Poster # T3427

An Alternative Banding Method for HPMC Liquid Fill Hard Shell Capsule

Haibo Wang, Ph.D., Edgar Jaynes, Ph.D., Ram Kasina, Ph.D., Anthony Qu, Ph.D.; Pharmaceutical Development Services, Patheon Inc.; www.patheon.com

OBJECTIVES

To evaluate the HPMC banding process and morphology using different banding agents, and compare HPMC banding and regular gelatin banding processes. To look for a possible new water based HPMC banding process and banding agent to replace the current alcohol/water based HPMC banding.

BACKGROUND

Hydroxypropyl methylcellulose (HPMC) is produced by synthetic modification of the natural polymer cellulose and is used as shell material for two piece hard shell capsules. HPMC capsules are considered to be an attractive alternative to gelatin capsules because of its vegetable source and little chance for crosslinking. To avoid leakage of the liquid formulation, or sometimes even solid formulation, through the gap between the cap and body of two piece hard shell capsules, capsules are usually sealed by banding the junction between the cap and body by using a banding agent. Gelatin capsule banding agents are water based gelatin solutions with a small amount of surfactant added. The gelatin solution melting point is at approximately 35ºC. The banding solution is kept warm and in a liquid state during banding, and turns to a gel after the band is applied. For HPMC capsule banding, usually the HPMC powder is dissolved in ethanol /water solution and capsules are banded at room temperature. The ethanol content is over 50 wt%. Since the banding solution chamber in the banding machine is not sealed, and the band drying tower is open to the process room, during the banding and drying process, a significant amount of flammable alcohol vapor will be released to the process room. Furthermore, in this two-solvent banding agent, ethanol evaporates faster than water. After the banding process proceeds for a certain amount of time, solvent dosing becomes necessary to keep the solution viscosity at a constant level and to control the HPMC amount at a constant percentage. The two- solvent system makes this dosing process difficult, since a simple solution viscosity test is not able to measure the ethanol/water ratio in solution. For these reasons several other candidates for water based HPMC banding agents and processes have been tried. Among them, a gelatin water solution is a successful banding agent for gelatin capsules. HPMC water solution is a purified water based solution. The most interesting banding agent is the HPMC solution containing a small amount of gelling agent.

METHODOLOGY

Size 00 opaque white Quali-V and Vcaps+ HPMC capsules filled with soybean oil and Miglyol 812 were banded with several different banding agents using an STI Laboratory Capsule Bander (Schaefer Technologies). Banding agents include: #1. 16% HPMC, 53% ethanol alcohol, 31% water solution; (This formulation is commonly used for HPMC banding.) #2. 22% gelatin water solution; #3. 22% HPMC water solution; and #4. 11% HPMC water solution with a gelling agent such as ~1% carrageenan, locust bean gum, and potassium chloride. In addition, 0.4~0.9% polysorbate 20 or 80 was added to these banding agents as a surfactant to improve the compatibility between solution and capsules, thus improving the band shape. Furthermore, different coloring agents were added to these banding agents to make the band easy to observe with the eye or under a microscope. In the banding process, only banding agent #1 was applied at room temperature. The other three banding agents were applied at 50~60ºC. Banding temperatures and solids loading in the banding agents was adjusted in order to obtain an optimal solution viscosity at 200~300 cps. After the band was air-dried for one day, the band quality was checked by visual observation of the band shape. A twenty-minute vacuum treatment at -0.2 atm was utilized to test the capsule leaking rate. The integrity of the band/capsule adhesion was checked by a capsule body area compression test using a TA.XT Plus Texture Analyzer (Texture Technologies) with a ¼" ball probe. The ball probe is pressed down 2 mm on capsule body and then retracted. The process is repeated three times and the band area is observed for band/capsule separation. Some of the banded capsules were cut open to observe the fusion of band and capsule wall at the cross-section under a microscope with a digital sensor. To evaluate band material tensile strength, banding agents were spread onto a flat surface to obtain dried band material sheets first. These sheets were then cut into rectangular strips for uni-axial tensile test using a Texture Analyzer.

