Supplementary Data

Electroconductive smart Polyacrylamide-Polypyrrole hydrogel: a device for controlled release of risperidone

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Hydrogel network parameter:

Hydrogel	K_s/r_0	ESR_{expt}/ESR_{cal}	$R^2/\chi^2/F$	Mc (g mol^{-1})	$\rho_c x10^{-18}$	$\xi(A^o)$
R1	0.0037/0.11	20.12/21.19	0.98/0.796/2268.37	40407.97	16.57	90.48
R2	0.00276/0.09	22.78/23.89	0.987/0.724/2958.72	80575.007	8.31	112.207
R3	0.00271/0.079	23.62/24.45	0.974/0.947/1472.02	161323.48	4.15	189.75
R4	0.0009/0.058	26.4725.39	0.965/0.84/729.08	241671.24	2.77	192.72

Table S1: **Swelling kinetic and network parameter of PAC-PPY hydrogel**

Raman Spectroscopy;

Electrochemical growth of polypyrrole inside the polyacrylamide hydrogel was analyzed by Raman Spectroscopy. It was observed that (Fig. S1) PAC-PPY hydrogel produced a strong band located at 1607 cm−1 representing the C C backbone stretching peak of polypyrrole. The peaks at 1394 and 1323 cm−1 could be attributed to the antisymmetrical C–N stretching of polypyrrole. The peaks at 729 and 1076 cm−1 were associated with the bipolaron and those at 982 and 1046 cm−1 to the polaron structure. The peaks at 1046 and 1076 cm^{-1} were assigned to symmetrical C–H in-plane bending. It could be also observed that at initial stage of polymerization no significant peak of PPY was observed whereas with progression of the number of scans and hence time, characteristic Raman band of PPY appeared confirming that the growth of PPY which started at Pt electrode spreaded out in the hydrogel matrix.

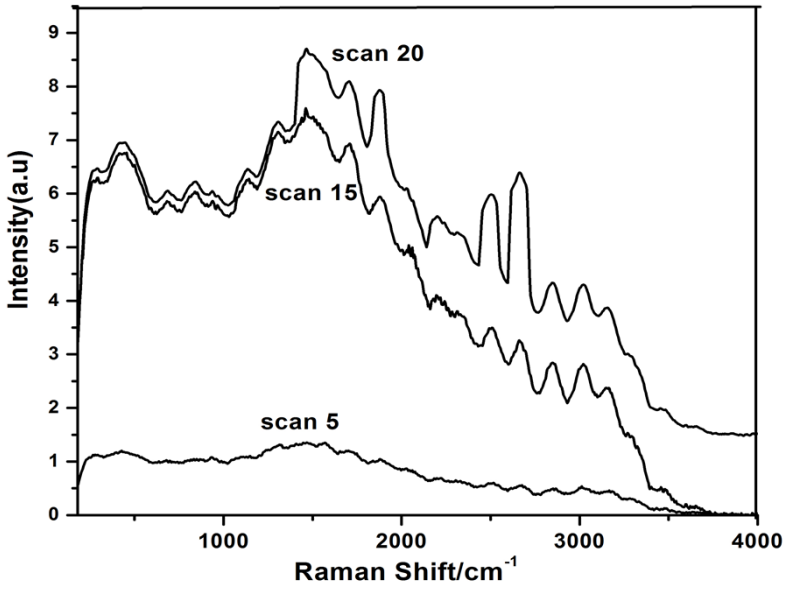

Fig. S1: Raman spectra of PAC-PPY hydrogel at different stages of polymerization

Risperidone release kinetic:

Four kinetic mathematical models were used to fit the obtained RISP release data, in order to select the one that described the release profiles for risperidone from PAC-PPY hydrogel best. The model equations are:

Zero-Order equation: $Q = k_0 t$ (1)

First-Order equation: $\ln Q = k_1 t$ (2)

Higuchi equation: $Q = k_H t^{1/2}$ (3)

Korsmeyer-Peppas equation: $Q = k_K t^n$ (4)

where, Q is the percentage cumulative amount of drug released at time t; k_0 the zero order release constant; k_1 the first order release constant; k_H the Higuchi release constant; k_K the Korsmeyer-Peppas release constant; and n the Korsmeyer-Peppas diffusional release exponent.

From Table S2 one could observe that the first order release model could not provide a high R^2 (goodness of fit) for release profiles of all formulations. This implied that drug release was not

dependent of the amount of drug remaining in the formulation whereas it followed zero order kinetics and it gave the highest linearity (R^2 = 0.97-0.99) at pH 6.8. Changes in pH of dissolution media could not affect significantly the release kinetic in case of formulation R2 whereas release pattern from R3 and R4 did not obey the linearity in case of pH 1.2 and 7.4. In such cases the Korsmeyer-Peppas model can be used which describes drug diffusion mechanism which followed a mixture of zero order diffusion and Higuchi type diffusion. Simultaneous swelling and erosion might be the mechanism of drug release from these matrix tablets. The Higuchi model describes diffusion controlled release from a homogeneous matrix, considering that the accessible dosage in the dissolution media changes with time. The 'n' value ranged from 0.8-1.1 for R2 formulation in all release media and this suggested that it was a super type II transport whereas formulation R4 and R1 exhibited a fickian diffusion and R3 followed a coupling of diffusion and erosion mechanism, the so called anomalous diffusion. Moreover all formulations exhibited slightly higher drug release at pH 6.8 that is correctable to the basic nature of drugs.

