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Supplementary material

SUPPLEMENTARY MATERIAL TO

Enhancement of the dissolution profile of the diuretic hydrochlorothiazide by elaboration of microspheres

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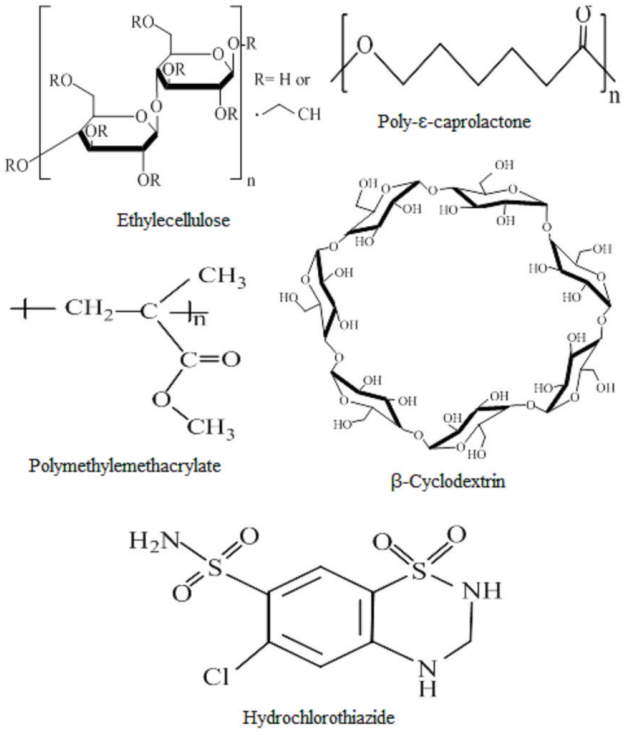

Scheme S-1. Structures of polymer carriers and HCTZ.

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PMMA CHARACTERIZATION

IR (cm^{-1}): 1721.50 (C=O ester), 1141.72 (C–O ester), 2949.52 (C–H, stretch), 1434.43 (CH_3 bending); ^{13}C-NMR (300MHz, $CDCl_3$), δ/ ppm): 178 (C=O), 52 O–CH_3, 31 (CH_2), 17 (C–**C**H_3); $\bar{M}_v$ (F1): 31903 g mol^{-1}, $\bar{M}_v$ (F2): 17576 g mol^{-1}, $\bar{M}_v$ (F3): 12075 g mol^{-1}; T_g (F1) = 152 °C, T_g (F2): 144°C, T_g (F3): 138 °C.

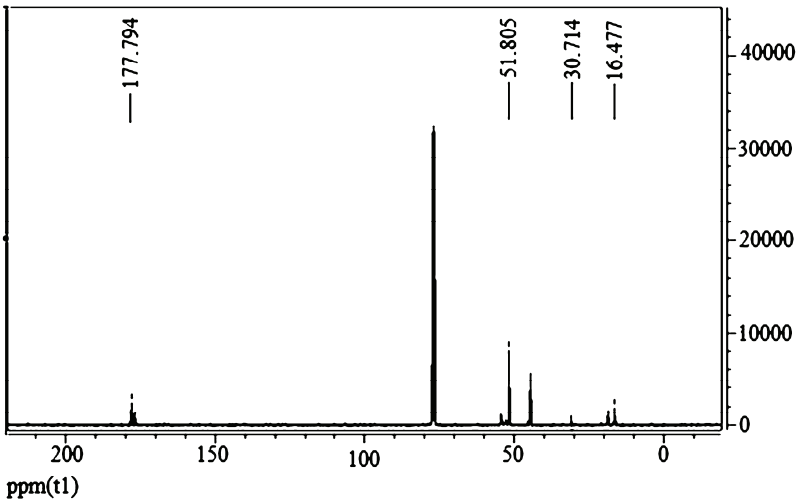

Fig. S-1. NMR spectrum of PMMA.

MICROSPHERES CHARACTERISTICS

*Determination of drug loading (*DL*)*. The drug content in the HCTZ microspheres was determined by extracting 10 mg of the microspheres dissolved in an adequate volume (20 mL) of methanol/water 1:1, after extracting the microspheres in an appropriate solvent under stirring at a rotation speed of 500 rpm for 24 h. The solution is examined at 273 nm to determine the content of HCTZ. Each determination was performed in triplicate.

