The Influence of Solvent System on the Performance of Polyvinyl Acetate Phthalate (PVAP) Delayed Release Coating Systems

ABSTRACT SUMMARY

Polyvinyl acetate phthalate (PVAP) or a fully-formulated delayed release coating system based on PVAP was dispersed in different solvents. Dispersion properties and coated tablet delayed release performance were evaluated. The neat polymer and formulated system yielded physically stable solutions and dispersions while the formulated system provided acceptable enteric protection and tablet disintegration.

INTRODUCTION

PVAP is a reaction product of phthalic anhydride and polyvinyl alcohol, used in pharmaceutical applications to provide enteric protection to solid dosage forms, or as a core seal-layer in the sugar coating process.[(1)]

Application of enteric coating systems from organic solvent mixtures continue in the marketplace despite well-known health and safety challenges associated with the process. These applications are limited, and appear largely due to the moisture sensitivity of certain active pharmaceutical ingredients and, potential long term stability of the finished delayed-release dosage form[(2)]. When using an organic system for the application of delayed release polymers, the choice of organic solvent is critical, as the type or ratio of solvents can significantly impact the quality of the resultant film.

One objective of this study was to characterize the effect of solvent type on the apparent dispersion pH and viscosity of the neat polymer, and a fully-formulated delayed release coating system (Opadry® Enteric). The second objective was to apply these dispersions to tablets and assess the film coating quality by analyzing enteric protection and disintegration time versus solvent mixture.

EXPERIMENTAL METHODS

Composition of Fully-Formulated System

Table 1 summarizes the concentration and function of each ingredient used in the fully-formulated system (Opadry Enteric, Colorcon).

Table 1. An Opadry Enteric Formulation Example

Ingredient	*Function*
PVAP	Enteric polymer
Titanium dioxide	Pigment
Stearic acid	Processing aid
Diethyl phthalate	Plasticizer

Dispersion Preparation

Polymer solutions or coating dispersions were prepared by dispersing either the neat polymer or the formulated system in a solvent mixture comprising isopropyl alcohol (IPA) and water (88:12 % w/w) or IPA and methylene chloride (MDC) (60:40 % w/w). Mixing was continued at low shear for 45 minutes. When using the IPA:water system, materials were first dispersed in IPA, followed by addition of the water with continued stirring.

Dispersion Characterization

The apparent pH of the coating dispersions was measured at 15% solids with a pH meter (model CL54, Toshniwal Instruments, Mumbai, India) after 45 minutes mixing, and after 72 hours of storage at ambient temperature. The viscosity of each dispersion was determined with a Brookfield DV-II+ Viscometer (Middleboro, USA) at similar intervals. Additionally, apparent pH and viscosity profiles were generated at 5, 10, and 15% total solids for the neat polymer and the formulated coating system, in each solvent mixture after 45 minutes mixing.

Tablet Coating

The fully-formulated coating dispersions were applied to 350 mg standard convex placebo tablets (5.2 kp breaking force, 0.12% friability) in a 12-inch conventional coating pan (Bectochem, Mumbai, India) located in a dedicated organic coating facility. Samples were collected for analysis at weight gains (actual) ranging from 5 to 7%.

The coating parameters for the different solvent systems are outlined in Table 2.

Table 2. Coating Process Parameters

Parameter	*IPA: Water*	*IPA: MDC*
Pan charge (g)	500	500
Inlet temperature (°C)	56	48
Exhaust temperature (°C)	37	36
Product temperature (°C)	40	38
Fluid delivery rate (g/min.)	2.2	3.2
Pan speed (rpm)	23-24	25-26
Atomization air pressure (bar)	2	2
Coating solids content (%)	15	6
Coating process time (5% wg, min.)	75	130

Disintegration Testing

Enteric coated tablets were reciprocated for 2 hours in 0.1N hydrochloric acid (HCl) using a USP compliant disintegration apparatus. Following this interval the samples were examined for any visual signs of “cracking, disintegrating, or softening” which would indicate a failure in enteric protection[3]. Samples were then transferred to phosphate buffer pH 6.8 USP, and the time for complete tablet disintegration determined.

