

Factors which influence sustained release from hot-melt extrudates

Supplementary Material

TABLES

Table S1 Percentage of target flurbiprofen content in the different segments of the extrudate threads from the pilot studies (n=3)

Flurbiprofen conc. (m/m)	Start	Middle	End	Mean	Rel. SD
20%	100.75%	101.53%	101.61%	101.3%	0.38%
25%	102.08%	101.77%	100.32%	101.39%	0.75%
33%	92.98%	93.05%	93.03%	93.02%	0.03%
25% + 3% Mg-Stearate	103.70%	103.86%	103.09%	103.55%	0.003%
25% with Eudragit RL PO + 4% stearic acid	101.13%	99.76%	100.08%	100.32%	0.71%

Results for Eudragit RL extrudates

Table S2. Dissolution performance of the Eudragit RL/flurbiprofen HME extrudates threads at different drug loads

<u>Eudragit RL/flurbiprofen extrudate threads at different drug loads</u>								
Drug Load	20% (m/m)		25% (m/m)		30% (m/m)		35% (m/m)	
Time in min	Release in %	Rel STD	Release in %	Rel STD	Release in %	Rel STD	Release in %	Rel STD
15	0.76	16.68	0.98	10.28	1.15	6.25	1.81	4.88
30	0.97	11.27	1.33	12.01	1.57	7.64	2.15	3.00
45	1.26	10.75	1.75	9.75	1.87	5.61	2.47	3.91
60	1.49	9.78	2.02	8.99	2.15	5.58	2.71	4.00
120	2.27	10.55	2.51	9.78	2.89	5.07	3.59	3.23
240	3.25	8.77	3.58	9.60	4.12	5.15	4.83	4.25
360	4.07	9.15	4.33	9.08	4.97	4.98	5.99	4.50
480	4.76	8.99	5.01	8.49	5.78	4.84	6.68	4.26
600	5.33	7.61	5.91	2.23	6.38	5.22	7.44	4.24
720	6.08	6.50	6.30	9.14	7.03	5.27	8.13	5.32

Table S3. Dissolution performance of the pulverized (particle size <125 µm) Eudragit RL/flurbiprofen HME extrudates at different drug loads

<u>Eudragit RL/flurbiprofen extrudate pulverized (particle size <125 µm) at different drug load</u>								
Drug Load	20% (m/m)		25% (m/m)		30% (m/m)		35% (m/m)	
Time in min	Release in %	Rel STD	Release in %	Rel STD	Release in %	Rel STD	Release in %	Rel STD
15	15.66	5.62	20.10	18.83	16.03	10.61	13.77	17.22
30	23.22	5.30	30.73	12.41	24.38	9.24	19.26	14.56
45	29.89	3.87	40.63	10.32	29.56	8.47	27.28	11.83
60	35.52	8.91	47.46	11.02	35.36	8.57	31.89	7.00
120	49.52	6.08	57.16	10.00	47.69	7.62	40.70	4.11
240	64.70	1.37	66.03	7.89	64.75	6.62	61.74	6.08
360	72.86	4.20	71.11	6.41	71.73	5.93	66.65	5.77
480	75.20	4.64	77.61	3.83	76.77	7.78	70.99	5.86
600	78.09	4.95	80.78	2.59	79.79	3.16	78.37	5.58
720	81.27	4.63	84.90	2.38	82.52	2.41	84.48	3.45

Table S4. Dissolution performance of the fractionated Eudragit RL/flurbiprofen HME extrudates at 25% (m/m) drug load

<u>Fractionated Eudragit RL/flurbiprofen extrudate at 25% (m/m) drug load</u>														
Drug Load	< 125 µm		125 µm – 250 µm		250 µm – 355 µm		355 µm – 630 µm		630 µm – 800 µm		800 µm – 2 mm		2 mm threads	
Time in min	Release in %	Rel STD	Release in %	Rel STD	Release in %	Rel STD	Release in %	Rel STD	Release in %	Rel STD	Release in %	Rel STD	Release in %	Rel STD
15	20.10	18.83	20.04	3.21	11.46	0.93	8.28	3.91	5.58	7.10	4.64	2.62	0.98	10.28
30	30.73	12.41	27.28	1.21	17.42	0.92	12.59	7.10	8.15	8.16	5.93	1.12	1.33	12.01
45	40.63	10.32	34.21	1.74	22.44	2.60	15.37	5.54	10.35	7.40	6.78	2.13	1.75	9.75
60	47.46	11.02	38.34	2.14	27.73	2.25	17.46	2.83	12.85	9.74	7.42	3.59	2.02	8.99
120	57.16	10.00	49.44	3.03	37.18	0.30	24.78	6.98	17.53	7.37	9.68	5.29	2.51	9.78
240	66.03	7.89	64.76	4.78	54.92	3.31	34.98	7.28	24.11	5.00	13.05	6.60	3.58	9.60
360	71.11	6.41	70.14	3.41	62.14	1.28	42.08	6.46	30.26	7.61	14.96	7.48	4.33	9.08
480	77.61	3.83	75.99	5.62	70.23	1.57	46.42	6.50	35.59	7.57	17.02	5.63	5.01	8.49
600	80.78	2.59	78.76	5.31	77.34	0.58	52.29	6.99	39.58	6.82	18.89	6.50	5.91	12.23
720	84.90	2.38	83.14	0.69	81.01	5.10	58.57	7.32	43.87	7.72	21.18	7.43	6.30	9.14

