

Drug Loaded 3D-Printed Poly(ϵ -Caprolactone) Scaffolds for Local Antibacterial or Anti-Inflammatory Treatment in Bone Regeneration

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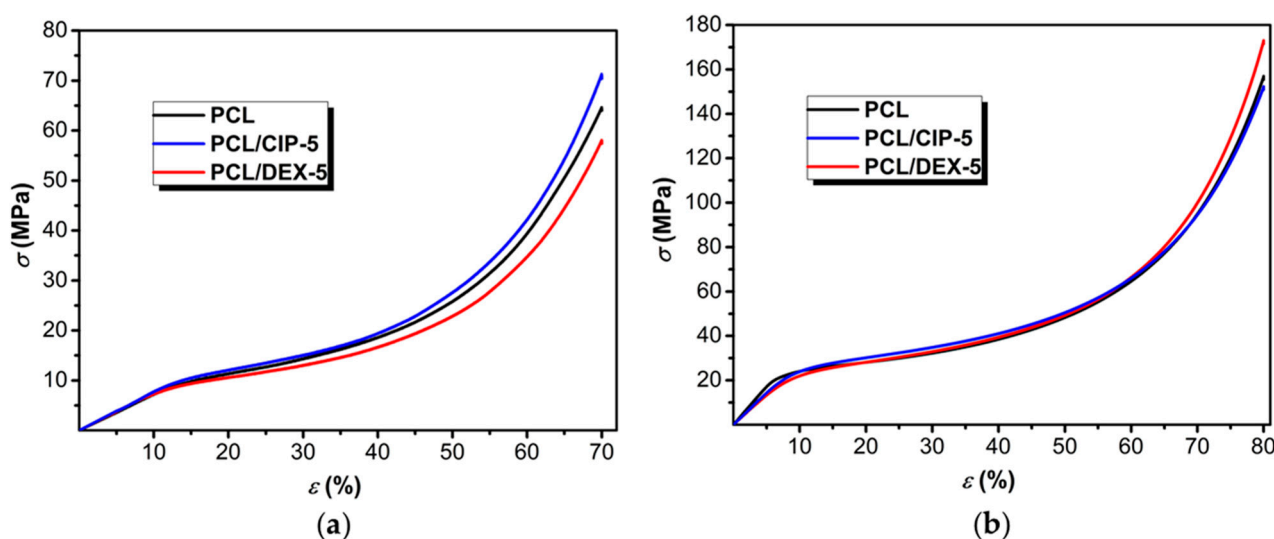


Figure S1. Compression stress-strain curves for 3D-printed (a) and monolithic (b) PCL specimens and its composites.

