Supporting

Modelling the Methacrylated Chitosan hydrogel properties through an experimental design approach, from composition to material property

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1. Materials and Methods

1.1. Optical Calibration

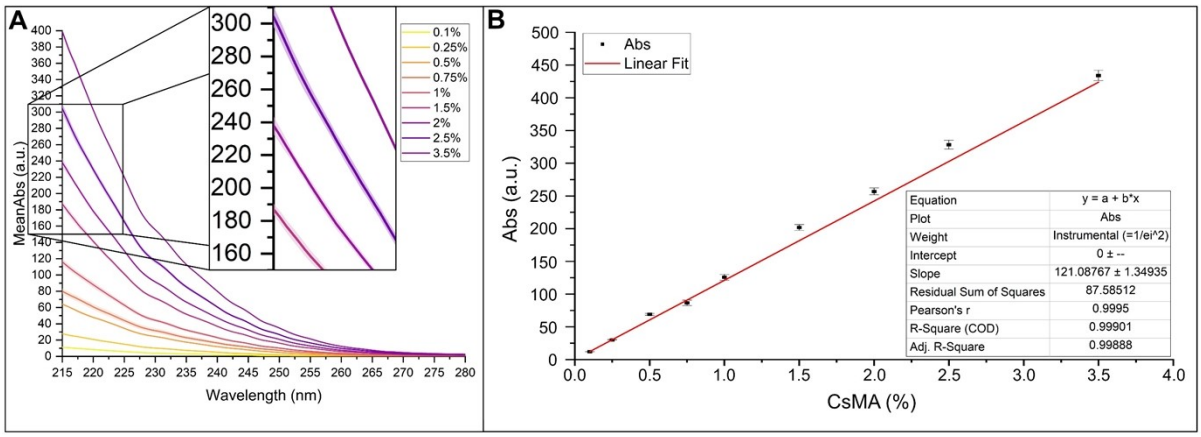

Figure S1: (**A**) UV Absorbance spectra of CsMA with increasing concentration: the intensity increased proportionally to the concentration of CsMA. The uncertainty on the UV-Vis curve (shown as a shadowed area) resulted to be extremely small, as reported by the magnification. (**B**) The increase in the UV-Vis intensity was linear and usable to obtain a calibration curve using the intensities at 215 nm.

In **Figure S1 A,** the UV absorbance spectra at different CsMA concentrations are reported. An increase in CsMA concentration increases the absorbance. Interestingly, the 95% CI reported as shadowed zone are extremely small, as can be seen by the magnification. Based on absorbance intensities at 215 nm a calibration curve was built (**Figure S1 B**). The data points were fitted by a straight line passing through the origin. The angular coefficient (m) resulted to be 121.09 this can be used to convert the intensity on CsMA concentration in percentage while the value 12.108767 was used to achieve the conversion in mg/mL (**Equation S1**). The high r^2 (0.999) ensured a good fitting of the calibration curve to the data.

$$[CsMA]\left(^{mg}/_{mL}\right) = \frac{I_{215}}{12.109} \quad \text{(S1)}$$

2. Results

2.1. Viscosity

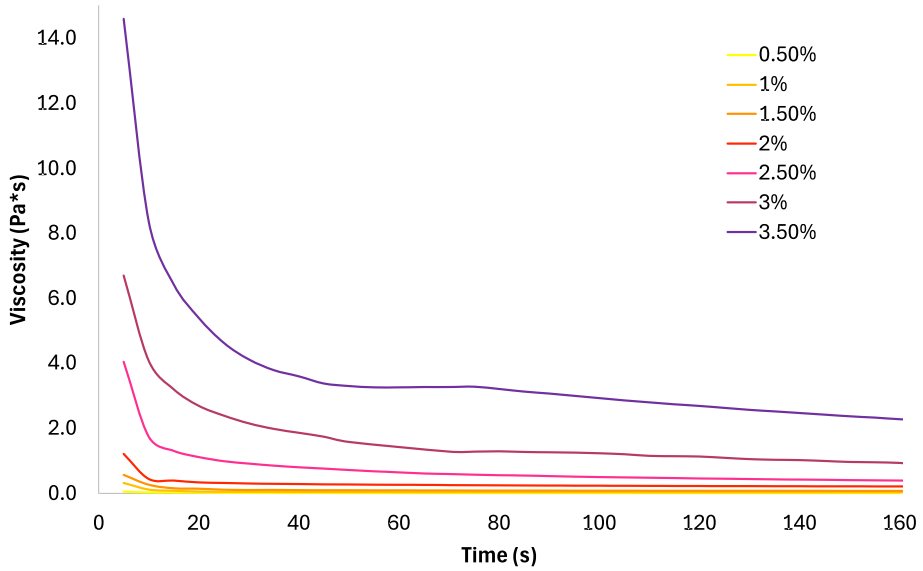

Figure S2: Viscosity plot as function of time during the rheological analysis for all the tested hydrogel solutions (from 0.5% to 3.5% of CsMA content). The shear rate was linearly increased in the 1 s^{-1}-100 s^{-1} range and shear stress and viscosity recorded.

