An investigation of the factors that causes the agglomeration of soft gelatin capsules coated with Methacrylic acid copolymer when stored in high humidity conditions

Kai Zhuang and Anisul Quadir

BASF Corporation, 1705 US HWY 46 W, Ledgewood, NJ 07852

BASF

The Chemical Company

Introduction

Coating soft gelatin capsules (SGC) with enteric film that does not dissolve in the stomach has become very common in the dietary supplement industry, especially for the fish oil SGC. Methacrylic acid copolymer (Kollicoat® MAE 30DP) has been successfully used to coat Vitamin E Acetate SGC.[1] However, it has been noted that these coated SGC tends to agglomerate during storage. There are evidences to show that the moisture absorbed by the film coated SGC can lower the glass transition temperature (Tg) of the film and thus cause the agglomeration.[1, 2, 3] Since plasticizer is commonly used to lower the Tg of the coating polymer, it is then interesting to see whether it is the moisture, or the type of plasticizer used, or the amount of plasticizer used that contribute most to the agglomeration of the enteric film coated SGC.

The purpose of this poster is then to investigate the effect of moisture, the type of plasticizer, and the amount of plasticizer on the tendency of capsule agglomeration, and to use experimental design and statistical analysis to elucidate the contribution of each factor to the cause of agglomeration.

Experimental

Material and Methods

Fish oil soft gelatin capsules (size 20 oval) were purchased from Capsule Works (Baypoint, NY). Kollicoat® MAE 30DP was obtained from BASF (Florham Park, NJ). Triethyl Citrate (TEC) was from Aldrich. Propylene Glycol (PG) was from Ruger. Triacetin was from J. T. Baker.

Coating was done in a Thomas Accela-coater equipped with a 19”perforate pan. Table 1 shows the typical coating condition. The effectiveness of the enteric coating was assessed by a modified USP disintegration method for enteric film coated tablets. Disintegration of the Kollicoat® MAE film-coated fish oil SGC was tested in 0.1N HCl for 1 hour. The capsules were then removed and blotted dry. The capsule weight differences before and after the test relative to the initial capsule weight were recorded as liquid uptake.

Kollicoat® MAE film-coated capsules were placed in open dish over saturated NaCl salt solution (75% relative humidity at room temperature, RT/75%RH) for one week. This storage condition has been shown to provide good correlation with the long term stability study in revealing capsule agglomeration tendency.[1] Moisture pick up by the capsules was accessed by drying the emptied shells in a 40°C oven for 4 days.

Inlet Air volume	220 CFM
Inlet air Temperature	35 - 45°C
Exhaust air temperature	24 - 30°C
Actual bed temperature (measured by a infared gun)	23 - 26°C
Pan speed	16 rpm
Spray rate	20 g/min
Atomize air	40 PSI

Table 1 – Coating parameters for fish oil SGC

Experimental Design

A 3 factor, 3 level full factorial design was applied to evaluate whether it was the type of plasticizer, the amount of plasticizer used or the absorbed moisture that contribute the most to cause the agglomeration. The coating level was used as an indirect indication of moisture absorption by the coated capsules, since Kollicoat® MAE film could prevent moisture penetration.[1, 4] Table 2 is the design of experiments selected by MINITAB® software. The solid content of the coating dispersion was fixed at 15%.

Statistical analysis was also performed by MINITAB® software.

Plasticizer level (%) Based on polymer content	Plasticizer type	Coating level (% Wt. Gain)
15%	TEC	6%
15%	TEC	9%
15%	TEC	12%
15%	Triacetin	6%
15%	Triacetin	9%
15%	Triacetin	12%
15%	PG	6%
15%	PG	9%
15%	PG	12%
20%	TEC	6%
20%	TEC	9%
20%	TEC	12%
20%	Triacetin	6%
20%	Triacetin	9%
20%	Triacetin	12%
20%	PG	6%
20%	PG	9%
20%	PG	12%
25%	TEC	6%
25%	TEC	9%
25%	TEC	12%
25%	Triacetin	6%
25%	Triacetin	9%
25%	Triacetin	12%
25%	PG	6%
25%	PG	9%
25%	PG	12%

Table 2 Experiment design selected by MINITAB®

Results and Discussion

Kollicoat® MAE film coating was successfully applied to the capsules for all experiments conducted. The film coated capsules withstood the USP disintegration test in 0.1N HCl. The capsules picked up very little liquid after the test, as indicated by figure 1. This ensured that the film had no leak, and any moisture picked up by the capsules had to permeate through the film.

