SUPPLEMENTAL INFORMATION

Summary of Millicylinder Formulation Strategies

PLGA millicylinders were prepared using different methods for loading of PVP-4HPR ASDs into the implant. Solubility of the components in various solvents and within the PLGA matrix were important considerations for delivery of the intact PVP-4HPR ASD. Challenges present included designing a system that accounted for the different chemical properties of hydrophobic 4HPR and hydrophilic PVP, which had differing affinities for the hydrophobic PLGA matrix. These differences allowed for rapid release of hydrophilic PVP into the aqueous release media, while the residual precipitated hydrophobic 4HPR was shielded from aqueous environment in the hydrophobic PLGA matrix. PLGA is soluble in the organic solvents DCM and acetone (typically used in solvent extrusion implant preparations due high volatility for drying of implants). PVP is insoluble in acetone, but soluble in DCM and MeOH. 4HPR has decreasing solubility in these solvents as follows: acetone > MeOH > DCM (14). For our *in vitro* release studies, a non-solubilizing buffer system was used (PBS 0.02% pH 7.4), and therefore any appreciable amount of 4HPR released will be indicative of release of the drug solubilized by the ASD.

Our first experiments (#1-5), loaded different ratios of PVP-4HPR particles into PLGA dissolved in acetone, and yielded poor 4HPR release kinetics (<10% after 28 days) due to rapid and nearly complete release of PVP after 3 days. These data reflect the challenge of co-delivery of drugs and excipients with different chemical properties. The next set of formulations (#6a-d) used DCM as a co-solvent, capable of co-dissolving 4HPR, PVP and PLGA. These implants were also coated with varying compositions of PLGAs (acid end-capped, addition of pore forming agent) with the aim of delaying the release of PVP. These formulations successfully provided controlled release of PVP possibly by entanglement of PVP and PLGA polymer chains. However, incomplete 4HPR release of only 10% after 6 weeks was observed.

Additionally, the #6 PLGA coated implants coated did slow PVP release as expected, but did not have a significant positive effect on 4HPR release kinetics.

Because PVP is a hydrophilic polymer, it will dissolve quickly in aqueous solutions with an expected large burst release of the excipient, which may contribute to dissociation of the drug-PVP ASD. To alleviate rapid PVP dissolution, TEAC was added to the PVP-4HPR ASD. Subsequent studies to assess millicylinders that contained PLGA-coated core PVP-4HPR or PVP-4HPR-TEAC ASDs were disappointing as nearly all of the PVP core had dissolved after the first few days, and >90% of the precipitated drug was left behind in the PLGA coatings. We determined that PLGA +3% $MgCO_3$ coatings do not adhere as tightly to the PVP-4HPR-TEAC implant compared to the PVP-4HPR implant. These data, which imply that TEAC perturbs PVP-PLGA or 4HPR-PLGA interactions, led to the question of whether 4HPR demonstrates a predilection for PLGA or PVP interaction. Decreased levels of PLGA in the implant has the potential to reduce 4HPR partitioning into PLGA, thereby preserving a more intact PVP-4HPR ASD.

The final formulation (#9) utilized PVP-4HPR-TEAC particles and the improved release was hypothesized to reflect an insulation of PVP-4HPR ASD by TEAC, and protect the amorphous character of the ASD and prevent 4HPR to partition into the PLGA polymer phase. This formulation (#9) had the most favorable 4HPR release, with 35% 4HPR released after 28 days, equating to a 5.6-fold increase in release compared to the formulation without TEAC (#1). The release from the control formulation #10 (no PVP, TEAC and PLGA) support the hypothesis that the enhanced 4HPR release was not attributable to PLGA plasticization, i.e. increased mobility of the polymer chains, induced by TEAC.

