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Towards a rational basis for selection of excipients: *Excipient Efficiency* for controlled release

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ABSTRACT

There are many factors influencing the drug release behaviour from a pharmaceutical formulation as the particle size of the drug and excipient, porosity of the system or geometrical phase transitions of the components. Therefore, the choice of the adequate excipient to achieve a specific drug release profile is mainly based on the experience and the trial and error method. Taking into account the directives towards the application of the "Quality by Design" approach, in this study the *Excipient Efficiency* (*EE*), a parameter able to quantify the capability of an excipient to control the drug release, has been developed. *EE* was initially calculated dividing the total porosity of the system by its diffusional release rate constant. The influence of several factors on this parameter has been evaluated. As a result, the final parameter has been corrected based on the drug solubility and the excipient particle size. *EE* provides a rational basis for identifying the most adequate excipients for a concrete formulation.

1. Introduction

In the last decades the importance of the role of excipients in drug formulation has increased as they can modify the onset, duration and intensity of drug action. Natural, semisynthetic and synthetic excipients have been employed as matrix tablet formers in different combinations and proportions trying to reach the desired release profiles. The reasons for modifying the drug release are varied and range from the slow release of highly water-soluble compounds, carrying of drugs to the target organ or cell, fitting to a predesigned release profile, reducing the number of daily administrations improving the patient compliance and minimizing side effects (Maderuelo et al., 2011).

Classically, excipients for matrix controlled release devices have been classified based on their ability for producing swelling, inert or lipid matrices, being the cellulose derivatives the more employed ones.

Several authors have thoroughly studied the factors that influence drug release from the matrix system, as for example particle size, viscosity or porosity (Langer and Peppas, 1981).

The polymer particle size has been related to the ability to form a gel layer, so that a slower drug release rate can be obtained employing small particles which produce faster a coherent gel layer (Caraballo, 2010; Maderuelo et al., 2011; Viridén et al., 2009).

With respect to viscosity, which influences the drug diffusion and the transport of water through the gel layer in hydrophilic matrices, an inverse relationship between release rate and gel viscosity has been shown (Brady et al., 2009; Onofre et al., 2009).

On the other hand, the influence of initial porosity is more related to inert matrices, increasing the transport properties of the system and therefore, having a positive influence on drug release. The initial porosity and the porosity developed due to the leaching of the drug are the main factors conditioning the release of the drug from inert matrix systems, i.e., nano, micro or macro systems where the drug is entrapped in a random network of insoluble and not swelling particles of excipient.

In order to provide a better knowledge of the internal structure of pharmaceutical systems, percolation theory has been extensively applied (Aguilar-de-Leyva et al., 2011; Fuertes et al., 2010; Miranda et al., 2007). This is a multidisciplinary theory which studies the distribution of the components of disordered and chaotic systems.

Percolation theory defines a cluster as a group of neighbor positions occupied by the same component in a lattice (Castellanos-Gil et al., 2008). When this cluster extends from one side to the other sides of the lattice it is called a percolating cluster. The main concept of this theory is the percolation threshold (pc) which can be defined as the concentration of a component at which there is a maximum probability of appearance of a percolating cluster of this substance.

The percolation threshold is a concentration of a component that usually corresponds to a region where important changes in

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the properties of the dosage form are expected. The application of percolation theory allows predicting the concentration range leading to an adequate distribution of the components in the dosage form. Furthermore, the identification of the critical points allows avoiding the vicinity of these regions of high variability, in order to obtain more robust dosage forms (Caraballo, 2010).

For example, the release behaviour of inert matrix systems is strongly influenced by the drug percolation threshold. At this concentration, the phase transition of the pores (adding the initial pores and the pores due to the dissolution of the soluble substances) is expected. When this pores network starts to span the whole matrix, the diffusion through the system is allowed, assuring the release of the whole dose of the drug.

On the other hand, the percolation threshold of the matrix forming polymer, constitutes an important critical point in hydrophilic matrices. Above this point, a coherent gel layer is obtained, allowing a controlled release of the drug. This hypothesis, formerly based on the kinetic parameters, has been confirmed by a recent work developed in collaboration between the Universities of Seville and Nottingham using Fluorescence Confocal Microscopy, which allows visualization of the structure of the gel layer at different time points (Mason et al., 2015).

