Consumer Specialties
ashland.com

PTR-106

Selection of Polymeric Carriers for Probucol Amorphous Solid Dispersions

Yonglai Yang, Vivian Bi, Rae-Ann Covington, Thomas Dürig
Ashland Specialty Ingredients, Wilmington, DE 19808 USA

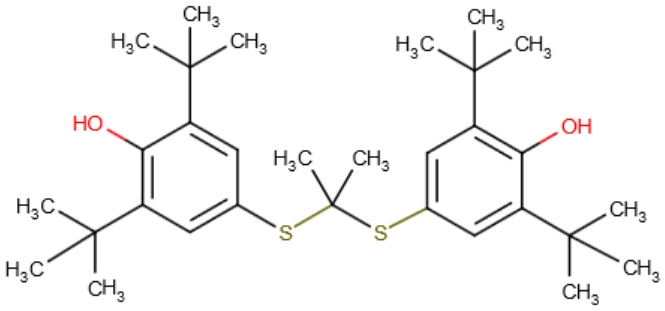
Introduction

Probucol is a poorly water-soluble compound with a high log P of 8.92. Its extremely hydrophobic nature makes solubility enhancement challenging. In this study, probucol was formulated into spray-dried amorphous solid dispersions (SDDs). Plasdone™ S-630 copovidone (PVP/VA), Plasdone™ K-29/32 povidone (PVP), Klucel™ EF hydroxypropylcellulose (HPC), Benecel™ E5 hydroxypropylmethylcellulose (HPMC) and AquaSolve™ L, M and H hypromellose acetate succinate (HPMCAS) were used as polymeric carriers at 20, 40 and 60% (*w/w*) drug loads. Stability and dissolution testing were conducted to evaluate the performance of probucol SDDs and determine the preferred formulations.

Methods

Materials

Probucol was purchased from RIA International LLC (East Hanover, NJ). The structure and selected properties of probucol are shown in Figure 1. Copovidone (Plasdone™ S-630), povidone (Plasdone™ K-29/32), HPC (Klucel™ EF), HPMC (Benecel™ E5) and HPMCAS (AquaSolve™ L, M and H grades) were manufactured by Ashland Inc. (Wilmington, DE).



Chemical formula: $C_{31}H_{48}O_2S_2$;
MW: 516.8; T_m: 125°C;
Log P: 8.92; p*K*a: 10.29;
Aqueous solubility: < 1 mg/L

Figure 1. Structure and selected properties of probucol (http://www.drugbank.ca/drugs/DB01599)

Note: This work was presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, October 25–29, 2015, Orlando, FL

Sample Preparation

Spray drying solutions were prepared by dissolving 5 wt% total solids into a 9:1 (*w/w*) mixture of methanol and water for HPMC; methanol was used as the solvent for all other polymers. Spray drying was performed using a GEA SD Micro™ spray dryer with a 1.0 mm two-fluid nozzle and operated in an open cycle configuration. The following spray drying process parameters were used: inlet temperature (90°C), outlet temperature (50°C), process gas flow rate (25 kg/h), atomization gas pressure (0.5 bar), and atomization gas flow rate (1.5 kg/h). The spray-dried samples were further dried at 40°C under vacuum overnight.

Characterization

The SDDs were characterized by X-ray powder diffraction (XRPD) before and after stability tests (5°C, 25°C/60% RH and 40°C/75% RH). The morphology of the SDDs was evaluated by scanning electron microscopy (SEM). Dissolution of the SDDs was assessed in fasted-state simulated intestinal fluid (FaSSIF) using a *p*ION µDISS Profiler™ under non-sink dissolution conditions.

Results and Discussion

Morphology

The particle morphologies of SDDs were evaluated by SEM. Representative SEM images for HPMCAS-L SDDs with 20, 40 and 60% drug loads are illustrated in Figure 2.