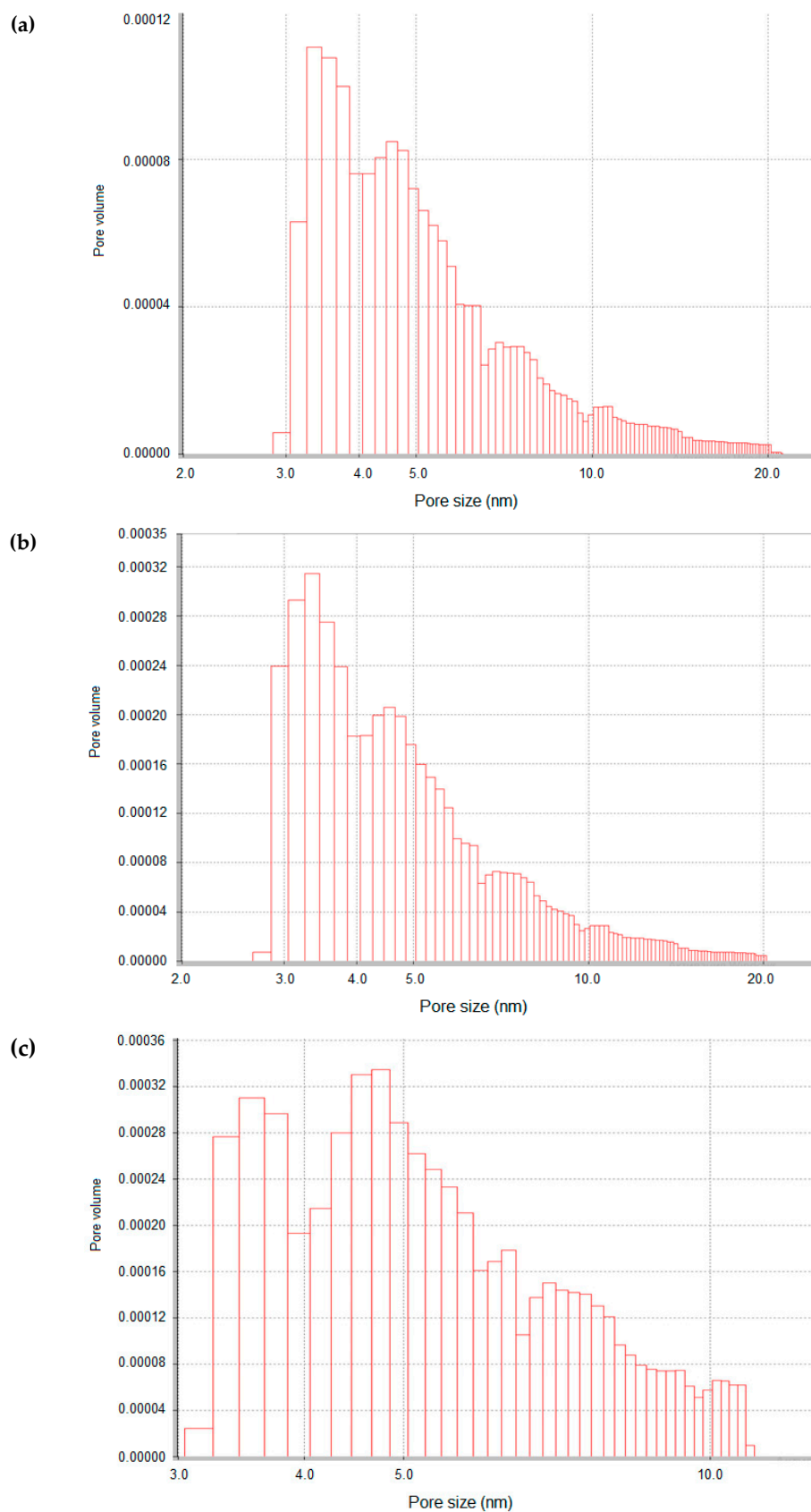


Figure S2. Pore size distribution of different 3D-printed scaffolds (BET):
(a) PCL; (b) PCL/CIP-1; (c) PCL/CIP-5.