RESULTS AND DISCUSSION

Table 1. Banding test results

Banding Agent	#1	#2	#3	#4
HPMC and Ethanol content	16% HPMC 53% Ethanol	22% Gelatin 0% Ethanol	22% HPMC 0% Ethanol	11% HPMC 0% Ethanol Gelling agents
Banding temperature	Room temp.	55ºC	50ºC	60ºC
Capsule leaking rate	2%	21%	8%	3%
Band/capsule separation rate after body compression test	0%	100%	0%	0%
Air bubbles rate at band area	3%	0%	70%	4%
Band morphology	5% irregular band edge. Almost no shrinkage	8% irregular band edge. Moderate band shrinkage	11% irregular band edge. Moderate band shrinkage	10% irregular band edge. Mild band shrinkage
Band material tensile strength	44.6 MPa	110.9 MPa	50 MPa	50.6 MPa

Banding test results for all four banding agents were listed in Table 1. Banding agent #1 is a liquid at room temperature. After banding, the band dries relatively quickly. The band layer is relatively thin and the band edge is smooth (Figure 1a). About 5% of these capsules show an irregular band edge. Almost no shrinkage or expansion was found on the band. That means that almost no capsule deformation was caused by this banding process. During a vacuum test at -0.2 atm, about 2% of capsules were found to be leaking. Leaking occurs at the cap and body junction. Under a magnifying glass, unbanded areas were found on these capsules and oil was drawn out from these areas under vacuum. More than 5 capsules were randomly chosen to do the capsule body compression test. No band/capsule or cap/body separation was found under a magnifying glass. A few small air bubbles were found at the cap/body junction. These bubbles were caused by air pressure relief inside the capsule.

Banding agent #2 is the banding agent that normally provides a quality band for gelatin capsules. Here the same banding process was used for HPMC capsule banding as for gelatin capsule banding. After drying, about 8% capsules showed an irregular band edge, which can also be found on gelatin capsule banding. No air bubbles were found in gelatin bands (Figure 1b). The difference is that gelatin banding causes some HPMC capsules to shrink at the band area, while gelatin capsules usually expand at the band area after banding. During a vacuum test, more than 1 out of 5 capsules showed apparent leaking. Under a magnifying glass, oil leaking was seen underneath the band. This indicates poor band/capsule binding. The capsule body compression test showed that the band can be easily separated from the capsule body by a low mechanical force. This separation is due to the poor compatibility between gelatin and HPMC.

Two HPMC/water solutions (15% and 22%) were tested to compare the effect of ethanol in banding agent #1. Without ethanol, the drying time is about one minute longer. A 15% HPMC/water solution was tried first. The same room temperature banding was used as that for banding agent #1. During drying, because capsules were horizontal inside the capsule carrier bars, the banding solution flowed down due to gravity and accumulated at the bottom of some of the capsules. After drying, small band material lumps formed on those capsules. Besides this, large size air bubbles were found in the band area. To eliminate these problems, a 22% HPMC/water solution was tried. Due to the high solution viscosity (~800cps) at room temperature, the solution had to be heated to 50ºC during the banding process to reduce viscosity. Once the capsules were banded, the attached solution cooled down and viscosity increased again. This eliminates the problem of banding solution flowing down, but the air bubble problem still exists. Large air bubbles were found on most capsule band areas (Figure 1c). These large bubbles and the unbanded area on some capsules led to 8% of the capsules leaking under vacuum. Besides the air bubble problem, some capsules show an irregular band edge and moderate shrinkage. However, due to the good compatibility between the banding solution and capsules, no band/capsule separation was found after the capsule body compression test.