Table S1: The Model F-value of 3736.17 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A, C, BC, A^2, B^2, C^2, ABC, A^2C, AB^2, AC^2, B^2C, BC^2, B^3, C^3 are significant model terms, the rest of the non-significant terms were added to maintain the model hierarchy. Applied transformation: natural log.

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	2132.96	17	125.47	3736.17	< 0.0001	significant
A-T	23.65	1	23.65	704.12	< 0.0001	***
B-Shear Rate	0.0010	1	0.0010	0.0308	0.8608	
C-Concentration	113.76	1	113.76	3387.51	< 0.0001	***
AB	0.0062	1	0.0062	0.1855	0.6669	
AC	0.0519	1	0.0519	1.55	0.2141	
BC	0.5245	1	0.5245	15.62	< 0.0001	***
A^2	1.20	1	1.20	35.71	< 0.0001	***
B^2	19.27	1	19.27	573.73	< 0.0001	***
C^2	25.76	1	25.76	766.95	< 0.0001	***
ABC	1.72	1	1.72	51.18	< 0.0001	***
A^2C	3.90	1	3.90	116.15	< 0.0001	***
AB^2	0.7622	1	0.7622	22.70	< 0.0001	***
AC^2	0.8419	1	0.8419	25.07	< 0.0001	***
B^2C	1.19	1	1.19	35.32	< 0.0001	***

BC^2	1.99	1	1.99	59.27	< 0.0001	***
B^3	9.32	1	9.32	277.51	< 0.0001	***
C^3	6.13	1	6.13	182.56	< 0.0001	***
Residual	22.67	675	0.0336			
Cor Total	2155.63	692				

Table S2: Initial assessment of the model, we choose the model that maximize R^2, adjusted R^2 (R^2_A), predicted R^2 (R^2_P) and minimize PRESS. The maximization of the R^2_A (R^2 adjusted on the number of model term), ensured that the increment of R^2 was only in minor part due to the increment in the number of terms. The increment of R^2_P and the minimization of PRESS indicates that the chosen model is predictive. R^2_A and R^2_P are in good agreement and in good agreement with R^2 (difference is lower than 0.2). This indicate that the chosen model well fit the collected data (excluding overfitting or underfitting). The adequate precision is a measure of the signal to noise ratio, a value higher than 4 is desirable, in our case due to the high number of point the value results to be around 260.

Source	StD	R^2	R^2_A	R^2_P	PRESS	Adq. Precision
Linear	0.3723	0.9557	0.9555	0.9551	96.79	
2FI	0.3724	0.9559	0.9555	0.9547	97.66	
Quadratic	0.2665	0.9775	0.9772	0.9765	50.65	
Cubic	**0.1833**	**0.9895**	**0.9892**	**0.9886**	**24.66**	**260.27**

Table S3: Coefficients in terms of coded factors (normalized in the [-1, 1] range). The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings.

Factor	Coefficient Estimate	Standard Error	95% CI Low	95% CI High
Intercept	-1.13	0.0174	-1.16	-1.09
A-T	-0.4247	0.0160	-0.4562	-0.3933
B-Shear Rate	-0.0057	0.0323	-0.0691	0.0578
C-Concentration	2.04	0.0350	1.97	2.11
AB	0.0061	0.0142	-0.0217	0.0339
AC	0.0159	0.0128	-0.0092	0.0410
BC	-0.0698	0.0177	-0.1044	-0.0351
A^2	-0.0965	0.0162	-0.1282	-0.0648
B^2	0.5306	0.0222	0.4871	0.5741
C^2	-0.5039	0.0182	-0.5396	-0.4682
ABC	0.1519	0.0212	0.1102	0.1936
A^2C	0.2611	0.0242	0.2135	0.3086
AB^2	0.1269	0.0266	0.0746	0.1792
AC^2	0.1096	0.0219	0.0666	0.1525
B^2C	-0.1963	0.0330	-0.2612	-0.1314
BC^2	-0.2340	0.0304	-0.2937	-0.1743
B^3	-0.7035	0.0422	-0.7864	-0.6206
C^3	0.4572	0.0338	0.3907	0.5236