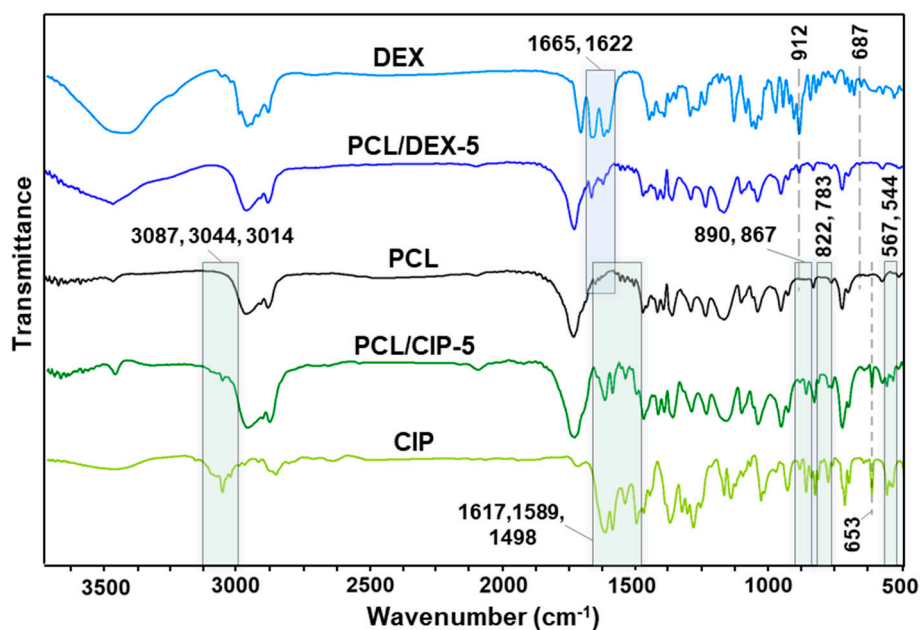


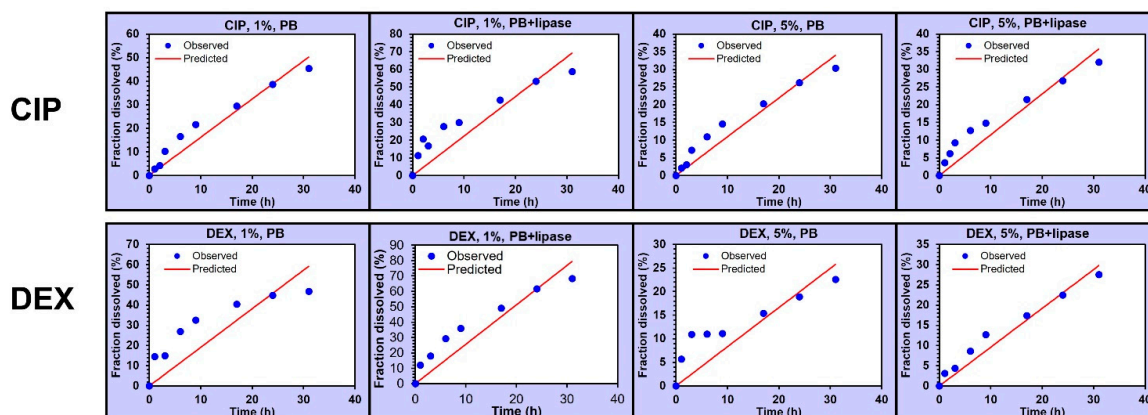
Figure S3. FTIR spectra of 3D-printed composite matrices with 5 wt% DEX (PCL/DEX-5) or CIP (PCL/CIP-5), as well as pristine PCL matrix and filler drugs.

Table S1. Correlation coefficients and calculated parameters with different mathematical models of release.

