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The Uses of Matrices in Drug Delivery: The Effect of Polymers On the Drug Release and the Kinetic Models

Hassan A. Alhmoud
Department of pharmaceutical sciences, College of pharmacy, Yarmouk University, Irbid, Jordan.
E- mail: hassan.alhmoud@yu. edu. jo

ABSTRACT

Matrices of polymer are commonly used in drug delivery and controlled release dosage form due to their simplicity, and patient compliance. Up to date, there are different types of matrices which are composed of a variety of polymers: hydrophilic and hydrophobic, and of both. This review discusses the effect of the polymers on the release rate of drug. The mechanisms of drug release from the matrices in the dissolution medium are also studied. Moreover, this study reviews the properties of polymers, their application in different preparation of pharmaceutical dosage forms, their role in drug delivery, and their therapeutic uses. Furthermore, the mathematical analysis to predict the model of drug release from the matrices is discussed. The field of controlled drug delivery is vast; therefore, this review will provide an overview of the applications of polymers in pharmacy, Medicine, their role in the mode of drug delivery and the most appropriate prediction of the drug release.
Key words*: polymers, matrix, drug release rate, mathematical models*

INTRODUCTION

A polymer is a large molecule, or a macromolecule, composed of many repeated subunits. Depending on their wide uses [1], both of the synthetic and natural polymers play an important role in our daily life.[2] Polymers varied from the synthetic plastics such as polystyrene to the natural polymers such as cellulose, DNA, silk and proteins. Both the natural and the synthetic polymers are formulated by polymerization of the monomers.

The natural polymeric materials such as shellac, amber, silk and natural rubber have been used since a long time. Cellulose is another natural polymer which is the main component of wood and paper

Polymer properties are classified into many classes according to their composition, as well as their physical basis [3]. The most basic property of the polymer is the identity of the monomers. Moreover, polymer properties depend on other properties such as the microstructure, which describes the arrangement of the monomers within the polymer at the scale of a single chain. These structural properties play an essential role in determining physical properties of the polymer, which predict the polymer behavior.

The physical properties of a polymer are also depending on the size and length of the polymer chain [4]. For example, increasing the chain length elevates the boiling temperatures of the polymer [5] .

The hydrophilic polymer matrices are widely used in the formulation of controlled release dosage forms [6 -10]. Also the hydrophobic polymers matrices have played an important role in the advancement of drug delivery technology by

providing therapeutic agents in constant doses over long periods in many occasions, and the controllable release of the drug from these matrices have been obtained [11 -14].

Tremendous progress has been made as a result of the exploration of diffusion controlled formulations in drug delivery [15 -17]. Hydrogels and other polymer carriers were developed to provide safe passage of the drugs to the site of action in the body. Polymers incorporated with therapeutics can be bioactive to provide their own therapeutic benefit [18] or can be biodegradable to improve release kinetics and prevent carrier accumulation [19]. Drugs have been incorporated to polymers to modify the release of drug or its half-life characteristics as well as to allow for passive and active targeting [12, 14, 20]. Finally, the latest drug delivery research using polymeric materials has produced systems and polymer carriers that facilitate the delivery of new cytoplasmic drug therapeutics [19].

The application of polymers in drug delivery was used since more than 6 decades by compression, coating, and encapsulation. The polymers used were included cellulose derivatives, poly (ethylene glycol) PEG, and poly (N-vinyl pyrrolidone) [21]. From a drug delivery perspective, polymer devices can be categorized as diffusion-controlled devices, swelling- or osmotically-controlled devices [22], biodegradable systems, or systems that are affected by external factors such as the pH, and temperature [23].

MATHEMATICAL MODELS USED TO DESCRIBE THE KINETIC OF DRUG RELEASE

Noyes – Whitney equation

This is the principal equation used to evaluate the kinetic of drug release. This equation was introduced by Noyes and Whitney in 1897. The equation is [24]. $DM/dt = KS (Cs – Ct)$ (1)

where M is the mass of solute dissolved in time t, dM/dt is the mass rate of dissolution (mass/time), K is the first order proportionality constant = D/h where D is the diffusion coefficient of the solute in solution, h is the thickness of the

diffusion layer, S is the surface area of the exposed solid, Cs is the solubility of the solid, and Ct is the concentration of solute in the bulk solution and at time t.

When Ct is less than15% of the saturated solubility of the drug Cs, Ct has a negligible influence in the dissolution rate of the solid, the dissolution of the solid is said to be represented under a sink condition.

Zero order models

$C = k_o t$ (2)

Where k_o is the zero order rate constant expressed in unit of concentration/time, and t is the time.

This relationship can be used to describe the dissolution of the drug of many controlled release dosage forms such as, matrices, coated forms, and osmotic devices [13, 25- 26].

First order models

$\mathbf{LogC = logC_o}- K_1 t/2.303$ (3)

Where $\mathbf{C_o}$ is the initial concentration of drug, K_1 is the first order constant, and t is the time. The first order models describe concentration dependent drug release for the system, log cumulative percent drug remaining plotted versus time. This relationship used in the dissolution of the pharmaceutical dosage forms which contain water soluble drugs that released from the pores of the matrices [27].