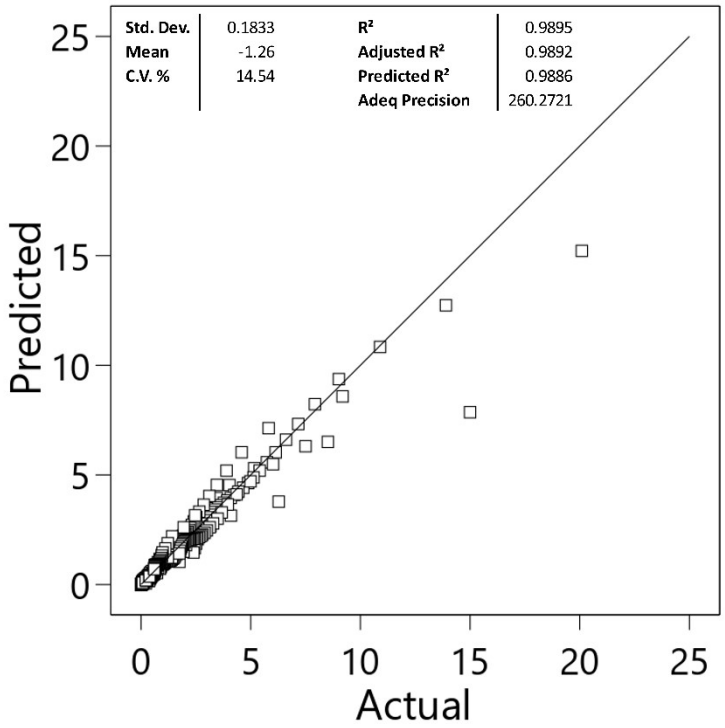

Figure S3: Predicted vs actual plot of the viscosity model. The points fall close to the diagonal indicating a god fit. The model well-fit the collected data with a R^2 value of 0.98. This value agrees with the adjusted R^2. The model is predictive with a predicted R^2 of 0.98. The adequate precision higher then 4 (260.3) indicates an appropriate signal to noise ratio.

$$\ln(\eta) = -4.70534 + 0.0718854 * A - 0.0722449 * B + 3.99273 * C * AC + 0.0103178 * BC - 0.0016331 * A^2 + 0.00113772 * B^2 + 0.000123983 * ABC + 0.000639313 * A^2C + 3.13922e-0 * AC^2 - 5.34099e-05 * B^2C - 0.00210119 * BC^2 - 5.79998e * C^3 \quad \text{(S2)}$$

2.2. Compression

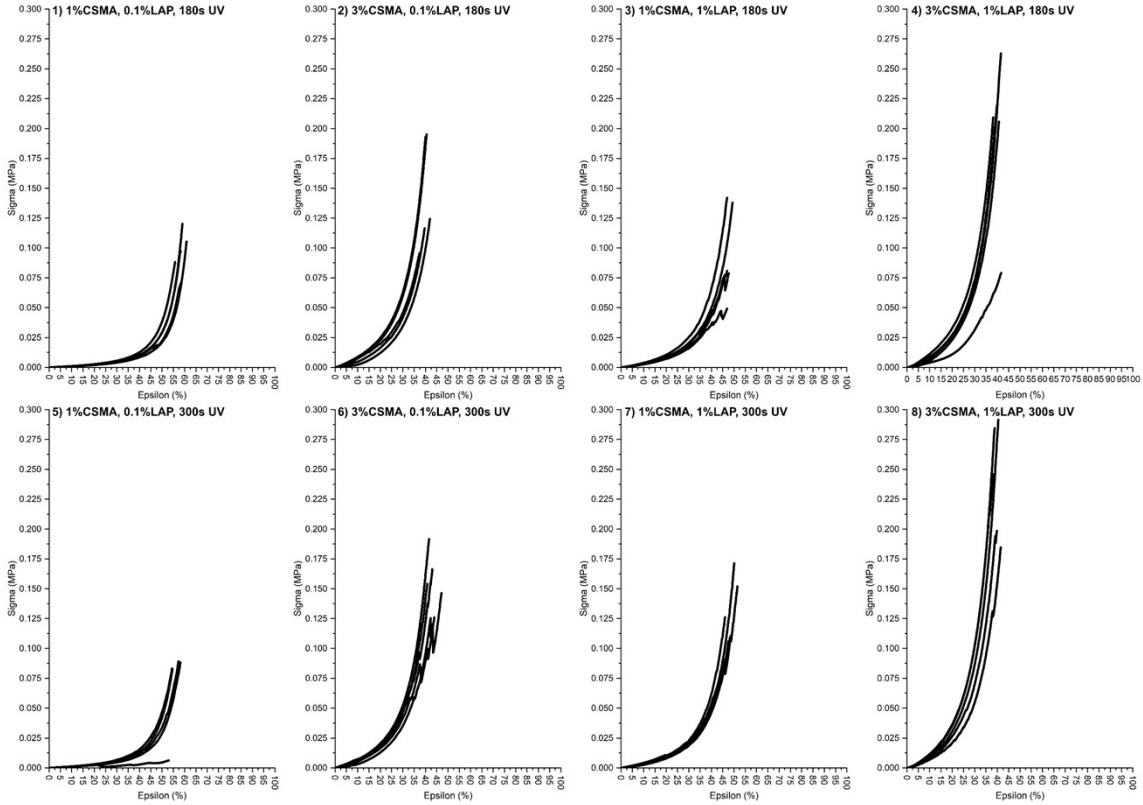

Figure S4: Stress-strain curves obtained in the compression test. Five samples were tested for each trial.

Table S4: The Model F-value of 74.81 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A, B, AB are significant model terms. The Lack of Fit F-value of 0.64 implies the Lack of Fit is not significant relative to the pure error. Applied transformation: Inverse square root.

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0.2133	4	0.0533	74.81	< 0.0001	significant
A-CSMA	0.1279	1	0.1279	179.53	< 0.0001	***
B-LAP	0.0497	1	0.0497	69.72	< 0.0001	***
C-UV Exp.	0.0024	1	0.0024	3.43	0.0726	
AB	0.0332	1	0.0332	46.57	< 0.0001	***
Residual	0.0249	35	0.0007			
Lack of Fit	0.0014	3	0.0005	0.6404	0.5946	not significant
Pure Error	0.0235	32	0.0007			
Cor Total	0.2382	39				

Table S5: Coefficients in terms of coded factors (normalized in the [-1, 1] range). The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjustments around that average based on the factor settings.

