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Analytical review

Monolithic Controlled Delivery Systems: Part I. Basic Characteristics and Mechanisms

Rumiana Blagoeva*, Assen Nedev

Institute of Mechanics – Bulgarian Academy of Science
Bl. 4, Acad. G. Bonchev Str., 1113 Sofia, Bulgaria
E-mail: rumi@imbm.bas.bg

**Corresponding author*

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Abstract: *The article considers contemporary systems for controlled delivery of active agents, such as drugs, agricultural chemicals, pollutants and additives in the environment. A useful classification of the available controlled release systems (CRS) is proposed according to the type of control (passive, active or self-preprogrammed) and according to the main controlling mechanism (diffusion, swelling, dissolution or erosion). Special attention is given to some of the most used CRS – polymer monoliths. The structural and physical-chemical characteristics of CRS as well as the basic approaches to their production are examined. The basic mechanisms of controlled agent release are reviewed in detail and factors influencing the release kinetics are classified according to their importance. The present study can be helpful for understanding and applying the available mathematical models and for developing more comprehensive ones intended for design of new controlled delivery systems.*

Keywords: *Controlled delivery, Drug release, Monolithic systems, Diffusion, Swelling, Dissolution, Erosion.*

Introduction

The design and investigation of active agent delivery systems is a multidisciplinary area which has attracted interest from various investigators – mechanical and chemical engineers, ecologists, pharmacists, physicians and others, over the last two decades. The possible applications of these systems include release of drugs, agriculture chemicals and pollutants from polymers, as well as additives from photoresist technology and microlithography into the environment [3, 8, 14, 18, 25, 26, 27, 30].

The traditional delivery systems are characterized by immediate and uncontrolled release kinetics of the delivered active agent. The drug release for example, usually undergoes a sharp increase in concentration followed by a similar decrease in concentration that may causes a dangerous approach to the toxic threshold or fall down below the effective therapeutic level [8].

The purpose of the contemporary delivery systems, or so called controlled release systems (CRS), is to maintain the agent concentration in the target medium at a desired value and to assure a control of the release rate and of the duration of the agent [9, 18, 26].

The object of the present considerations is controlled drug delivery systems, the design and production of which has been rapidly developing especially in the pharmaceutical industry (pills, implants, spray form drugs etc). Controlled drug release systems are of critical importance for the implementation of contemporary therapeutic treatment, which places a stress on drug effectiveness and patient compliance. The design of new more effective CRS brings engineers and pharmacists to work together with a common aim. The development of appropriate mathematical models predicting the realization of the drug delivery is an important and necessary activity for the design of CRS. Mathematical modeling is performed under reasonable assumptions for the structural characteristics of the systems and for the mechanisms of the transfer and physicochemical processes during the drug release.

The aim of the present study is to analyze and systemize the available information for the basic characteristics and mechanisms of the CRS from the point of view of mathematical modeling of controlled agent delivery.

General classification of CRS

Three different categories of CRS can be distinguished: passive preprogrammed, active preprogrammed and active self-programmed [16, 24]. While in the first category the release rate is predetermined and is irresponsive to external biological stimuli, in the second category it can be controlled by a source external to the body as in the case of insulin delivery. The last category which has the greatest potential of the three is characterized by the possibility of self-control induced by biological stimuli such as sugar concentration in the blood.

Two major types of biocompatible materials are used for designing such systems: inorganic (metals, ceramics and glasses) and polymeric (synthetic and natural) [15]. The most common mechanism that controls the drug delivery is diffusion. Two kinds of diffusion controlled systems have been developed. The first is a reservoir system in which the bioactive agent represents a core surrounded by an inert diffusion barrier (Fig. 1), such as a membrane, a capsule, a microcapsule, a liposome, fiber. The second type is a monolithic system in which the active agent is dispersed or dissolved in an inert polymer and its release is controlled mainly by the diffusion as shown schematically on Fig. 2. Chemical control can also be achieved using: biodegradable (bioerodible) systems (see Fig. 3) in which the polymeric matrix converses from insoluble in water into soluble one or pendant chain systems where the drug is covalently bound to the polymer.

