

Supplementary Materials: Development of Sedative Dexmedetomidine Sublingual In Situ Gels: In Vitro and In Vivo Evaluations

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Table S1. Physical state of various *in situ* gelling systems. CP 934 = Carbopol 934, HEC = Hydroxyl ethyl cellulose. HEC, BCK and boric acid are included in each formulation as 0.2, 0.01 and 0.5% *w/v*, respectively, and the final volume of each formulation is 100 mL.

Code	CP 934	Chitosan	Na Alginate	HEC	Physical State at Non-Physiological Condition	Physical State at Physiological Condition (37 °C, pH 7.4)
	Concentration (% <i>w/v</i>)					
F1 [*]	0.1	-----	-----	0.2	Clear transparent solution	Clear transparent viscous solution
F2	0.25	-----	-----	0.2	Clear transparent solution	Clear transparent gel
F3	0.3	-----	-----	0.2	Clear transparent solution	Clear transparent gel
F4 [*]	0.5	-----	-----	0.2	Clear transparent gel	Clear transparent gel
F5 [*]	-----	0.25	-----	0.2	Clear transparent solution	Clear transparent viscous solution
F6	-----	0.5	-----	0.2	Clear transparent solution	Clear transparent gel
F7	-----	0.75	-----	0.2	Clear transparent solution	Clear transparent gel
F8 [*]	-----	1.0	-----	0.2	Clear transparent gel	Clear transparent gel
F9 [*]	-----	-----	0.25	0.2	Clear transparent solution	Clear transparent viscous solution
F10	-----	-----	0.5	0.2	Clear transparent solution	Clear transparent gel
F11	-----	-----	0.75	0.2	Clear transparent solution	Clear transparent gel
F12	-----	-----	1.0	0.2	Clear transparent solution	Clear transparent gel

*excluded formulations due to their lack of flowing property at non-physiological conditions.

Table S2. Hot plate reaction times in rats following sublingual administration of DEX *in situ* gel, oral and intravenous (IV) administrations of DEX free drug solutions.

Groups	Reaction Time (s)						
	Before treatment	10 min	20 min	30 min	45 min	60 min	120 min
Control	8.5 ± 1.2	9.4 ± 0.8	8.5 ± 1.0	8.8 ± 1.1	9.5 ± 0.7	9.1 ± 0.9	9.5 ± 0.89
DEX oral	8.6 ± 0.9	9.3 ± 1.0	10.2 ± 1.2	11.5 ± 1.1	11.9 ± 0.8	11.3 ± 0.9	10.7 ± 1.22
DEX IV	9.5 ± 1.1	13.2 ± 1.3#	16.3 ± 1.5#	17.8 ± 1.0#	16.4 ± 0.6#	13.9 ± 0.8**	11.2 ± 0.95#
DEX sublingual (<i>in situ</i> gel F3)	9.2 ± 0.9	11.9 ± 1.5*	15.8 ± 1.6*	17.2 ± 1.4*	17.4 ± 1.3*	16.4 ± 1.0*	12.6 ± 1.1

Data are represented as means ± SD ($n = 6$). *Significant differences compared to that of the DEX oral solution ($p < 0.05$). #Non-significant differences compared to that of the DEX sublingual *in situ* gel. **Significant differences compared to that of the DEX sublingual *in situ* gel ($p < 0.01$).

Table S3. Effect of sublingual administration of DEX *in situ* gel, oral and intravenous (IV) administrations of DEX free drug solutions on the blood pressure in rats.

Groups	Mean systolic Blood Pressure						
	Before treatment	10 min	20 min	30 min	45 min	60 min	120 min
Control	92 ± 4.5	89 ± 5.3	90 ± 4.3	93 ± 6.1	92 ± 3.7	88 ± 2.5	90 ± 4.2
DEX oral	87 ± 3.8	86 ± 6.3#	85 ± 4.2#	88 ± 5.6#	85 ± 4.3#	86 ± 3.8#	87 ± 3.2#
DEX IV	88 ± 2.9	84 ± 6.8#	79 ± 5.8*	68 ± 4.2**	65 ± 3.7**	60 ± 5.8**	57 ± 4.9**
DEX sublingual (<i>in situ</i> gel F3)	83 ± 5.5	82 ± 4.7#	82 ± 5.3#	77 ± 4.8#	79 ± 5.2#	81 ± 3.8#	80 ± 2.9#

Data are represented as means ± SD ($n = 6$). #Non-significant differences compared to the measured blood pressure before treatment. *Significant differences compared to the measured blood pressure before treatment ($p < 0.05$). **Highly Significant differences compared to the measured blood pressure before treatment ($p < 0.01$).

Table S4. Heart rates in rabbits following sublingual administration of DEX *in situ* gel, oral and intravenous (IV) administrations of DEX free drug solutions.

Groups	Heart Rate						
	Before treatment	10 min	20 min	30 min	45 min	60 min	120 min
Control	294 ± 6.5	289 ± 7.2	290 ± 5.8	295 ± 4.9	288 ± 6.4	297 ± 5.8	293 ± 7.6
DEX oral	286 ± 4.8	283 ± 5.6#	288 ± 4.9#	286 ± 6.3#	290 ± 7.1#	285 ± 6.6#	291 ± 5.8#
DEX IV	300 ± 5.3	270 ± 6.4*	264 ± 4.8*	255 ± 7.3*	249 ± 6.6*	238 ± 4.8*	230 ± 3.9*
DEX sublingual (<i>in situ</i> gel F3)	328 ± 5.1	324 ± 4.7#	322 ± 5.3#	324 ± 3.8#	326 ± 3.9#	322 ± 5.2#	327 ± 6.2#

Data are represented as means ± SD ($n = 5$). #Non-significant differences compared to the measured blood pressure before treatment. *Highly significant differences compared to the measured blood pressure before treatment ($p < 0.01$).