Factor	Coefficient Estimate	Standard Error	95% CI Low	95% CI High
Intercept	0.2003	0.0042	0.1918	0.2089
A-CSMA	-0.0566	0.0042	-0.0651	-0.0480
B-LAP	-0.0352	0.0042	-0.0438	-0.0267
C-UV Exp.	-0.0078	0.0042	-0.0164	0.0008
AB	0.0288	0.0042	0.0202	0.0374

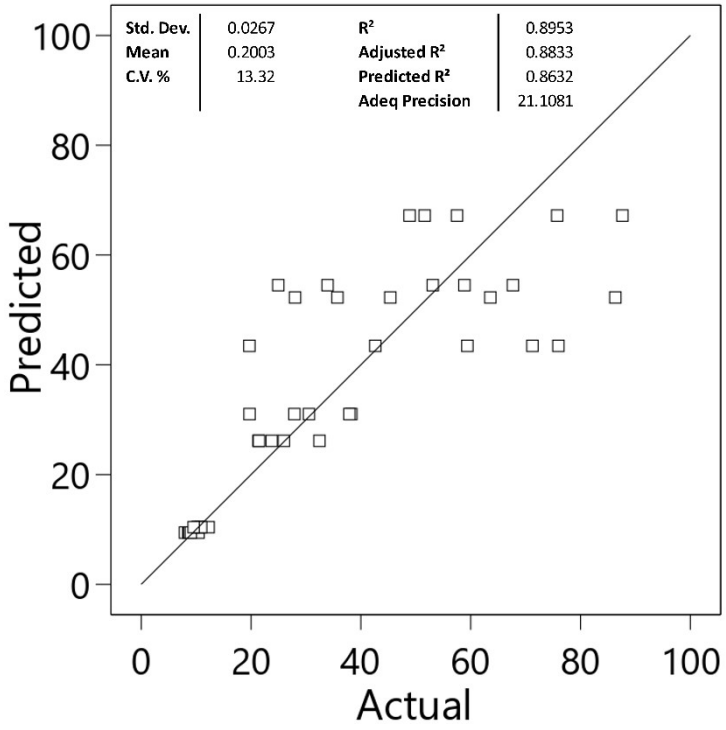

Figure S5: Predicted vs actual plot of the compression Young's modulus model. The points are scattered along the diagonal indicating a reasonable agreement between the model and the data points. The model well-fit the collected data with a R^2 value of 0.89. This value agrees with the adjusted R^2 (0.88). The model is predictive with a predicted R^2 of 0.86. The adequate precision higher then 4 (21.1) indicates an appropriate signal to noise ratio.

$$1/\sqrt{E} = 0.458191 - 0.0917612 * A - 0.206342 * B - 0.000130222 * C + 0.0640121 * . \quad \text{(S3)}$$

2.3. Area

Table S6: Kruskal-Wallis test with a Dunn's multicomparison on the distributions of pore areas. Almost all the differences resulted to be statistically different. This clearly indicate an impact of the process factors (both composition and UV-exposure) on the hydrogel's structures.

Samples	Mean rank diff.	Significant	Summary	Adjusted P Value
1 vs. 2	-1693	Yes	****	<0.0001
1 vs. 3	-4174	Yes	****	<0.0001
1 vs. 4	-5146	Yes	****	<0.0001
1 vs. 5	-2178	Yes	****	<0.0001
1 vs. 6	-2219	Yes	****	<0.0001
1 vs. 7	-1473	Yes	****	<0.0001
1 vs. 8	-2011	Yes	****	<0.0001
2 vs. 3	-2481	Yes	****	<0.0001
2 vs. 4	-3454	Yes	****	<0.0001
2 vs. 5	-485.6	No	ns	0.053
2 vs. 6	-526.1	No	ns	0.072
2 vs. 7	219.6	No	ns	>0.9999
2 vs. 8	-318.1	No	ns	>0.9999
3 vs. 4	-972.2	Yes	*	0.0321
3 vs. 5	1996	Yes	****	<0.0001
3 vs. 6	1955	Yes	****	<0.0001
3 vs. 7	2701	Yes	****	<0.0001
3 vs. 8	2163	Yes	****	<0.0001
4 vs. 5	2968	Yes	****	<0.0001
4 vs. 6	2928	Yes	****	<0.0001
4 vs. 7	3673	Yes	****	<0.0001
4 vs. 8	3136	Yes	****	<0.0001
5 vs. 6	-40.47	No	ns	>0.9999
5 vs. 7	705.2	Yes	***	0.001
5 vs. 8	167.5	No	ns	>0.9999
6 vs. 7	745.7	Yes	**	0.001
6 vs. 8	208	No	ns	>0.9999
7 vs. 8	-537.7	Yes	*	0.046

2.4. Diameter

Table S7: Kruskal-Wallis test with a Dunn's multicomparison on the distributions of pore equivalent diameter. Almost all the differences resulted to be statistically different. This clearly indicate an impact of the process factors (both composition and UV-exposure) on the hydrogel's structures. It should be noticed that being the equivalent diameters a derived value the results of the test are identical of the previous table.

