

Figure 1

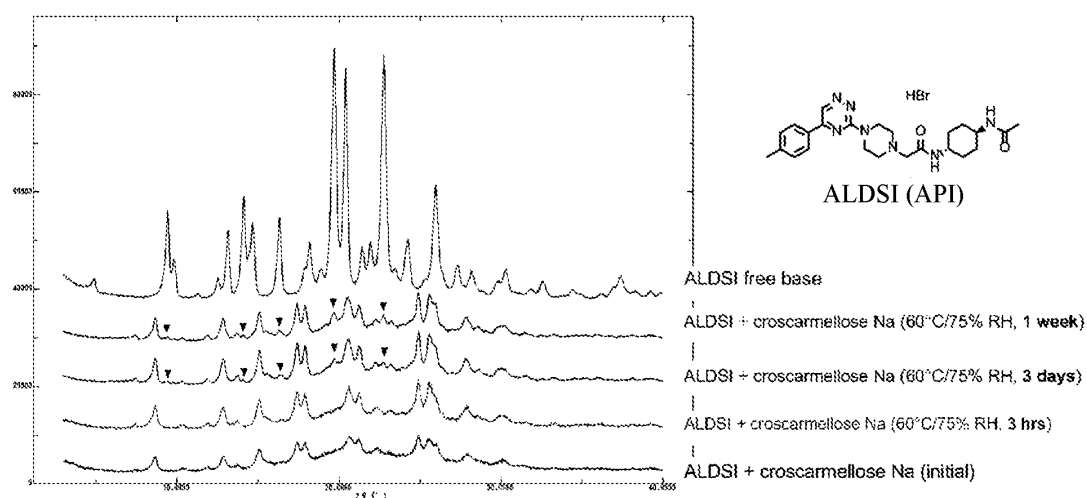


Figure 2

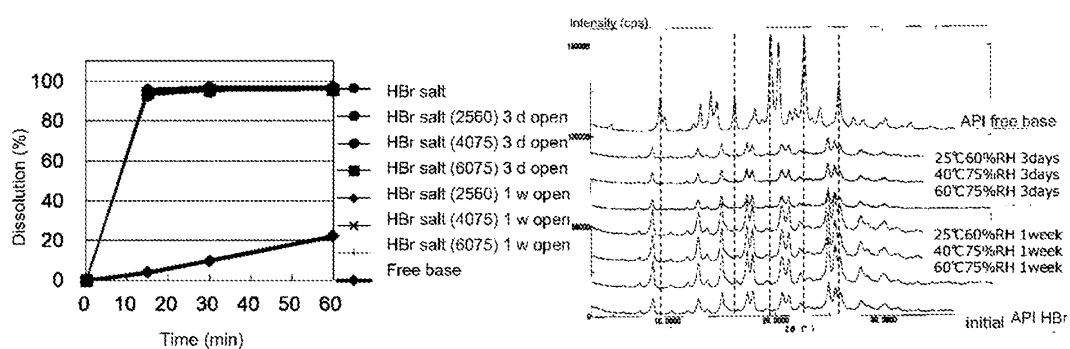


Figure 3

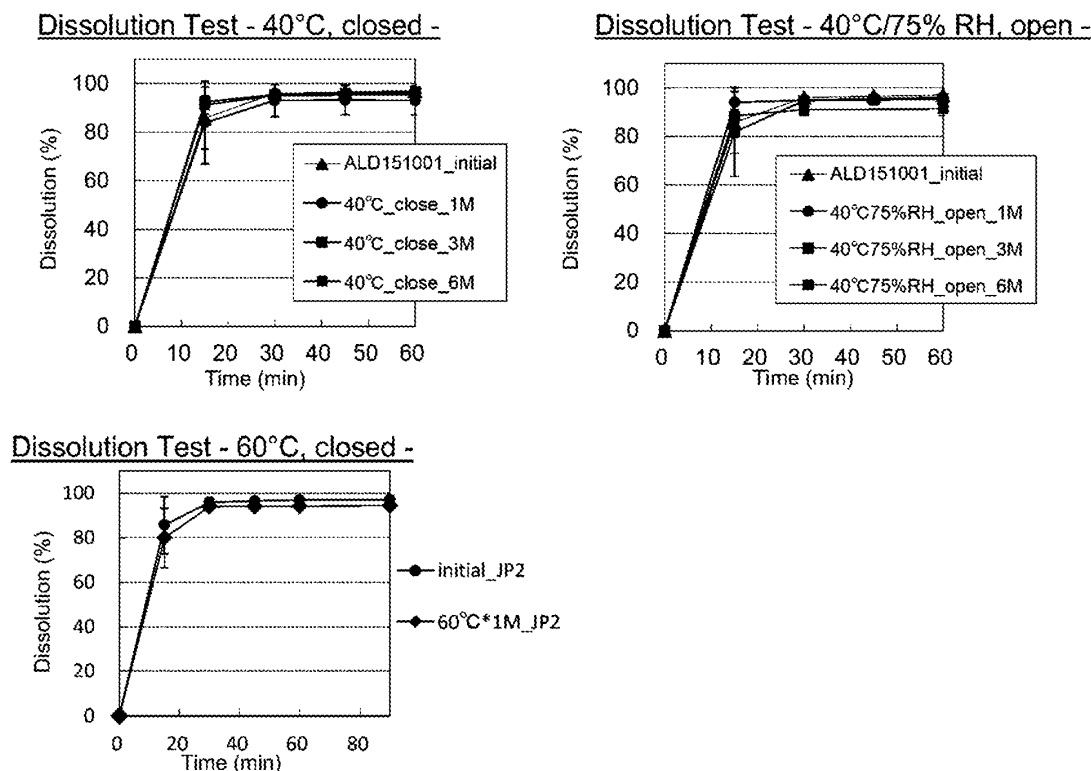


Figure 4

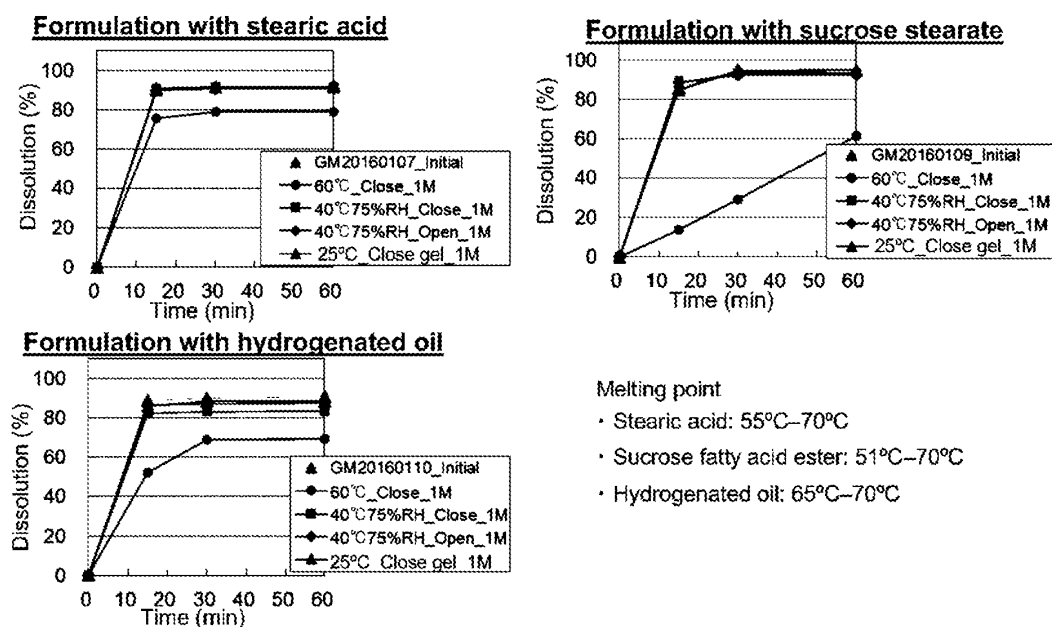


Figure 5: XRPD diffractograms of final blend and uncoated tablet for DC lot 1.

