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Controlled supersaturation experiments in the presence of formulation excipients

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PURPOSE

To study the effect of common excipients on the nucleation rate of a supersaturated API in simulated gastrointestinal media (SGIM).

METHOD

The supersaturation experiments were conducted on a Sirius inForm using the Controlled Supersaturation assay. Here, 40 mL of the medium was dispensed into the vessel, the temperature was controlled to 37°C and the pH adjusted to 2.0 or 6.5. A volume of a concentrated stock solution of the API in solvent was then added to the medium to generate a supersaturated solution. UV spectra were collected by an immersion probe for a specified duration and used to determine in-situ concentration and follow the nucleation and crystal growth events.

The medium was prepared from FaSSIF v2 powder supplied by Biorelevant.com and NaCl, but the maleic acid buffer system was replaced with the v1 phosphate buffer system to enable in situ UV quantitation. For simulated gastric fluid 0.15 M NaCl at pH 2.0 was used.

The supersaturation experiments were repeated in the presence of excipients to mass ratios of 1:1 and 1:10, sample:excipient. The excipients studied were mannitol (a sugar), two grades of PVP (polyvinylpyrrolidone polymer, often used as crystallisation inhibitors) and two grades of methocel (hydroxypropylmethylcellulose polymer, also often used as crystallisation inhibitors).

RESULTS

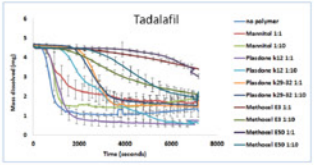
The resulting data had a sigmoidal shape to the profile with upper and lower plateaux and a decaying slope. The data on the upper plateau represents the maximum concentration (supersaturation level) of the drug. After a period of time, the concentration reduces as crystals start to form and the lower plateau represents the solubility obtained in the medium (buffer containing excipient).

The data on the upper plateau was used to determine nucleation induction time which is the reciprocal of nucleation rate (Figure 1a). Here, the RMSD of the data on the plateau was determined and the induction time was found from the first data point that exceeded 2 standard deviations from the mean plateau concentration.

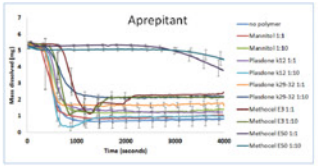
The induction times were tabulated against the five excipients used in this study at low and high levels.

Tadalafil

- 5 mg of excipient was used for a 1:1 ratio and 50 mg for a 1:10 ratio. The medium used was FaSSIF v2 at pH 6.5.
- Mannitol had a negligible effect on the induction time.
- Plasdone k12 increased the induction time by a factor of < 2 at the low ratio and 3 at the high ratio.
- Plasdone k29-32 increased the induction time by a factor of 5 for both the low and high ratios.
- Methocel E3 increased the induction time by a factor of 8, but only at the low ratio.
- Methocel E50 increased the induction time by a factor of 9, but only at the low ratio.



Excipient	Level	Induction time (s)	+/- (s)
No excipient	-	338	111
Mannitol	Low	467	57
	High	359	33
Plasdone k12	Low	478	107
	High	1025	49
Plasdone k29-32	Low	1595	155
	High	1538	167
Methocel E3	Low	2381	327
	High	1318	157
Methocel E50	Low	3123	338
	High	2115	366



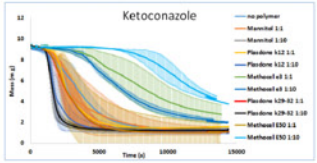
Excipient	Level	Induction time (s)	+/- (s)
No excipient	-	282	15
Mannitol	Low	265	92
	High	347	67
Plasdone k12	Low	316	77
	High	358	27
Plasdone k29-32	Low	342	16
	High	464	61
Methocel E3	Low	631	41
	High	441	82
Methocel E50	Low	2321	198
	High	3098	177

Aprepitant

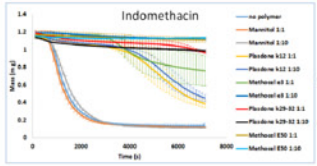
- 5 mg of excipient was used for a 1:1 ratio and 50 mg for a 1:10 ratio. The medium used was FaSSIF v2 at pH 6.5.
- Mannitol, Plasdone k12, Plasdone k29-32 and Methocel E3 all had a negligible effect on the induction time.
- Methocel E50 increased the induction time by a factor of 9 for the low ratio and a factor of 10 for the high ratio.

Ketocoanzole

- 9 mg of excipient was used for a 1:1 ratio and 90 mg for a 1:10 ratio. The medium used was FaSSIF v2 at pH 6.5.
- Mannitol increased the induction time by a factor of 2, but only at the low ratio.
- Plasdones k12 and k29-32 had a negligible effect on the induction time.
- Methocel E3 increased the induction time by a factor > 4, but only at the high ratio.
- Methocel E50 increased the induction time by a factor of 8, but only at the high ratio.



Excipient	Level	Induction time (s)	+/- (s)
No excipient	-	885	98
Mannitol	Low	1641	166
	High	791	103
Plasdone k12	Low	1162	180
	High	923	131
Plasdone k29-32	Low	928	155
	High	776	150
Methocel E3	Low	653	33
	High	3419	334
Methocel E50	Low	1458	117
	High	6449	855



Excipient	Level	Induction time (s)	+/- (s)
No excipient	-	528	55
Mannitol	Low	409	58
	High	491	100
Plasdone k12	Low	3931	533
	High	4137	558
Plasdone k29-32	Low	6618	438
	High	7200	0
Methocel E3	Low	2543	60
	High	7200	0
Methocel E50	Low	7200	0
	High	7200	0

Indomethacin

- 1.2 mg of excipient was used for a 1:1 ratio and 12 mg for a 1:10 ratio. The medium used was 0.15 M NaCl at pH 2.0.
- Mannitol had a negligible effect on the induction time.
- Plasdone k12 increased the induction time by a factor of 8 at both the low and high ratio.
- Plasdone k29-32 increased the induction time by a factor of 13 for the low ratio and the high ratio maintained supersaturation indefinitely.
- Methocel E3 increased the induction time by a factor of 5 for the low ratio and the high ratio maintained supersaturation indefinitely.
- Methocel E50 maintained supersaturation indefinitely at both ratios.

CONCLUSION

The cellulose polymers Methocel E3 and Methocel E50 were found to extend the induction time of the API's tested here whilst mannitol had very little effect. The effects of the plasdone polymers K12 and K29-32 were more variable.

This data may be useful when designing a formulation to sustain a supersaturated state of an API for oral delivery.

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