Review Article

Controlled drug release rate and contemporary issues in oral drug delivery formulations

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Abstract

Principles of controlled drug delivery are the release of the drug in a controlled manner for prolong period. These types of dosage forms need were to maintain the drug concentration for a long period. The treatment of disease states has traditionally involved the use of multiple daily dosing of a therapeutic agent using a conventional dosage form, e.g., tablets. The development of such systems is the role of pharmaceutical polymers. In light of the current and continuing importance of this category of drug delivery system, the following section provides a concise overview of the range of designs of controlled release drug delivery systems. The controlled or sustained drug delivery systems, required the drug is homogeneously dispersed, either at the molecular scale or as solid particles, within a carrier system. The most usual using oral dosage form, like matrix tablets therefore in this review we are discussed matrix tablets. The matrix tablet formulations are affected by various factors that affected the release rate of drugs through the oral drug delivery Systems. This information can be very valuable for the development of such type of formulation.

Keywords: Controlled drug delivery, Sustained release drug delivery, Polymers, Matrix tablets

Introduction

The treatment of disease states has traditionally involved the use of multiple daily dosing of a therapeutic agent using a conventional dosage form, e.g., tablets. Following administration, the drug is absorbed into the systemic circulation in a stepwise fashion involving: Drug diffusion through the matrix of the dosage form. The drug dissolves into the aqueous fluid of the gastrointestinal tract. The solution is diffusion through the aqueous fluid of the gastrointestinal tract to the surrounding tissue, e.g., the villi of the small intestine. The absorption of the drug is across the wall of the gastrointestinal tract. The drug enters into the systemic circulation and is deposition at the required site of action. In conventional oral drug delivery systems, the drug is released from the dosage form within a short (defined) period allowing subsequent absorption into the systemic circulation. Under these circumstances, the onset and duration of the effect of a therapeutic agent are controlled by the absorption step. It is assumed that by ensuring greater concentrations of the drug at the site of action or absorption, the mass and rate of drug absorption will increase and this will, in turn, result in greater concentrations of drug in the systemic circulation (Chien et al., 1992; Sweta et al., 2015; Agrawal et al., 1999; Turner et al., 2004; Carstensen et al., 1977; Sen et al., 2015; Garg et al., 2016).

Controlled or sustained drug delivery systems

The controlled or sustained drug delivery systems are delivering the drug in a controlled, and sustained manner for a prolonged period (Sweta et al., 2017). The various dosage forms are available n the market that delivers the drug at the desired rate in the selected site of the body. The controlled or sustained drug delivery systems are nanoparticles, microspheres, coating technology, and tablet formulation, etc (Pandey et al., 2012, Shukla et al., 2012, Pandey et al., 2012). Most commonly available

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dosage forms which are using to deliver of drug that is available in the market. These types of formulation release the drug at the controlled or sustained manner (Shukla et al., 2017, Shukla et al., 2016, Gour et al., 2016).

Factors affecting release rate of the drug from matrix tablets

Over the past four decades, an interest has developed in the design and formulation of dosage forms that control the subsequent release of drugs from the dosage form into the surrounding biological fluids. Consequently, this rating process effectively controls the pharmacological properties of the therapeutic agent. The development of such systems is the role of pharmaceutical polymers. In light of the current and continuing importance of this category of drug delivery system, the following section provides a concise overview of the range of designs of controlled release drug delivery systems and the contribution/significance of polymers to their function. The reader should be reminded that the following sections are designed to provide an overview of controlled release drug delivery systems and where necessary references to more specialist literature are included. The controlled or sustained drug delivery systems, required the drug is homogeneously dispersed, either at the molecular scale or as solid particles, within a carrier system. The most usual using oral dosage form, like matrix tablets therefore in this review we are discussed matrix tablets. The matrix tablet formulations are affected by various factors that affected the release rate of drugs through the oral drug delivery Systems. The following factors that are release rate of a drug are

1. Effect of viscosity

Viscosity can be defined as a measure of the resistance of a fluid to flow. The viscosity of drug solution is can be controlled by polymers about polymer solutions, viscosity depends upon the molecular weight of the polymer (Indian Academy of Sciences, 2010). The viscosity of polymer solutions is the result of polymer chain hydration through hydrogen bonding of oxygen atoms by their ether linkages that causing them to extend and form relatively open random coils. The hydrated coils continue to hydrogen bond to additional water molecules holds within the coils (The Dow Chemical Company, 2000). These water molecules initially dissolve the drug and hold it, and swell and form a network-like structure called matrix that decreases the release of the drug due to higher viscosity through the hydrophilic matrices (Rahman et al., 2011). Therefore good viscosity grades having HPMC polymer used in matrix systems for the formulation of oral controlled release or sustained drug delivery systems. The viscosities of HPMC are used like K100M, K15M, K4M, and K100LV, etc. The drug release from the higher viscosity grade K100M releases the drug compared to the lower viscosity grade K100LV. The release of a water-insoluble drug like diclofenac sodium from the HPMC K100M matrix is prolonged. It can stay away from gastrointestinal side effects. Many researchers have been reported and