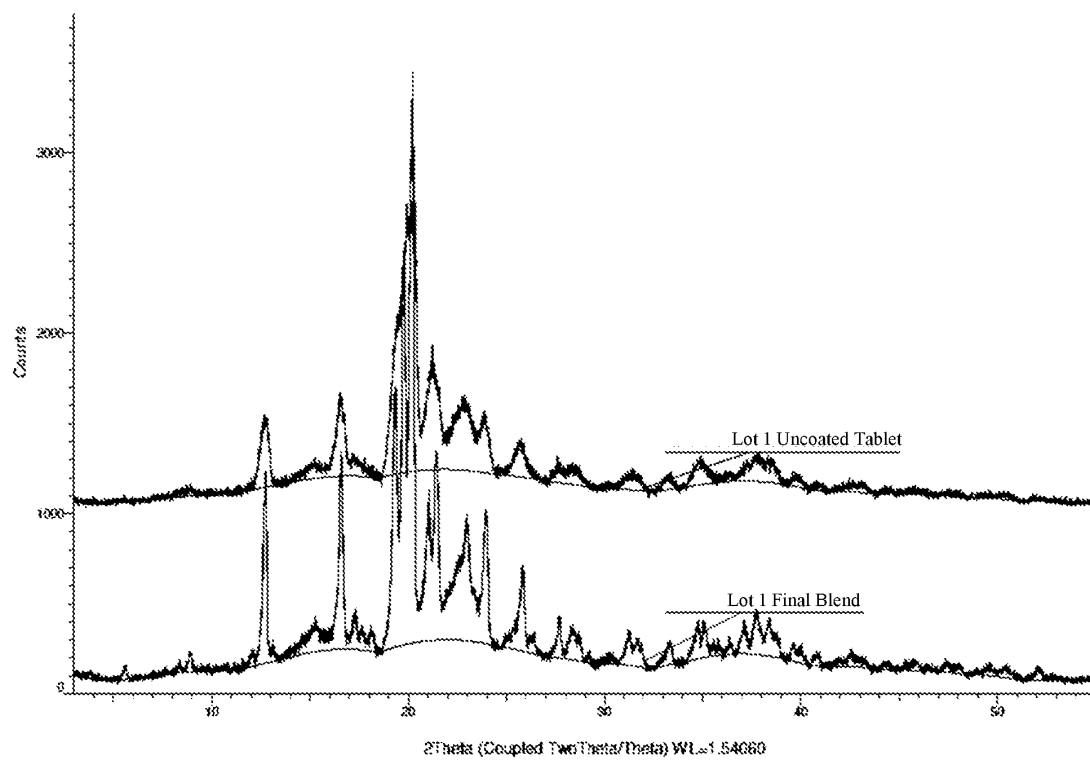


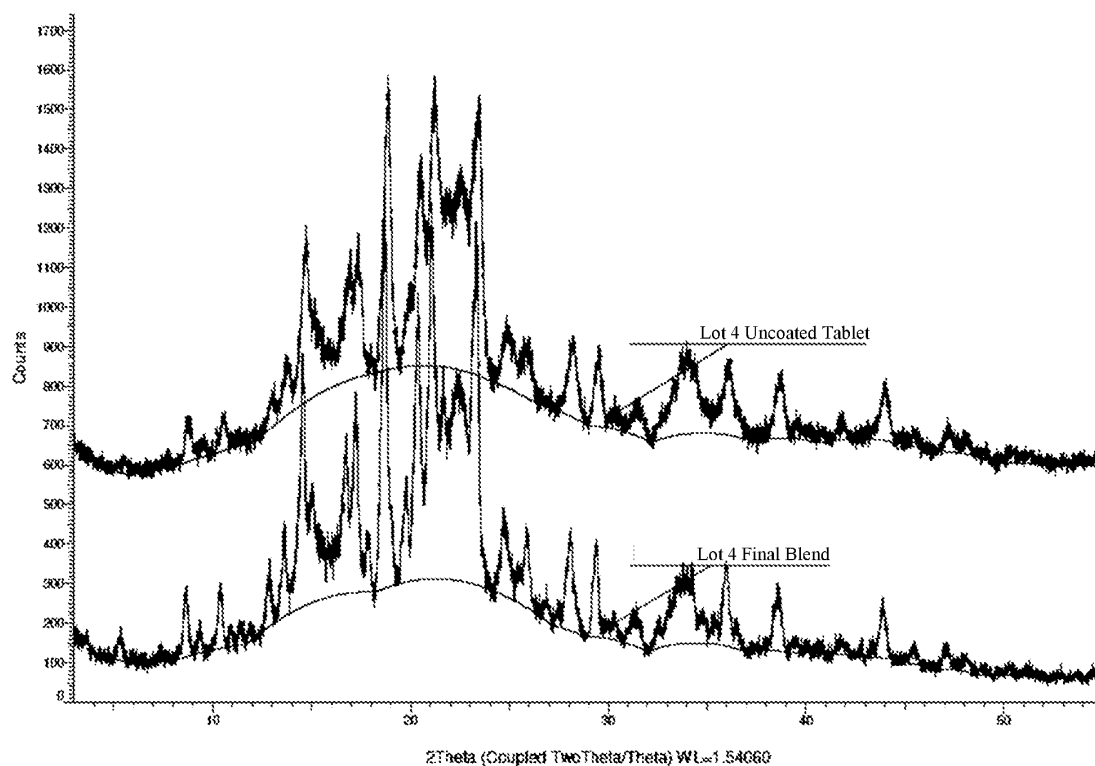
Figure 6: XRPD diffractograms of final blend and uncoated tablet for DC lot 4.

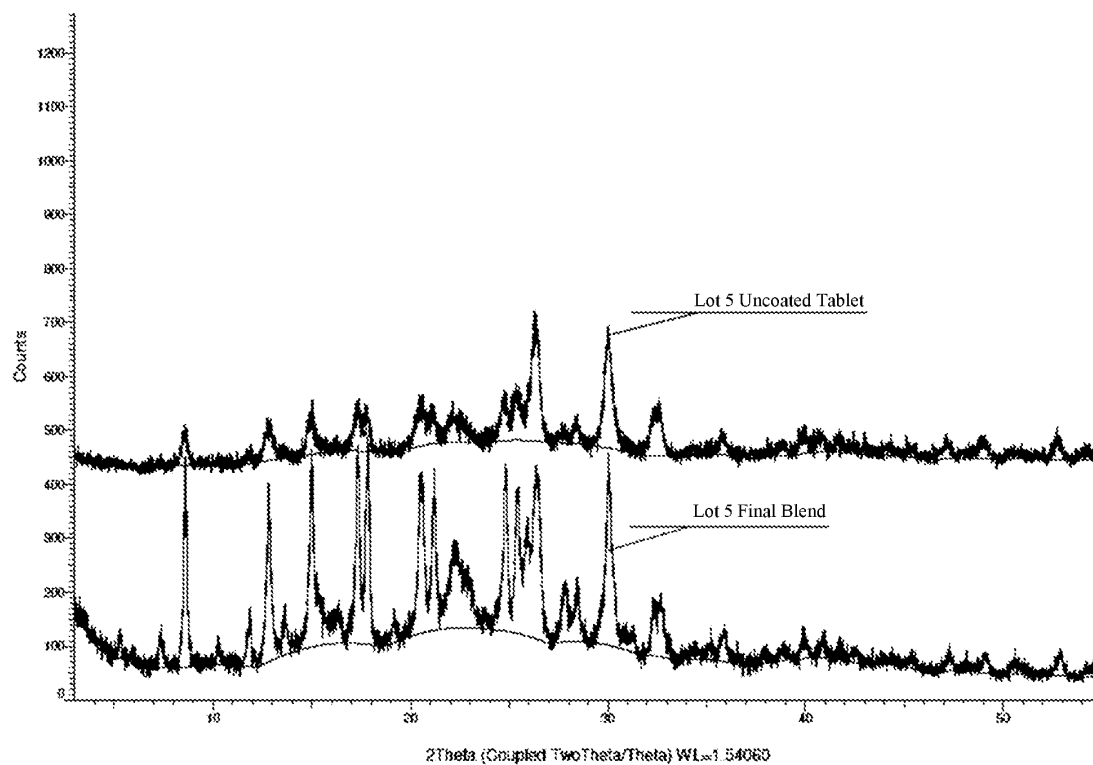
Figure 7: XRPD diffractograms of final blend and uncoated tablet for DC lot 5.