PLGA- PVP-4HPR Millicylinder Implant Erosion Morphology

The morphology of formulations 1-5 was examined by SEM prior to and after 28 days of *in vitro* release (Fig. S1). These images depict the initial crystallinity and miscibility of 4HPR or PVP in PLGA, and also the extent of implant erosion after 28 days. The greatest implant homogeneity is observed in

formulation #1 (PLGA 503H+ 9/1 PVP-4HPR), but as the PVP/4HPR ratio decreases (requiring a lesser amount of the ASD to be loaded into implant to achieve 5% 4HPR loading in formulations #2 and #3), more crystals (likely 4HPR precipitation) are present. In formulations #4 and #5, greater crystal formation was observed in PLGA 503 ester end-capped, which is likely a reflection of insolubility of both PVP and 4HPR in PLGA 503, and correlates with the faster 4HPR and PVP release. An opposite implant erosion trend was observed based on the release profiles, where that erosion rate increased as the PVP level was decreased, most notably for implant #3 (7/3 PVP-4HPR) that nearly fell apart after 28 days.

Upon visual inspection, the implants with a lower PVP-4HPR ratio loaded implants had greater swelling (for 503H formulations), slower erosion, and has slower release of both PVP and 4HPR. Also on day 28, the PLGA 503 implants (#4, 5) appeared to have underwent limited erosion, but the formation of a pore network was present.

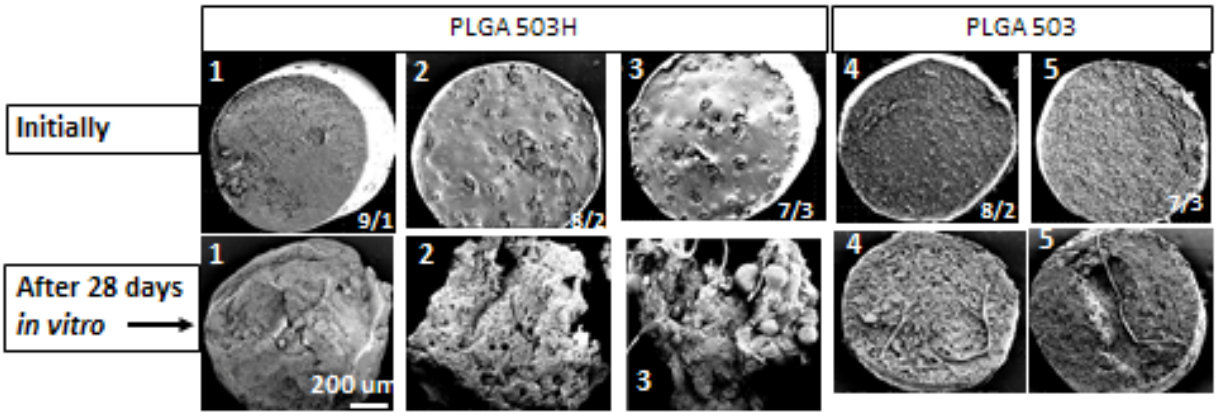

Figure S1: SEM images of cross sections of PLGA millicylinder implants (#1-5) loaded with PVP-4HPR particles with varying ratios prior to and after 28 days in in vitro release media. Numbers correspond to formulations: #1-3 prepared with PLGA 503H, and #4, 5 with PLGA 503. #1: PVP/4HPR 9/1 particles, #2, 4: PVP/4HPR 8/2 particles, #3, 5: PVP/4HPR 7/3 particles.

Effects of PLGA Coating Type on PVP-4HPR Core Implants on Drug Release

The effect of PLGA coatings on PVP and 4HPR release were evaluated in formulations 6, 7, and 8. As seen in Figs. 7 and 8, all of the formulations coated with PLGA 503H had the slowest PVP (3 days

for 80% release), while the addition of the basic pore forming salt $MgCO_3$ into the PLGA coating accelerated PVP release. This could be attributed to neutralization of the PLGA's acidic end groups by $MgCO_3$. The least favorable coating for delaying PVP release was PLGA 503, and nearly 100% PVP was released after first day. This result may be due to the greater hydrophobicity of the ester end-capped PLGA. In the SEM images (Fig. 8c), the PLGA coatings containing 3% $MgCO_3$ do not adhere as tightly to the PVP-4HPR-TEAC implant compared to the PVP-4HPR implant, suggesting that TEAC may play a role in repulsion of PVP to PLGA or of 4HPR to PLGA. Although these formulations (#7, 8) did not perform well *in vitro*, insight was gained into how PLGAs and TEAC affect the release rate of the PVP-4HPR complex.