Table 1. Classification of oral controlled drug delivery systems (OCDDS)

Category	Type
Diffusion-controlled-OCDDS	Matrix-type systems, Hydrophobic matrix systems, Hydrophilic matrix systems, Reservoir-type systems, Transdermal, Drug in adhesive systems, Monolithic adhesive systems, Multilaminate adhesive systems, Inert matrix systems, Semisolid matrix systems, Reservoir matrix systems, Other diffusion controlled systems, Intrauterine devices and intravaginal rings, Intraocular inserts, Subcutaneous implants
Dissolution-controlled-OCDDS	Based on dissolution-controlled release of solid particles Based on dissolution-controlled release coated technologies Based on dissolution-controlled release matrix technologies
Osmotic controlled-OCDDS	Osmotic delivery systems for solids Type I: single compartment Type II: multiple compartments Osmotic delivery systems for liquids
Biodegradable polymeric- OCDDS	Microparticles Nanoparticles Implants
Ligand-based targeting- OCDDS	Pulsatile systems
Programmable-OCDDS	Feedback-controlled systems
Stimulus responsive	Physically modulated: Temperature Chemically modulated: pH dependent

concluded that the higher viscosity grade of HPMC (K100M) can strengthen the gel layer and delay the penetration of water into the dry matrix core. This results in delayed release of water-soluble and water-insoluble active molecules (Alderman, 1984).

Effect of pH

The gastrointestinal (GI) pH is one of the key factors of GI fluids and that varies significantly along the digestive tract underfed and its environment (Charman et al., 1997). It influences the dynamics of HPMC hydrophilic matrix systems. It can change the gel layer formation (Tritt-Goc et al., 2005). In addition, the gel layer formation by the polymer depends on their nonionic character. The viscosities of HPMC polymers are normally maintained over a wide pH range of 3-11. This means if the drug solubility is pH-dependent that drug release through the HPMC matrix surface will also be pH-dependent (Asare-Addo et al., 2011). The transit time exhibits the time taken for food to move through the different segments of the GI tract.

Transit time and pH values affect the water-soluble drug-like theophylline through the theophylline release from HPMC matrix tablets. The higher drug release from low viscosity HPMC in acidic pH 1.2, consequences that indicated which continued to decrease the rate of drug release as the pH increased to alkaline. In addition, this study has been studied and reported that pH and molecular mass of HPMC affect the hydration effects or swelling behavior (Tritt-Goc and Kowalczuk et. al., 2005). The swelling nature of HPMC gell like character at different time intervals is studied by using magnetic resonance imaging (MRI). The gelling nature of polymer increases as time is increased. It shows the development of the gel layer with time and increases the surface area of the polymer, and decreases the dry core. They were revealed that the drug release is higher in acidic conditions (i.e. stomach) for low viscosity HPMC as the gel layer is thinner thus allowing penetration of water.

Effect of ionic strength

The ionic strength property of GI fluids is a key factor. It affects the rate of drug release from HPMC matrices (Asare-Addo et al., 2011; Charman et al., 1997). The ionic strength property of GI fluid is based on food composition, which is taken by a person. The ionic concentration is maintained at a steady level in the jejunum due to water and ion secretion. It is expected to be approximately 0.14 M in fasted conditions (Asare-Addo et al., 2011; Bonferoni et al., 1995; Lindhal et al., 1997). Generally, the ionic concentration strength of the GI tract under both fed and fasted states. It is a range of 0-0.4 M (Johnson et al., 1993). A study by Asare-Addo et al., 2011) investigated, and found that the ionic strength of polymer increased the amount of theophylline drug released rate. The ionic concentration strengths mimicked the potential effects of food, 0.2 M: low content of food and 0.4 M: high content of food. The results represented ionic concentration had significant produce on the release pattern of the drug through the K100LV matrices. They were found that the K100M matrices had the lowest drug release rate and produced a strong gel layer, and revealed that the high viscosity grades are the best candidates for producing controlled release profiles that are less affected by food.

Effect of cations

The modified polymers have been developed by researchers by using various different cations such as Al3+, Ca 2+, Zn2+ and Mg2+ with alginate (Al-Musa et al., 1999; Nokhodchi and Tailor, 2004). These developed modified polymers forming good network-like bridges due to presence of cations within a matrix (Braccini 1999; Ching et al., 2008), and forming a network structure and it is called a hydrogel. The hydrogel-like network can also be explained with the egg-box model. This egg-box model has explained the bonding between alginate and divalent cations such as Ca2+ and Zn2+, respectively using a two-dimensional approach (Grant et al. 1973). It is found that the divalent cations like aluminum ions have an extra positive charge per unit of surface allows cross-linking to a greater extent (Mohammadi, 2009). The formation of hydro-gels modulates drug release from sustained-release formulations and has been used in microspheres, beads, and film coating (Chan et al., 2006; Lee et al. 2005; Shukla et al., 2019). These cations are widely used in the development of cross-linking in natural gum, and the derived gum used for the formulation of matrix tablets. These derived natural gums preserve the matrix structure and keep away from the early disintegration of the matrix tablets (Ching et al., 2007). This property of derived polymers makes it suitable for the development of a controlled release agent. However, the concentration of cation in polymer affects an important role, in controlling quickly or slowly drug released rate of drug (Nokhodchi and Tailor 2004; Ching et al., 2007; Mohammadi et al., 2009).