Figure 8: XRPD diffractograms of at various steps of HSWG manufacturing process for lot 6.

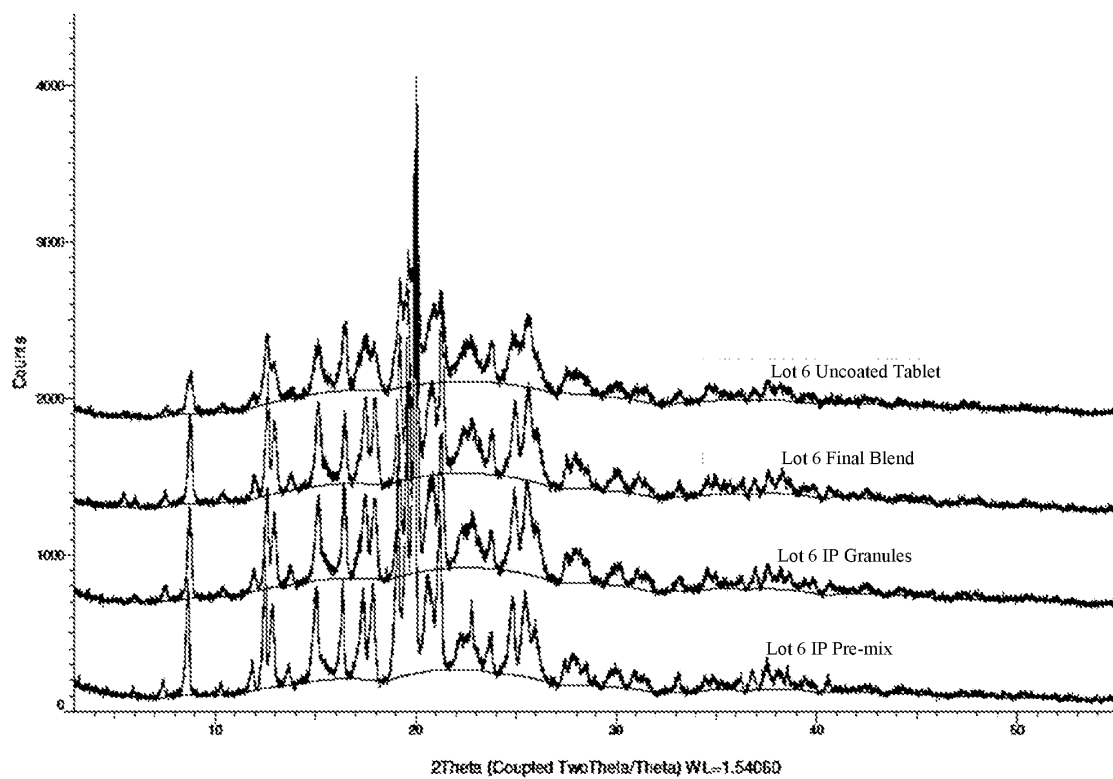


Figure 9: XRPD diffractograms of lot 11 final blend, uncoated tablet, and film coated tablet.

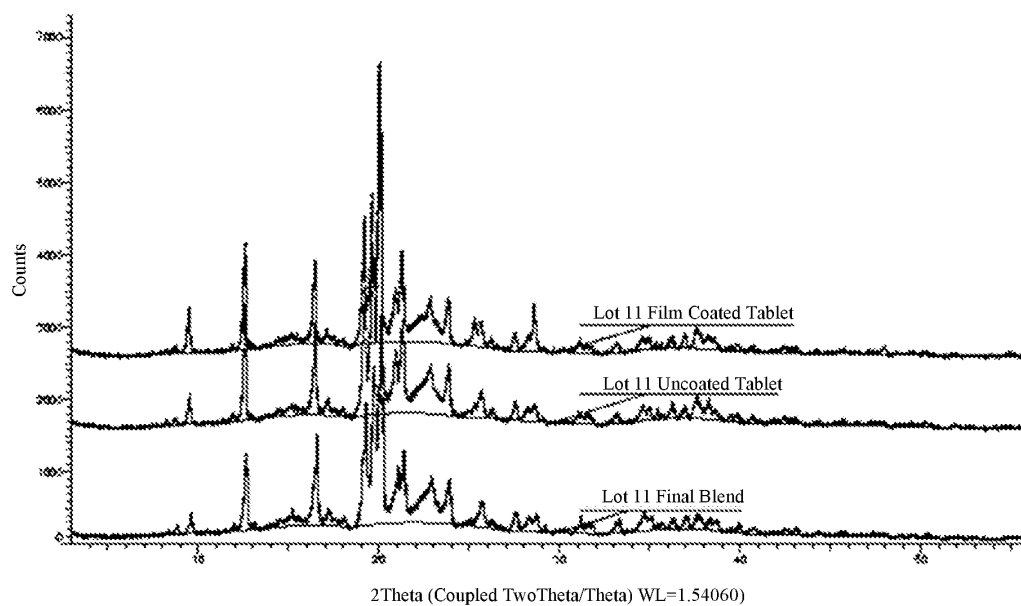


Figure 10: XRPD diffractograms of lot 13 final blend, uncoated tablet, and film coated tablet.