Table S5. Dissolution performance of 125 – 250 µm fraction of the fractionated Eudragit RL/flurbiprofen HME extrudates at 25% (m/m) drug load at 50,75 and 100 rpm

Fractionated Eudragit RL/flurbiprofen extrudate at 25% (m/m) drug load, 125 – 250 µm particle size						
Rpm	50 rpm		75 rpm		100 rpm	
Time in min	Release in %	Rel STD	Release in %	Rel STD	Release in %	Rel STD
15	20.04	3.21	21.52	4.44	16.25	6.43
30	30.73	1.21	34.31	5.03	24.69	5.73
45	40.63	1.74	40.46	4.33	31.31	4.76
60	47.46	2.14	46.17	4.34	36.77	4.90
120	57.16	3.03	60.09	2.78	51.28	3.32
240	66.03	4.78	73.58	2.30	68.80	2.83
360	71.11	3.41	79.64	2.11	76.93	1.26
480	77.61	5.63	81.66	1.61	81.56	2.46
600	80.78	5.31	83.15	0.91	85.66	1.94
720	84.90	0.69	83.39	1.26	91.83	0.80

Table S6. Dissolution performance of 800 µm – 2 mm fraction of the fractionated Eudragit RL/flurbiprofen HME extrudates at 25% (m/m) drug load at 50,75 and 100 rpm

Fractionated Eudragit RL/flurbiprofen extrudate at 25% (m/m) drug load, 800 µm–2 mm particle size						
Rpm	50 rpm		75 rpm		100 rpm	
Time in min	Release in %	Rel STD	Release in %	Rel STD	Release in %	Rel STD
15	4.64	2.62	3.35	7.90	2.22	7.19
30	5.93	1.12	5.40	3.37	3.46	4.94
45	6.78	2.13	6.10	4.57	4.33	5.01
60	7.42	3.59	7.16	0.90	5.36	4.93
120	9.68	5.29	9.72	3.63	7.45	4.55
240	13.05	6.60	13.74	0.85	10.93	3.71
360	14.96	7.48	17.01	0.70	13.33	4.29
480	17.02	5.63	19.33	1.52	16.40	3.35
600	18.89	6.50	22.09	0.47	18.68	4.72
720	21.18	7.43	22.90	1.48	20.95	3.44

Table S7. Dissolution performance of the Eudragit RS/flurbiprofen HME extrudate threads at different drug loads

<u>Eudragit RS/flurbiprofen extrudate threads at different drug load</u>								
Drug Load	20% (m/m)		25% (m/m)		30% (m/m)		35% (m/m)	
Time in min	Release in %	Rel STD	Release in %	Rel STD	Release in %	Rel STD	Release in %	Rel STD
15	1.19	8.50	1.98	3.60	1.65	5.32	3.31	5.02
30	1.35	4.53	2.05	3.64	1.68	6.91	3.44	8.00
45	1.47	6.10	2.18	3.47	1.87	5.20	3.68	4.81
60	1.55	6.41	2.27	3.47	2.06	4.25	3.84	4.67
120	1.90	6.94	2.67	2.70	2.75	4.51	4.27	4.66
240	2.41	6.10	3.27	1.95	3.57	3.96	5.07	7.46
360	2.81	6.31	3.69	2.14	4.24	4.43	5.48	4.79
480	3.19	7.60	4.09	1.99	4.90	4.42	5.95	4.50
600	3.38	6.65	4.30	2.22	5.34	4.45	6.37	4.73
720	3.68	4.01	4.59	2.15	5.53	5.17	6.76	4.68

Results for Eudragit RS extrudates

Table S8. Dissolution performance of the Eudragit RS/flurbiprofen HME extrudate threads at different drug loads

