Carrageenan-based solutions for the sealing of liquid-filled pullulan hard capsules

Nicole M. Szweda[1]; Marie N. Rapin[2]; Paul Evans[2]; Sebastian Braun[1]; Michael C. Hacker[1]

[1] Heinrich Heine University Duesseldorf, MNF, Institute of Pharmaceutics and Biopharmaceutics, Universitaetsstrasse 1, 40225 Duesseldorf

[2] NextPharma Edinburgh, Units 1 - 8 Oakbank Park Way, Livingston EH53 0TH. Paul.evans@nextpharma.com

INTRODUCTION

Background

Two types of hard capsules are commonly used for liquid filling with lipid-based formulations (useful for poorly soluble and poorly bioavailable drugs): gelatin and hydroxypropyl methyl cellulose (HPMC). Pullulan capsules are a sustainable plant-based third alternative with superior qualities (oxygen barrier) [2], which may help the pharmaceutical industry satisfy the demand for green alternatives [1]. Hard capsules are routinely sealed to prevent leakage using the main biopolymer of the capsule parts or a suitable alternative.

Objective

The objective of this paper is to develop a sealing solution for pullulan capsules (Figure 1). The seaweed-based biopolymer κ-carrageenan, stable up to 90°C and capable of forming strong but brittle films at room temperature, is an interesting candidate. Its performances were studied as a single component, as well as in the presence of KCl and ethanol (acting as gelation promoters and strength enhancers) and compared to standard gelatin and HPMC sealing solutions (Figure 2).

Figure 2. Contents and preparation of sealing solutions. *Colour codes and abbreviations are used throughout the poster. AT: ambient temperature*

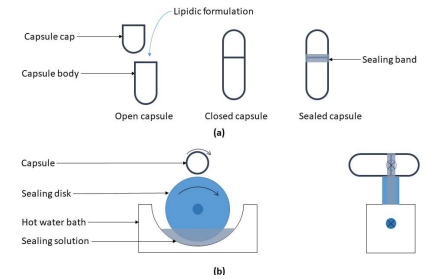

Figure 1. Capsule sealing method. *(a) From left to right: open capsule; closed unsealed capsule; closed sealed capsule. (b) Left: front view of the banding apparatus; Right: side view of the banding apparatus*

RESULTS: PRELIMINARY TESTS

Viscosity

Viscosity of sealing solutions should be maintained at 200-500 cP to ensure satisfactory processability on banding machine (Figure 3).

- Gelatin & HPMC solutions are routinely maintained at 60°C and 25°C
- Viscosities of Car and CarK were below 200 cP at 55°C
- Viscosity of CarE was below 200 cP at 45°C.

Gelation of the sealing solutions

Gelation or film formation at handling temperature is a critical event that compromises the sealing process. The solutions was evaluated visually for possible changes in petri dishes held at temperature in a water bath.

- All sealing solutions remained processable for over 90 minutes (average duration for use of a sealing solution) at their respective handling temperatures.

Speed of drying

Drying time has to be evaluated as prolonged drying times could make the formulations inappropriate for banding process. Drying was measured through weight loss of thin films incubated at ambient conditions.

- HPMC, gelatin, Car, CarK and CarE were touch-dry and solvent-free after 24 hours.

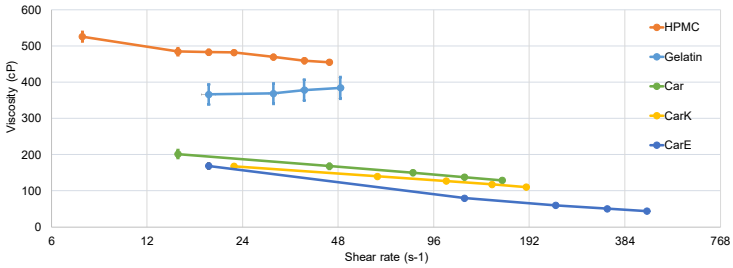

Figure 3. Viscosity of sealing solutions at their respective handling temperatures. *Viscosities measured at constant temperature on a Brookfield DV-III rheometer equipped with cone-plate geometry (CP-40), with a step-wise speed ramp method. Experiments conducted in triplicate, standard deviations displayed as bar errors. Handling temperatures during analysis: HPMC 25 ° C, gelatin 60 ° C, Car, CarK at 55 ° C and CarE at 45 ° C*

RESULTS: FILM MECHANICAL ASSESSMENT

Texture analysis

The burst strength of thin films from sealing solutions was measured as a proxy for the capsule seal performance.

