Utilizing crystallization inhibition to maximize drug bioavailability from softgel formulations

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Introduction

Poorly water-soluble drugs are the bulk of new APIs coming to market, and as such, methods to increase dissolution or maintain solubility in the body are needed. Softgels are a unique, liquid dosage form that is ideal for enhancing bioavailability of difficult APIs from solution by pre-dissolving and maintaining the API into a liquid based system. However, when the liquid contents are released, typically in the stomach, or the intestine, poorly water-soluble drugs often crash out of solution through recrystallization in the gastrointestinal fluid. During the 4 to 6-hour gastrointestinal transit time, poorly water soluble APIs must remain in solution for a significant time window in order to be available for absorption.

Drugs inside the body or in an in vitro dissolution apparatus will exhibit an equilibrium concentration, where the dissolved drug reach a maximum available concentration in the fluid of choice; for poorly water soluble compounds, this level is very low. Common solubilizers often result in an overall increase to this equilibrium concentration. However, in the relatively large volume of the body or an in vitro dissolution test, the increase to the equilibrium concentration is comparably small. Consequently, upon release from the dosage form, the drug quickly becomes supersaturated. A classical solubilizer will often result in what is known as the “spring model”, where the drug concentration rapidly increases, but within only seconds or minutes the drug nucleates, crystallizes and reverts back near a new equilibrium concentration. On the other hand, utilizing an excipient with crystallization inhibition characteristics instead allows for a slow return down to the equilibrium concentration; this is known as the “parachute model”. Both of these are represented in Figure 1.

Crystallization inhibitors typically work utilizing one of two mechanisms, one through preventing or delaying the nucleation of the drug, thus extending the absorption window, or alternatively, by a strong adsorption to the drug crystal surface, which slows down the growth of the drug crystal and extends the absorption window.[1]

Softgel capsules are a proven and well accepted drug formulation for bringing poorly water-soluble drugs to market. The liquid core allows for APIs to be solubilized in a liquid matrix that is rapidly dispersible within the gastrointestinal tract upon dissolution of the gelatin shell. It is well known and practiced by softgel formulators that low molecular weight polyvinylpyrrolidone exhibits crystallization inhibition effects, particularly Kollidon® 12 and Kollidon® 17 PF. In this work, novel techniques using the Pion Inform® are used to monitor recrystallization rates in the presence of various polymers and surfactants in an effort to uncover additional excipients that can be utilized within the softgel form in order to maximize the drug bioavailability window.

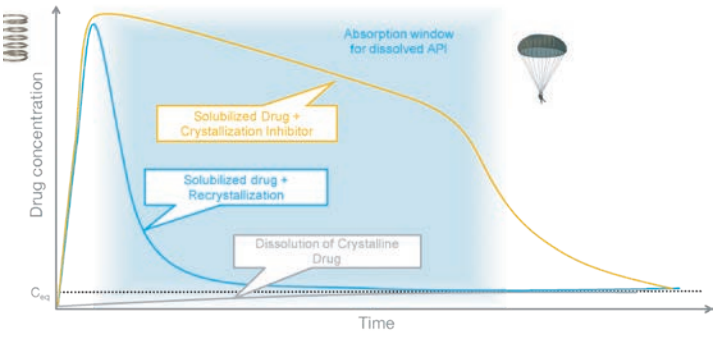


Figure 1: Comparison of the “Spring Model” vs. the “Parachute Model” to maximize drug bioavailability

Methods

500 µL softgel formulations were produced to mimic a suitable and practical volume of softgel fill. Formulations contained Kollisolv® PEG 400 LA as a hydrophilic softgel base fill.

5% of surfactants Kolliphor® RH 40, Kolliphor® EL, Kolliphor® HS 15 or polymers Kollidon® 12, Kollidon® 17 PF, Kollidon® 30, Kollidon® 90, and Kollidon® VA 64 were tested as polymeric excipients. All were miscible at the 5% level and exhibited a viscosity usable in softgel manufacturing (< 700 cPs); these were pre-dissolved in the PEG fill with the target API. Each formulation was injected into the Pion InForm® in a 50 mL of Buffered solution at either a pH of 2.0 for stomach conditions or 6.8 for intestinal; an image of the apparatus is shown in Figure 2. The API concentration in solution was monitored and plotted over time.

Three key drugs were utilized, Danazol, Nifedipine, and Loratadine, and studied at supersaturated conditions. Key drug properties are shown in Table 1.[2]

Following injection, crystallization was monitored using UV probes and turbidity measurements over a minimum of 30 minutes in order to monitor the recrystallization behavior.

