## Molecular Insights on Warfarin Sodium 2-Propanol Solvate Solid Form Changes and Disproportionation Using a Low Volume 2-Stage Dissolution Approach.

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Appendix A - Supplementary Document





Figure. S1. PXRD patterns of EFIWIZ, WAR<sub>C</sub> (as received) and WAR<sub>NC</sub>



Figure. S2 (a) DSC and TGA thermogram of WAR<sub>C</sub> (b) DSC and TGA thermogram of WAR<sub>NC</sub>



Figure. S3 (a) X-ray diffraction data of warfarin crystalline 2-propanol solvate (WAR<sub>C</sub>) and noncrystalline WAR<sub>C</sub> (WAR<sub>NC</sub>) post solubility studies at pH 1.2, pH 4.5, pH 6.8 and pH 7.4, (b) DSC data of WAR<sub>C</sub> and WAR<sub>NC</sub> post solubility studies at pH 1.2, and warfarin free acid (WAR).



Figure S4. X-ray diffraction data of NaCl (Blue), WAR (Green) and WAR<sub>C</sub> (Red).



Figure S5. The amount of sodium determined in  $WAR_C$ ,  $WAR_{NC}$ , WAR (from 0.1N HCl) and sodium chloride (obtained from filtered solution)



Figure S6. FTIR Spectra a) Warfarin Sodium 2-propanol Solvate (WAR<sub>C</sub>), b) a) Non-crystalline Warfarin Sodium (WAR<sub>NC</sub>), c) Warfarin (WAR, reference), d) WAR<sub>C</sub> (after 0.1N HCl solubility studies) and e) WAR<sub>NC</sub> (after 0.1N HCl solubility studies)



Figure S7. a) Polarized light microscopy images and b) Scanning electron microscopy images of WAR<sub>C</sub> (Warfarin Sodium 2-propnaol Solvate), WAR<sub>NC</sub> (Non-crystalline Warfarin Sodium) and WAR (Unionized Warfarin).

	WAR <sub>C</sub> Equilibrium pH (24 h)	WAR <sub>NC</sub> Equilibrium pH (24 h)
0.1N HCl	$3.5 \pm 0.2$	$3.2 \pm 0.3$
pH 4.5 (Acetate buffer)	5.4 ± 0.1	5.6 ± 0.1
pH 6.8 (Phosphate buffer)	8.8 ± 0.3	8.5 ± 0.2
pH 7.4 (Phosphate Buffer)	$9.4 \pm 0.2$	$9.2 \pm 0.3$
Water	$7.9 \pm 0.7$	7.6 ± 0.5

Table S1. Equilibrium pH of  $WAR_C$  and  $WAR_{NC}$  in different dissolution media at 24 h time point

Table S2. Difference factors (f1) at individual stages of 2-stage dissolution

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Comparison	Stage 1	Stage 2			
A1/B1	52.83	12.42			
A1/C1	66.69	14.16			
B1/C1	29.38	1.98*			
A2/B2	60.72	14.86*			
A2/C2	64.89	21.06			
B2/C2	19.12	7.28*			

\* similar dissolution

Table S3. Results of One Way ANOVA test at individual stages of 2-stage dissolution

Comparison	Source of Variation	SS	df	MS	F	P-value	F crit
A1/B1/C1	Between Groups	1505.55	2.00	752.78	26.78	1.02E-03	5.14
Stage 1	Within Groups	168.64	6.00	28.11			
_	Total	1674.19	8.00				
A1/B1/C1	Between Groups	1198.56	2.00	599.28	1442.97	3.59E-28	3.35
Stage 2	Within Groups	11.21	27.00	0.42			
_	Total	1209.78	29.00				
A2/B2/C2	Between Groups	3848.70	2.00	1924.35	48.37	1.81E-06	3.89
Stage 1	Within Groups	477.37	12.00	39.78			
_	Total	4326.07	14.00				
A2/B2/C2	Between Groups	1805.49	2.00	902.75	109.76	7.61E-12	3.47
Stage 2	Within Groups	172.72	21.00	8.22			
_	Total	1978.21	23.00				

SS: Sum of squares, Df: Degree of freedom, MS: Mean squares