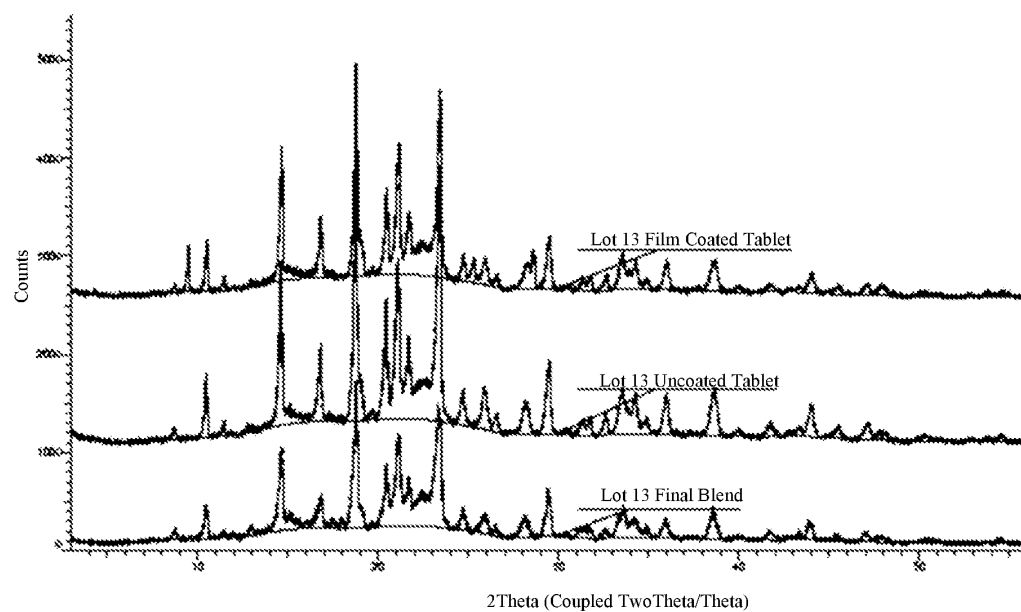


Figure 11: XRPD diffractograms of lot 15 final blend, uncoated tablet, and film coated tablet.

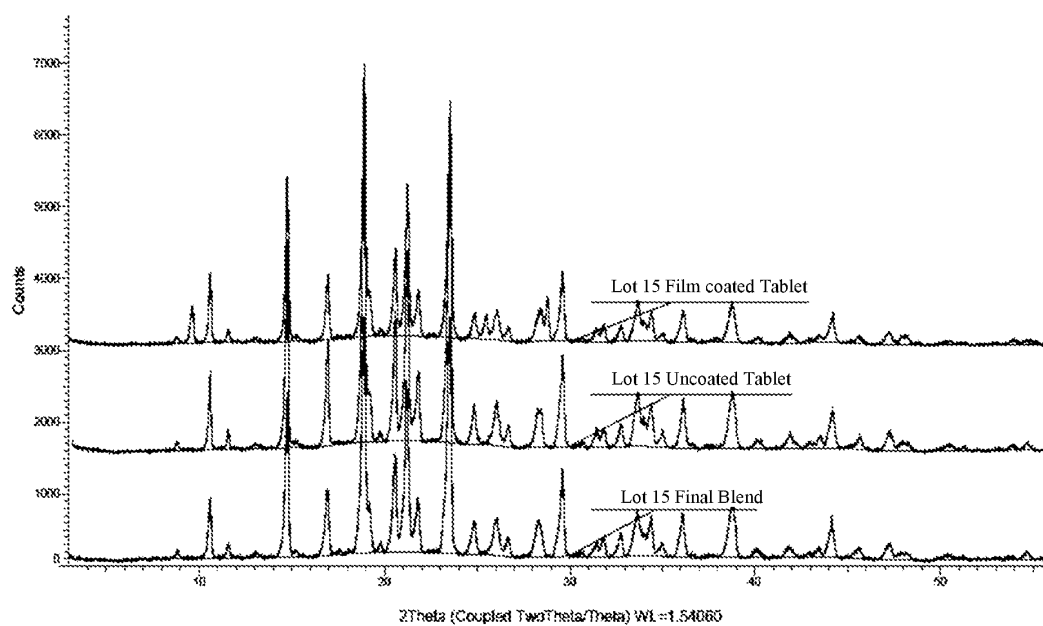


Figure 12: XRPD diffractograms of 17 final blend, uncoated tablet (Trials #1 & #2), and film coated tablet (Trials #2).

