HPMC AND THEOPHYLLINE CO-PRECIPITATION FROM SUPERCRITICAL CO_2: EXPERIMENTAL AND THEORETICAL ANALYSIS OF RELEASE KINETICS FROM TABLETS

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Among the many kinds of controlled delivery systems, a very important class is represented by those constituted by hydrophilic polymers. The aim of this work is to study experimentally and theoretically study the release kinetics from tablets made up by a compressed theophylline-HPMC powder obtained by means of co-precipitation from supercritical CO_2. It is expected that with this a deeper contact between drug and polymer with respect to the tablets prepared with the untreated materials is reached. This fact, together with a pronounced variation of particle morphology after CO_2 treatment, introduces also a change in the internal morphology of the CO_2-matrix and may lead to a slower release of the drug compared to the matrices based on untreated materials
In order to understand the key mechanisms ruling drug release from tablets, a semi-empirical model was developed to fit our experimental data.
presented and discussed.

INTRODUCTION

The use of hydrophilic polymers is currently the most applied method in controlling the release of drugs from oral pharmaceutical dosage forms. Hydroxypropylmethylcellulose (HPMC) is a polymer frequently used in formulation of controlled release devices, for its ability to form rapidly a gel layer at the matrix periphery exposed to aqueous media [1]. Up to now several sustained-released systems of drug have been elaborated using supercritical fluid processes [2-4]. Furthermore many authors reported the capability of supercritical fluids, and in particular of CO_2, to change size and morphology of the processed particles. It seemed to be very interesting to test the effect of this medium on the physical and morphological characteristics of two different molecular weights of hydroxypropylmethylcellulose (HPMC) E5 and K100 and a drug. Choosing the theophylline as model drug, the capability of promoting a sustained-release of the drug by HPMC is studied and the release of the drug is modelled in order to evidence the influence of the supercritical fluid technology treatment.

I - EXPERIMENTAL RESULTS

A mixed solvent (1:1 mixture of dichloromethane/ethanol) was chosen for the antisolvent precipitation process.

Theophylline, E5 and binary systems having low content of E5 were easily precipitated.
On the other hand, systems containing HPMC K100 were more difficult to precipitate and very scarce yields were obtained. This was probably due to the high affinity of CO_2 for the polymer.
Physical characterization of drugs and polymer before and after the treatment with the supercritical fluid does not evidence any variation except morphological changes.
In order to test the effect of the inclusion of the drug in the polymer different dissolution tests were performed at different pH.

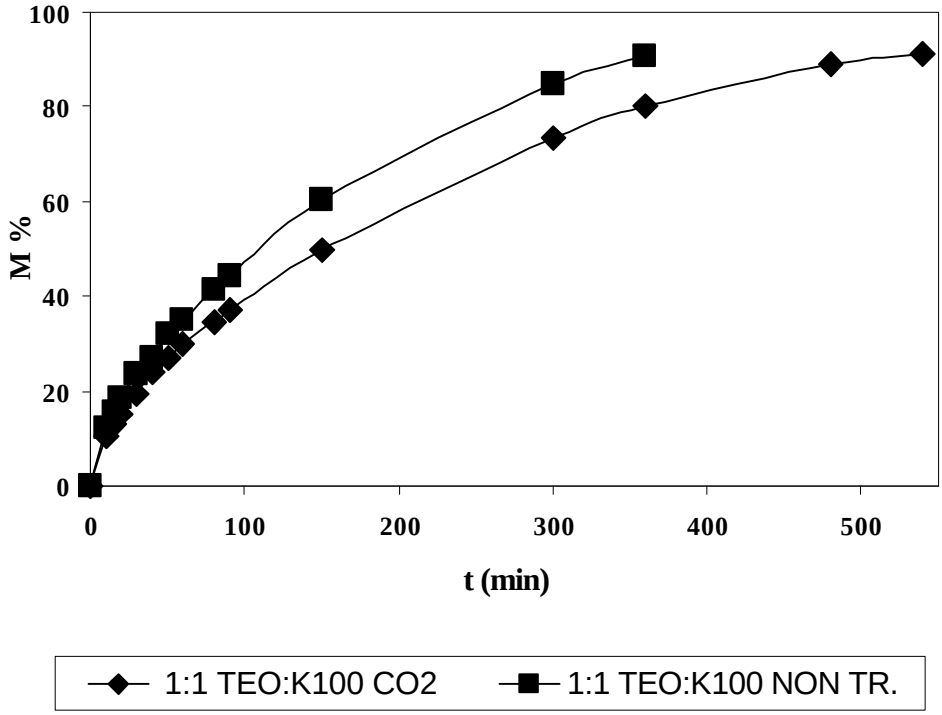

Figure 1: Comparison release profiles obtained with the materials obtained by antisolvent coprecipitation and with the untreated materials