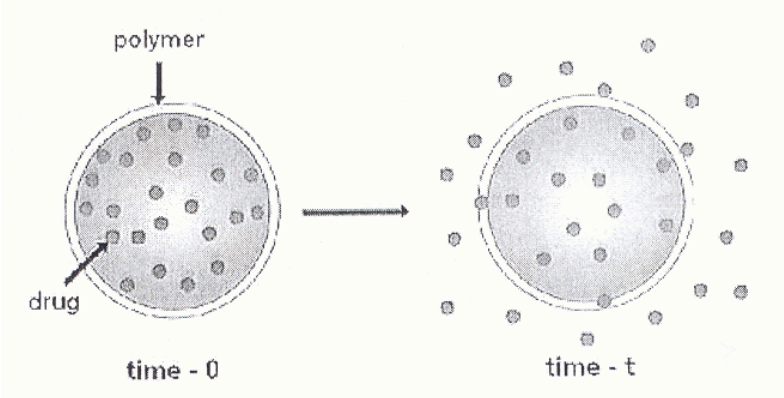

Fig. 1 Schematic representation of reservoir diffusion controlled release systems

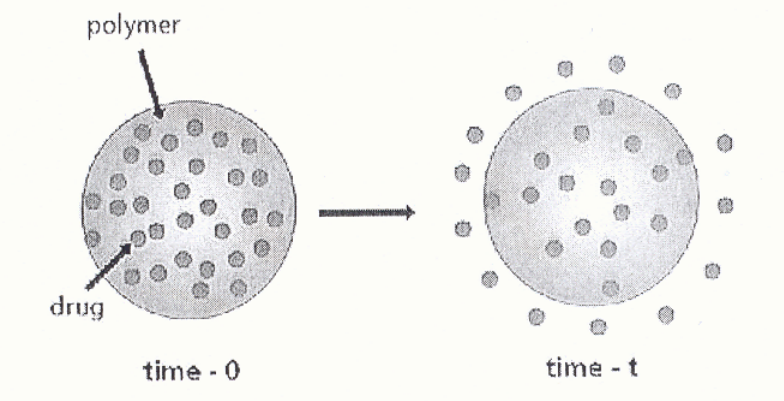

Fig. 2 Schematic representation of monolithic diffusion controlled release systems

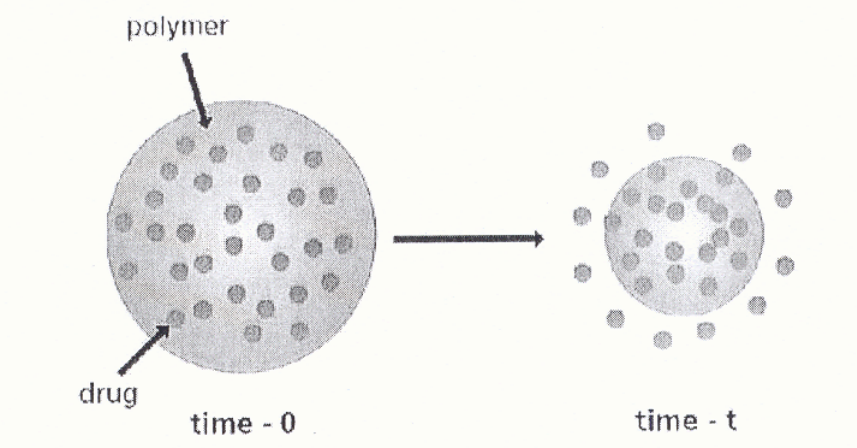

Fig. 3 Schematic representation of biodegradable release systems

Having in mind the large diversity of CRS applications (in contraception, ophthalmic and odontoiatric field, cancer, alcoholism or diabetes treatment e.g.) we can conclude that a complete description of such systems is a heavy task in the frame of the present paper. We focus our attention on a set of the most used CRS – monolithic or matrix systems.

Monolithic systems. Basic Characteristics.