Formulation	Zero order		First order		Higuchi Model		Korsemeyer Peppas Model	
	R^2	K_0	R^2	K_1	R^2	K_H	R^2	n
pH 1.2								
R1	0.89	0.933	0.86	0.009	0.91	5.313	0.97	0.31
R2	0.98	2.31	0.97	0.04	0.95	17.45	0.98	1.14
R3	0.92	1.86	0.89	0.035	0.97	22.98	0.96	0.736
R4	0.93	1.3	0.91	0.02	0.84	9.2	0.95	0.52
pH 7.4								
R1	0.98	1.753	0.96	0.032	0.96	12.13	0.94	0.69
R2	0.99	2.35	0.96	0.052	0.92	17.49	0.91	0.88
R3	0.76	1.61	0.76	0.034	0.93	5.5	0.85	0.30

R4	0.89	1.2	0.84	0.016	0.87	8.4	0.82	0.41
pH 6.8								
R1	0.94	1.54	0.82	0.025	0.94	8.18	0.97	0.32
R2	0.98	2.1	0.93	0.04	0.91	15.22	0.99	0.89
R3	0.98	1.884	0.96	0.04	0.95	15.56	0.92	0.72
R4	0.97	1.7	0.90	0.032	0.89	12.41	0.87	0.58

Table S2: Evaluation of drug release kinetic of different hydrogel formulation for Risperidone release

Evaluation of cytotoxicity in HepG2 cell:

The sample of human HepG2 cells a obtained from ATCC (American type culture collection, USA) was seeded in 96- well plates with a cell density of 8500 per well. Two hundred microliters of DMEM (Dulbecco modified enriched medium) supplemented with 10% of fetal bovine serum, penicillin (100 U/ml), and streptomycin (100 U/ml) were used as growth medium (Invitrogen Life Technologies, Merelbeke, Belgium). Cells were incubated for 48 h at 37oC in 5% CO2. The culture medium was then replaced with 180 µl of fresh media and 20 µL of different concentration (0.5 to 150 µg/ml) hydrogel in PBS buffer. Triton X-100 (1% w/v) and 10 µM Doxorubicin were used as positive controls. The cells were incubated at 37oC for 72 h under 5% CO2 before determining the metabolic activity of each well by a colorimetric assay. After removal of the solutions, 25 µl of 3-(4,5- dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT; Sigma, Bornem, Belgium) solution in PBS buffer was added to each well. Cells were again incubated for 4 h at 37oC. The media was removed from all the wells and 100 µl of the extraction buffer (DMSO; Merck, Darmstadt, Germany) was added to dissolve the formazan by-product.

In order to estimate the effect of PAC-PPY hydrogel on metabolic activity and viability/ proliferation of cells, MTT assay was conducted. The cytotoxicity of hydrogel matrix with or

without an incorporated drug (i.e risperidone) was evaluated using a microtiter well protocol in which HepG2 cells were exposed to sterile pieces of PAC-PPY hydrogel of different concentrations over 72h time course. From The optical micrographs of the HepG2 cells after 24 h incubation time shown in Fig. S2. Usually HepG2 cells are epithelial in morphology, i.e polygonal in shape with more regular dimension (Fig. S2a). It was observed that in presence of positive control using 0.1 wt% Triton-X or 10 μM Doxorubicin most of the cells undergo apoptosis (Fig. S2b & Fig. S2c) i.e. complete program cell death. After treatment with pristine hydrogel (Fig. S2d-f) and drug loaded hydrogel particle (Fig. S2g-i) of various concentrations (0.5 -150 μg/ml) no significant change of cell morphology was observed compared with the control cell (Fig. S2a). Even for high concentration of hydrogel (150 μg/ml) most of the cells maintained polygonal shape with epithelial morphology (Fig S2f and Fig. S2i). The data obtained from cell viability by MTT assay after 72 h incubation is shown in Fig. S3. It was also observed both PAC-PPY and RISP loaded PAC-PPY did not reduce the cell growth or cell density.