Samples	Mean rank diff.	Significant	Summary	Adjusted P Value
1 vs. 2	-1693	Yes	****	<0.0001
1 vs. 3	-4174	Yes	****	<0.0001
1 vs. 4	-5146	Yes	****	<0.0001
1 vs. 5	-2178	Yes	****	<0.0001
1 vs. 6	-2219	Yes	****	<0.0001
1 vs. 7	-1473	Yes	****	<0.0001
1 vs. 8	-2011	Yes	****	<0.0001
2 vs. 3	-2481	Yes	****	<0.0001
2 vs. 4	-3454	Yes	****	<0.0001
2 vs. 5	-485.6	No	ns	0.053
2 vs. 6	-526.1	No	ns	0.072
2 vs. 7	219.6	No	ns	>0.9999
2 vs. 8	-318.1	No	ns	>0.9999
3 vs. 4	-972.2	Yes	*	0.032
3 vs. 5	1996	Yes	****	<0.0001
3 vs. 6	1955	Yes	****	<0.0001
3 vs. 7	2701	Yes	****	<0.0001
3 vs. 8	2163	Yes	****	<0.0001
4 vs. 5	2968	Yes	****	<0.0001
4 vs. 6	2928	Yes	****	<0.0001
4 vs. 7	3673	Yes	****	<0.0001
4 vs. 8	3136	Yes	****	<0.0001
5 vs. 6	-40.47	No	ns	>0.9999
5 vs. 7	705.2	Yes	***	0.001
5 vs. 8	167.5	No	ns	>0.9999
6 vs. 7	745.7	Yes	**	0.001
6 vs. 8	208	No	ns	>0.9999
7 vs. 8	-537.7	Yes	*	0.046

2.5. Mean Diameter

Table S8: The Model F-value of 38.95 implies the model is significant. There is only a 0.64% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A, B, C, BC are significant model terms. Applied transformation: None.

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	3286.25	4	821.56	38.95	0.0064	significant
A-CsMA	293.20	1	293.20	13.90	0.0336	*
B-LAP	898.86	1	898.86	42.62	0.0073	**
C-UV Exp.	441.72	1	441.72	20.94	0.0196	*
BC	1652.48	1	1652.48	78.35	0.0030	**
Residual	63.27	3	21.09			
Cor Total	3349.53	7				

Table S9: Coefficients in terms of coded factors (normalized in the [-1, 1] range). The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjusted around that average based on the factor settings.

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High
Intercept	68.42	1	1.62	63.25	73.59
A-CsMA	6.05	1	1.62	0.8866	11.22
B-LAP	10.60	1	1.62	5.43	15.77
C-UV Exp.	-7.43	1	1.62	-12.60	-2.26
BC	-14.37	1	1.62	-19.54	-9.20

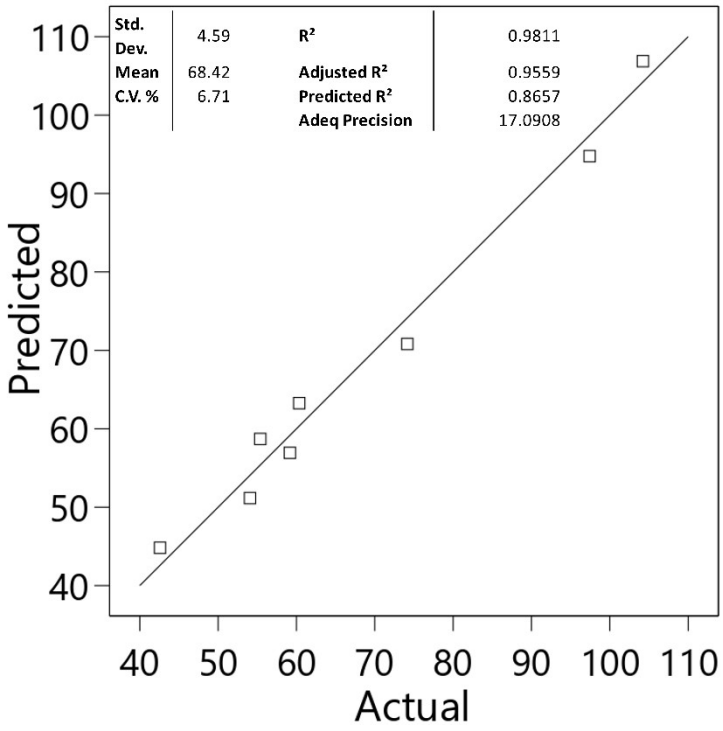

Figure S6: Predicted vs actual plot of the pores' mean diameter model. The points falls along the diagonal indicating a good agreement between the model and the data points. The model well-fit the

collected data with a R^2 value of 0.98. This value is in agreement with the adjusted R^2 (0.95). The model is predictive with a predicted R^2 of 0.87. The adequate precision higher then 4 (17.1) indicates an appropriate signal to noise ratio.

$$D_{Mean} = 2.81606 + 6.05393 * A + 15.1308 * B + 0.168922 * C - 0.0532303 * BC \quad \text{(S4)}$$

2.6. Median Diameter

Table S10: The Model F-value of 34.74 implies the model is significant. There is only a 2.82% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case B, BC are significant model terms. Applied transformation: Natural log.