No remarkable influence of the antisolvent precipitation process was observed the pure theophyline.
For the solid dispersed forms (SD) the increased amount of HPMC E5 does not influence the dissolution rate which is also unaffected by the change of pH. The HPMC K100 has a better effect on the dissolution rate in respect to the HPMC E5 and both celluloses modify the dissolution rate of the pure drug towards the desired effect. However the influence is not so dramatic.
Matrix systems were prepared both with untreated materials and with materials obtained through the supercritical antisolvent precipitation.
In figure 1 as an example the release profiles obtained with the matrix obtained with the materials coprecipitated with the antisolvent (1:1 TEO:K100 CO2) and with the matrix prepared with the untreated materials (1:1 TEO:K100 NON TR) are reported. The

comparison demonstrates a significantly slower drug release rate thanks to the broader contact of the drug with the carriers and the subsequent change in the internal morphology of the matrices.

II - MODELING

Drug release kinetics from compacted systems made up by hydrophilic polymers is affected by many factors such as polymer swelling, polymer erosion and drug dissolution characteristics, beside drug/polymer ratio and the tablet geometric features. Indeed, upon contact with the release fluids (water or physiological media), the polymer glassy dry state progressively transforms into a rubbery swollen one and, consequently, drug dissolution takes place. Firstly, the release fluid (solvent) dissolves the drug amount present at tablet/release environment interface giving origin to a pronounced burst effect in the release profile [5], then, it penetrates into the tablet according to the local porosity and to the polymer physical properties. As soon as the local penetrant concentration exceeds a threshold value, the polymeric chains become to unfold so that the glassy / rubbery polymer transition occurs and a gel layer surrounding the tablet begins to appear [6]. The glassy - rubbery transition enormously increases polymer chains mobility, so that the drug can diffuse through the gel layer. Initial burst apart, the release kinetic is heavily ruled by the gel thickness, which in turn depends on the relative position of the eroding front (separating the release environment from the gel and moving outwards) and the swelling front (separating the dry glassy tablet core from the gel layer and moving inward). Additionally, in the case of sparingly soluble drugs, a third front, the diffusion front, can appear between the outer portion of the gel, where the drug is completely dissolved, and the inner part, where the drug is not yet dissolved despite the rubbery state of the polymer [7]. Accordingly, one aim of this work is to develop a new mathematical model of semi-empirical nature, but founded on reasonable assumptions, leading to an analytical solution.
The main idea is to generalize the classical equation describing the dissolution of a solid drug in sink conditions [8]:

$$\frac{\mathrm{d}C_\mathrm{r}}{\mathrm{d}t} = -\frac{k_\mathrm{d}\,A}{V_\mathrm{r}} C_\mathrm{s} \qquad (1)$$

where t is time, C_r and C_s are drug concentration and solubility in the release environment, respectively, A is the release surface area, V_r is the release environment volume and k_d is the dissolution constant, by properly incorporating in it the effect of the gel layer resistance R and the tablet composition at the swelling front. So, bearing in mind that the global resistance to diffusion of a multi-layered membrane is given by the sum of the resistance of each layer [9] and $1/k_d$ can be thought as the drug dissolution resistance, eq(1) can be re-written as:

$$\frac{\mathrm{d}C_\mathrm{r}}{\mathrm{d}t} = -\frac{x_\mathrm{d}\,A}{V_\mathrm{r}} \frac{C_\mathrm{s}}{\left(\frac{f}{k_\mathrm{d}} + R\right)} \qquad (2)$$

where x_d is the drug volume fraction at the swelling front and f is a parameter accounting for the fact that, due to gel presence, the drug dissolution constant k_d will be lower than that relative to pure solid drug dissolution [10]. x_d accounts for the fact that drug release also depends on the effective drug dissolution area at the swelling front.
In order to choose a reasonable, although empirical, expression for R, we suppose that its value is mainly affected by the gel layer thickness. A proper expression can be given by:

$$R = B\left(1 - \exp^{-bt}\right) \qquad (3)$$

where B and b are two model parameters to be determined by data fitting (of course, gel permeability P is equal to 1/R).
In order to complete the model, the time variation of the release area A has to be estimated. At this purpose A is identified with the geometrical area competing to the diffusion front (in so doing we assume that what is crucial for drug delivery is not the tablet geometrical area, coinciding with the area of the eroding front, but the area at the diffusion front) [11]. Moreover, for the sake of simplicity, we assume that the ratio K between the height h and the radius R of the cylinder delimited by the diffusion front does not modify with time and it is equal to the unswollen tablet height/radius ratio. Accordingly, A modifies with time in the following way:

$$A = 2\mathrm{p}(1+K)R^2(t) \tag{4}$$

In other words, the problem of the A time dependence is shifted on the R one that can be determined by means of the following mass balance:

$$M_0 = V_\mathrm{r} C_\mathrm{r}(t) + \mathrm{p}KR^3(t)C_0 \tag{5}$$

where M_0 is the drug amount initially contained in the tablet. In writing eq.(5), we implicitly assume that the drug amount contained in the tablet portion delimited by the erosion and diffusion front is negligible. The combination of eqs.(4) and (5) yields the time variation of A(t) that inserted into eq.(2) gives model final form whose solution is:

$$C_\mathrm{r}^+ = \frac{C_\mathrm{r}}{M_0/V_\mathrm{r}} = 1 - \left(1 - \frac{2(1+K)x_\mathrm{d}}{M_0^{1/3}}\left(\frac{\mathrm{p}}{K^2C_0^2}\right)^{1/3} F(t)\right)^3 \tag{6}$$

$$F(t) = C_\mathrm{s}\left[\frac{t}{B + 1/f\,k_\mathrm{d}} + \frac{\ln\left(1 + B\left(1 - \mathrm{e}^{-bt}\right)k_\mathrm{d}/f\right)}{(B + 1/f\,k_\mathrm{d})b}\right] \tag{7}$$

III – RESULTS OF THE MODELING

Figure 2 shows the comparison between the model best fitting and the experimental data referring to matrix prepared with the materials coprecipitated with the antisolvent process and using HPMC K100 (1:1 TEO:HPMC K100 PH 1.2 CO2). It can be appreciated the very good data description in the entire range of the experimental time. This means that the hypotheses on which the model was build are reliable and the degree of approximation introduced is acceptable. The fitting procedure is led knowing that M_0 = 75 mg, K = 0.154, x_d = 0.5, C_0 = 565 mg/cm^3, C_s = 12.5 mg/cm^3, and k_d = 0.188 cm/min. The resulting fitting parameters are f = 0.34, B = 72 min/cm and b = 0.028 1/min. One of the most important aspect of this model relies in the possibility of reducing all the information contained in the experimental data into a simple curve indicating the time evolution of tablet resistance to release the drug (represented by R in our model) or, equivalently, to tablet permeability (P = 1/R) as indicated in figure 3. According to this theoretical analysis, we can affirm that at the beginning, tablet permeability is high, while it rapidly decreases with time until reaching a threshold value associable to tablet permeability in the swollen state.