Higuchi Model

Higuchi in 1961 [28] described the release rate of drug based on Fickian diffusion as a square root of time- dependent process from swellable insoluble matrix. Cumulative percentage of drug released plotted versus square root of time.

$Q = K_H t^{1/2}$ (4)

K_H is the Higuchi dissolution constant.

This relation can be applied for describing the drug dissolution from the types of modified release pharmaceutical dosage forms such as transdermal and matrix tablets [12, 14, and 29].

Hixson- Crowell's Model

Hixson and Crowell in 1931 [30] correlated the release from systems with polymer erosion/dissolution resulting in a change in surface area and diameter of particles or tablets. The cube root of percentage drug remaining plotted versus time.

$$Q_o^{1/3} - Q^{1/3} = K_{HC}t \quad (5)$$

Where Q is the amount of drug released in time t, Q_o is the initial amount of drug in the tablet, and K_{HC} is the constant rate for the Hixson and Crowell rate equation.

This model is applied on the tablet dosage forms where the dissolution occurs in planes that are parallel to the drug surface if the tablet dimensions proportionally, and the initial geometric form remains constant all the time [12].

Korosmeyer- Peppas model

The model of (Korsmeyer 1983 and Peppas, 1985) describes a drug release from a polymeric system. The values of 60% drug release were fitted in Korsmeyer-Peppas model [12, 31].

$$Mt/M\infty = M_{kp}t^n \quad (6)$$

Where $Mt/M\infty$ is the fraction of drug release at time t, k is the release rate constant. The n value is used to characterize the different release mechanisms as shown in the table 1 for cylindrical shaped matrices.

Table 1: Diffusion exponent (n), and drug release mechanism for cylindrical shape.

Diffusion exponent (n)	Mechanism of drug release
0.45 0.45 < n < 0.89 0.89 n > 0.89	Fickian diffusion (case ı) Non- Fickian diffusion Case ıı transport Super case ıı transport

The value for *n* depends on the type of transport, and geometry. Case I or Fickian diffusion describes the condition in which diffusion is slow compared with the rate of chain relaxation. This condition is correlated to $n = 0.50$ for thin film geometries.

For cylindrical and spherical geometries, the characteristic *n* values are 0.45 and 0.43, respectively [32 – 33]. For Case II diffusion, the system is relaxation controlled because the chain relaxation rate is the kinetically limiting component, thus $n = 1$.

Systems with values of *n* ($0.43 < n < 1$) experience anomalous transport and indicate that diffusion and relaxation mechanisms are similar in rate.

Degradation and erosion of polymers

The degradation and erosion of polymers had been discussed [34-35]. Due to degradation, the volume of the material decreases during the bulk erosion causing a decrease over time. Therefore, bulk erosion rates are difficult to control since it is not zero order [36], the difference between degradation and erosion is that scission of the covalent bond by chemical reactions occurs in degradation. While dissolution of chain fragments in noncrosslinked systems without chemical alterations to the molecular structure occurs by Erosion.

Degradation and erosion occur at the surface or in the bulk. The surface degradation occurred by removing the polymer gradually from the surface of the matrix, [13, 37] while, the polymer volume fraction remains unchanged. In the bulk degradation, a less change occurs in the size of the polymer carrier until the entire matrix degraded or eroded. In the case of biodegradable polymers, no evidence indicates if they produce a toxic fragment sizes. The administration of parenteral polymers degrades it into small, metabolic and nontoxic because they are small enough and less complicated elimination mechanisms [38-40].

Polymers types and their uses in medicine and pharmacy

Some polymers are composed of a large variety of linear and branched (co)polymers or cross-linked polymer networks. The properties of these polymers are their ability to undergo a dramatic physical or chemical change in response to an external stimulus. Temperature has a major effect on the polymer systems that respond to temperature due to the ease of conversion of these polymers to be used in the drug delivery applications [41-42].

The pH varies systematically in the body, particularly along the GI tract, where the pH in the stomach is ≈ 1. 2, degrades the polymers molecules. The small intestine is more alkaline, with pH of ≈ 6.8 - 7.2. The pH profiles will also change among cellular compartments. For example, endosomes typically exhibit pH values of 5.0 - 6.8 and lysosomes 4.5-5.5 [43 -44].

The majority of the used polymers for drug delivery are classified as hydrogels, micelles, polyplexes, or polymer drug incorporates. Hydrogels are hydrophilic polymeric networks capable of containing large amounts of water or biological fluids [45]. Physical or covalent crosslinks render hydrogels insoluble in water. Hydrogels can be prepared as a response to various stimuli [46] and have shown good utility in the fields of medicine and pharmacy.