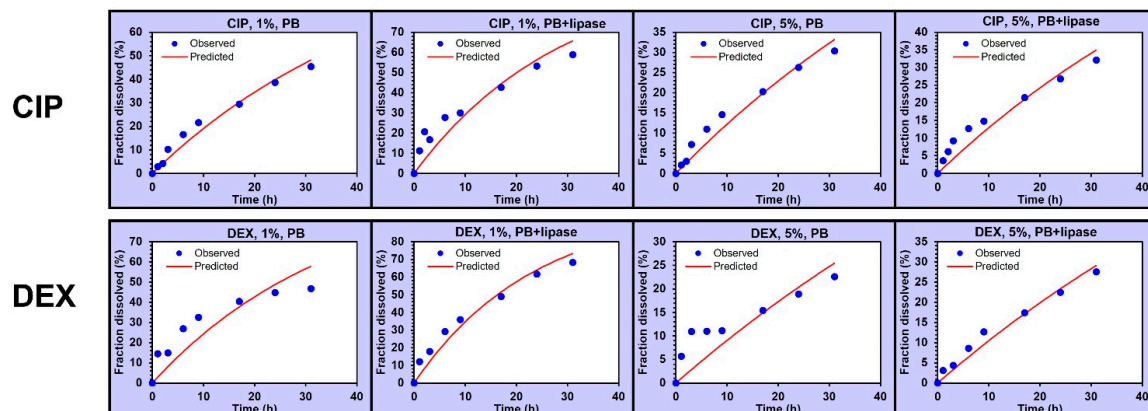
| Model | Correlation coefficients and parameters | CIP | | | | | DEX | | | | |
|------------------|---|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| | | PB | | PB+Lipase | | | PB | | PB+Lipase | | |
| | | 1 % | 5 % | 1 % | 5 % | 0.5 % | 1 % | 5 % | 0.5 % | 1 % | 5 % |
| Zero-order | R^2 | 0.9805 | 0.9802 | 0.9579 | 0.9779 | 0.8616 | 0.9071 | 0.9290 | 0.8747 | 0.9689 | 0.9879 |
| | k_0 | 1.62 | 1.10 | 2.23 | 1.15 | 0.23 | 1.91 | 0.83 | 0.26 | 2.56 | 0.96 |
| First-order | R^2 | 0.9905 | 0.9875 | 0.9761 | 0.9848 | 0.9055 | 0.9417 | 0.9345 | 0.9248 | 0.9917 | 0.9924 |
| | k_1 | 0.02 | 0.01 | 0.03 | 0.01 | 0.003 | 0.03 | 0.01 | 0.004 | 0.04 | 0.01 |
| Higuchi | R^2 | 0.9903 | 0.9915 | 0.9903 | 0.9962 | 0.9726 | 0.9819 | 0.9770 | 0.9776 | 0.9984 | 0.9880 |
| | k_H | 7.48 | 5.06 | 10.67 | 5.41 | 3.20 | 9.35 | 4.03 | 3.70 | 12.18 | 4.46 |
| Korsmeyer-Peppas | R^2 | 0.9933 | 0.9948 | 0.9901 | 0.9978 | 0.9965 | 0.9896 | 0.9808 | 0.9971 | 0.9986 | 0.9963 |
| | k_{KP} | 4.415 | 3.023 | 11.600 | 4.447 | 8.488 | 12.455 | 6.163 | 9.179 | 10.730 | 2.608 |
| | n | 0.68 | 0.68 | 0.47 | 0.56 | 0.30 | 0.41 | 0.34 | 0.31 | 0.55 | 0.68 |
| Hixon-Crowell | R^2 | 0.9833 | 0.9827 | 0.9616 | 0.9743 | 0.8915 | 0.9312 | 0.9328 | 0.9095 | 0.9869 | 0.9911 |
| | k_{HC} | 7.0×10^{-3} | 4.0×10^{-3} | 1.1×10^{-3} | 5.0×10^{-3} | 9.7×10^{-3} | 8.0×10^{-3} | 3.0×10^{-3} | 1.2×10^{-3} | 1.2×10^{-2} | 4.0×10^{-3} |
| Hopfenberg | | | 3 | 2 | 3 | 4 | 3 | | | | |
| | R^2 | 0.9905 | 0.9875 | 0.9761 | 0.9848 | 0.8314 | 0.9416 | 0.9345 | 0.9406 | 0.9916 | 0.9923 |
| | k_{HB} | 3.9×10^{-5} | 1.0×10^{-5} | 1.7×10^{-5} | 1.2×10^{-5} | 7.1×10^{-5} | 3.2×10^{-5} | 3.3×10^{-5} | 5.6×10^{-7} | 3.2×10^{-5} | 1.0×10^{-4} |
| Weibull | | | 5 | 5 | 5 | 7 | 5 | | | | |
| | R^2 | 0.9972 | 0.9980 | 0.9908 | 0.9976 | 0.9986 | 0.9907 | 0.9799 | 0.9955 | 0.9975 | 0.9974 |
| | α | 19.484 | 26.822 | 8.989 | 24.183 | 5.101 | 7.630 | 17.555 | 15.263 | 10.707 | 43.009 |
| | β | 0.71 | 0.66 | 0.59 | 0.64 | 0.19 | 0.47 | 0.41 | 0.45 | 0.72 | 0.76 |

| | | | | | | | | | | | |
|---------|----------|--------|--------|--------|--------|--------|--------|--------|----------------------|----------------------|--------|
| Makoid- | R^2 | 0.9963 | 0.9972 | 0.9942 | 0.9985 | 0.9990 | 0.9920 | 0.9902 | 0.9968 | 0.9989 | 0.9976 |
| Banakar | k_{MB} | 3.946 | 2.681 | 12.493 | 4.571 | 6.346 | 11.413 | 6.866 | 9.982 | 10.898 | 2.596 |
| | n | 0.776 | 0.785 | 0.397 | 0.526 | 0.392 | 0.505 | 0.187 | 0.296 | 0.541 | 0.672 |
| | k | 0.008 | 0.009 | 0.007 | 0.004 | 0.001 | 0.010 | 0.017 | 1.1×10^{-4} | 3.6×10^{-4} | 0.002 |
| Peppas- | R^2 | 0.9975 | 0.9981 | 0.9940 | 0.9983 | 0.9991 | 0.9918 | 0.9826 | 0.9967 | 0.9989 | 0.9976 |
| Sahlin | k_1 | 15.61 | 10.37 | 9.76 | 4.32 | 5.97 | 11.85 | 4.60 | 9.41 | 10.97 | 0.55 |
| | k_2 | 18.10 | 12.19 | 2.32 | 0.18 | 0.19 | 0.71 | 1.15 | 0.14 | 0.01 | 2.07 |
| | m | 0.21 | 0.21 | 0.35 | 0.52 | 0.45 | 0.55 | 0.29 | 0.30 | 0.54 | 0.37 |