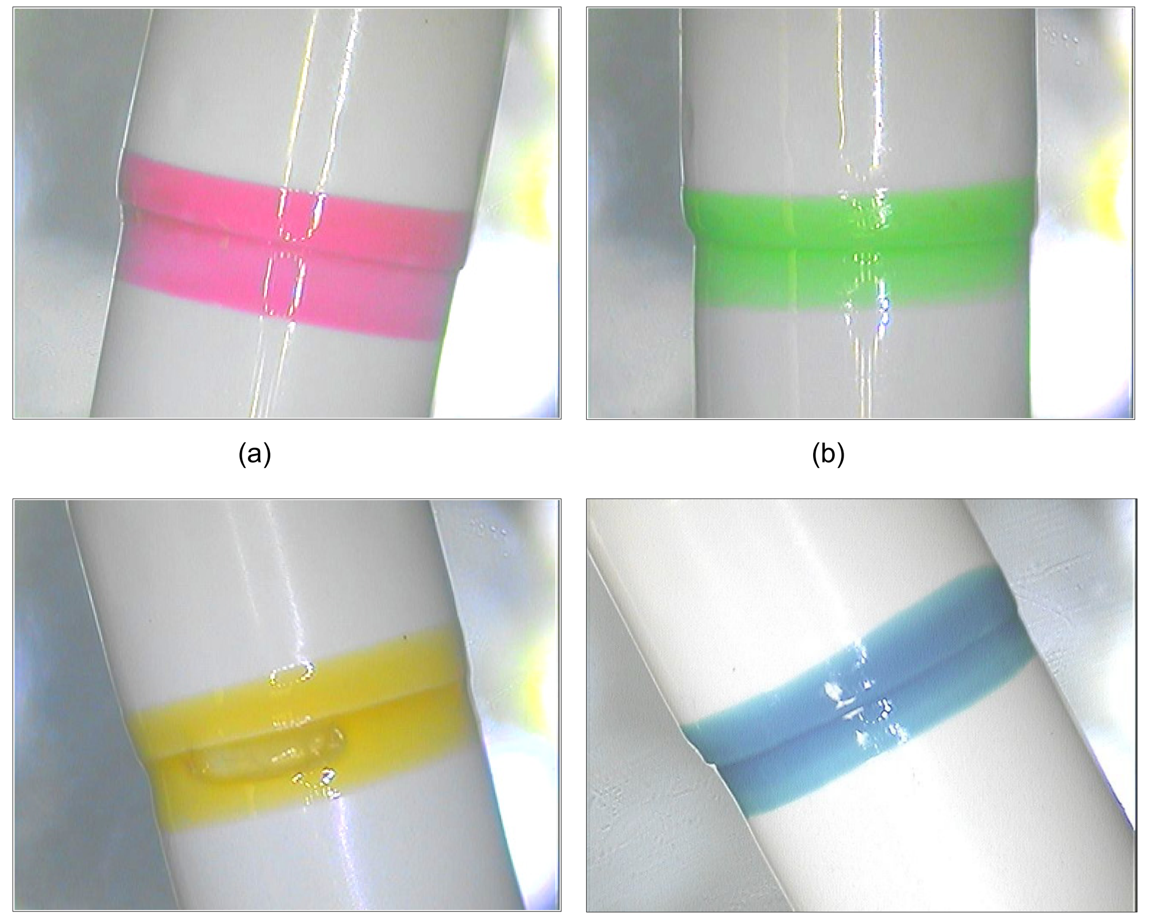

Figure 1. Banded capsules under microscope. (a) 16% HPMC and ethanol alcohol/water. (b) 22% gelatin water solution. (c) 22% HPMC water solution (d) 11% HPMC water solution with gelling agents.

Banding agent #4 contains a small amount of carrageenan and KCl as gelling agents, such that the banding agent is a liquid solution at high temperature and a solid gel at low temperature. During the process, the liquid banding solution is applied onto the capsule surface and quickly gels after banding. This process is physically similar to the gelatin banding process. In this way, the band material will not flow down the capsule and the strong gel blocks most of the air bubble venting from the capsules. After drying, the air bubble formation rate was about 4%. A few capsules showed an irregular banding edge and mild band area shrinkage. About 3% of the capsules were found to be leaking after the vacuum test. All the leaking was caused by unbanded areas on the capsules. No band/capsule separation was found after the capsule body compression test.

The band material tensile strength test result measures the dried band material strength after drying. Band material #1, 3, and 4 have very similar tensile strength. The gelling agents in banding agent #4 don't affect the material strength. Band material #2 gelatin shows a strength about twice as high as all the HPMC based band materials.

To observe capsule banding material fusion with the capsule, capsules randomly selected from these four groups were cut longitudinally into halves. Figure 3 shows the longitudinal cross-sections of the band areas. The thin colorful layer is the band material. Visually, the band and capsule fuse into one using banding agents #1, 3, and 4. No gap, bubble, or separation was observed between capsule and band (Figure 3a, c, and d). However no fusion was observed on #2 gelatin banded HPMC capsules (Figure 3b). The cap can be easily separated from the band with no damage to either cap or band. These results are consistent with the leaking test and the capsule body compression test.