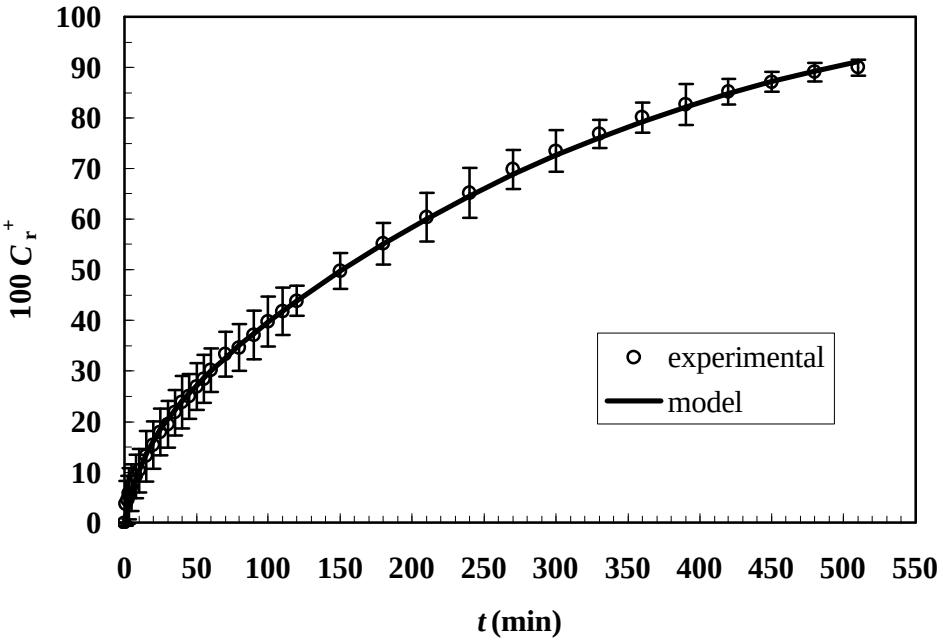

Figure 2: Comparison between the model best fitting (solid line) and experimental data (open circles) referring to tablets 1:1 TEO:HPMC K100 PH 1.2 CO2 (vertical bars indicate datum standard error).

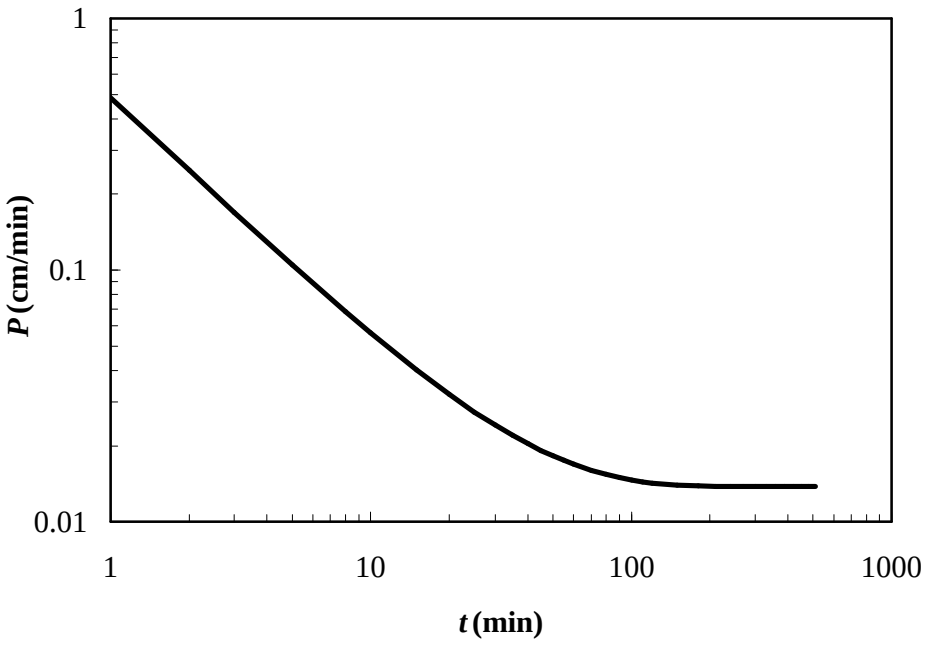

Figure 3: Tablet permeability (P) time dependence coming from model data fitting performed on data shown in figure M1.

This behaviour can be explained remembering that our permeability (or resistance) accounts for both drug dissolution and diffusion through the developing gel layer.

Accordingly, initially, the only resistance is that of the dissolution of the drug present in the outer tablet layer as no gel stratum has yet built up (in this situation, R is very small and P very high being equal to k_d/f). Then, as gel stratum develops, the resistance rapidly grows up and permeability is considerably lowered. Due to the simplification adopted in model building, we must renounce to use this final permeability value to estimate real gel permeability and, consequently, drug diffusion in it. Nevertheless, we can perform relative comparisons between different P vs t curves associated to different drugs and tablets.

CONCLUSION

On the basis of experimental results analyzed with the model developed in the present work it is possible to evidence the differences in the release profiles obtained with the different systems prepared. Two different mechanisms of released are showed by the tablets prepared with the untreated and with the materials obtained by antisolvent precipitation technique.

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