Results and Discussions

The apparent pH of the coating dispersions depended on the choice of solvent system. However the apparent pH and viscosity of the coating dispersions exhibited no substantial change after 72 hours of storage, irrespective of the solvent mixture utilized to prepare the Opadry Enteric dispersion (Tables 3 and 4).

Table 3. Apparent pH of Dispersions (15% w/w)

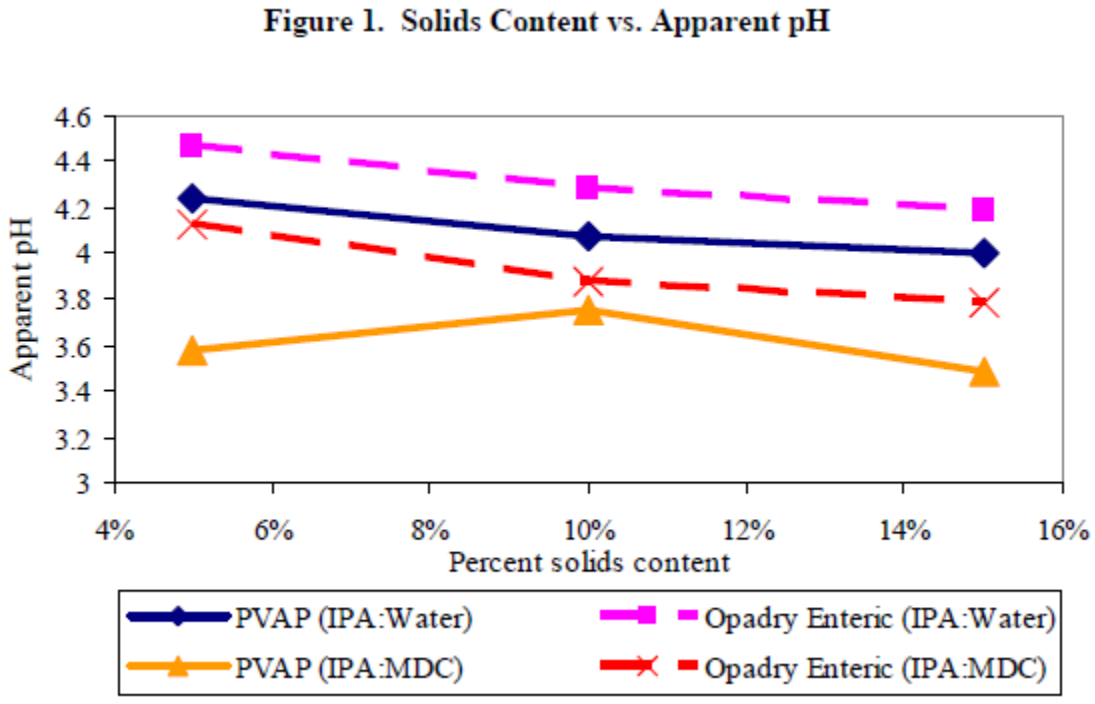
Solvent System	*Initial*	*After 72 hours*
IPA: Water	4.25	4.15
IPA: MDC	3.92	3.92

Table 4. Dispersion (15% w/w) Viscosity

Solvent System	*Initial*	*After 72 hours*
IPA: Water	22cp	23cp
IPA: MDC	17cp	18cp