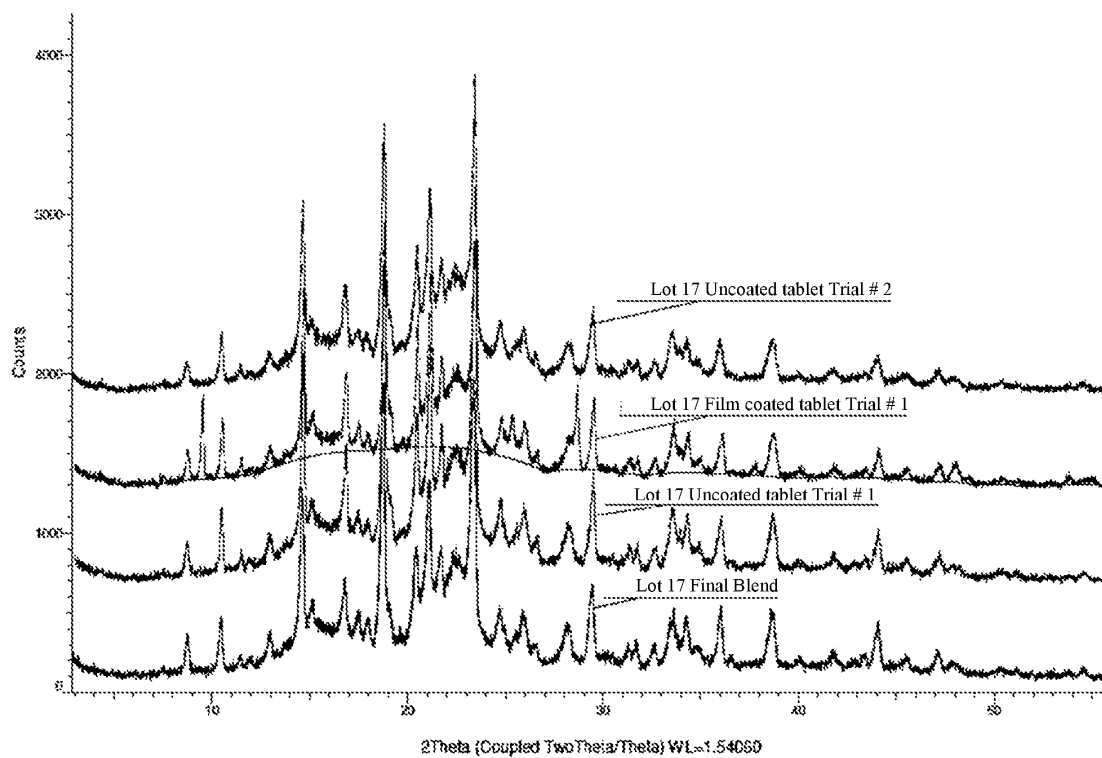


Figure 13: XRPD diffractograms of 18 final blend, uncoated tablet (Trials #1/#2 & #3), and film coated tablet (Trials #2).