Due to the high number of factors influencing the release behaviour from sustained release drug delivery systems, currently the choice of the excipient responsible for the controlled release of a pharmaceutical formulation is mainly based on the trial and error method.

The current regulatory environment established in the directives of the *International Conference on Harmonisation* (ICH Expert Working Group, 2009), encourages the application of the concept of "Quality by Design" during pharmaceutical development in order to increase product and process understanding. "Quality by design" principles can also facilitate innovation and continuous improvement of the product.

With this aim, Caraballo proposed a new parameter called *Excipient Efficiency*. This parameter was calculated as the ratio between the total porosity of the matrix, determined as the addition of the initial porosity plus the porosity due to the dissolution of the drug, and the slope of the Higuchi constant. This study was distinguished with one of the Prices of the Controlled Release Society in its 28th Symposium in San Diego, California (Controlled Release Society, 2001).

The objective of the present study is to develop a parameter able to quantify the ability of an excipient to control the drug release from a pharmaceutical formulation, allowing an easy comparison between different excipients and providing a rational basis for identifying the most adequate excipients for a concrete formulation.

2. Materials and methods

2.1. Materials

The following drugs were employed in the manufacture of the different matrix tablets:

Potassium chloride (Acofarma, Spain), Verapamil HCl (Recordatti, Italy), Carbamazepine (Fagron, Spain), Sodium Diclofenac (Fagron, Spain), Acyclovir (Kern Pharma, Spain), Theophylline (Roig Farma, Spain), Acetaminophen (Roig Farma, Spain), Ranitidine HCl (Acofarma, Spain).

The following materials were employed as matrix forming excipients:

Eudragit RS-PM (Hüls Española, Spain), ETHOCEL 7 FP, ETHOCEL 10 FP, Methocel K100 LV CR, Methocel K100 LV, Methocel K4 M CR, Methocel K4 M (Colorcon Phamaceutics, UK).

Lactose Fast Flo (Foremost, U.S.A), and Microcrystalline cellulose (AVICEL PH 102) (FMC BioPolymer, Ireland) were employed as fillers.

Magnesium stearate (Fagron, Spain) and Colloidal silicon dioxide (AEROSIL 200) (Evonik, Germany) were employed as lubricant and flow aid, respectively.

2.2. Tablet manufacturing

The composition of the studied matrices is shown in Table 1. The mixing process was carried out in a Turbula mixer (Willy A.

Table 1
Composition of the studied matrices.

Matrices		Compression	Composition (%w/w)	
Inert	Binary	Ultrasound	KCl	10,20,30,40,50,60,70,80,90%
			Eudragit	90,80,70,60,50,40,30,20,10%
		Eccentric	KCl	10,20,30,40,50,60,70,80,90%
			Eudragit	90,80,70,60,50,40,30,20,10%
	Multicomponent	Eccentric	Carbamazepine	30%
			Ethocel (7 FP, 10 FP)	40%
			Lactose	29%
			SiO_2	0.50%
			MgSt	0.50%
Hydrophillic	Binary	Eccentric	KCl (25–50, 150–200, 250–300, 300–350 μm)	20,30,40,50,60,70,80,90%
			HPMC K4M (25–50, 150–200, 250–300 μm)	80,70,60,50,40,30,20,10%
		Eccentric	Drug (ranitidine, aciclovir, theophylline, acetaminophen)	60,70,80,90,95%
			HPMC K4M	5,10,20,30,40%
	Multicomponent	Eccentric	Verapamil	30%
			HPMC (K4M, K4MCR, K100LV, K100LVCR)	15,20,25,30%
			Microcrystalline cellulose	35,30,25,20%
			Lactose	19%
			SiO_2	0.50%
			MgSt	0.50%
	Multicomponent	Eccentric	Carbamazepine	30%
			HPMC (K4M, K4MCR, K100LV, K100LVCR)	15,20,25,30%
			Microcrystalline cellulose	19%
			Lactose	35,30,25,20%
			SiO_2	0.50%
			MgSt	0.50%