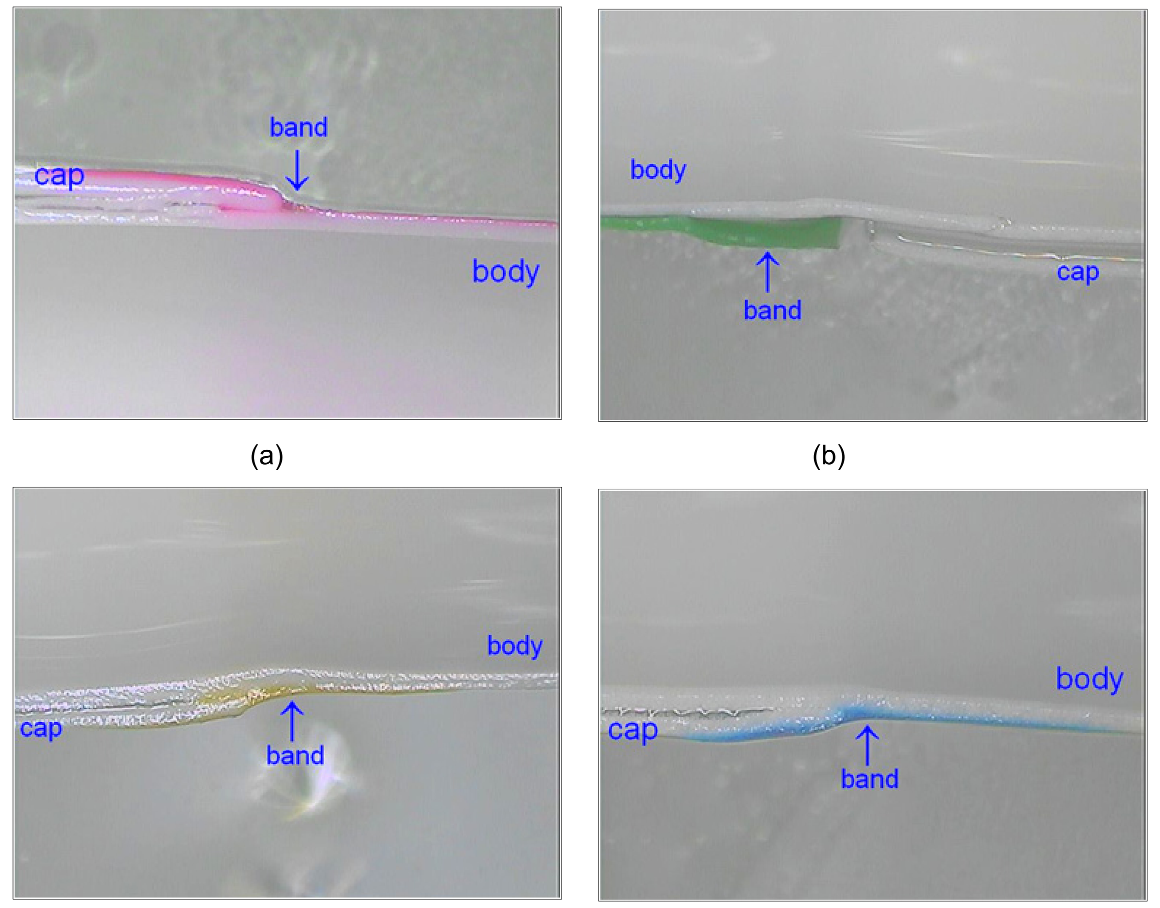

Figure 2. Cross-section of capsule banded area under microscope. (a) 16% HPMC and ethanol alcohol/water. (b) 22% gelatin water solution. (c) 22% HPMC water solution (d) 11% HPMC water solution with gelling agents.

The high amount of ethanol in the first HPMC banding agent formulation makes the banding solution dry quickly and the band edge smooth. When most of the ethanol evaporates, the solution viscosity quickly increases to several thousand centipoise. This explains the low air bubble formation rate in the band area. Gelatin gel has a relatively high gel strength, so no air bubbles form in the gelatin band. With gelling agents, HPMC gel can also successfully prevent most bubbles from forming at the band area.

Band morphology is influenced by many factors, including banding agent viscosity, presence of surfactant, band wheel condition, wheel heights and speed, processing temperature, and so forth. Unbanded areas may be caused by a combination of these items. The banding process need to be fine-tuned to optimize the result. A uniform band thickness at the cap and body junction area is critical to prevent capsules from leaking due to the relatively low solid loading in HPMC banding agents. Gelling of banding agent #4 helps to maintain a uniform band thickness at the junction area. It is difficult to avoid band shrinkage for HPMC capsules. After banding, water migrates from the banding agent into the capsule shell. This helps the binding and fusion between the banding material and the capsule shell, but can soften the capsule shell underneath the band, causing capsule shell shrinkage after drying. Usually, a minimal band thickness and fast drying can reduce the band shrinkage. With a gelling agent, more water has been retained in the band material instead of being absorbed by the capsule shell after banding. This may be the reason for relatively low capsule shrinkage at the banding area.

CONCLUSIONS

The HPMC capsule banding process is more difficult than is gelatin capsule banding. The high percentage of ethanol commonly used in HPMC banding solution is present to reduce drying time, and thus reduce capsule shrinkage, the air bubble formation rate, and the leaking rate. Three possible water based replacement banding agents were tried. Among them, the gelatin banding agent has a low air bubble formation rate, but the binding strength between band material and capsule shell is extremely low. Thus, the capsule leaking rate is the highest among all groups. The banding agent with only HPMC and water can't prevent air venting from capsules, thus air bubbles were frequently found at the band area. Bubbles cause leakage as well as cosmetic issues. Incorporating gelling agents in an HPMC banding solution can solve the air bubble formation issue and afford relatively low leakage rates and mild band shrinkage.