<u>Eudragit RS/flurbiprofen extrudate threads at different drug load</u>								
Drug Load	20% (m/m)		25% (m/m)		30% (m/m)		35% (m/m)	
Time in min	Release in %	Rel STD	Release in %	Rel STD	Release in %	Rel STD	Release in %	Rel STD
15	1.19	8.50	1.98	3.60	1.65	5.32	3.31	5.02
30	1.35	4.53	2.05	3.64	1.68	6.91	3.44	8.00
45	1.47	6.10	2.18	3.47	1.87	5.20	3.68	4.81
60	1.55	6.41	2.27	3.47	2.06	4.25	3.84	4.67
120	1.90	6.94	2.67	2.70	2.75	4.51	4.27	4.66
240	2.41	6.10	3.27	1.95	3.57	3.96	5.07	7.46
360	2.81	6.31	3.69	2.14	4.24	4.43	5.48	4.79
480	3.19	7.60	4.09	1.99	4.90	4.42	5.95	4.50
600	3.38	6.65	4.30	2.22	5.34	4.45	6.37	4.73
720	3.68	4.01	4.59	2.15	5.53	5.17	6.76	4.68

Table S9. Dissolution performance of the pulverized Eudragit RS/flurbiprofen HME extrudates
(particle size < 125 µm) at different drug load

<u>Eudragit RS/flurbiprofen extrudate pulverized (particle size <125 µm) at different drug load</u>								
Drug Load	20% (m/m)		25% (m/m)		30% (m/m)		35% (m/m)	
Time in min	Release in %	Rel STD	Release in %	Rel STD	Release in %	Rel STD	Release in %	Rel STD
15	19.28	4.19	16.92	4.54	16.86	3.92	14.99	3.66
30	26.19	2.66	23.84	3.65	25.13	6.65	21.65	4.02
45	29.87	2.41	26.70	4.17	30.13	3.36	26.08	4.54
60	33.65	2.92	29.94	4.32	32.59	3.13	28.40	4.63
120	40.71	2.68	36.86	4.39	42.07	3.35	37.90	3.96
240	49.60	2.56	44.05	2.54	50.94	2.81	47.95	4.23
360	56.28	3.11	48.40	1.83	57.34	2.84	54.72	1.71
480	60.68	2.84	55.31	2.59	59.86	1.90	61.16	1.38
600	63.49	2.62	59.01	2.41	61.84	1.15	65.77	2.32
720	66.76	2.53	62.26	3.20	63.83	1.97	70.28	2.66

Table S10. Dissolution performance of the fractionated Eudragit RS/flurbiprofen HME extrudates at 25% (m/m) drug load

<i>Fractionated Eudragit RS/flurbiprofen extrudate at 25% (m/m) drug load</i>														
Drug Load	< 125 µm		125 µm – 250 µm		250 µm – 355 µm		355 µm – 630 µm		630 µm – 800 µm		800 µm – 2 mm		2 mm threads	
Time in min	Release in %	Rel STD	Release in %	Rel STD	Release in %	Rel STD	Release in %	Rel STD	Release in %	Rel STD	Release in %	Rel STD	Release in %	Rel STD
15	16.92	4.54	15.27	3.10	7.34	3.76	5.26	6.25	3.26	3.75	2.66	1.51	1.98	3.60
30	23.84	3.65	19.63	2.87	10.11	1.53	7.23	3.42	4.63	3.84	3.54	1.55	2.05	3.64
45	26.70	4.17	23.67	2.44	12.56	1.18	8.81	2.23	5.65	3.48	4.25	1.76	2.18	3.47
60	29.94	4.32	26.10	2.13	13.49	0.41	9.38	0.72	6.48	2.89	4.83	1.60	2.27	3.47
120	36.86	4.39	33.13	3.37	19.07	2.36	13.19	1.87	9.31	4.98	6.79	2.85	2.67	2.70
240	44.05	2.54	43.78	4.24	26.66	1.35	18.38	1.89	12.76	4.69	9.05	0.69	3.27	1.95
360	48.40	1.83	48.63	3.81	32.80	2.33	22.47	1.75	15.61	4.73	11.10	1.31	3.69	2.14
480	55.31	2.59	54.23	1.85	36.84	1.13	25.36	0.31	17.83	3.64	12.70	1.56	4.09	1.99
600	59.01	2.41	56.01	1.46	39.79	2.24	27.48	1.08	20.15	2.85	14.34	1.46	4.30	2.22
720	62.26	3.20	58.09	1.78	42.38	2.06	29.06	0.77	22.13	2.91	15.67	1.65	4.59	2.15

Table S11. Dissolution performance of 125 – 250 µm fraction of the fractionated Eudragit RS/flurbiprofen HME extrudates at 25% (m/m) drug load stirred at 50,75 and 100 rpm