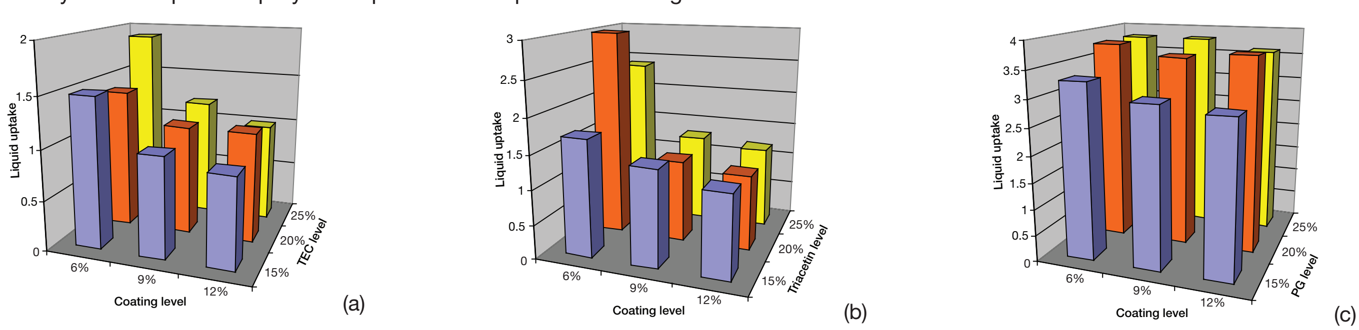

Figure 1 – Liquid uptake by enteric coated capsules after 1 hr disintegration test in 0.1N HCl. (a) TEC as plasticizer (b) Triacetin as plasticizer (c) PG as plasticizer

All coated capsules were put in open dish and stored over saturated NaCl solution (RT/75% RH). After 1 week the capsules were observed for agglomeration. The result is presented in Table 3.

Statistical analysis showed that the plasticizer level had a significant effect on the agglomeration tendency ($P < 0.05$). Plasticizer type also had an effect; however the effect is not significant. Figure 2 clearly shows the main effect for agglomeration.

	TEC level			Triacetin level			PG level		
Coating level	15%	20%	25%	15%	20%	25%	15%	20%	25%
6%	—	—	agglomerated	—	—	agglomerated	agglomerated	agglomerated	agglomerated
9%	—	—	agglomerated	—	—	agglomerated	agglomerated	agglomerated	agglomerated
12%	—	—	agglomerated	—	—	agglomerated	agglomerated	agglomerated	agglomerated

— Did not form agglomerate

Table 3 – Agglomeration tendency of coated capsules after 1 week at RT/75%RH

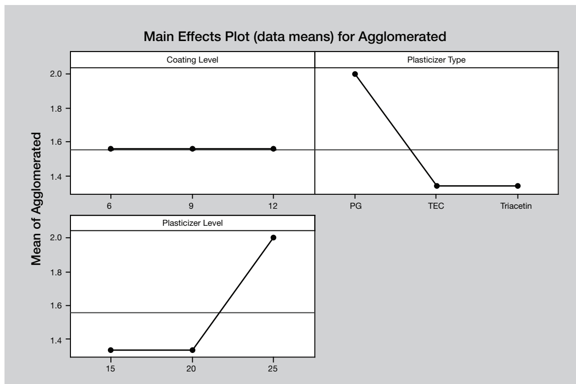

Figure 2 – Main effects plot using agglomerate as response.

It was surprising that the coating level did not have any effect on the agglomeration tendency. The moisture uptake study clearly showed that coating level had the largest effect on the absorption of moisture by the film coated capsules at high humidity ($P < 0.05$). Figure 3 shows the main effect plot for moisture pick up, and figure 4 shows a surface response plot for moisture pick up.

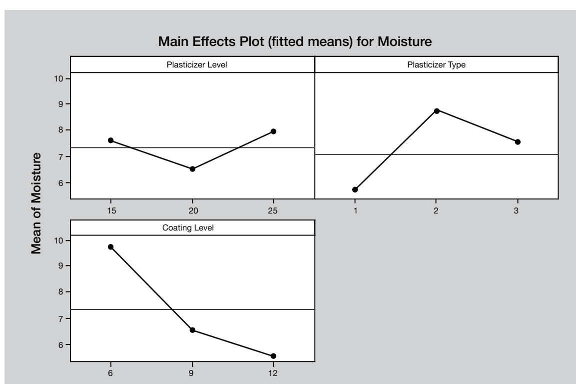

Figure 3 – Main effect plot of Moisture pick up

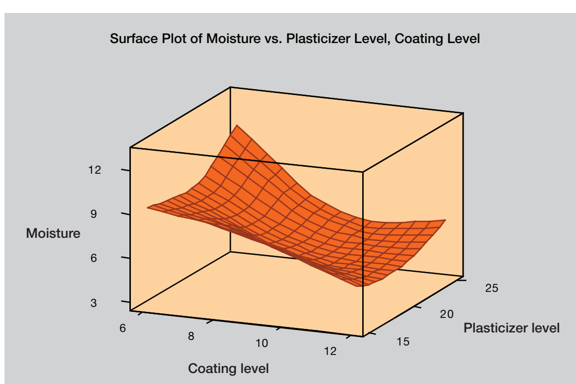

Figure 4 – Surface plot for moisture pick up

High coating level reduced the absorption of moisture by the film coated capsules. This was true for all 3 plasticizers used and for all levels of plasticizer. It was evident that Kollicoat® MAE film could prevent moisture penetration into the soft gelatin shells and this effect depended on the film thickness.