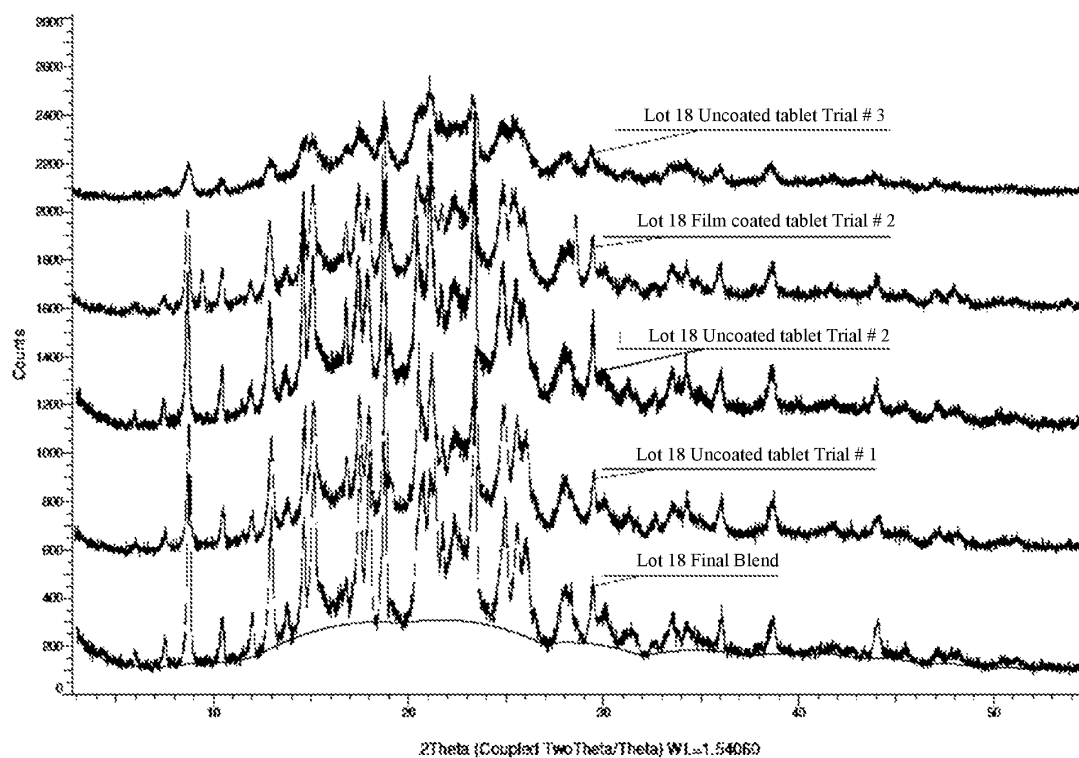


Figure 14: Summary of Analytical data for prototype formulations

Lot	1			4			5			6			
Dose strength (mg)	12.5			25			100			100			
Description (Visual)	White, round biconvex tablet			White, round biconvex tablet			White, round biconvex tablet			White, round biconvex tablet			
Assay	%LC			%LC			%LC			%LC			
	98.7			98.8			98.8			100.1			
	Method revision			R&D 01			R&D 01			R&D 01			
Related Substances	Total Impurities:			No impurity $\geq 0.05\%$			No impurity $\geq 0.05\%$			No impurity $\geq 0.05\%$			
	Method revision			R&D 01			R&D 01			R&D 01			
Dissolution (n=3) 900ml of water Paddles @ 50rpm	Time (min)	%LC	individuals	%LC	individuals	%LC	individuals	%LC	individuals	%LC	individuals		
	10	50	45, 53, 61	67	87, 88, 87	70	78, 61, 61	60	65, 47, 70				
	15	52	47, 55, 54	71	89, 74, 70	73	80, 53, 85	83	84, 81, 85				
	30	55	50, 57, 57	72	70, 76, 71	73	81, 54, 85	86	87, 86, 86				
	45	56	50, 56, 58	73	71, 75, 72	73	80, 54, 85	87	88, 86, 86				
	60 (ramp)	58	54, 80, 60 ^a	75	73, 76, 75 ^a	76	80, 64, 84 ^a	87	87, 86, 86 ^a				
	Method revision			R&D 01			R&D 01			R&D 01			