The drug loading (*DL*) is defined as the ratio of HCTZ mass in microspheres and the mass of microspheres and is calculated according to Eq. (1):

$$DL\,/\,\% = 100\frac{\text{Mass of HCTZ in microspheres}}{\text{Mass of microspheres}} \quad (1)$$

Yield of microspheres. The yield of microsphere was calculated according to Eq. (2):

$$Y/\%= \ 100\frac{\text{Practical mass of microspheres}}{\text{Theoretical mass of microspheres}} \quad (2)$$

where the practical mass of microspheres is the mass of the microspheres recovered and the theoretical mass of microspheres is the mass of the carrier and the drug used in the formulation.

Particle size. The microspheres were also examined by optical microscopy (Optika 4083.B1) to determine the size distribution of the various sphere preparations. The mean microparticle diameter was measured by examining more than 500 microparticles and the

number mean diameter (d_{10}), the surface mean diameter (d_{32}), the weight mean diameter (d_{43}) and size distribution (δ) were calculated as follows:

$$d_{10} = \sum n_i d_i / \sum n_i \quad (3)$$

$$d_{32} = \sum n_i d_i^3 / \sum n_i d_i^2 \quad (4)$$

$$d_{43} = \sum n_i d_i^4 / \sum n_i d_i^3 \quad (5)$$

$$\delta = d_{43}/d_{10} \quad (6)$$

where i is the index of the population, d_i is the particle diameter of population i and n_i is the number of particles in class i.

Scanning electron microscopy (SEM). The surface structure and porosity of the HCTZ microspheres were investigated by scanning electron microscopy (EDX Quanta 250 tungsten wires from the company FEI) at 50 Pa under a 10 kV acceleration voltage.

XRD analysis. To confirm the effective HTCZ encapsulation, microspheres were characterized by XRD with a RIGAKU MINIFLEX 600 logical acquisition mini flex (y=1.541A°) in the 2θ range from 5 to 70°. X-Ray diffractograms of pure HCTZ, carriers and drug microspheres were compared.

Differential scanning calorimetry (DSC). Thermal analysis (DSC) was performed on the microspheres using a Netzsch DSC 214 Polyma DSC21400A-0514-L differential scanning calorimeter. All the samples were prepared by weighing (12 mg of pure HCTZ, 13 mg of ethyl cellulose, 19 mg of β-cyclodextrine and 10 mg of microspheres). The analysis was made at a rate of 10 °C min^{-1} within the temperature range 27–400 °C.

Infrared spectroscopy. The samples were characterized by infrared spectroscopy using an Alpha Bruker IR spectrometer in the spectral wavelength range from 400 to 4000 cm^{-1}.

Table S-I. Data of amount of HCTZ released after 1, 2 and 8 h

Lot	HCTZ released, % (at pH 1.2)			HCTZ released, % (at pH 7.4)		
	1 h	2 h	8 h	1 h	2 h	8 h
L1	66	69	72	94	98	100
L2	27	31	35	39	52	58
L3	18	27	47	16	37	77
L4	57	73	89	65	89	100
L5	82	91	99	95	100	100
L6	64	71	84	69	87	100
L7	68	83	87	100	100	100

RELEASE MECHANISMS AND MATHEMATICAL ANALYSIS

In the literature, many theoretical or empirical models are described to explain the process of mass transfer. In this study, four of these models were chosen for quantitative prediction of controlled drug delivery. The selected models were the zero-order, the first order, the Higuchi and the Korsmeyer models.[1–4] Thus, the choice of the best model was based on the value of correlation coefficient, r^2, obtained after tracing experimental results according to the equations corresponding to the selected model:

Zero-order:

$$Q_t = Q_0 + K_0 t \tag{7}$$

First Order:

$$\log Q_t = \log Q_0 + \frac{K_1 t}{2.303} \tag{8}$$

Higuchi:

$$Q_t = k_H t^{1/2} \tag{9}$$

Korsmeyer–Peppas:

$$M_t / M_{t\infty} = k_{KP} t^n \tag{10}$$

where Q_t/Q_0 is the fractional drug release at time t; K_0, K_1, K_H and K_{KP} are the zero order, first order, Higuchi and Korsmeyer release constants, respectively; and n the release exponent that indicates of the mechanism of release.

In fact, the Higuchi model is able to describe the release of a soluble or poorly soluble drug in water from a semi-solid or solid matrix system.[3] Therefore, the value of n was used by Peppas[5] in order to characterize the various release mechanisms. Thus, when $n = 0.5$, the release mechanism is Fick diffusion and is time-dependent, and as a non-Fickian model if n is between 0.5 and 1.0, case II transport if $n = 1.0$, and super case II transport if $n > 1.0$. Then, if $n < 0.5$, the diffusion mechanism could be related to the quasi-Fickian model.

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