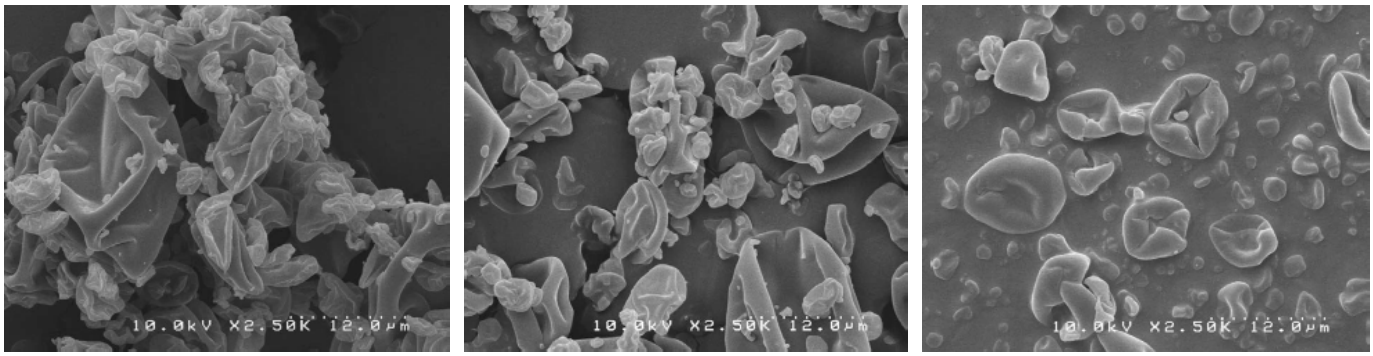


Figure 2. SEM images of HPMCAS-L SDDs with 20, 40 and 60% drug loads

Physical Stability

The physical stability of all SDDs was evaluated using XRPD after storage at 5°C, 25°C/60% RH and 40°C/75% RH conditions (Table 1). The lower drug loading (20%) SDDs with all three grades of HPMCAS were the most stable as they were the only SDDs that remained amorphous at 40°C/75% RH after three months.

Table 1. Stability results for all probucol SDDs up to three months

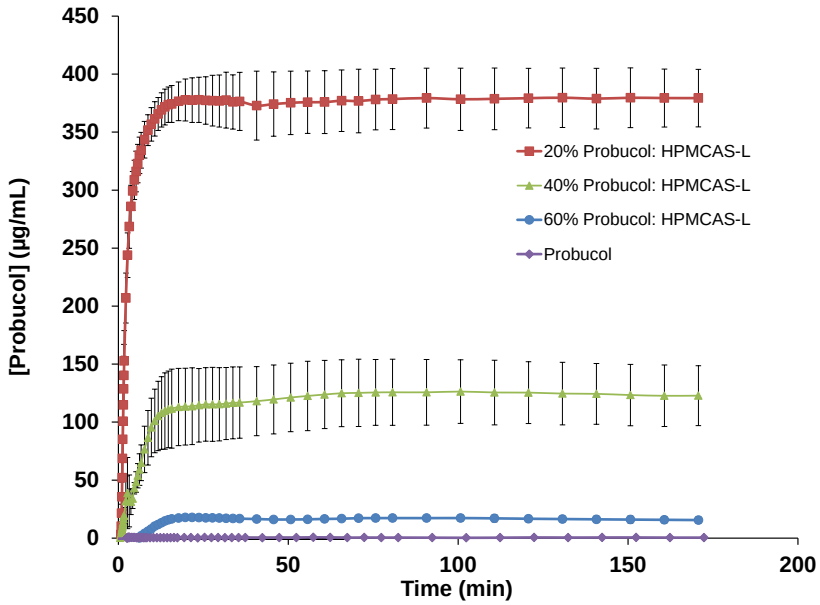
Drug load	Polymer	Initial	1 month (5 °C)	1 month (25 °C/60% RH)	1 month (40 °C/75% RH)	3 month (5 °C)	3 month (25 °C/60% RH)	3 month (40 °C/75% RH)
20	PVP	amorph	NT	NT	amorph	NT	amorph	glass
40	PVP	amorph	NT	amorph	cryst	NT	amorph	N/A
60	PVP	amorph	NT	amorph	cryst	amorph	cryst	N/A
20	PVP/VA	amorph	NT	amorph	cryst	NT	amorph	N/A
40	PVP/VA	amorph	NT	amorph	cryst	NT	amorph	N/A
60	PVP/VA	amorph	NT	amorph	cryst	amorph	cryst	N/A
20	HPMCAS-L	amorph	NT	NT	amorph	NT	amorph	amorph
40	HPMCAS-L	amorph	NT	amorph	cryst	NT	amorph	N/A
60	HPMCAS-L	amorph	NT	amorph	cryst	amorph	cryst	N/A
20	HPMCAS-M	amorph	NT	NT	amorph	NT	amorph	amorph
40	HPMCAS-M	amorph	NT	amorph	cryst	NT	amorph	N/A
60	HPMCAS-M	amorph	NT	amorph	cryst	amorph	cryst	N/A
20	HPMCAS-H	amorph	NT	NT	amorph	NT	amorph	amorph
40	HPMCAS-H	amorph	NT	amorph	cryst	NT	amorph	N/A
60	HPMCAS-H	amorph	NT	amorph	cryst	amorph	cryst	N/A
20	HPMC	amorph	amorph	cryst	cryst	amorph	N/A	N/A
40	HPMC	cryst	N/A	N/A	N/A	N/A	N/A	N/A
60	HPMC	cryst	N/A	N/A	N/A	N/A	N/A	N/A
20	HPC	cryst	N/A	N/A	N/A	N/A	N/A	N/A
40	HPC	cryst	N/A	N/A	N/A	N/A	N/A	N/A
60	HPC	cryst	N/A	N/A	N/A	N/A	N/A	N/A