Fractionated Eudragit RS/flurbiprofen extrudate at 25% (m/m) drug load, 125 – 250 µm particle size						
Rpm	50 rpm		75 rpm		100 rpm	
Time in min	Release in %	Rel STD	Release in %	Rel STD	Release in %	Rel STD
15	15.27	3.10	11.40	4.81	7.94	1.27
30	19.63	2.87	16.75	5.92	11.58	2.21
45	23.67	2.44	19.95	4.93	14.33	3.20
60	26.10	2.13	23.43	6.76	16.98	4.00
120	33.13	3.37	32.34	3.65	24.28	4.17
240	43.78	4.24	44.00	2.62	34.70	4.12
360	48.63	3.81	51.67	3.84	41.19	3.72
480	54.23	1.85	56.93	3.69	46.64	3.72
600	56.01	1.46	61.90	3.31	51.20	3.07
720	58.09	1.78	62.50	2.21	56.79	3.66

Table S12. Dissolution performance of the 800 µm – 2 mm fraction of the fractionated Eudragit RS/flurbiprofen HME extrudates at 25% (m/m) drug load stirred at 50, 75 and 100 rpm

Fractionated Eudragit RL/flurbiprofen extrudate at 25% (m/m) drug load, 800 µm–2 mm particle size						
Rpm	50 rpm		75 rpm		100 rpm	
Time in min	Release in %	Rel STD	Release in %	Rel STD	Release in %	Rel STD
15	2.66	1.51	3.46	2.74	0.90	9.79
30	3.54	1.55	4.25	2.44	1.55	10.47
45	4.25	1.76	4.72	2.66	1.99	7.90
60	4.83	1.60	5.31	4.09	2.51	6.09
120	6.79	2.85	6.78	3.96	3.61	6.17
240	9.05	0.69	8.83	3.56	5.44	4.38
360	11.10	1.31	10.52	4.14	6.81	3.87
480	12.70	1.56	11.93	4.35	8.42	5.05
600	14.34	1.46	13.27	4.68	9.77	4.13
720	15.67	1.65	13.78	4.48	10.96	4.45

Results for the commercial product, Cebutid

Table S13. Dissolution performance of the commercial sustained release product at stirring rates of 50,75 and 100 rpm

Dissolution performance Cebutid LP sustained release capsules						
Rpm	50 rpm		75 rpm		100 rpm	
Time in min	Release in %	Rel STD	Release in %	Rel STD	Release in %	Rel STD
15	0.55	11.52	2.29	8.37	3.02	3.25
30	1.14	10.57	4.50	8.63	5.30	1.48
45	1.42	7.63	7.10	5.47	7.33	1.51
60	1.84	6.64	9.22	4.04	9.67	1.65
120	3.49	4.53	17.54	2.21	17.00	0.82
240	6.30	2.08	31.28	1.83	29.13	1.48
360	8.69	2.46	43.06	1.46	38.42	1.35
480	10.65	2.73	52.38	1.53	47.48	1.26
600	12.24	2.03	59.79	1.61	54.59	0.80
720	14.13	1.36	66.38	1.86	57.06	1.23

Figure S1. DSC of pure flurbiprofen, pure excipients, physical mixtures and extrudates