From an engineering point of view, the term "matrix" indicates a three-dimensional network, more often polymeric, fabricated for a particular application and containing an active agent (drug) and other substances such as solvents and excipients. The matrices can be hydrophilic (such as hydroxypropyl methylcellulose – HPMS, methylcellulose, sodium carboxymethyl-cellulose, alginates and scleroglucan) or hydrophobic (such as wax, polyethylene, polypropylene and ethylcellulose) [16, 30].

There are three main approaches for preparation of polymer monolithic systems [8]. The first one is based on mixing the drug, as a thin powder, with the prepolymer and subsequently placing the whole mixture in the polymerization reactor. A matrix can be prepared in advance and then put in contact with a highly concentrated drug solution able to swell the matrix. The solvent is then removed, for example by a physical treatment.

The second approach is based on mechanic-chemical activation, which allows the loading of a drug into a polymeric carrier, thus avoiding the use of solvents whose elimination can be very expensive and delicate operation. Additionally, matrices can be drug-loaded using supercritical fluid techniques. The supercritical fluids are dense as liquid but viscous as gas,

and easily swell the matrix (bringing the drug inside the matrix or extracting solvents) and can be later removed by decreasing pressure.

The simplest way for preparing a monolithic system is to compress, in a proper ratio, the polymer, the drug and the required excipients.

The newest CRS are connected with nanotechnologies and consist of nano or micro particles containing an active agent implemented in a biodegradable polymeric matrix [32].

Although polymeric matrices are characterized by different physical and chemical properties (neutral, polyelectrolyte, liphophilic e.g.), they posses the same structural characteristics [9, 20]. They can be considered as coherent systems with mechanical characteristics in between those of solids and liquids, and as made up by a continuum medium in which high molecular weight molecules are dispersed and collocated to form a continuum three dimensional network [20]. The presence of crosslinks between the polymeric chains hinders polymer dissolution in the liquid phase that can only swell the network. In the case of strong crosslinks (typically chemical covalent bonds) the network does not change over time that is as opposed to the case of prevailing weak crosslinks (typically physical interactions such as Coulombic, van der Waals, dipole-dipole etc.). Distribution of the crosslinks is time-dependent due to Brownian motion of the chains and segments of chains even when the crosslink density is constant with time. As a consequence, each network can undergo erosion depending on the polymer-polymer junction weakness. The picture is more complex when the matrix is constituted by an ensemble of small matrix domains embedded in a continuum.

There exist also contemporary matrices with two networks (interpenetrating structures) originated by two different polymers [17]. These matrices are produced by an initial swelling of a monomer, followed by a reaction to form a second intermeshing network.

According to the porosity, matrix systems can be classified as follows: macro porous with pores dimension between 0,1-1μm; micropores with pores dimension between 50-200 Å, slightly larger than diffusant molecules size; non porous [16]. In the first two categories drug diffusion occurs essentially through pores, while in nonporous systems the drug molecules diffuse through network mesh.

Polymer matrices may gain anisotropy in the process of their manufacturing due to operations predominant in one direction (tablets compression is performed in the axial direction e.g.) [33]. The matrix particles may deform more in one direction, which may induce dissimilar residual stresses and change the porosity, tortuosity and geometric obstructions differently in different directions. Thus the anisotropic structure of the pores can affect the drug diffusion coefficient in different directions.

According to some studies, in certain crystals and polymer sheets, the molecules have a preferential orientation which can result in anisotropic behavior [33]. It has been established that the rate of solvent penetration in a direction parallel to the orientation axis is less than the rate of penetration in the perpendicular direction, which is due to the anisotropic diffusion coefficients of the penetrant.