The effect of polymers on drug release

Over the past decades, a large number of studies were accomplished using a variety range of hydrophilic/hydrophobic polymers of different physical and chemical properties. The effect of these polymers had shown a tremendous effect on the release rate of the drug in the vitro experiments [47 -53]. The drug releases from these matrices had been occurred by one or more of the following mechanisms. Firstly, the wetting mechanism, after imbedding the hydrophobic based matrices in the dissolution medium and adequate wetting of the surface has been achieved, there must be a soluble component in the matrix that dissolved easily with a result of pore forming and sometimes disruption of the matrices in some other fashion [54-56]. The drug release is controlled by the permeation through the matrix [54]. Also wetting is not the same for the entire hydrophobic polymer based matrices. The content of soluble quaternary ammonium groups in Eudragit Rl100 is more than that in Eudragit RS100, this property increases the wettability of the matrices by using Eudragit RL100 and increases the release of the drug [55- 56].

Swelling is the second, mechanism which occurs mostly from the hydrogel polymers, the capability of hydrogels to swell in water is due to the hydrophilic groups present in the polymer chains, while its mechanical resistance is due in part to the physical or chemical network cross-linking [57- 59]. It was found that the ratio of the hydrophilic hydrophobic polymers in the matrices had a significant effect on the drug release when the soluble propranolol HCl used as a model drug. When the ratio of the hydrophobic polymer Eudragit RS 100 was 50% with 17% NaCMC and 32% propranolol HCl from tablets of 500mg each, the drug release was completed in less than 4 hours [13]. While using Eudragit RL 100, in a ratio of 20% of NaCMC and 59% RL and 20% of propranolol HCl from tablets of 400mg each, a complete drug release was obtained after 5 hours [37]. The difference between RL100 and RS100 may be referred to their content of the amount of the soluble quaternary ammonium groups which retard the disruption of the polymer and retard the drug release by one hour. By incorporation, the hydrophilic polymers sodium carboxymethylcellulose to the propranolol hydrochloride tablets containing the hydrophobic polymer Eudragit RL100

an alteration on the ratios of drug release from tablets was obtained [13,37]. Because after embedding the matrices in the dissolution medium, the hydrophilic polymer absorbed water and the matrices were swelled, and regulated the drug release. By changing the ratios of hydrophobic/hydrophilic polymer, a controlled release rate of drug was obtained. These results had been used in other studies to investigate the effect of surfactants on the release rate of drug [11 – 12,14]. The swelling behavior of any polymer network depends upon the nature of the polymer, polymer solvent compatibility and degree of crosslinking. However, in the case of ionic networks, swelling kinetics depend upon mass transfer limitations, ion exchange and ionic interaction [20]. The swelling of pH-sensitive hydrogels and the influence of this parameter in chemical, biological and physiological systems had been studied [60, 13].

The third mechanism is the wetting and erosion which was observed when a combination of hydrophilic, hydrophobic polymer and other soluble materials (drug, excipients, etc.) are used in the tablet matrix [40]. By imbedding the tablets in the dissolution medium, the solution started to wet, penetrate the tablets and dissolve the soluble materials from its front, and release the drug from the formed pores within the tablets in the dissolution medium [26, 13].

Finally, the mechanisms' wetting, swelling, and erosion may occur simultaneously when combination of hydrophilic, hydrophobic polymer and other soluble materials (drug, excipients, etc.) are used. In this mechanism, after the tablets were imbedded in the dissolution medium, the solution started to wet the front of the tablets and dissolve the soluble materials, later it penetrated the tablets and caused the release of the drug. At the same time, the dissolution medium penetrates the tablets and an erosion of the hydrophobic polymer occurs from the surface of the tablets and increases the drug release. Meanwhile, the hydrophilic polymer within the matrix accommodates an amount of the dissolution medium; this causes the swelling of the matrix and regulation of the drug release.

To predict the kinetic of drug release from these types, the application of one or more of the above models is useful [11-12].

The therapeutic effects of polymers as drug carrier

Polymer plays an important role in the area of biopaharmaceutics, in which a linear or branched polymer chain behaves either as bioactive or as inert carrier to which a therapeutic is covalently linked, as in the case of polymer-drug conjugates, polymer-protein conjugates, polymeric micelles, and multicomponent polyplexes [61]. Conjugation of the therapeutic to the polymer improves the pharmacokinetic and pharmacodynamic properties of biopharmaceuticals through a variety of measures, including increased plasma half-life, protection of the therapeutic from proteolytic enzymes, reduction in immunogenicity, enhanced stability of proteins, enhanced solubility of low MW drugs, and the potential for targeted delivery [61, 63].

CONCLUSION

The polymers are successfully used since a long time in all the human daily life. Meanwhile, over the past decades, polymers of natural and synthetic origin with other excipients are widely used in pharmacy as drug carriers to modify and regulate the drug release. These mechanisms include dissolution, swelling, diffusion, and erosion. The goal of the polymer use is to maintain a durable therapeutic effective and safe dosage forms. Also, the biodegradable polymers have been used in mediating of safe and effective delivery of bioactive agents to treat an enormous variety of medical conditions.

The kinetic modeling used to predict the drug release; the models are established to describe the relationship between the shape and geometry of the dosage form and its dissolution. Finally, no single model is solely accepted to determine if dissolution profiles are the same. The model dependent methods approve an acceptable model approach to the true relationship between the dependent and independent variables of the dissolution data.

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