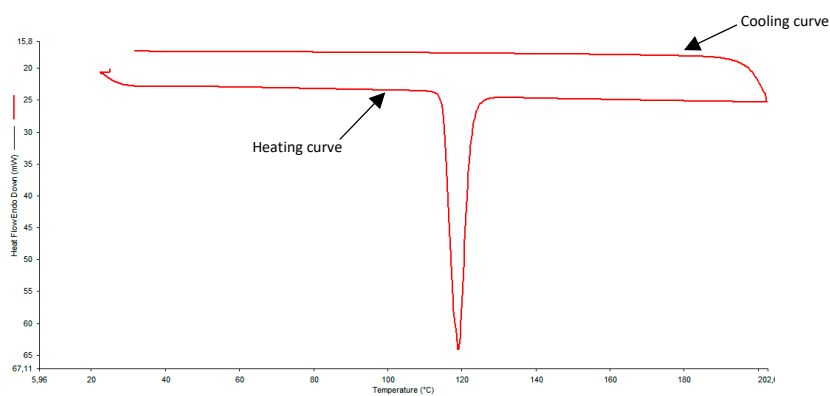


Figure S1.1 pure flurbiprofen

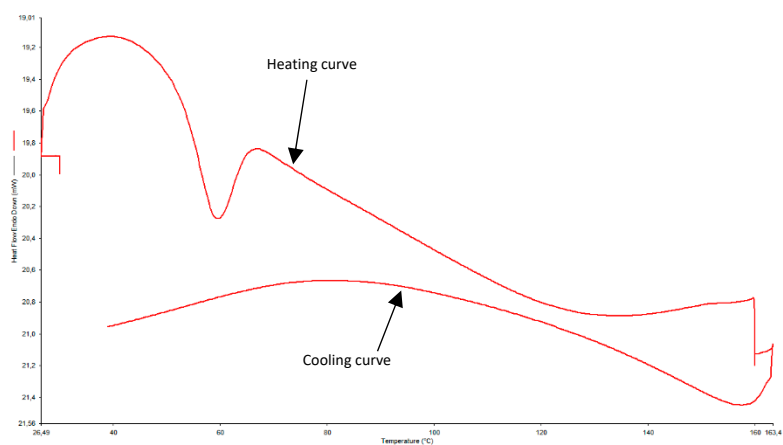


Figure S1.2. of pure talcum

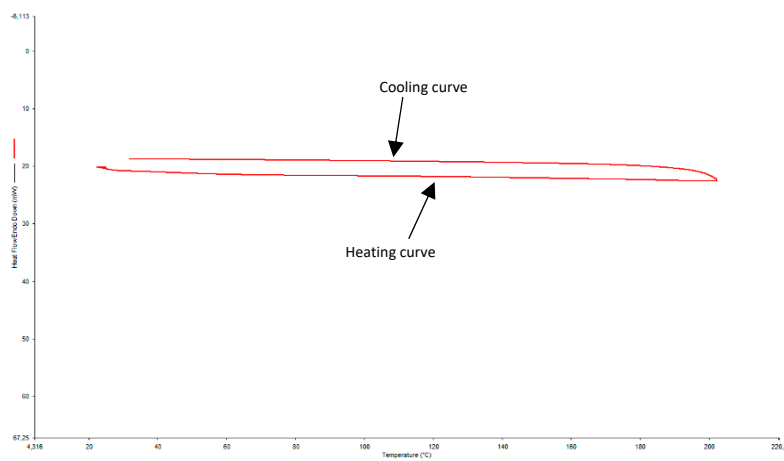


Figure S1.3. pure stearic acid

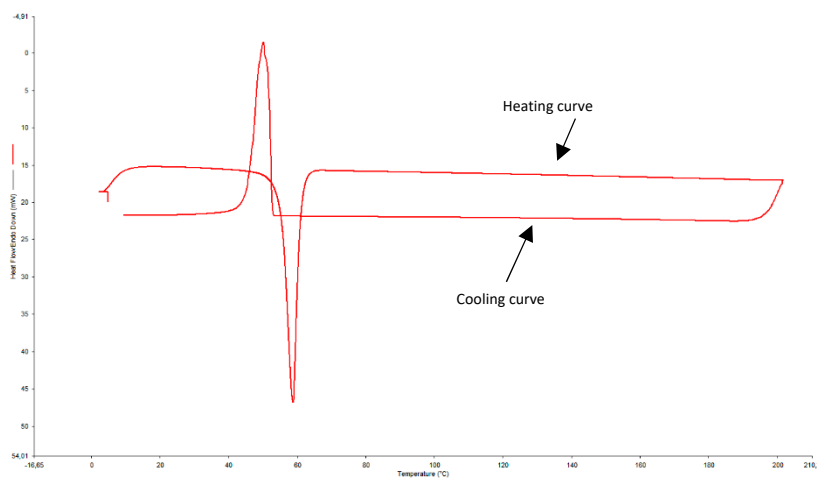


Figure S1.4. pure Eudragit RL

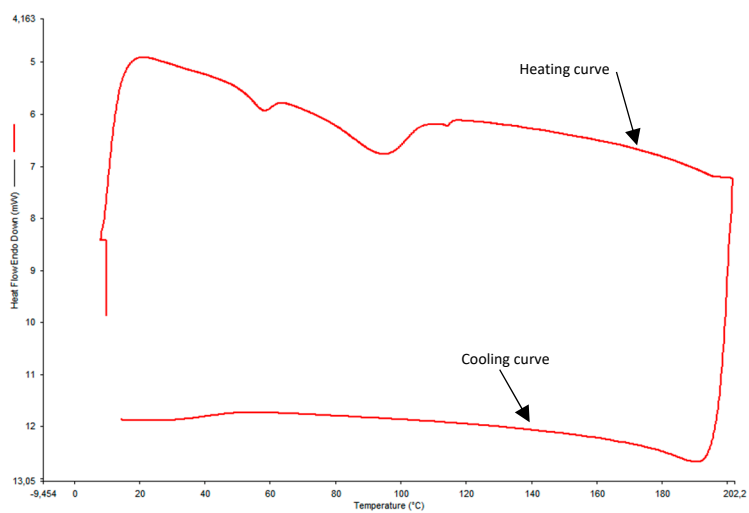


Figure S1.5 pure Eudragit RS

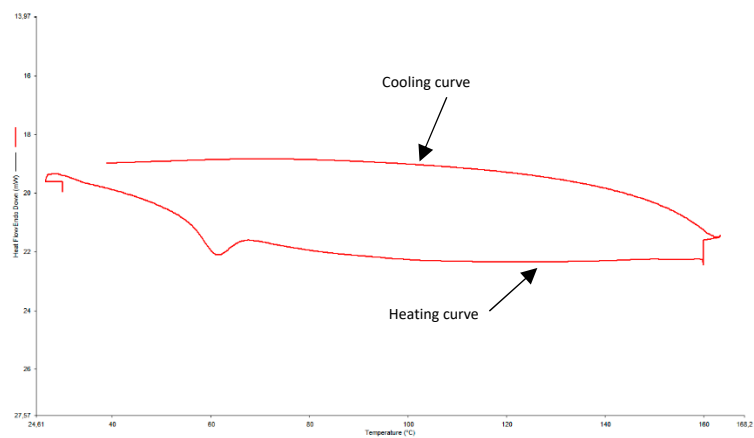