Mechanisms of controlled agent release from the matrix

Except in some rare cases, matrix systems are stored in dry, shrunken state (without any liquid phase inside) before usage, due to stability and dosing requirements [8, 10]. In that state of the matrix, the drug is in the form of microcrystal, of nanocrystals or in an amorphous state, diffusion through the network meshes dose not exist [21], and the state is known as a ”glassy” one [10]. Upon contact with the release fluids (water or physiological media) penetrating from the surroundings the matrix begins to swell and drug dissolution can take place (for polymers with a transition temperature higher than room temperature). The process of swelling implies the transition from a glassy state to a “rubbery”, swollen one. As soon as the liquid penetrant concentration exceeds a threshold value, the polymer chains unfold and as a consequence of the above mentioned transition, a gel-like layer, surrounding the matrix dry core, begins to appear [9]. This transition implies a molecular rearrangement of the polymeric chains that tend to reach a new equilibrium condition. The time required for this rearrangement denoted by t_r, commonly depends on the temperature and on the concentration of the penetrating solute [10]. When t_r is much greater than the characteristic (relaxation) time of diffusion t_d (defined as the ratio of the diffusion coefficient of the penetrating solvent at equilibrium and the square of a characteristic length of the matrix), then the Fickian solvent diffusion [6] with constant diffusivity takes place. If t_r is much lower than t_d, the solvent penetration may be described by means of Fick’s law with concentration dependent diffusivity. When $t_r \approx t_d$ (up to second exponent order of their ratio), the penetrant absorption does not follow the classical Fikcian law [2, 9, 28, 29]. In this case the macroscopic release of the drug becomes anomalous or non classical [6], while in the other cases it behaves classically, despite the fact that drug release rate usually depends on the solvent concentration distribution. The last dependency can be accounted by the drug diffusivity.

The glassy-rubbery transition significantly increases polymer chain mobility, so that the network mesh enlarges and the drug can dissolve and diffuse through the gel layer. Nanocristal and amorphous drugs are characterized by a higher solubility in aqueous medium with respect to the microcrystal drug (especially for radius smaller than 10 nm), as solubility depends on crystal size. An inverse process of re-crystallization occurs simultaneously due to the lack of thermodynamic equilibrium with unavoidable solubility reduction. Dissolved drug re-crystallization can take place inside the matrix but also in the release environment during the release process. This phenomenon can be characterized by different re-crystallization constants (for details see [11]).

Drug diffusion through the swelling network system depends on polymer/drug physical-chemical characteristics as adsorption and desorption processes are possible on the polymer chains [12]. It depends also on the ratio between the diffusant and mesh size as well as on the matrix topology. Matrix systems can be considered as fractal media for their internal high disorder degree due to complex network topology. It can be demonstrated the diffusion process through fractal (percolative) networks differs a lot from diffusion in non fractal networks [1].

The initial drug distribution in the matrix (the concentration profile) can significantly influence the release kinetics. It is established [22] that very different release kinetics can be achieved by selecting uniform, sigmoidal, steps or parabolic drug concentration. In the case of uniform distribution the dissolution of the drug present at the matrix/release environment

interface can give origin to a burst effect in the release profile followed by a slower release [8]. This effect is observed more significantly in hydroxypropyl methylcellulose (HPMC) matrix systems characterized by a high swellability [26].

According to Langer and Peppas [19], diffusion, swelling and erosion are the most important rate-controlling mechanisms of commercially available CRS. Nevertheless, dissolution and other possible physicochemical interactions can influence CRS behavior in a different extent. When investigating the simultaneous processes in a matrix system two different diffusion types processes should be distinguished – penetration of the external fluid into the matrix (penetrant uptake) and the drug release from the matrix. The penetrant uptake gives origin to the formation of three fronts [4, 5, 8] (as it is shown on Fig. 4). The eroding front is the outer interface which separates the matrix from the release environment. It moves outwards when swelling kinetics is predominant on the erosion process or inwards when erosion is predominant. The position of this front depends on the environment influence as well as structural and physicochemical properties of the matrix. The swelling front, separating the glassy core from the swelling area, moves inward and its rate depends on the polymer/solvent system characteristics (namely, the viscous-elastic properties of the system). In porous matrices this front depends on the system porosity also.