Amorphous Character of PVP-4HPR particles and PLGA-PVP-4HPR +TEAC Millicylinders Determined by DSC

The extent of drug solubility in the polymer is an important aspect of ASD, and the level of solubility can be assessed by measuring the T_g of the system via DSC, and drug activity can be obtained and used calculate the Flory-Huggins interaction parameter (X) (32). While this data is useful for selection of the optimum polymer for ASD's, it is not within the scope of this paper. The T_g of a mixture can be estimated according to the Fox equation:

$$\frac{1}{T_{g,mix}} = \frac{w_1}{T_{g1}} + \frac{w_2}{T_{g2}}$$

Where $T_{g,mix}$ is the glass transition temperature of the mixture (in Kelvin), and *w* is the weight fraction of each component. A limitation of the Fox equation is that it can only be applied to blends with weak intermolecular interactions. Factors affecting the T_g include molecular size and shape, and extent and strength of hydrogen bonding, all of which can affect the packing or free volume. It is likely that PVP and 4HPR exhibit strong hydrogen bonding, and therefore this equation may not lead to accurate predictions. It is important to note that any residual water present can act as a plasticizer and leads to a decrease in T_g. For example, if 5% water (T_g = -138 ˚C for water) is present in 100% PVP (T_g=164 ˚C), the T_g of the hydrated excipient will decrease to 120 ˚C. Because the T_m of 4HPR and T_g of PVP are so similar, 164

°C and 174 °C respectively, the heat flow peaks are note easily resolved, and DSC data proves difficult for the calculation of ratios of the excipient, drug, and ASD complex. As depicted in the thermogram in **Figure S2**, the Tm of pure 4HPR is 174°C. Because 4HPR exists as a crystalline solid, the heat flow curve showing a sharp spike is indicative of a Tm. Compounds that exist in a glassy state exhibit a Tg, which can be calculated from the midpoint of the inflection curve derived from the heat flow from thermogram, and are therefore easily distinguishable from a Tm.

The T_g of the PVP-4HPR particles was measured to determine if the formulation was in an amorphous state, indicated by having a T_g less than that of the PVP polymer (163 °C). The T_g of the dried PLGA-PVP-4HPR millicylinders was also measured to determine if PVP or 4HPR affected the Tg of PLGA, implying miscibility into the PLGA encapsulating matrix.

Figure S3 shows thermograms of a representative PLGA-PVP-4HPR millicylinder formulation with and without TEAC, compared to that of PVP-4HPR particles with PVP/4HPR weight ratios of 9/1. The T_g values of formulations #8a and #8c (PVP-4HPR coated with 503H or 503+3% $MgCO_3$) were similar, 126 °C and 121 °C respectively, but an additional T_g is present in #8a at 34 °C, representing PLGA 503H. These PVP-4HPR 9/1 core implants have a much lower T_g than the corresponding particles (155 °C), possibly due to residual solvent or water present. The PVP-4HPR-TEAC core implants coated with PLGA 503H (formulation #7a), displayed two T_g values at 30 °C and 97 °C, while the corresponding particles has a T_g of 87°C. The 10 °C difference could be due to precipitation of the PVP in presence of the PLGA coating and TEAC. Finally, formulation #7 contained the PVP-4HPR-TEAC 9/1/1 particles loaded into PLGA 503H, and exhibited two T_g values at 37 °C and 140 °C. The later T_g is much greater than that of the corresponding particles (87 °C) and the core implant coated with PLGA 503H (97 °C). These elevated T_g values in formulations #9 and the 9/1 PVP-4HPR particles (compared to the 8/2 and 7/3 ratios) may play a role in the favorable release and solubility enhancement of 4HPR.