Kinetics of drug release rate

The release characters of drugs from hydrophilic matrices can be mathematically explained by the using equation which is known as Higuchi equation:

$M = k.t00.5$

Where k is a constant and M is the amount of drug released at time t.

The Higuchi's equation primarily was applicable only for

planar matrix systems, and after that, it was modified to regard as diverse geometrical shapes and matrix characteristics mutually with porous structures (Lapidus and Lordi,1966, 1968, Higuchi 1963; Desai et al., 1965, 1966, Shukla et al., 2019). It should be reserved in mind that the classical equation. It was derived underneath pseudo-steady state assumptions. It cannot be applied to real controlled release systems (Peppas 1984; Kumar et al., 2019; Verma et al., 2020). The final equation of kinetic equation shows that if a system is chiefly diffusion-controlled, then it is predictable that a plot of the drug release beside the square root of time, and will exhibit a straight line.

The mechanism of drug release from hydrophilic matrix tablets after ingestion is complex but it is based on diffusion of the drug through, and erosion of, the outer hydrated polymer on the surface of the matrix. In the case of a greatly soluble drug, this occurrence may lead to an opening disintegrate release due to the incidence of the drug on the surface of the matrix tablet. The gel layer (rubbery state) swell with time increases, and more water enters into the core of the matrix film, thereby increasing the thickness of the gel layer and providing a diffusion barrier that controlled and decrease the drug release (Rajabi-Siahboomi et al., 1996; Garg et al., 2018; Sahu et al., 2019). The gel layer thickness behavior is crucial in describing the release kinetics of swellable matrices. Water continues to penetrate the matrix surface of the tablet and many other formulations through the gel layer, and drug release by the eroding surface of matrix tablets (Lee and Peppas 1987; Narasimhan and Peppas 1997; Kumar et al., 2018; Mishra et al., 2019). The release rate of the drug depends on the thickness, sewlling or rheological properties of the gel layer (Caramella et al., 1989). The good thickness, sewlling or rheological properties of the gel layer represented that the interactions between polymer-polymer and polymer-solvent are very important for controlling the gel network structure and erosion. In addition, the strength of gel can play a major role in controlling the drug release from this type of matrices.

Others factors

The various factors that affect the release rate of drug through the surface of the matrix layer. These factors are discussed below under like as

1. Types of Formulation

The types of formulation are key factors that affect the release of a drug like if nanoparticles, microsphere, and tablets formulation, etc. The drug solubility is proportional to the surface area of dosage formulation if more surface area induces more drug solubility. Therefore these factors also affect the drug release rate (Shukla et al., 2020, Yadav et al., 2020).

2. Methods

The various methods are employing for the formulation of controlled or sustained release drugs. The solubility of drug molecules depends on the methods like matrix tablet formulation. The matrix formulation can develop by using the direct or wet granulation method. The direct compression-based developed matrix tablets, having good swelling index character than wet granulation-based develop tablets. The wet granulation-based developed tablets not having a good swelling index value but they formed a more rigid network on the surface of the tablet, and water does not penetrate it. So that the selection of method is depends on nature of drug candidates and polymers, and also the target site of the drug (Jain et al., 2020; Shukla et al., 2020).

3. Nature of Polymers

The nature of polymers affect the release of a drug like if water-soluble drug then for the formulation of controlled or sustained dosage form were developed by using water-insoluble that deliver the drug into the intestine or pH-dependent, respectively.

4. Nature of Active Ingredient

The nature, type, and site of delivery affect the release rate of drug molecules. The drug may be water-soluble or water-insoluble so that, the nature of drug molecules key factors in the affecting release rate of drug.

5. Dose of drug

The dose and period for action of the drug also affect the dosage formulation, and that affect the release of the drug (Shukla et al., 2017).

Conclusion

The oral controlled drug delivery dosage formulations are most common systems that are using by patients. These formulations deliver the drug into the body, and maintain the concentration of drug in blood for long time. In the present review article we are covered all the different factors that affecting the release rate of drug that are types of formulation, nature of polymers, nature of drug viscosity of polymer, pH, ionic strength, cross-linking with cations, and site of drug targeting. The developments of ideal controlled release formulation need to follow these factors, and remove dose dumping diffects. The natural, synthetic polymers and their modified forms were studied in terms of their release kinetics when used in a variety of oral dosage formulations. Hence, it is this behavior based on which a drug formulation could be prepared to give sustained, and controlled type of effect. Thus, it was concluded that the potential controlled and sustained release oral dosage

formulation must follow factors which affect the rate of release of drug. In-addition, keep in mind above concept before the designing or development of oral controlled release of drug.

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