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0.6039	5	0.1208	34.74	0.0282	significant
A-CsMA	0.0356	1	0.0356	10.24	0.0854	.
B-LAP	0.2040	1	0.2040	58.68	0.0166	*
C-UV Exp.	0.0525	1	0.0525	15.09	0.0603	.
AC	0.0425	1	0.0425	12.22	0.0730	.
BC	0.2693	1	0.2693	77.45	0.0127	*
Residual	0.0070	2	0.0035			
Cor Total	0.6108	7				

Table S11: Coefficients in terms of coded factors (normalized in the [-1, 1] range). The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjusted around that average based on the factor settings.

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High
Intercept	3.52	1	0.0208	3.43	3.61
A-CsMA	0.0667	1	0.0208	-0.0230	0.1564
B-LAP	0.1597	1	0.0208	0.0700	0.2494
C-UV Exp.	-0.0810	1	0.0208	-0.1707	0.0087
AC	-0.0729	1	0.0208	-0.1626	0.0168
BC	-0.1835	1	0.0208	-0.2732	-0.0938

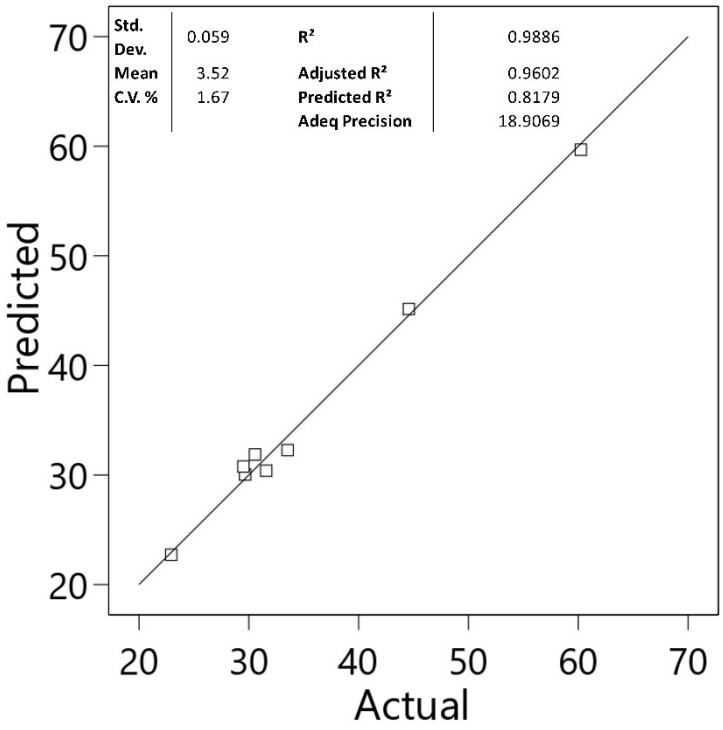

Figure S7: Predicted vs actual plot of the pores' median diameter model. The points are falls in the diagonal indicating a good agreement of the model and the collected data points. The model well-fit the collected data with a R^2 value of 0.99. This value agrees with the adjusted R^2 (0.96). The model is predictive with a predicted R^2 of 0.82. The adequate precision higher then 4 (18.9) indicates an appropriate signal to noise ratio.

$$ln(D_{Median}) = 2.03894 + 0.358213 * A + 0.198575 * B + 0.00481685 * C - 0.000679522 * BC \quad \text{(S5)}$$

2.7. Weight Loss

Table S12: Mean values and standard deviations of the bare weight loss expressed as relative percentage respect to the initial hydrogel weight (at t_0).

time		1		2		3		4		5		6		7		8	
		Mean	StD	Mean	StD	Mean	StD	Mean	StD	Mean	StD	Mean	StD	Mean	StD	Mean	StD
day	hr	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%
	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	0.5	8.56	2.08	-6.92	5.82	12.67	2.73	0.34	6.67	10.11	1.48	-1.56	2.76	5.28	2.18	-0.57	5.37
	1	15.04	1.89	-14.04	2.28	15.52	2.97	2.17	5.66	11.60	2.41	-0.57	11.94	8.62	2.19	6.43	6.60
	2	22.65	10.63	1.74	5.71	20.39	6.18	5.69	8.28	18.60	7.05	9.88	7.29	14.72	4.41	21.83	7.21
	3.5	24.47	7.79	19.88	17.45	24.89	6.11	31.50	9.23	20.56	4.45	21.20	9.56	19.54	4.85	19.11	12.28
1	17	36.37	8.66	35.12	10.23	35.01	6.57	36.76	11.93	34.45	9.92	35.50	12.82	30.78	5.42	30.58	4.89
2	48	36.48	9.26	37.83	10.01	35.79	7.73	45.56	7.82	33.73	10.04	41.83	11.51	28.15	5.46	39.11	4.81
3	72	39.73	10.25	33.21	14.59	33.77	7.88	44.06	8.65	36.64	7.80	37.16	12.31	27.43	9.07	36.75	6.05
4	96	37.41	12.89	40.35	9.43	34.14	6.00	47.63	8.63	36.36	8.11	37.67	10.13	22.06	7.92	35.94	3.58
7	168	40.03	9.34	42.42	8.14	38.33	7.19	46.29	10.67	38.30	8.67	36.06	14.93	32.85	8.06	37.89	1.94
14	336	43.95	8.98	43.14	9.24	43.25	9.57	49.69	10.74	42.52	7.78	43.79	10.34	46.76	13.06	38.26	2.91
22	528	42.58	11.41	41.41	7.82	55.24	8.70	48.37	8.20	41.86	7.89	40.00	8.61	48.98	7.11	35.14	3.28
30	720	42.94	10.72	38.33	11.87	51.54	12.75	46.71	7.03	42.36	9.84	42.41	7.49	46.34	13.37	37.80	7.62
60	1440	46.27	11.99	42.09	10.33	56.86	9.27	45.17	11.19	45.72	6.93	46.04	9.13	46.39	14.85	36.82	3.15