Figure S1.6 physical mixture of Eudragit RS, stearic acid and talcum containing 25% m/m flurbiprofen

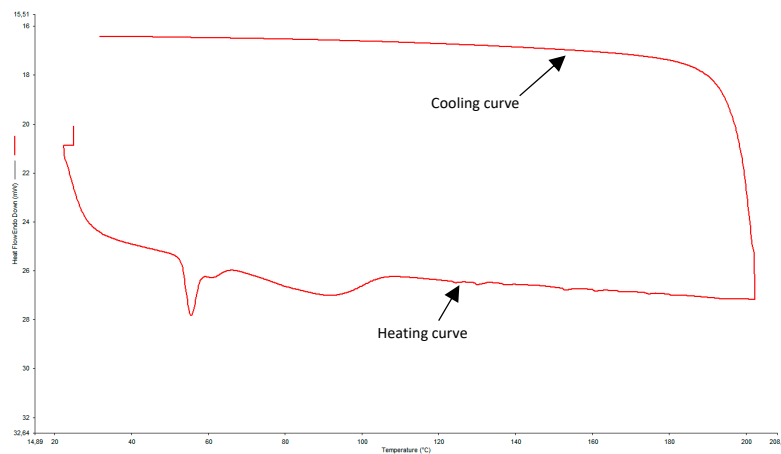


Figure S1.7. DSC thermogram of a physical mixture of Eudragit RL, stearic acid and talcum, containing 25% m/m flurbiprofen

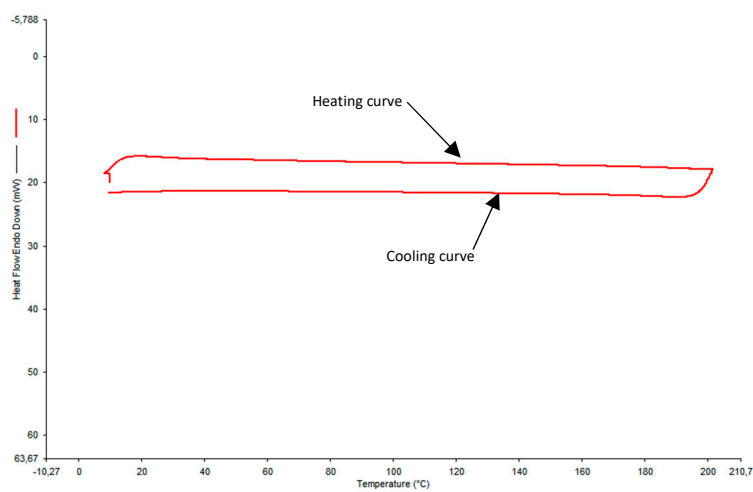


Figure S1.8. extrudate containing Eudragit RS, stearic acid, talcum and 20% m/m flurbiprofen