Zero-order $F=k_0 \cdot t$



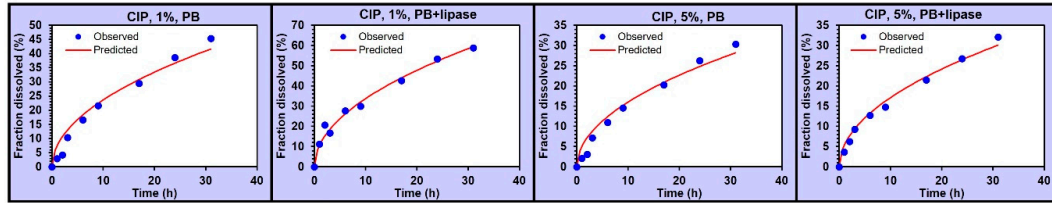
First-order $F=100 \cdot [1 - \exp(-k_1 \cdot t)]$



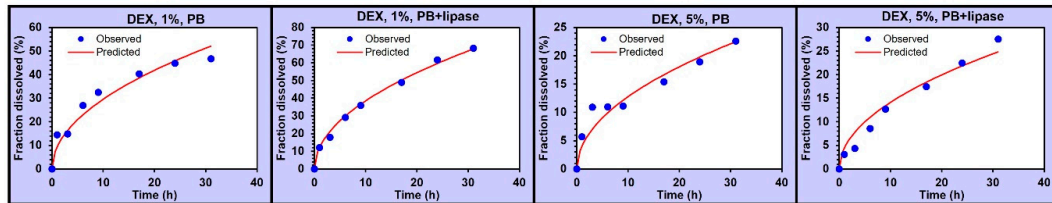
Higuchi

$$F = k_H \cdot t^{0.5}$$

CIP



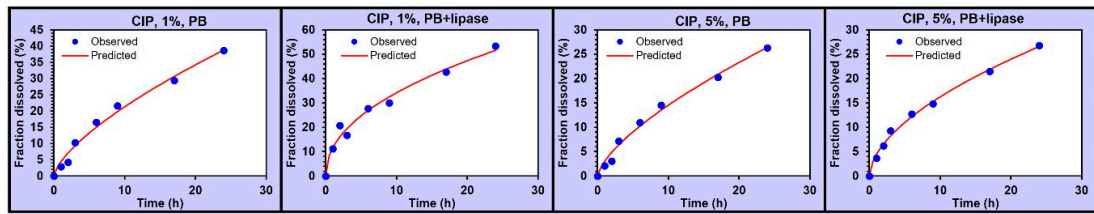
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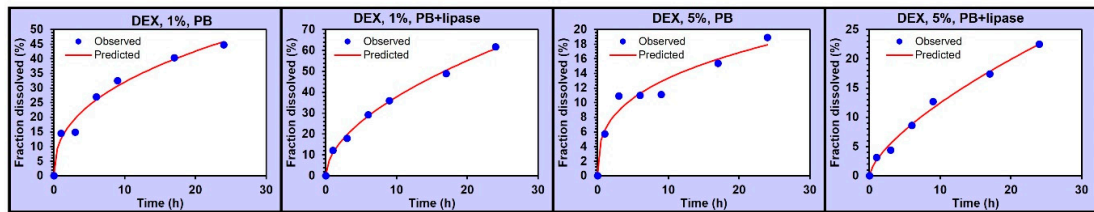
Korsmeyer-Peppas