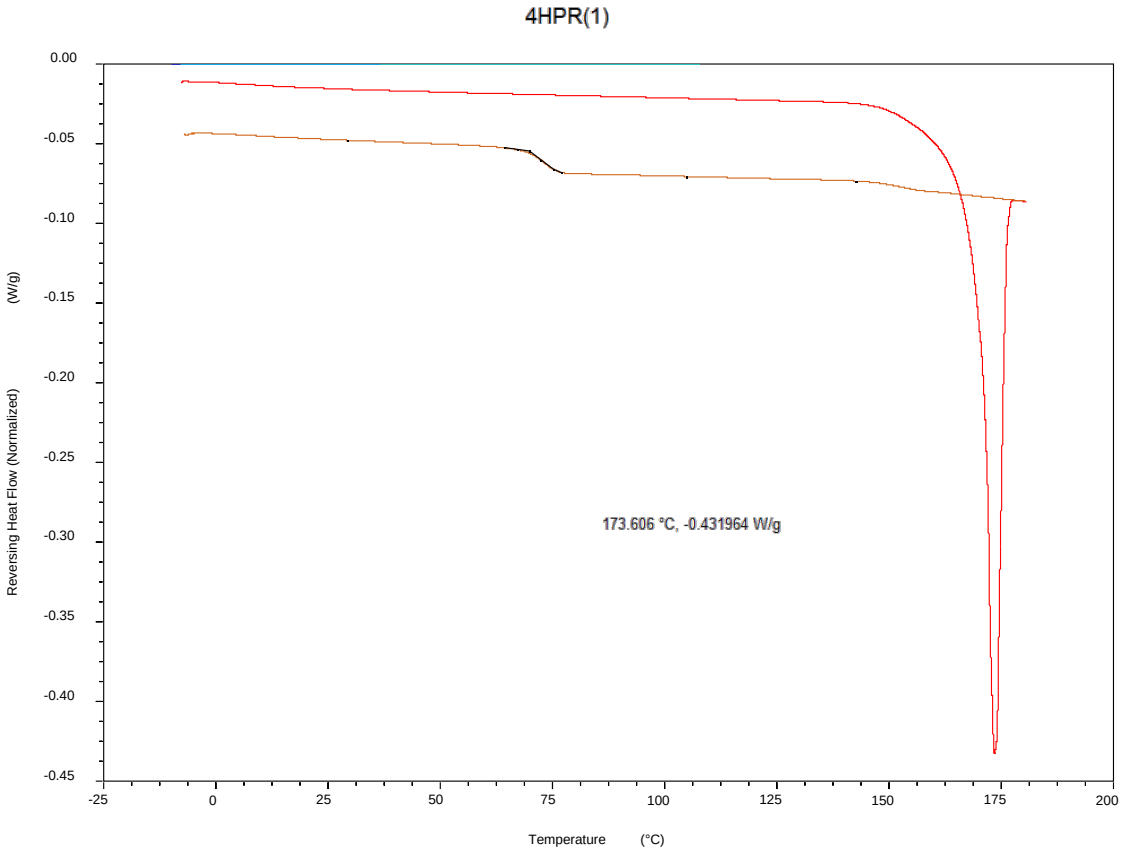

Figure S2: DSC thermogram of 4HPR, with T_m of 174 °C annotated Red line indicates the heat flow curve, which is used to derive the brown line (derivative of heat flow) showing any inflection points, indicative of a T_g.

