1 Introduction

1.1 Tablet: definition and types

According to the USP, tablets are defined as solid dosage forms containing medicinal substances with or without suitable diluents (USP 31 NF 26 2008). Within this definition, tablets can be classified in different types depending on the formulation and the manufacturing process (compressed, molded, coated, dragée, lozenge, chewable, buccal, sublingual, effervescent, etc…). The most commonly used tablets are compressed tablets. In this case, the tablets are prepared by the application of high pressure to a powder or granules using steel punches and dies.

Tablets can be also classified in three major groups depending on their release behavior: immediate release, where the drug is immediately released after ingestion; delayed-release, where the drug is released after a lag time to avoid a possible destruction or inactivation of the drug in the gastric fluid as well as irritation of the gastric mucosa. The third group corresponds to the sustained release tablets, where the drug is released over an extended period of time. The present study will focus on sustained release tablets.

Sustained release tablets are divided into multiparticle and monolithic tablets (Bauer et al. 2006). In multiparticle tablets several units (crystals, particles, granules, pellets) are embedded maintaining their physical and chemical properties. Multiparticle tablets disintegrate in contact with biological fluids releasing the units with intact properties. The monolithic tablets can either be coated with an inert polymer that releases the drug through diffusion or be matrix tablets, where the drug is embedded in a sponge-like structure and released through different mechanisms (Ritschel et al. 2002).

The release of a drug through a polymer can usually be described by Fick's laws of diffusion.

Fick's first law, is shown in equation (1.1):

$$J_1 = -D_{12}\frac{\partial c}{\partial z} \qquad (1.1)$$

J_1 = *molar flux of drug [mol/cm^{2}s]*

D_{12} = *diffusion coefficient of the drug in the polymer [cm^2/s]*

∂c = *concentration of the drug [mol/cm^3]*

∂z = *length diffusion path [cm]*

This equation is normally used for the description of reservoir-type, diffusion-controlled systems at steady-state diffusion and release. To determine the variation of the drug concentration in the medium with time, Fick's second law is used (equation 1.2):

$$\frac{\partial c_1}{\partial t} = D_{12} \frac{\partial^2 c_1}{\partial z^2} \qquad (1.2)$$

∂c = *concentration of the drug [mol/cm^3]*

∂t = *time [s]*

D_{12} = *diffusion coefficient of the drug in the polymer [cm^2/s]*

∂z = *length diffusion path [cm]*

A simple equation (equation 1.3) was presented by Ritger and Peppas (Ritger et al. 1987) to describe the release behavior from controlled release polymeric devices. The exponent *n* represents the diffusional exponent and depending on its value defines one or other release mechanism.

$$\frac{M_t}{M_\infty} = kt^n \qquad (1.3)$$

M_t = *amount of drug released at a certain time t [kg]*

M_∞ = *total amount of drug released [kg]*

k = *dissolution velocity constant [1/s]*

t = *time [s]*

n = *diffusional exponent*

The values for the diffusional exponent differ depending on the geometry of the system (Peppas 1985; Ritger et al. 1987; Lindner et al. 1996) as shown below (Table 1)

Table 1 Diffusional exponent and mechanism of diffusional release from various non-swellable controlled release systems

Diffusional exponent *n*			Drug release mechanism
Thin film	Cylindrical sample	Spherical sample	
0.50	0.45	0.43	Fickian diffusion
0.50<n<1.00	0.45<n<0.89	0.43<n<0.85	Anomalous (non Fickian) transport
1.00	0.89	0.85	Zero-order release: erosion or relaxation control

There are three main mechanisms to classify controlled release systems (Langer et al. 1983). These mechanisms are shown in Table 2. The mechanisms written in bold letters are those directly related with this study.

Table 2 Classification of controlled release systems by mechanisms

Diffusion controlled
Reservoirs (membranes)
Matrices (monoliths)
Chemically controlled
Erosion
Pendant chain
Solvent activated
Osmotic pressure
Swelling

1.1.1 Diffusion controlled: reservoirs (membranes)

The membrane diffusion controlled systems are the most widely used. The diffusion of the drug takes place through the thin layer that separates the core of the drug from the media. This layer remains intact along the complete gastro intestinal (GI) tract and controls the release by diffusion of the drug through the layer (Bauer 1998).

1.1.2 Diffusion controlled: matrices (monoliths)

The matrices can be classified into systems where the drug is dissolved, into systems where the drug is dispersed or into porous matrix systems.

In the case where the drug is dissolved in the polymer, the drug release is controlled by the solubility of the drug in the polymer. The controlled release mechanism can be explained by Fick's second diffusion law (equation 1.2).

When the drug is dispersed, the release is controlled by the dissolution of the drug (Narasimhan 2000). The kinetic release can be explained with the equation (1.4):

$$Q = A\sqrt{Dc_s \cdot (2c_0 - c_s) \cdot t} \qquad (1.4)$$

Q = *amount of drug released at a certain time t [mol/cm^2]*

A = *cross sectional area of the polymer film [cm^2]*

D = *diffusion coefficient of the drug in the polymer [cm^2/s]*

c_0 = *total concentration of the drug in the matrix [mol/cm^3]*

c_s = *saturation concentration of the drug [mol/cm^3]*

t = *time [s]*

The same equation can be used to explain the release of the drug through the pores of a matrix system, considering the porosity and tortuosity of the structure, as described in equation (1.5):

$$Q = \sqrt{D\frac{\varepsilon}{\tau}(2c_0 - \varepsilon \cdot c_s)c_s \cdot t} \qquad (1.5)$$

Q = *amount of drug released at a certain time t [mol/cm^2]*

D = *diffusion coefficient of the drug in the liquid in the pores [cm^2/s]*

ε = *porosity of the matrix*

τ = *tortuosity from the pores*

c_0 = *total concentration of the drug in the matrix [mol/cm^3]*

c_s = *saturation concentration of the drug [mol/cm^3]*

t = *time [s]*

1.1.3 Chemically controlled: erosion

The erosion type of controlled release system can be used in both reservoirs and matrices. The release from the reservoirs is dependent upon the permeability and thickness of the layer. These variables will define the release.