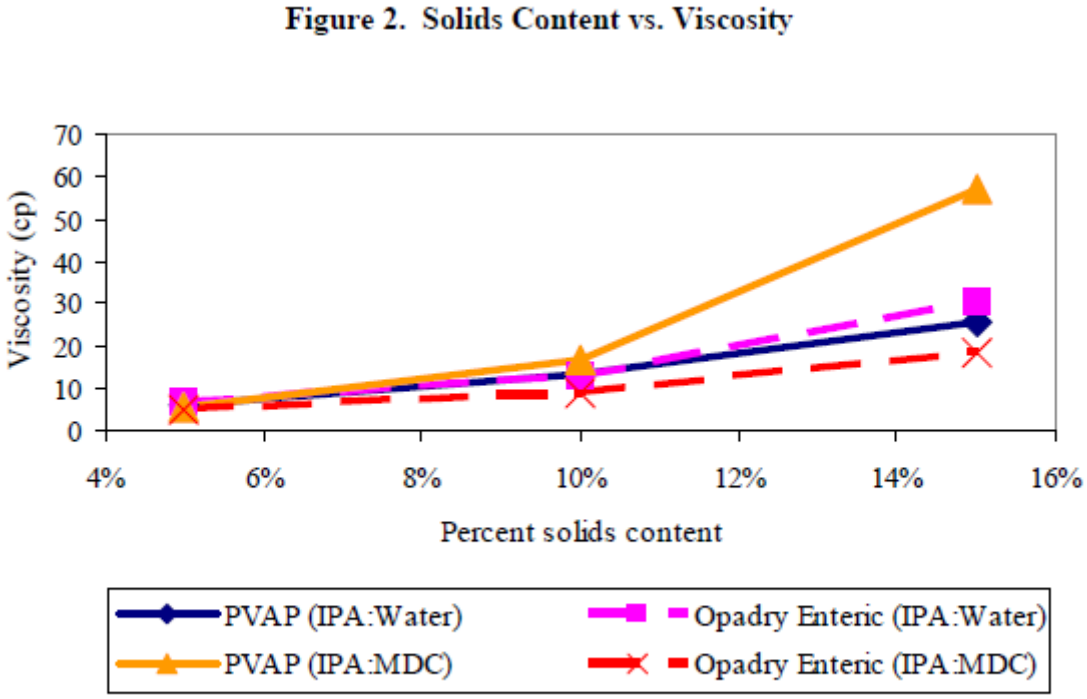
Increasing the concentration of PVAP or the formulated coating system resulted in a decrease in the apparent pH of the dispersion (Figure 1). Higher pH values were found for samples prepared in IPA:Water compared to IPA:MDC.

Figure 1. Solids Content vs. Apparent pH



Solution viscosity increased as the polymer concentration increased, irrespective of the solvent mixture used (Figure 2). A higher solution viscosity was obtained when PVAP was dissolved in IPA:MDC in comparison to IPA:Water at 15% solids content. This trend was not observed for the formulated systems.

Figure 2. Solids Content vs. Viscosity



Enteric protection was achieved for placebo tablets coated with Opadry Enteric from either IPA:Water or IPA:MDC as the solvent mixture, and across various weight gains (Table 5). Reproducible tablet disintegration was observed in phosphate buffer 6.8 with the time for disintegration slightly increasing as the actual coating weight gain increased.

Table 5. Delayed Release Disintegration

Weight Gain (Actual)	*Enteric Protection*	*Disintegration Time (min)*
Uncoated placebo	N/A	1.9 ± 0.20
IPA: Water		
5%	PASS	10.66 ± 0.92
6%	PASS	10.83 ± 1.00
7%	PASS	14.32 ± 0.20
IPA: MDC		
5%	PASS	8.89 ± 1.29
6%	PASS	10.26 ± 1.32
7%	PASS	10.48 ± 1.62

CONCLUSION

The choice of organic solvent system used affected viscosity and pH of solutions and dispersions of both neat PVAP and a fully-formulated Opadry Enteric coating system. The most significant difference in viscosity was observed at the highest solids content (15%), where PVAP dissolved in IPA:MDC generated a higher viscosity than PVAP dissolved in IPA:Water. Opadry Enteric provided enteric protection and reproducible disintegration irrespective of the solvent system, at coating levels as low as 5% weight gain.

REFERENCES

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Reprint of poster presented at the 2007 Annual Controlled Release Society Meeting. Authors: Kurt Fegely, Viena Dias, Laxmikant Patil, Vaibhav Ambudkar and Ali R. Rajabi-Siahboomi

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