Figure 2: Pion InForm® utilized for measuring precipitation kinetics in this study

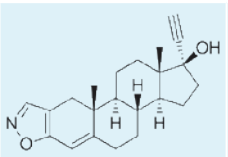
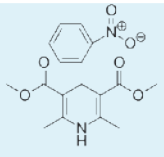
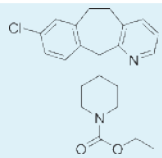
Danazol	Nifedipine	Loratadine
		
Synthetic Steroid	Calcium Channel Blocker	Antihistamine
337.46 g/mol	346.33 g/mol	382.88 g/mol
LogP: 3.62	LogP: 2.49	LogP: 4.55
pKa: 0.25	pKa: 5.33	pKa: 4.33

Table 1: Drugs properties of Danazol as model drug for solubility

Results and Discussion

Danazol is a classic poorly water soluble drug used as a model compound for challenging BCS Class II drugs. It is generally regarded as non-ionizable and therefore the effect of pH was expected to be insignificant. Select results under stomach conditions are shown in Figure 3.

The drug dissolved only in Kollisolv® PEG 400 LA resulted in a low equilibrium concentration with limited bioavailability window. The addition of a typical crystallization inhibitor, Kollidon® 12 resulted in limited increase in the bioavailability window. Kolliphor® RH 40, a known potent solubilizer instead produced the classic "spring model" behavior, with a sharp increase in concentration followed by a rapid decline within two minutes. The equillibrium concentration was notably increased. What is notable about this data is the strong effects of Kollidon® VA 64. While typically utilzed as a matrix polymer in hot melt extrusion and spray drying, this copolymer of polyvinylpyrrolidone and polyvinylacetate resulted in a strong parachute model effect significantly extending the bioavailability window at 5% w/w. It is important to note that this result is emblematic of the behavior, and a much longer parachute effect under optimal formulation conditions may be further established; nonetheless, the polymer influence is remarkable. Entering into the intenstinal model, the data is shown in Figure 4.

In the higher pH of the intestine, the danazol recrystallization behavior shown in the stomach is mimicked, with Kollidon® VA 64 again exhibiting a strong parachute model at the modest concentratoin of only 5% w/w. Kolliphor® RH 40 also continued to highlight a "spring model" behavior, as the effect of pH on non-ionic surfactant behavior had been hypothesized to be minimal.

Utilizing an alternative drug, Nifedipine, the experimental conditions were repeated again utilizing 5% w/w additive; the results in the stomach, low pH model are shown in Figure 5.

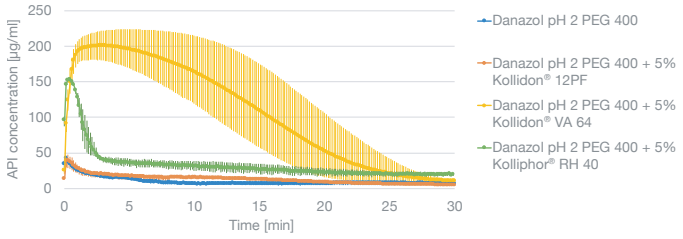


Figure 3: Danazol recrystallization behavior under stomach conditions at 5% w/w additive

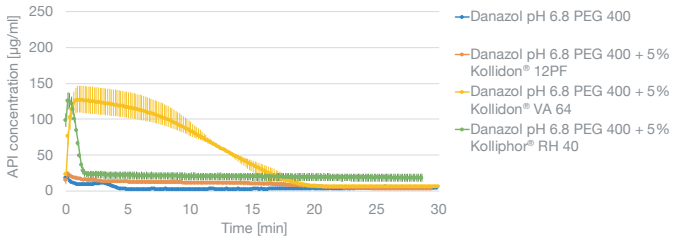


Figure 4: Danazol recrystallization behavior under intestinal conditions at 5% w/w additive

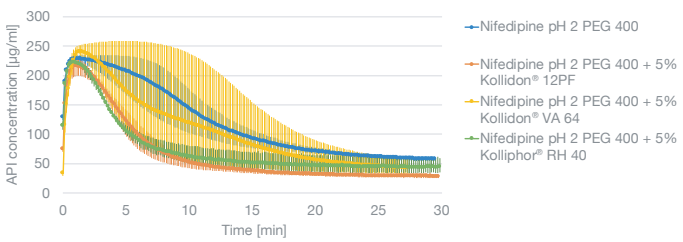


Figure 5: Nifedipine recrystallization behavior under stomach conditions at 5% w/w additive

Under stomach conditions, reduction of crystal growth was not statistically significant, regardless of formulation additive; but it is important to note the slow recrystallization behavior when compared to Danazol. However, under intestinal conditions, where the pH is now higher than the published pKa of Nifedipine of 5.33, the results were more notable; these are shown in Figure 6.