The release from matrices is controlled by a combination of diffusion and erosion. The erosion can be homogeneous or heterogeneous. When the erosion is taking place in the entire matrix structure the erosion is homogeneous; when the erosion starts on the surface of the polymer matrix it is heterogeneous.

1.1.4 Chemically controlled: pendant chain

This kind of controlled release is not as extensively used as are the cases described before. The drug is chemically bonded to the polymer and is released through an enzymatic or hydrolytic reaction that separates the drug from the polymer structure.

1.1.5 Solvent activated: osmotic pressure

The release of the drug is controlled by the tablet structure (OROS= Osmotic Release Oral System). The tablet is made of a drug containing core where the drug is embedded, and a semi permeable membrane with an orifice. The solvent diffuses through the membrane, the volume of medium dissolves the drug and an equal volume of dissolved drug is released through the orifice (Conley 2006).

1.1.6 Solvent activated: swelling

This controlled release mechanism takes place in polymeric systems where the drug is dissolved or dispersed in the polymer. The moment the system comes in contact with the medium, the polymer swells, lowering its glass transition temperature and the polymer allows the drug to dissolve. It is possible to recognize two main interfaces. The first separates the glassy state from the rubbery state (swelling interface) moving inwards to the center of the core, and the other separates the rubbery state from the medium (polymer interface) moving outwards. In the last case the polymer normally dissolves (Langer et al. 1983).

Between the glassy and the rubbery state a macromolecular relaxation takes place. This relaxation affects the drug diffusion through the polymer, giving Fickian or non-Fickian diffusion (Colombo 1993).

The transport of the drug through the polymer can be controlled by the macromolecular relaxation or by the diffusion of the drug through the rubbery polymer. The Deborah number, described in the equation (1.6), is used to characterize this transport:

$$De = \frac{\lambda}{\theta} \qquad (1.6)$$

De =*Deborah number*

λ = *Relaxation time [s]*

θ = *Diffusion time [s]*

When the Deborah number is greater than 1, the transport is completely relaxation-controlled. A number lower than 1 means the transport is completely diffusion-controlled. When the value is close to 1 an anomalous diffusion behavior takes place, because the relaxation and diffusion time are similar (Vrentas et al. 1975).

To determine if the release of the drug follows zero-order release or Fickian diffusion, the swelling interface number, described in the equation (1.7), is used:

$$Sw = \frac{v\delta(t)}{D} \qquad (1.7)$$

Sw = *"Swelling interface" number*

v = *velocity of the swelling interface [cm/s]*

δ = *sample thickness [cm]*

t = *time [s]*

D = *diffusion coefficient of the drug in the polymer [cm^2/s]*

When the *Sw* is lower than 1, a zero-order release can be expected. A *Sw* greater than 1 means Fickian diffusion.

This overview provides necessary knowledge of the different possible release mechanisms required to discuss the topic of this investigation, manufacturing of matrix tablets to provide

sustained release of highly soluble by combining countercharged poly(meth)acrylic polymers. The next point to discuss is the variety of excipients that can be used to build a matrix.

1.2 Excipients used to build a matrix

Matrix formulations are commonly chosen for controlled release due to the several advantages they offer. The manufacturing of these tablets does not require special equipment. In several cases, the drug release velocity depends on the matrix structure and not on other factors like intestine motility, electrolyte concentration of the medium or pH. Compared to coated tablets, matrix tablets are more robust. Coated tablets are also more likely to lead to a dose dumping effect if the film is not properly formed or is physically damaged post manufacture (Ritschel et al. 2002).

The excipients used to build a matrix can be classified by their chemical structure and by their properties as hydrophilic, inert, lipidic, biodegradable and resin matrices (Gandhi et al. 1999).

1.2.1 Hydrophilic (Cellulose ethers and esters)

These excipients are the most widely option to use for matrix tablets to provide sustained release. These polymers are semisynthetic products obtained by alkylation of cellulose. The differences between the various types reside in the different degree of substitution and degree of polymerization varying also the total molecular weight (Figure 1), and therefore their release characteristics. The release is based on swelling process leading to a gel layer formation (Vueba et al. 2005).

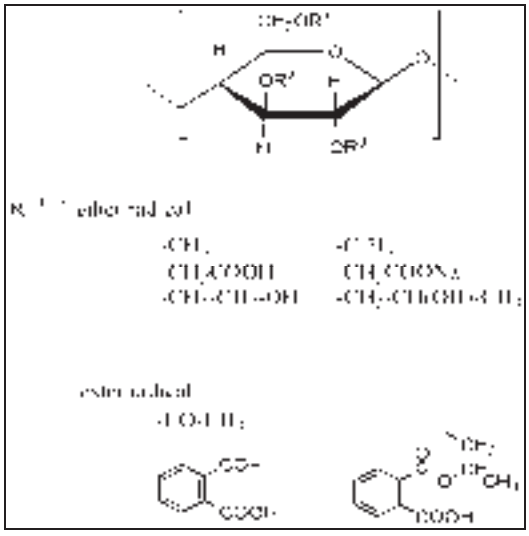

Figure 1 Structures of cellulose esters and ethers