- Gelatin films were by far the strongest and most plastic (no rupture)
- CarE films were the most brittle
- CarK and Car films were comparably strong and withstood stress twice as high as CarE
- HPMC films were the most deformable.

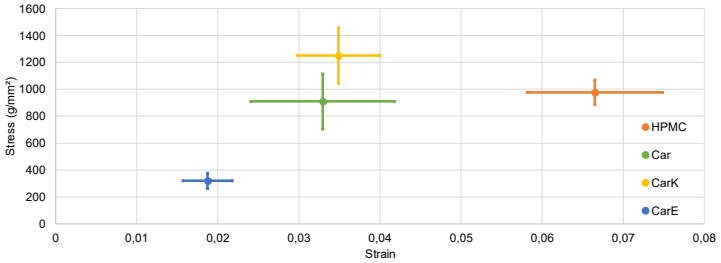

Figure 4. Evaluation of the mechanical properties of polymeric films. *Burst strength of dried films (comparable wet weight) examined using a texture analyser (TA.XTplus, Stable Micro Systems, UK) by penetration through a cylindrical sample held between metallic clamps (speed: 1 mm/s, maximum penetration: 5 mm). Experiment conducted on 10 samples per formulation; standard deviation displayed as error bars. Gelatin films not shown as they did not rupture during the experiment*

RESULTS: SEAL ASSESSMENT

Sealing process

Sealing performance was tested on a bench-scale banding apparatus for up to 10 minutes. The main limitation of the process for carrageenan-based solutions was rapid viscosity increases, whereas gelatin and HPMC sealing solutions remained processable for minimum 90 minutes.

- Car performance was satisfactory at 55°C
- CarK and CarE performances were satisfactory at 65°C but resulted in distorted capsules, indicating that pullulan capsules may soften or dissolve when exposed to the aqueous sealing solutions at that temperature.

Seal evaluation

Gelatin, the most common polymer used for banding, gave homogeneous, thick and smooth seals, whereas HPMC, Car, CarK and CarE seals were thinner and less homogeneous (Figure 5).

When integrity of the seal was tested under vacuum, no leakage was observed for all sealing formulations used for banding.

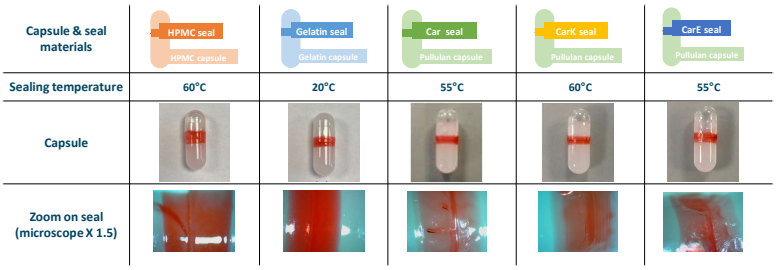

Figure 5. Hard capsules sealed with different polymeric materials. *Visual examination of the quality of the seals after complete drying (24 hours). Introduction of a red dye in the sealing solutions to enhance the contrast between sealing material and capsule material.*

DISCUSSION & CONCLUSION

Car, CarK & CarE solutions were suitable for pullulan capsule sealing and showed comparable performances during pre-testing and formed seals of comparable quality. Overall, Car was preferable to CarK and CarE for the capsule sealing process as these solutions remained processable for a longer time and could be handled at a lower temperature.

The addition of KCl and ethanol to yield CarK and CarE, respectively, was intended to enhance the films' properties but did not achieve the intended benefit. This may be due to a low concentration (KCl), or to acceleration of localised precipitations, which promoted the formation of a discontinuous and fragile carrageenan film (ethanol). The presented reliability of carrageenan seals could indicate the presence of molecular interactions between carrageenan and pullulan.

In the future, the sealing solutions could be further optimized through the addition of plasticizers, to improve processability, or through the addition of ι-carrageenan or other biopolymers, to enhanced film properties. Moreover, additional understanding of carrageenan-pullulan interactions may shed light on the quality of the seal. Finally, a range of pharmaceutical tests (dissolution, stability, robustness) will be necessary to ensure the new sealing solutions do not significantly alter the capsule properties.

References

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