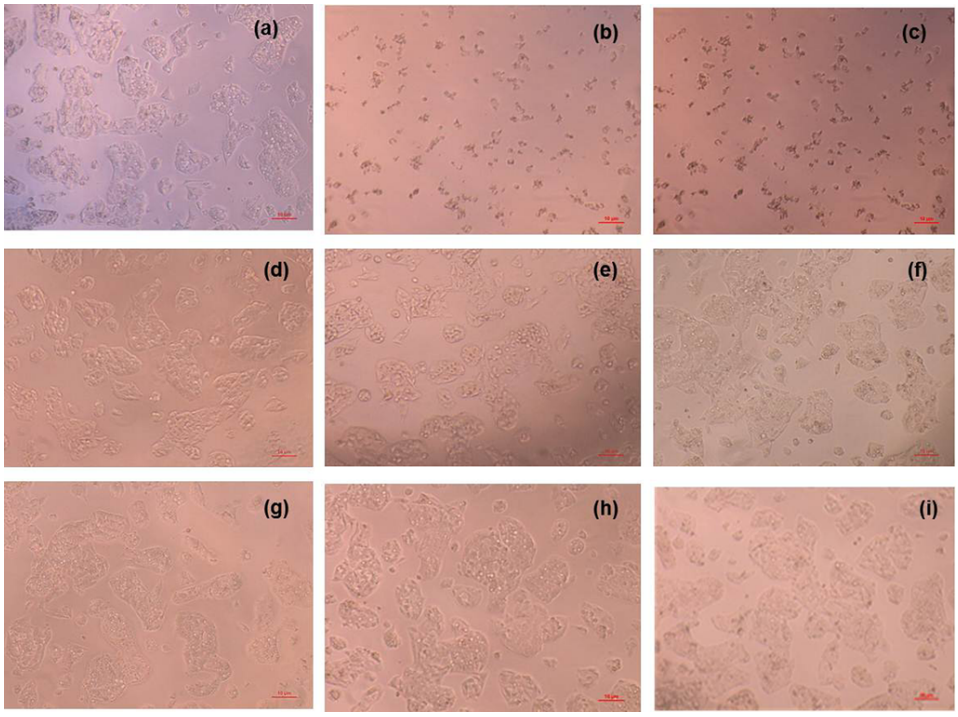

Fig. S2 : Phase contrast optical micrographs HepG2 cell after incubation with (a) medium control (b) 0.1% TritonX-100 (c) 10 µM Doxorubicin (d)-(f) 50, 70, 150 µg/ml PAC-PPY (g)-(i) 50, 70, 150µg/ml RISP loaded PAC-PPY

Fig. S2. It was also observed both PAC-PPY and RISP loaded PAC-PPY did not reduce the cell growth or cell density. Thus it could be said that cell viability was not depended on dose of polymer hydrogel. This PAC-PPY hydrogel can form easily excretable Glycidamide utilizing cytochrome P450 enzyme in liver without any cell damage.Therefore this smart hydrogel could be considered as biocompatible and nontoxic to human body.

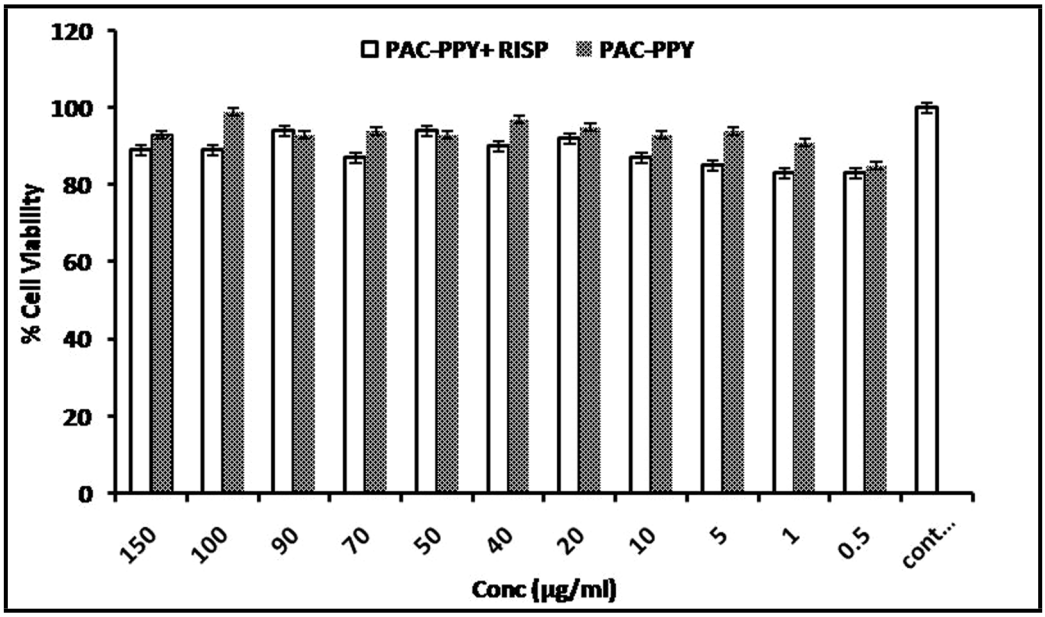

Fig. S3: Effect of polymer concentration on the cytotoxicity of PAC-PPY and RISP loaded PAC-PPY hydrogel measured by MTT assay after 72 h

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