2.8. Degradation/Swelling

Table S13: Mean values and standard deviations of the degradation/swelling expressed as the mass of the detached hydrogel in relative percentage respect to the initial hydrogel weight (at t_0).

time		1		2		3		4		5		6		7		8	
		Mean	StD	Mean	StD	Mean	StD	Mean	StD	Mean	StD	Mean	StD	Mean	StD	Mean	StD
day	hr	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%
	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	0.5	8.60	2.09	-6.86	5.82	12.72	2.73	0.72	6.71	10.15	1.47	-1.49	2.77	5.32	2.18	-0.45	5.36
	1	15.12	1.90	-13.90	2.28	15.61	2.97	2.36	5.68	11.66	2.39	-0.42	11.95	8.70	2.19	6.69	6.57
	2	22.78	10.64	1.97	5.71	20.53	6.18	6.28	8.33	18.70	7.03	10.11	7.29	14.83	4.41	22.23	7.18
	3.5	24.64	7.80	20.20	17.44	25.08	6.11	32.31	9.29	20.69	4.43	21.52	9.57	19.70	4.85	19.65	12.24
1	17	36.58	8.66	35.51	10.20	35.24	6.57	37.73	11.99	34.64	9.90	35.90	12.82	30.97	5.42	31.23	4.82
2	48	36.73	9.27	38.29	9.98	36.06	7.73	46.69	7.90	33.96	10.03	42.29	11.52	28.37	5.45	39.88	4.73
3	72	40.02	10.26	33.72	14.56	34.08	7.88	45.34	8.71	36.90	7.78	37.67	12.32	27.69	9.06	37.63	5.96
4	96	37.74	12.91	40.92	9.39	34.48	6.00	49.05	8.71	36.65	8.10	38.23	10.14	22.35	7.91	36.92	3.47
7	168	40.39	9.35	43.04	8.09	38.71	7.19	47.84	10.75	38.62	8.65	36.67	14.95	33.17	8.07	38.97	1.82
14	336	44.35	8.99	43.81	9.19	43.66	9.57	51.37	10.81	42.87	7.76	44.44	10.36	47.11	13.07	39.46	2.78
22	528	43.01	11.43	42.14	7.76	55.68	8.70	50.19	8.27	42.24	7.87	40.70	8.63	49.37	7.12	36.45	3.13
30	720	43.40	10.73	39.10	11.81	52.01	12.75	48.67	7.05	42.77	9.82	43.16	7.51	46.75	13.39	39.22	7.45
60	1440	46.78	12.01	42.92	10.25	57.38	9.26	47.27	11.27	46.16	6.93	46.84	9.15	46.84	14.87	38.36	2.96

2.9. Solubilization

Table S14: Mean values and standard deviations of the solubilization expressed as the mass of the solubilized hydrogel in relative percentage respect to the initial hydrogel weight (at t_0).