	Observations	Coring observed after 5 minutes; all tablets were completely disintegrated before 15 min.			Coring observed after 5 minutes; all tablets were completely disintegrated before 15 min.			Coring observed after 5 minutes; all tablets were completely disintegrated before 15 min.			Coring observed after 5 minutes; all tablets were completely disintegrated before 15 min.		
	Dissolution (n=3) 900ml of 0.1N HCl Paddles @ 50rpm	Time (min)	%LC	individuals	%LC	individuals	%LC	individuals	%LC	individuals	%LC	individuals	
		10	88	85, 88, 90	88	88, 78, 92	75	88, 48, 87	94	20, 28, 51			
15		94	92, 94, 95	95	94, 95, 95	94	98, 82, 93	87	54, 63, 85				
30		98	95, 97, 96	94	94, 91, 95	90	93, 78, 96	93	85, 88, 95				
45		97	97, 98, 96	98	95, 98, 97	93	99, 83, 97	97	102, 92, 98				
60 (ramp)		98	98, 98, 97	98	95, 96, 97	101	100, 100, 101	99	103, 93, 99				
Method revision			R&D 01			R&D 01			R&D 01				
Observations		Coring observed after 5 minutes; all tablets were completely disintegrated before 15 min.			Coring observed after 5 minutes; all tablets were completely disintegrated before 15 min.			Coring observed after 5 minutes; all tablets were completely disintegrated before 15 min.			Coring observed after 5 minutes; all tablets were completely disintegrated before 15 min.		

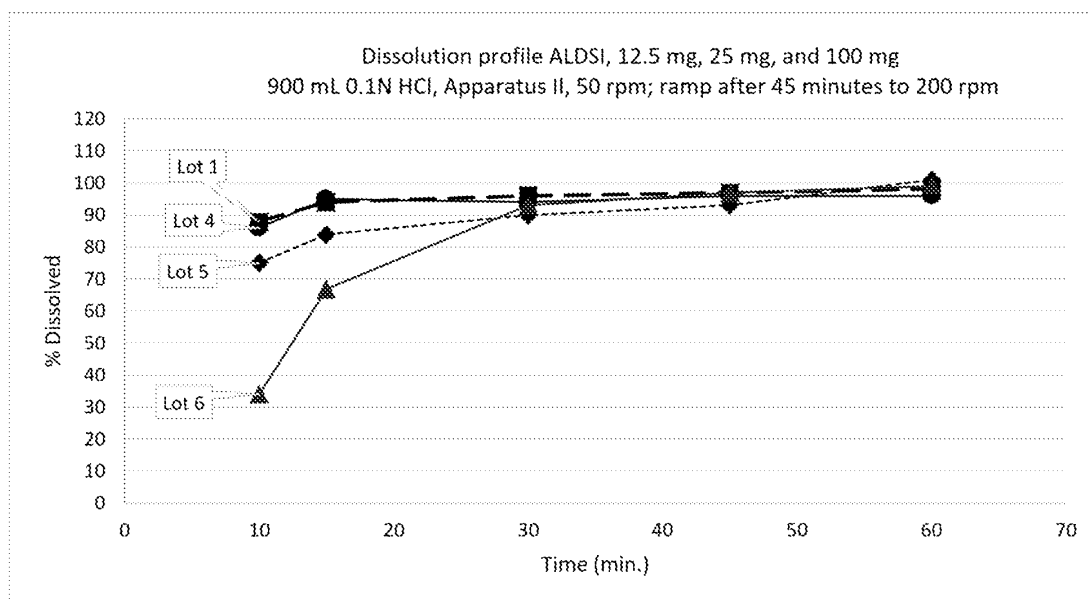
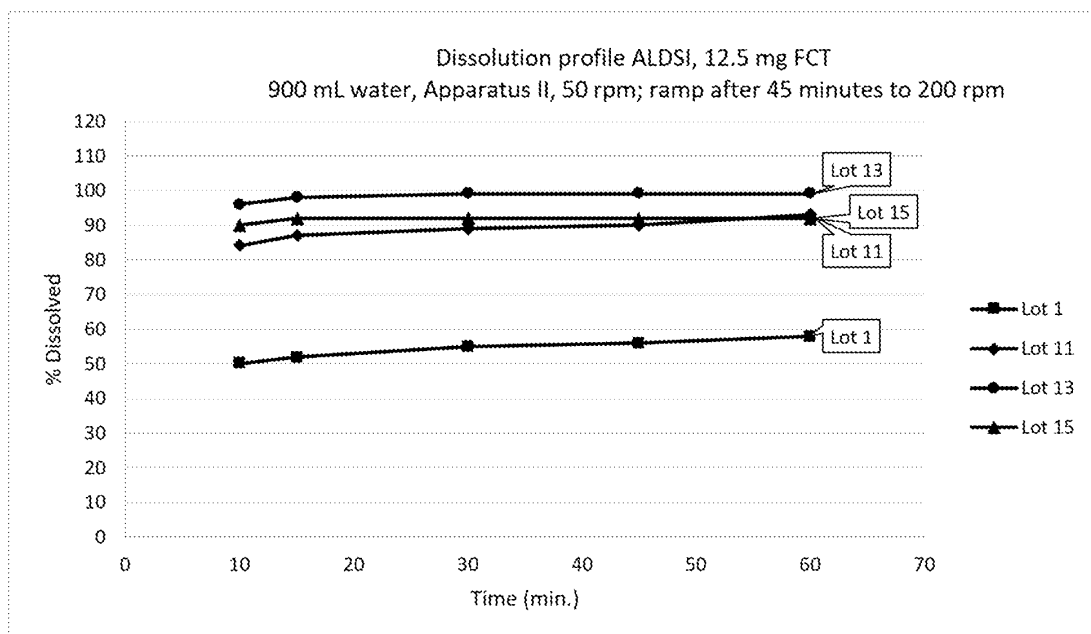
Figure 15: Dissolution profile of 12.5 mg, 25 mg, and 100 mg tablet prototypes in 0.1 HCl