$$F = k_{KP} \cdot t^n$$

CIP



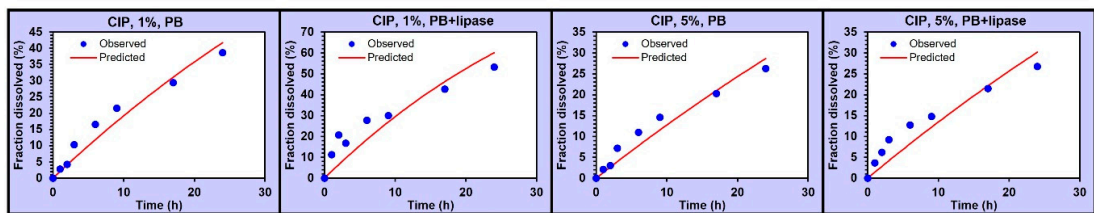
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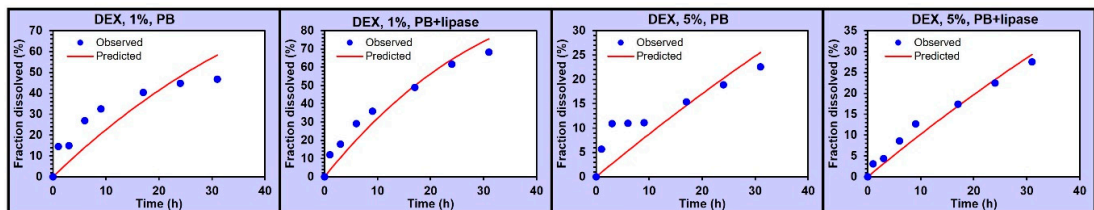
Hixon-Crowell

$$F = 100 \cdot [1 - (1 - k_{HC} \cdot t)^3]$$

CIP



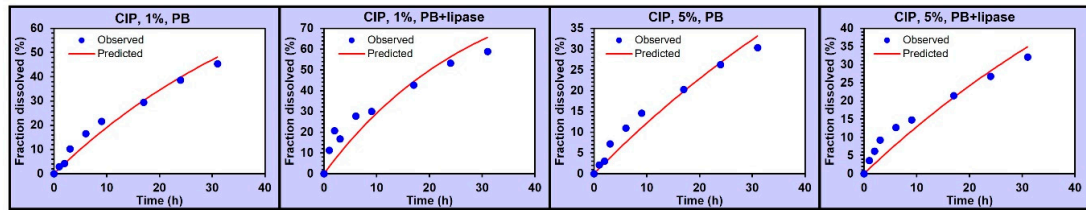
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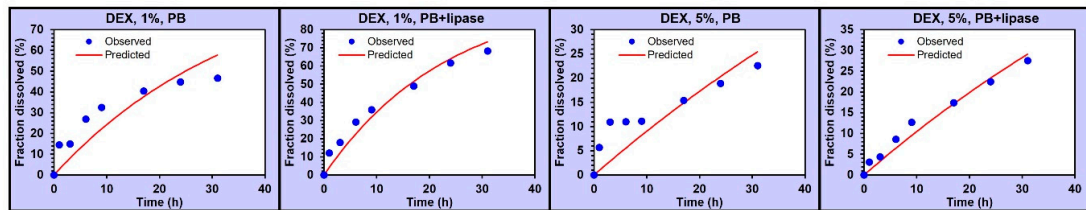
Hopfenberg

$$F=100*[1-(1-k_{HB} *t)^n]$$

CIP



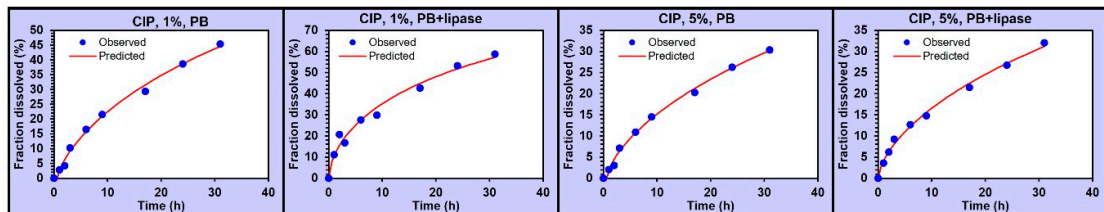
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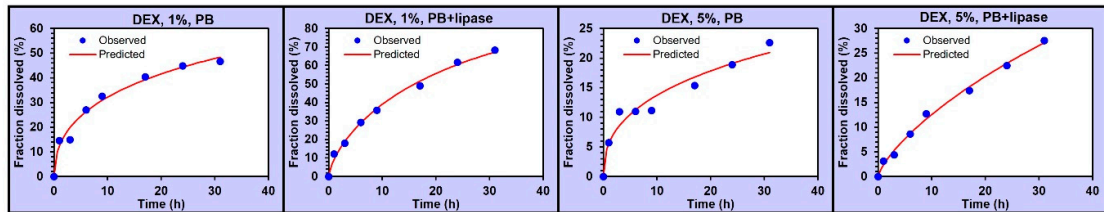
Weibull