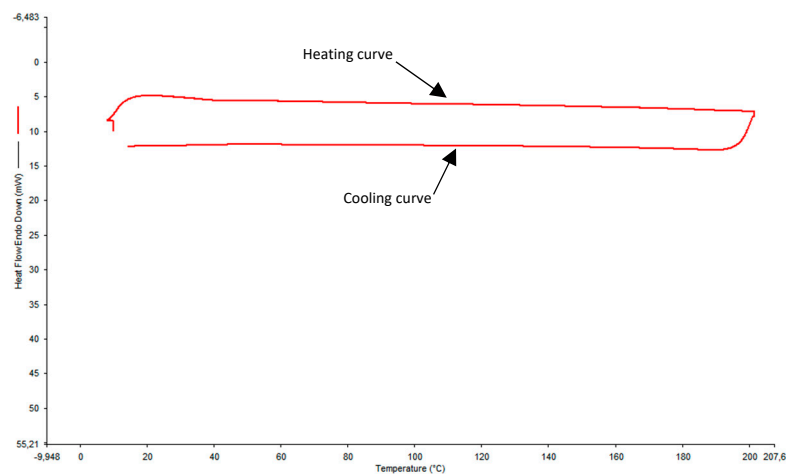


Figure S1.9 extrudate containing Eudragit RS, stearic acid, talcum and 25% m/m flurbiprofen

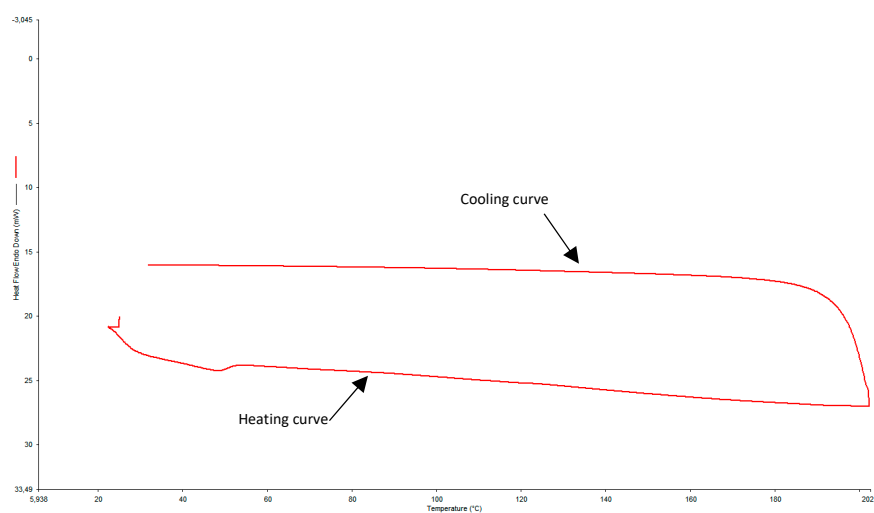


Figure S1.10. extrudate containing Eudragit RS, stearic acid, talcum and 30% m/m flurbiprofen

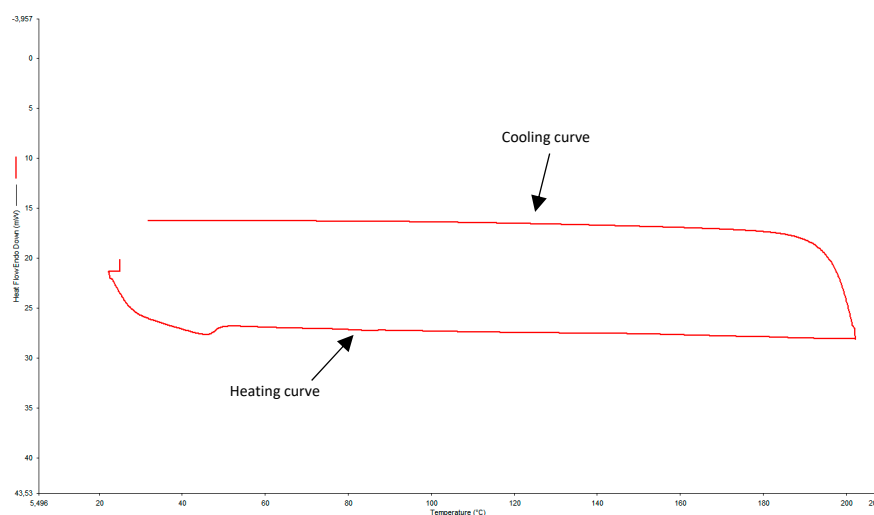


Figure S1.11. extrudate containing Eudragit RS, stearic acid, talcum and 35% m/m flurbiprofen