Figure 16: Summary of Analytical data for prototype formulations

Lot		11		13		15	
Dose strength (mg/tablet)		12.5		12.5		12.5	
Description (Visual)		White round biconvex film coated tablets		White round biconvex film coated tablets		White round biconvex film coated tablets	
Assay ^A	%LC	98.8 (97.2, 100.4)		98.7 (98.7, 98.6)		88.5 (88.5, 88.5)	
	Method revision	R&D03		R&D03		R&D03	
Related Substances % LC	Total Impurities:	No impurity $\geq 0.05\%$		No impurity $\geq 0.05\%$		No impurity $\geq 0.05\%$	
	Method revision	R&D03		R&D03		R&D03	
Dissolution (n=3) 900 ml of water Paddles @ 50 rpm	Time (min)	%LC	individuals	%LC	individuals	%LC	individuals
	10	84	92, 83, 78	96	96, 95, 96	90	91, 93, 86
	15	87	93, 87, 81	98	99, 96, 97	92	92, 96, 87
	30	89	94, 88, 84	99	100, 99, 97	92	92, 96, 88
	45	90	95, 90, 86	99	100, 99, 98	92	92, 96, 88
	60 (ramp)	93	97, 92, 90	99	100, 99, 97	92	92, 95, 88
	Method revision	R&D 01		R&D 01		R&D 01	
	Observations	Coning observed; all tablets were completely disintegrated at 10 min; back pressure was observed during filtration.		Coning observed; all tablets were completely disintegrated at 10 min; back pressure was observed during filtration.		All tablets were completely disintegrated at 10 min, back pressure was observed during filtration.	
	Time (min)	%LC	individuals	%LC	individuals	%LC	individuals
	10	84	80, 81, 91	86	84, 85, 90	85	81, 85, 87
Dissolution (n=3) 900 ml of 0.1N HCl Paddles @ 50 rpm	15	87	84, 85, 93	96	99, 93, 97	89	87, 91, 88
	30	90	88, 89, 94	98	101, 94, 98	89	87, 93, 88
	45	92	90, 91, 95	98	101, 94, 98	89	87, 92, 89
	60 (ramp)	98	97, 98, 99	97	101, 94, 98	89	87, 92, 88
	Method revision	R&D 01		R&D 01		R&D 01	
	Observations	Coning observed; all tablets were completely disintegrated at 10 min.		All tablets were completely disintegrated at 10 min.		Tablets not completely disintegrated at 10 min.	

Lot #		12.5 mg tablets		
		11	13	15
Content Uniformity USP <905>	Tablet #	%LC	%LC	%LC
	1	95.3	95.9	93.9
	2	98.1	95.6	90.9
	3	98.5	89.9	91.0
	4	100.3	97.9	88.9
	5	99.3	91.7	88.8
	6	97.2	99.3	87.1
	7	100.5	99.4	93.7
	8	99.0	97.4	87.6
	9	97.4	96.8	87.1
	10	95.1	97.9	87.2
	Average	98.1	96.2	89.6
	%RSD	1.9	3.3	3.0
	Min	95.1	89.9	87.1
	Max	100.5	99.4	93.9
	AV	4.9	9.8	15.3
	Method revision	R&D 0	R&D 0	R&D 0

Figure 17: Dissolution profile of 12.5 mg tablet prototypes in water**Figure 18: Dissolution profile of 12.5 mg tablet prototypes in 0.1N HCl**