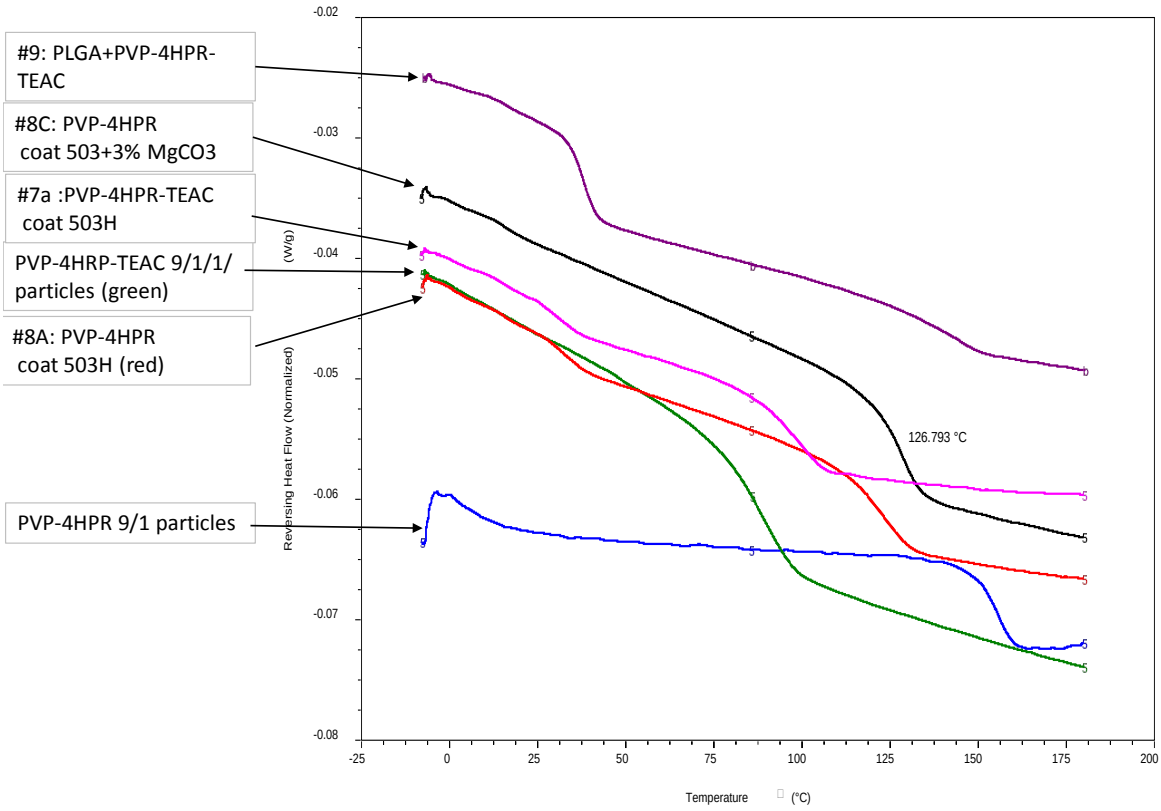

Figure S3: DSC thermograms displaying T_g values of PLGA-PVP millicylinder formulations (#7a, #8a, #8c, #9) compared to those of the PVP-4HPR 9/1 or PVP-4HPR-TEAC 9/1/1 particles.

Residual Solvent in Implants Determined by TGA Analysis

The TGA analysis shows <5% residual solvent present after drying implant after ready mass loss at 100 °C in Figure S4.

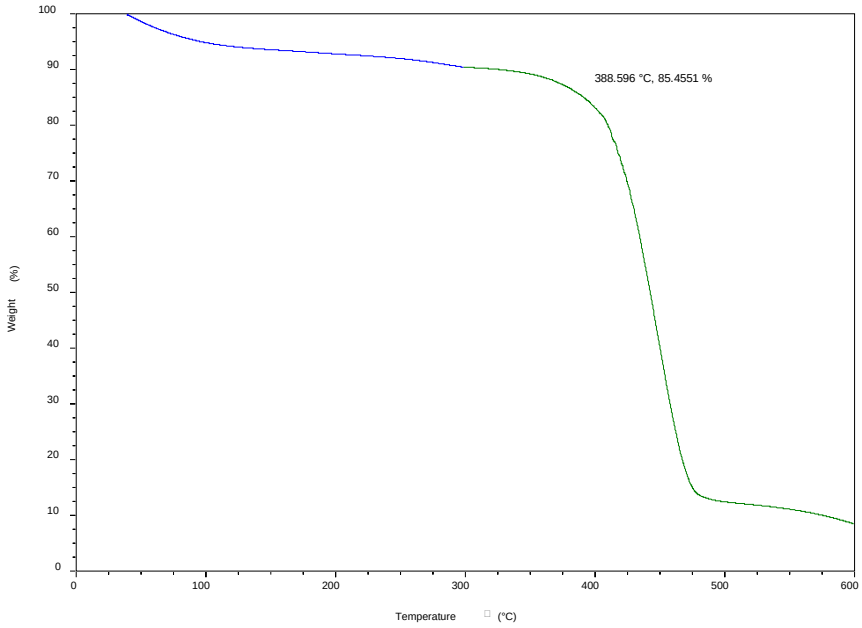

Figure S3: TGA spectra of (A) #7d PVP-4HPR 9/1 core (uncoated) vs. (B) #7a coated with PLGA 503H.