time		1		2		3		4		5		6		7		8	
		Mean	StD	Mean	StD	Mean	StD	Mean	StD	Mean	StD	Mean	StD	Mean	StD	Mean	StD
day	hr	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%	%
	0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	0.5	0.039	0.002	0.064	0.002	0.047	0.001	0.385	0.044	0.035	0.002	0.075	0.005	0.039	0.002	0.064	0.002
	1	0.080	0.004	0.144	0.001	0.096	0.005	0.182	0.023	0.060	0.023	0.156	0.004	0.075	0.001	0.144	0.001
	2	0.123	0.005	0.230	0.008	0.137	0.001	0.595	0.062	0.098	0.021	0.238	0.004	0.111	0.003	0.230	0.008
	3.5	0.166	0.008	0.318	0.015	0.184	0.001	0.805	0.079	0.137	0.021	0.324	0.006	0.151	0.004	0.318	0.015
1	17	0.215	0.009	0.392	0.028	0.227	0.003	0.971	0.085	0.192	0.022	0.397	0.009	0.192	0.005	0.392	0.028
2	48	0.258	0.011	0.457	0.033	0.266	0.003	1.133	0.093	0.225	0.022	0.457	0.011	0.225	0.009	0.457	0.033
3	72	0.295	0.013	0.515	0.040	0.302	0.003	1.281	0.094	0.257	0.021	0.509	0.013	0.261	0.016	0.515	0.040
4	96	0.331	0.016	0.570	0.045	0.340	0.003	1.411	0.108	0.288	0.021	0.559	0.013	0.291	0.017	0.570	0.045
7	168	0.363	0.017	0.621	0.050	0.374	0.001	1.546	0.106	0.319	0.022	0.608	0.016	0.322	0.019	0.621	0.050
14	336	0.393	0.017	0.671	0.054	0.404	0.001	1.680	0.106	0.347	0.022	0.651	0.018	0.351	0.018	0.671	0.054
22	528	0.435	0.016	0.725	0.060	0.442	0.002	1.823	0.108	0.379	0.020	0.702	0.020	0.384	0.022	0.725	0.060
30	720	0.469	0.016	0.773	0.068	0.473	0.002	1.959	0.109	0.409	0.021	0.748	0.023	0.413	0.021	0.773	0.068
60	1440	0.511	0.015	0.831	0.083	0.516	0.003	2.106	0.110	0.444	0.021	0.799	0.023	0.452	0.023	0.831	0.083

Table S15: The Model F-value of 264.59 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A, B, C, AB are significant model terms. The Lack of Fit F-value of 1.99 implies the Lack of Fit is not significant relative to the pure error. There is a 15.54% chance that a Lack of Fit F-value this large could occur due to noise. Applied transformation: Inverse square root.

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	2.24	4	0.5592	264.59	< 0.0001	significant
A-CsMA (%)	1.78	1	1.78	842.58	< 0.0001	***
B-LAP (%)	0.2131	1	0.2131	100.84	< 0.0001	***
C-UV Exp (s)	0.0464	1	0.0464	21.97	0.0002	***
AB	0.1965	1	0.1965	93.00	< 0.0001	***
Residual	0.0402	19	0.0021			
Lack of Fit	0.0109	3	0.0036	1.99	0.1554	not significant
Pure Error	0.0292	16	0.0018			
Cor Total	2.28	23				

Table S16: Coefficients in terms of coded factors (normalized in the [-1, 1] range). The coefficient estimate represents the expected change in response per unit change in factor value when all remaining factors are held constant. The intercept in an orthogonal design is the overall average response of all the runs. The coefficients are adjusted around that average based on the factor settings.

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High
Intercept	1.24	1	0.0094	1.22	1.26
A-CsMA (%)	-0.2724	1	0.0094	-0.2920	-0.2528
B-LAP (%)	-0.0942	1	0.0094	-0.1139	-0.0746
C-UV Exp (s)	0.0440	1	0.0094	0.0243	0.0636
AB	-0.0905	1	0.0094	-0.1101	-0.0709

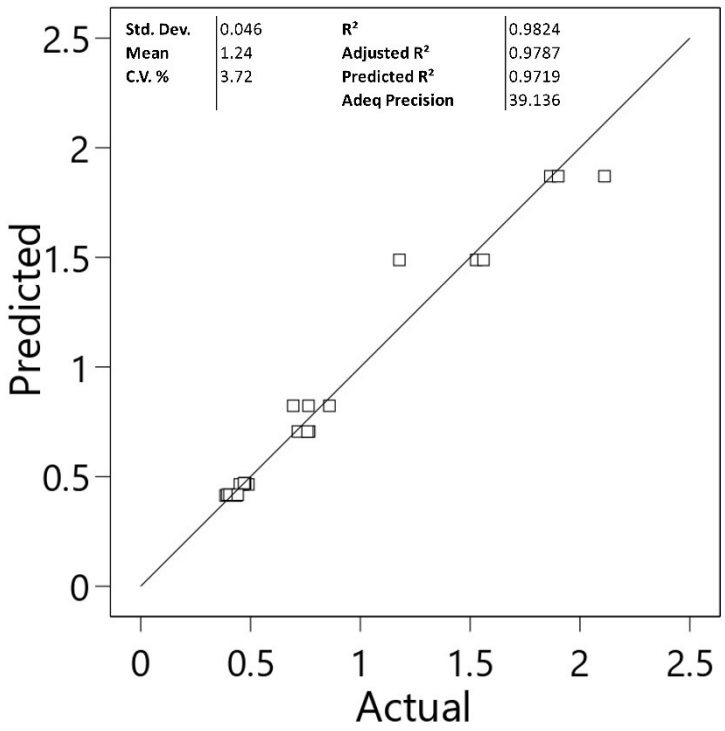

Figure S8: Predicted vs actual plot of the solubilization model. The points are falls in the diagonal indicating a good agreement of the model and the collected data points. The model well-fit the collected data with a R^2 value of 0.98. This value agrees with the adjusted R^2 (0.97). The model is predictive with a predicted R^2 of 0.927. The adequate precision higher then 4 (39.1) indicates an appropriate signal to noise ratio.

$$\frac{1}{\sqrt{(Sol)}} = 1.23657 - 0.272393 * A - 0.0942322 * B + 0.0439805 * C - 0.0904962 * \quad \text{(S6)}$$