Amorph: amorphous; Cryst: crystalline; N/A: not analyzed due to previous failure at given condition; NT: not tested due to lack of crystallization at a more aggressive condition.

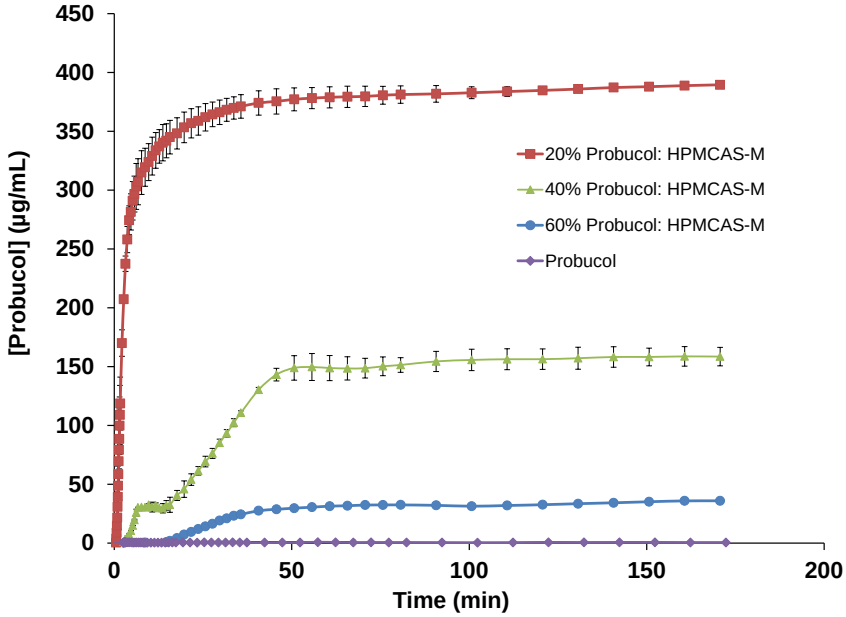
Dissolution

Dissolution testing of crystalline probucol and all SDDs was performed using a *p*ION µDISS Profiler™ in pH 6.5 FaSSIF media at 37°C with a stirring speed of 300 rpm. The *in situ* concentration-versus-time profiles were collected. Probucol SDDs with HPMCAS-L, M, H, or HPMC significantly enhanced dissolution over the crystalline probucol, as shown in Figures 3 and 4. Other SDDs did not exhibit significant solubility enhancement over the crystalline drug; one representative dissolution profile is shown in Figure 5.

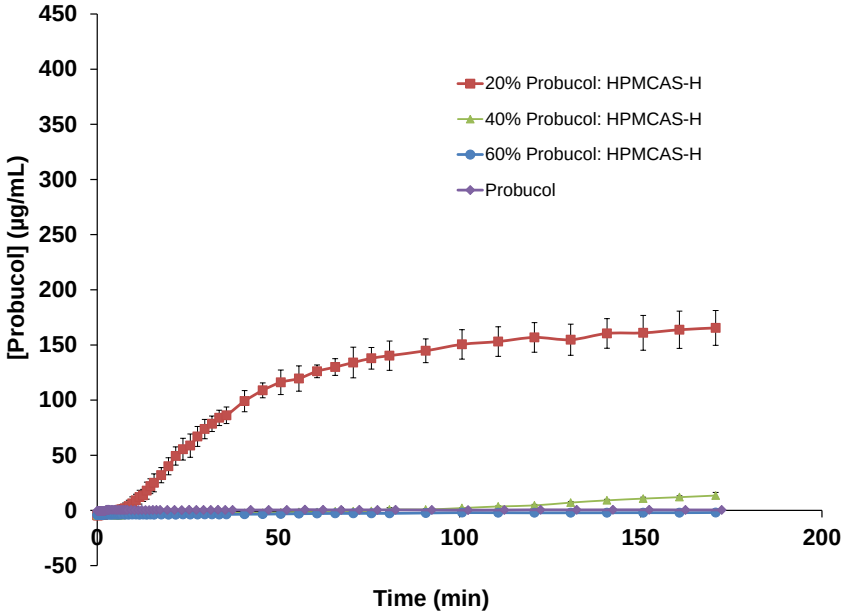
As shown in Figure 3, the SDDs with a lower drug load (20%) provided increased solubility enhancement over the SDDs at higher drug loads (40 and 60%). This is due to the fact that a drug with a high log P requires a high level of polymeric carrier, which may enable a strong interaction between the drug and polymer. It also can be seen that SDDs comprising HPMCAS-L and M with 20% drug load achieved a higher initial dissolution rate and supersaturation than the HPMCAS-H SDD, which is attributed to the higher degree of succinoyl substitution (hydrophilic group) for L and M grades. The reason for supersaturation sustainment may be due to the formation of amorphous drug/polymer nanostructure for HPMCAS SDDs in aqueous solution.