$$F=100*\{1-Exp[-((t-Ti)^{\beta}/\alpha)]\}$$

CIP



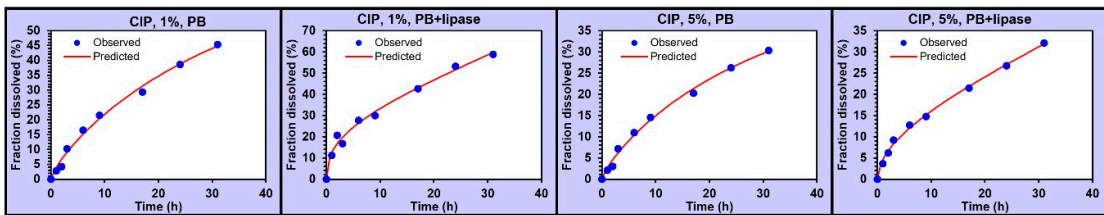
DEX



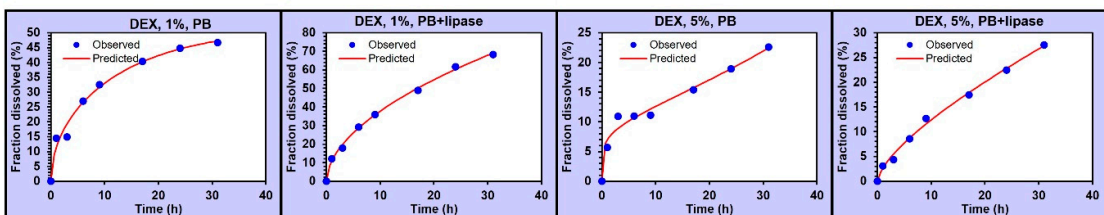
Makoid-Banakar

$$F=k_{MB} *t^n*Exp(-k*t)$$

CIP



DEX



Peppas-Sahlin

$$F = K_1 \cdot t^m + K_2 \cdot t^{(2 \cdot m)}$$

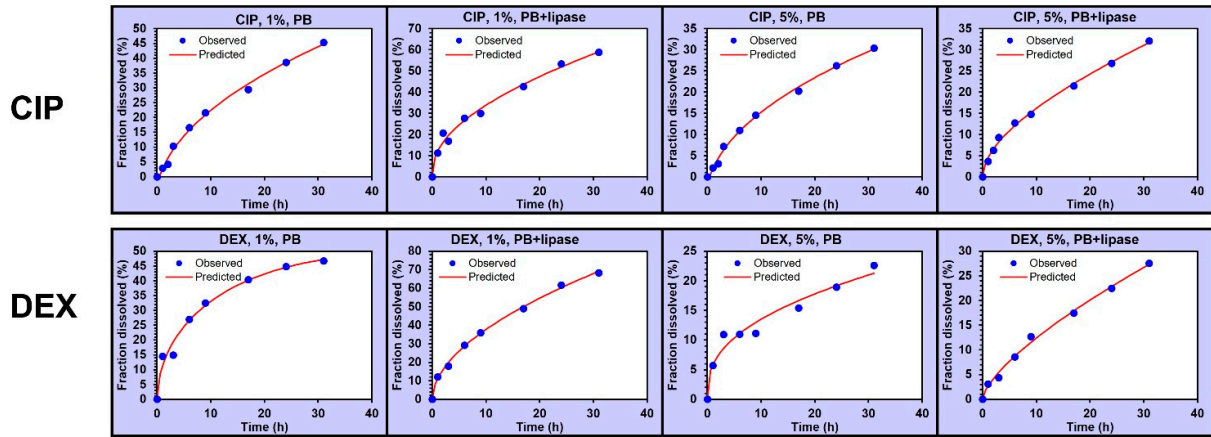


Figure S4. Regression curves obtained with different dissolution mathematical models of release.