High moisture level in the gelatin capsules is believed to cause agglomeration of Methacrylic acid copolymer coated SGC.[1, 2, 3] By lowering the moisture absorbed by the film coated capsules, the chance for these capsules to agglomerate is also reduced However, our data indicated a different scenario. For Kollicoat® MAE film coated capsules with 25% of plasticizer, even at 12% coating level, and low moisture uptake, the capsules still agglomerated.

One explanation may be due to the plasticizers incorporated into the polymeric films. The thermal and mechanical properties of Methacrylic acid co-polymer film can be affected by the addition of plasticizer.[5, 6] The degree of plasticization depends on the interaction between the plasticizer and the polymer, as well as the amount of plasticizer. As can be seen from figure 5, DSC studies show that TEC, Triacetin and PG differ in their efficiency in lowering the Tg of Kollicoat® MAE films. With 25% of plasticizer, the Tg of the Kollicoat® MAE film was very low. With the help of absorbed moisture, the capsules agglomerated quickly. PG was most efficient in lowering Tg of Kollicoat® MAE film, and it was not surprising that at all 3 levels, the capsules agglomerated.

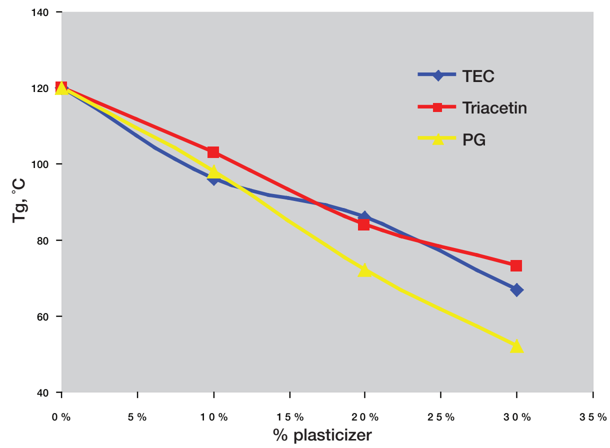

Figure 5 – Lowering of the Tg of Kollicoat® MAE film by different plasticizers

To see if this hypothesis is true, another coating trial was carried out using only 10% PG as plasticizer. The coating also passed the disintegrating test, and the capsules were tested in high humidity condition. After 1 week of exposure the capsules did not agglomerate. This result supported the theory that low Tg caused the agglomeration of Kollicoat® MAE film coated SGC. Moisture pick up helps to further lowering the Tg, but is not a significant factor in causing agglomeration.

Conclusion

Our data indicates that for Kollicoat® MAE film coated fish oil capsules, the amount of plasticizer applied in the coating dispersion plays a significant role in causing the coated capsules to agglomerate. Agglomeration can happen very quickly when the capsules are stored in a very high humidity condition. However, the moisture in the environment only facilitates the agglomeration by further lowering the Tg of the film. Agglomeration of Kollicoat® MAE film coated fish oil SGC can be easily prevented by reducing the amount of plasticizer used.

Acknowledgement

The authors want to thank Dr. Anping Wang (BASF Corp., Wyandotte) and Dr. Yidan Lan (BASF Corp., Ledgewood) for their support in providing DSC data and statistical analysis.

References

1. Zhuang, K., Onyiuke, C., Quadir, A., 2008 AAPS Poster.
2. Felton, L.A., Haase, M.M., Shah, N.H., Zhang, G., Infeld, M.H., Malick, A.W., McGinity, J.W., Int. J. Pharm. 127 (1996) 203 – 211
3. Felton, L.A., Shah, N.H., Zhang, G., Infeld, M.H., Malick, A.W., McGinity, J.W. Int. J. Pharm. 113 (1995) 17 – 24
4. Scheiffele, S., Kolter, K., and Schepky, G., Drug Devel. And Ind. Pharm., 24(9), 807 – 818 (1998)
5. Flober, A., Kolter, K., Reich, H.-B., and Schpky, G., Drug Development and Industrial Pharmacy, 26(2), 177 -187 (2000)
6. Gutierrez-Rocca, J. C., and McGinity, J. W., Int. J. Pharm. 103 (1994) 293-301