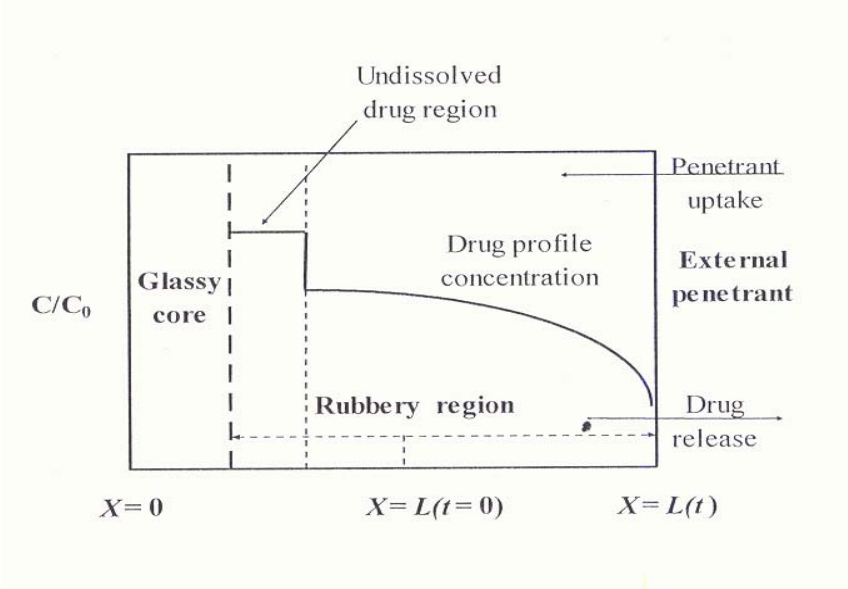

Fig. 4 Three fronts induced by the external fluid penetration:
the swelling front, the diffusion front and the erosion front

In the case of a dissolvable drug, an additional front appears in the swelling area, namely the diffusion front. It separates the part of the matrix, where the drug is dissolved, from that of the undissolved (dispersed) drug and follows the swelling front in its motion. When drug diffusion is much slower than its dissolution, drug release is accepted to be diffusion controlled [15, 33]. Usually it is assumed drug dissolution is realized very rapidly in respect to the rate of its release and the main control is performed on diffusion. There exist few investigations accounting the effect of the finite drug dissolution rate [5, 7]. The role of dissolution and diffusion increases with decreasing of the matrix swelling degree, especially in porous matrices [13].

The scheme on Fig. 4 is a simplified consideration of the real mechanisms of the controlled drug release. The results from the numerical simulations of the considered processes [2, 6, 7,

9, 22, 23, 26, 28, 29, 31, 32] show that except for rare cases, both solvent and drug concentrations have a sigmoidal profile in the matrix rather than a steps profile. Nevertheless this scheme can be very useful in understanding the whole complex of interconnecting processes.

On the basis of the above considerations we can conclude that the most important factors (processes and parameters) for drug release kinetics are as follows:

- mass transfer of the penetrating solvent (Fickian or non-Fickian diffusion); relaxation time of the penetrant diffusion and polymer transition relaxation time;
- agent release as Fickian diffusion with diffusivity dependent on the solvent concentration;
- degree of matrix swelling due to penetrating solvent;
- degree of matrix erosion;
- agent dissolution rate and its solubility limit;
- matrix geometry (planar, cylindrical, spherical and others);
- structural characteristics (such as porosity, distribution of the initial agent loading) and degree of anisotropy;
- physicochemical interactions and parameters of the polymer-agent system.

Generalizing, the agent release behavior can be considered as a function of the above factors if each type of CRS is defined by a set of characteristic values and appropriate operators, representing quantitatively the processes in the system. The detailed evaluation of the domain of this function is an object of next considerations.

Conclusion

A systematic review of the contemporary systems for controlled delivery of active agent has been performed. After some basic classifications according to the type of control, the widely used monolithic CRS have been chosen as a main object under considerations.

The structural and physical-chemical characteristics of polymeric matrix CRS as well as the basic approaches to their production are studied. All key mechanisms that undergo in the monolithic CRS are analyzed and a useful classification of the factors influencing the active agent release kinetics is derived.

The present study can serve as a basis when applying the proposed so far mathematical models and when developing more comprehensive ones, intended for design of contemporary monolithic controlled drug delivery systems.

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