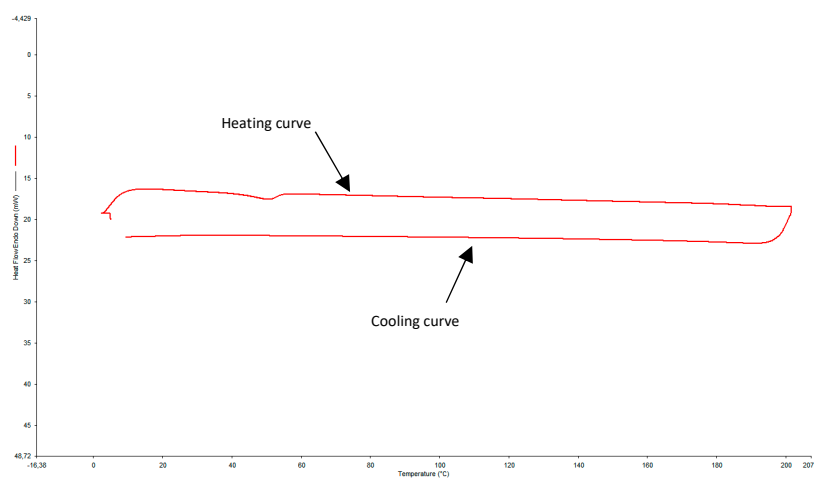


Figure S1.12. extrudate containing Eudragit RL, stearic acid, talcum and 20% m/m flurbiprofen

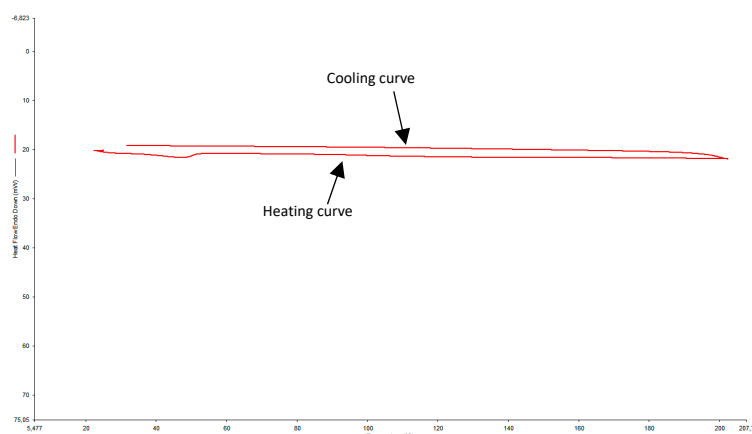


Figure S1.13. extrudate containing Eudragit RL, stearic acid, talcum and 25% m/m flurbiprofen

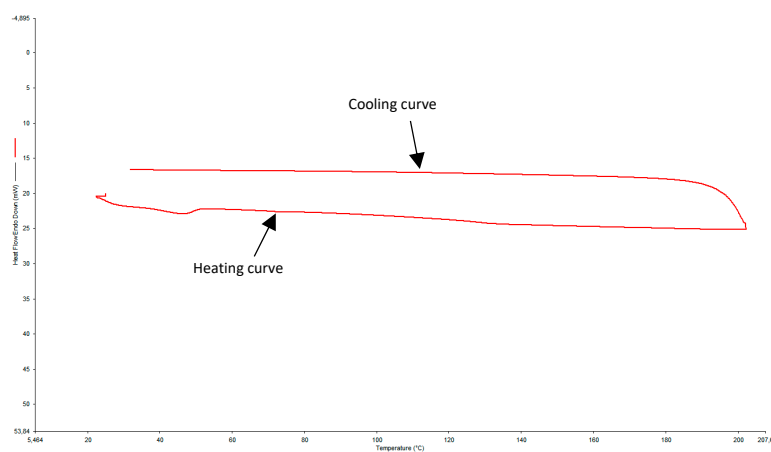


Figure S1.14. extrudate containing Eudragit RL, stearic acid, talcum and 30% m/m flurbiprofen

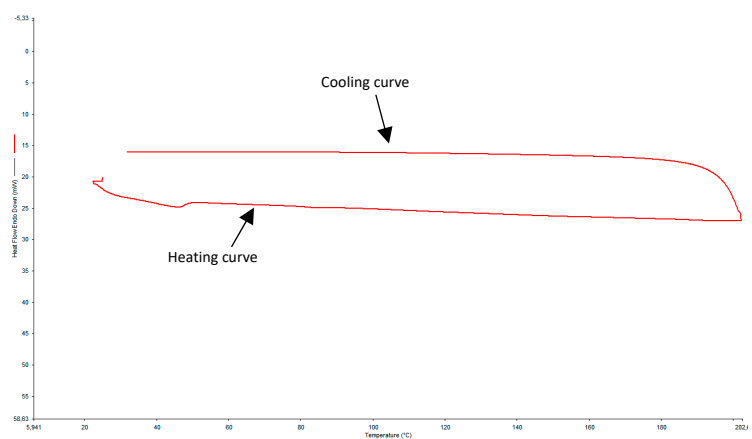


Figure S1.15. extrudate containing Eudragit RL, stearic acid, talcum and 35% m/m flurbiprofen