(a)



(b)



(c)

Figure 3. Dissolution results for HPMCAS SDDs: (a) L grade; (b) M grade; (c) H grade

HPMC SDD formulations also provided improved solubility, albeit to a lesser extent than HPMCAS SDDs, as shown in Figure 4. Other hydrophilic carriers, like PVP, PVP/VA, and HPC, were unable to provide increased solubility for probucol, as shown in Figure 5 using PVP/VA as an example. The hydrophilic characteristic of these carriers may provide an initial fast dissolution; however, the API will rapidly crystallize because the polymer lacks hydrophobic groups to interact with the drug molecule and sustain the supersaturation.

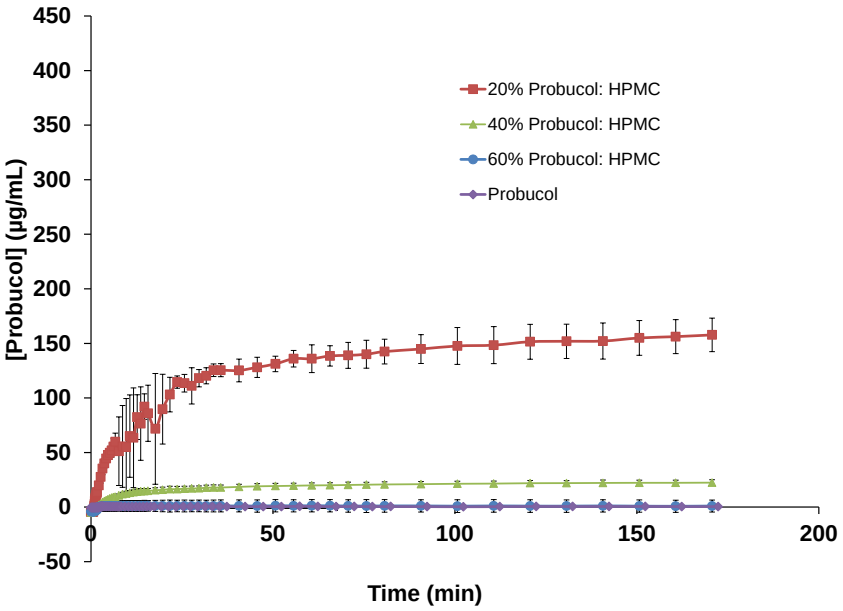


Figure 4. Dissolution results for HPMC SDDs

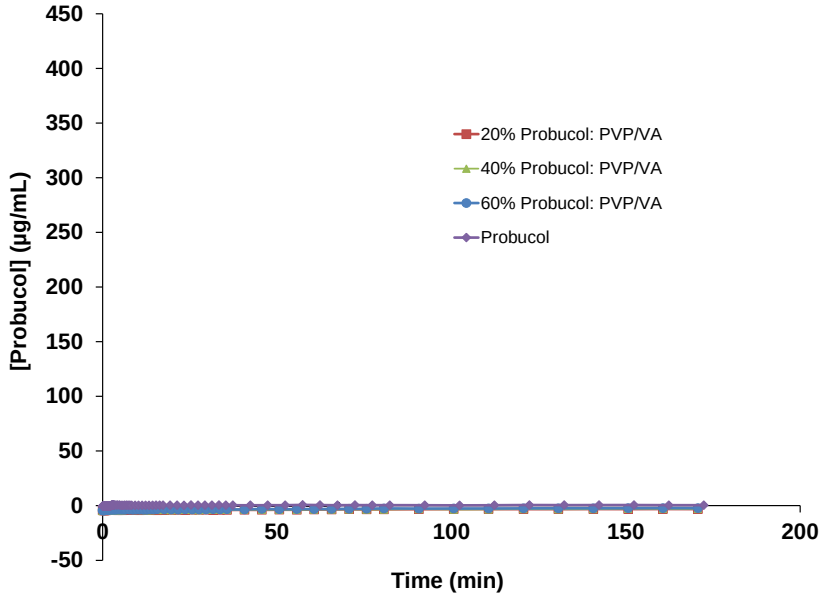


Figure 5. Dissolution results for PVP/VA SDDs

The dissolution data were summarized into two terms, relative AUC_{120} and C_{120}/C_{max}. Relative AUC_{120} is equal to the AUC_{120} of the selected formulation over the reference, *i.e.,* crystalline API. C_{120}/C_{max} is indicative of the degree of precipitation that has occurred over the first 120 min. Relative AUC_{120} versus C_{120}/C_{max} for 21 SDDs were plotted in Figure 6. Note that "X" on the plot indicates the crystalline probucol API, which was used as a