Under intestinal conditions, Nifedipine had a slower growth rate than noted in the Danazol experiments from the Kollisolv® PEG 400 LA softgel fill. The addition of solubilizer Kolliphor® RH 40 did not significantly influence the recrystallization behavior. However, both Kollidon® 12 and Kollidon® VA 64 exhibited a statistically significant increase in concentration and noted parachute pattern at the low concentration of 5% w/w. It is hypothesized that the polyvinylpyrollidone moiety of the Kollidon® VA 64 is therefore the portion of the polymer that is interacting with the drug surface during growth.

The common OTC medication, Loratadine was then tested for recrystallization. This is shown in Figure 7 under stomach conditions.

Clearly, due to the low pH combined with the published pKa of 4.33, the Loratadine is fully solubilzed during the tested transit time of the stomach. However, this brings an interesting issue. As the pH downstream subsequently increases in the intestine, the drug will have a propensity to "crash out" from recrystallization. The results under intestinal conditions are shown in Figure 8.

In this case, the low concentration of 5% w/w showed in interesting pattern, where a slight increase in availability was noted for Kollidon® VA 64, while the longest increase to the absorption window was noted by Kolliphor® RH 40. Clearly, this highlights the need for a multitude of excipients available to formulators, as different moieties will have different interactions with alternate APIs. Consequently, higher concentrations of Kolliphor® RH 40 which are practical for a softgel form may be highly effective to increase the bioavailability of Loratadine following transit from the stomach to the intestine.

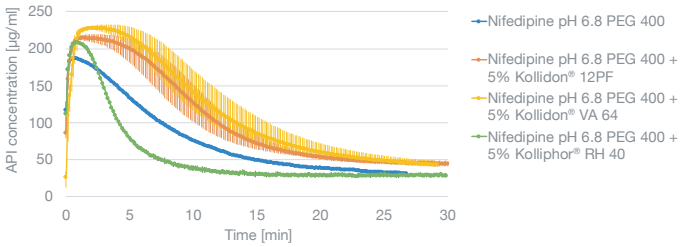


Figure 6: Nifedipine recrystallization behavior under intestinal conditions at 5% w/w additive

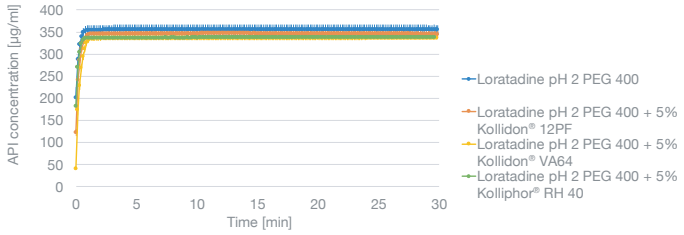


Figure 7: Loratadine recrystallization behavior under stomach conditions at 5% w/w additive – full dissolution achieved

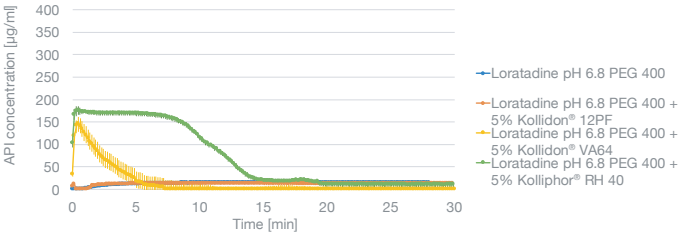


Figure 8: Loratadine recrystallization behavior under intestinal conditions at 5% w/w additive

Conclusion

- In common BCS Class II compounds such as Danazol, with limited effect of pH present, classical solubilizers, such as Kolliphor® RH 40 provided an initial increase in solubility in both stomach and intestinal conditions, but shortly thereafter a "spring" model reduction in solubility to near base-line levels.
- Polymeric excipients, such as Kollidon® 12 and Kollidon® VA 64 provided a much slower recrystallization emblematic of the classic "parachute" model.
- Surprisingly, Kollidon® VA 64, an excipient more renowned for use in amorphous solid dispersions, emerged as a promising additive to slow recrystallization and maximize bioavailability during the therapeutic window.
- Future studies will focus on extending the absorption window to longer transit times by utilizing higher concentrations of polymer and surfactant excipients.
- Care should be taken during the transition between stomach, low pH conditions to the higher pH conditions of the GI tract, as many poorly soluble drugs may exhibit a propensity to recrystallize at the point of pH shift.
- Formulators should utilize a number of excipients in order to effectively screen for crystallization inhibitors.

References

[1] Adapted from Dr. Ferdinand Brandl – How to keep your API in supersaturation? – Ludwigshafen 10/12/2017.

[2] Wishart DS, Knox C, Guo AC, Shrivastava S, Hassanali M, Stothard P, Chang Z, Woolsey J. DrugBank: a comprehensive resource for in silico drug discovery and exploration. Nucleic Acids Res. 2006 Jan 1;34 (Database issue): D668-72.

Kollidon® VA 64

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