Table S2. Viability of THP-1 cells after 24 h *in vitro* co-cultivation with different concentrations of dexamethasone (DEX). Data are presented as mean \pm SD ($n \geq 9$); the data are shown as the percentages of viable cells.

| Series | Cell viability (%) | | | | | |
|---------------------|--------------------------------|----------------------|---------------------|-----------------------------|----------------------|----------------------|
| | without TNF α treatment | | | with TNF α treatment | | |
| | Viable | early Ap | late Ap/Necrosis | Viable | early Ap | late Ap/Necrosis |
| Negative control | 94.43 \pm 0.21 | 4.36 \pm 0.24 | 1.06 \pm 0.07 | 94.09 \pm 0.41 | 4.10 \pm 0.37 | 1.61 \pm 0.12 |
| DEX, 5 μ g/mL | 94.82 \pm 0.20 | 4.19 \pm 0.23 | 0.87 \pm 0.06 | 92.16 \pm 0.27 ** | 5.47 \pm 0.22 * | 2.12 \pm 0.12 * |
| DEX, 10 μ g/mL | 94.75 \pm 0.25 | 3.77 \pm 0.29 | 1.07 \pm 0.09 | 90.06 \pm 1.12 *** | 6.86 \pm 0.74 ** | 2.70 \pm 0.41 |
| DEX, 20 μ g/mL | 93.81 \pm 0.26 | 4.55 \pm 0.20 | 1.41 \pm 0.14* | 83.13 \pm 1.28 *** | 11.71 \pm 1.08 *** | 4.64 \pm 0.45 *** |
| DEX, 30 μ g/mL | 93.60 \pm 0.33 | 4.49 \pm 0.30 | 1.63 \pm 0.12 *** | 83.51 \pm 1.39 *** | 11.49 \pm 0.98 *** | 4.50 \pm 0.52 *** |
| DEX, 50 μ g/mL | 94.96 \pm 0.31 | 3.13 \pm 0.22 ** | 1.90 \pm 0.21 ** | 85.34 \pm 1.08 *** | 11.45 \pm 1.00 *** | 3.021 \pm 0.12 *** |
| DEX, 100 μ g/mL | 86.73 \pm 0.87 *** | 11.46 \pm 0.81 *** | 1.81 \pm 0.07 ** | 59.41 \pm 1.79 *** | 33.78 \pm 1.69 *** | 6.81 \pm 0.19 *** |

*, **, *** – the difference with negative control (THP-1 cell without dexamethasone) were significant with $p < 0.05$, $p < 0.01$ and $p < 0.001$ according to non-parametrical Mann–Whitney U test; ‘Viable’ – YO-PRO-1–PI– cells; ‘early Ap’ – THP-1 cell in early steps of apoptosis with YO-PRO-1+PI– phenotype; ‘late Ap/Necrosis’ – dead THP-1 cells with YO-PRO-1+PI+ phenotype.

Table S3. CD54 expression by THP-1 cells in response to *in vitro* stimulation with different concentrations of dexamethasone. Data are presented as mean \pm SD ($n \geq 9$); the data are shown as CD54 MFI.

| Series | CD54 expression (MFI) | |
|---------------------|----------------------------|-----------------------------|
| | w/o TNF α treatment | with TNF α treatment |
| Negative control | 0.773 \pm 0.084 | 5,397 \pm 1,008 |
| DEX, 5 μ g/mL | 0.718 \pm 0.027 | 2.489 \pm 0.489 ** |
| DEX, 10 μ g/mL | 0.744 \pm 0.031 | 2.083 \pm 0.253 * |
| DEX, 20 μ g/mL | 0.855 \pm 0,043 | 2.237 \pm 0.097 * |
| DEX, 25 μ g/mL | 1.022 \pm 0.068 * | 2.398 \pm 0.218 * |
| DEX, 30 μ g/mL | 0.852 \pm 0.066 | 1.998 \pm 0.075 ** |
| DEX, 50 μ g/mL | 0.792 \pm 0.029 | 1.696 \pm 0.082 *** |
| DEX, 100 μ g/mL | 0.852 \pm 0.033 | 1.403 \pm 0.085 *** |

*, ** – the difference with negative control (THP-1 cell without dexamethasone) were significant with $p < 0.05$ and $p < 0.01$ according to non-parametrical Mann–Whitney U test.