reference. Formulations in the upper right corner are the best performers, which exhibit the highest supersaturation and sustainment ability. The results showed that the HPMCAS-L and M SDDs with 20% drug load had relative AUC values over 750, followed by 20% HPMCAS-H and HPMC, and 40% HPMCAS-L and M.

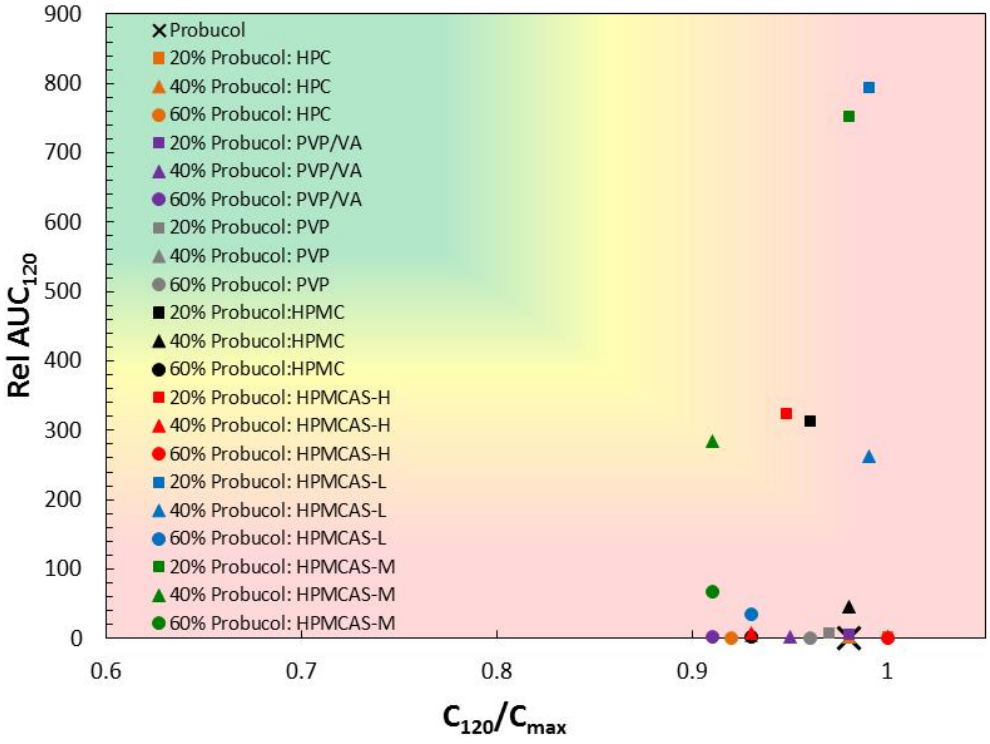


Figure 6. A novel approach to characterize dissolution of the probucol SDDs using relative AUC (compared to API) versus C_{120}/C_{max}

Conclusions

Twenty-one probucol spray-dried dispersions were prepared and characterized. The experimental results demonstrated that a lower drug load (20%) is required for the polymeric carriers to sufficiently stabilize this insoluble drug with a high log P both in solid state and during dissolution. HPMCAS as a carrier in probucol solid dispersions offered an optimal combination of enhanced stability and solubility at 20% drug load. The dissolution profiles suggested that HPMCAS-L and M SDDs enabled faster initial release than HPMCAS-H SDDs, which was attributed to the relatively higher levels of hydrophilic substitution for L and M grades. In addition, a novel approach of plotting the key dissolution parameters offered a means of rational selection of polymeric carriers for amorphous solid dispersions.