waxes [54].

Polymers used in the formulation of controlled release drug delivery systems

Various types of polymers have been widely used in the matrix formulations of controlled release drug delivery systems. Most of them work under the same principle by embedding or conjugating the drug in polymer matrices. In general, the choice of polymer used in controlled release matrices depends on the nature of polymer used (hydrophilic, hydrophobic and amphiphilic). A brief review on these different types of polymers used in matrices is discussed below.

Hydrophilic polymers

These types of polymers contain polar or charged functional groups rendering them to be soluble in water. Most hydrophilic polymers are grouped by the chemistry of their structure. HPMC and hypromellose are considered the most widely used hydrophilic polymers in oral controlled release drug delivery systems [55]. HPMC has been studied and examined as a thickening agent a coating polymer, a bioadhesive in solid dispersion and as a binder. HPMC hydrates rapidly and forms a gelatinous barrier layer around the tablet when in contact with water. The rate of drug release from the HPMC matrix is dependent on many factors, such as the type of polymer used, the drug model, the polymer/drug ratio the particle size and fillers used [56]. This type of polymer is chemically inert, physically it has good viscosity, is stable in pH media between 3 ~ 11, and is nontoxic and it is non-irritating [57]. On the other hand, many factors can control the choice of HPMC in the matrix such as drug solubility. Highly water soluble drugs need higher amounts of HPMC. The higher viscosity of HPMC or amount of HPMC in the tablet can decrease the drug release rate [58]. The preparation method can also affect the dissolution profile of many drugs using preparation. For example, the direct compression technique is suitable with HPMC applications [58].

Hydrophobic polymers

These types of polymers contain non-polar or charged functional groups in the chemical structure rendering their surfaces not being wetted by water. Most hydrophobic polymers are classified into different types based on chemical class and monomer functionality. Polystyrene has been widely used and it is considered as one of the most widely used materials in the advanced plastic industry [59].

Amphiphilic polymers

These types of polymers have two components that confer both a hydrophobic and hydrophilic characteristic to drug dosage forms. One example are gelucires, which have been used considerably as pharmaceutical excipients in controlled release drug delivery systems.

Gelucires

They are a mixture of glyceride-based materials and esters of polyethylene glycol (PEG) which can be used in the preparation of controlled release drug dosage forms. These polymeric materials contain mixtures of mono-, di- and triglycerides with esters of PEG. The presence of these components offers hydrophobic and hydrophilic natures to the dosage form. The nature and proportion of these components can control the hydrophobicity and drug release properties in the drug dosage forms [60].

Gelucires are inert, semi-solid, waxy, amphiphilic excipients with surface-active properties that spontaneously form a fine dispersion or emulsion upon exposure to water [61]. They are available in different types. Different types of gelucires can be identified by two numbers/values. These two numbers are the melting point of the base (varies from 33 °C-65 °C) and the HLB value of the proportion of water-soluble, parts to fat-soluble in each gelucire (varies from 1 to 14). The wide range of the melting point and the proportion of hydrophile-lipophile components in gelucires make it widely applicable in the preparation of different types of dosage forms, especially in the preparation of both fast and slow release formulations [62]. Gelucires with low HLB values in lipid matrices can decrease the dissolution rate of the drugs from the lipid matrices [63; 64, 65], whereas gelucires with high HLB values can accelerate the release rate of the drugs from the lipid matrices [66, 67].

Several previous researches have reported the use of gelucires as a base in the preparation of controlled release drug delivery systems [68]. In addition, the uses of gelucires to enhance the oral bioavailability of poorly water-soluble drugs have been reported. These drugs include the antiviral agent UC781 [69, 70], the antimalarial drug halofantrine [71], the HIV protease inhibitor DMP 323 [72] and theophylline [73]. Also the uses of gelucires in the oral formulation of nicotine [74] in the controlled release drug delivery system of salbutamol [75-77], oxprenolol [78], lithium sulphate [79], benzonatate [80], nifedipine [64], quinidine gluconate and theophylline [81] have been reported. In addition, a number of studies have reported the use of gelucires in drug-loaded spheres [82-85] as a compressed tablet dosage form [86].

CONCLUSION

On the basis of the obtained review, the controlled release drug delivery systems of many fast release drugs could be prepared and achieved by incorporating the drugs in various polymeric materials. The successful preparation of a controlled drug delivery system is dependent on the nature and ratio of both the drug and the polymer in the matrix. Different types of controlled drug delivery systems can be approachable by using different types of polymers. Polymeric material can be useful in the design of different types of dosage forms as a drug carrier for different ways of drug administration.

CONFLICT OF INTERESTS

Declared None

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