Gelatin-free Softgel Studies: Development of Novel Shell Compositions and Processes Suitable for the 'Hot Filling' of High Viscosity and Semi-solid Fill Materials.

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INTRODUCTION

Purpose

- To develop polysaccharide-based shell formulations and elevated temperature filling processes suitable for the encapsulation of high viscosity and semi-solid, pharmaceutical fill formulations.

Background

- Pharmaceutical fill formulations that exist as solid-like or semi-solid systems at room temperature and melt at temperatures greater than 40°C pose a challenge for the softgel formulator. These types of formulations typically do not lend themselves readily to encapsulation using traditional gelatin-based encapsulation films, since during capsule formation the films have a sealing limit of approximately 38°- 42°C. In recent years the potential of polysaccharide-based encapsulating films for 'hot filling' high melting point fill formulations has been investigated. This poster summarizes the results obtained from studies that have been conducted using 'high melting point' encapsulating films containing iota-carrageenan and hydroxypropylated starch, as the shell-forming polymers.

Scope

- Investigate the melting point and temperature dependency of the viscosity and viscoelasticity of fill formulations that exist as solid-like or semi-solid materials at room temperature.

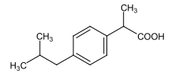
- Establish the filling and sealing temperatures for satisfactory capsule formation using
  1) conventional gelatin-based encapsulating films, and
  2) polysaccharide-based encapsulating films, containing iota-carrageenan and hydroxypropylated starch

MATERIALS

Drug substance

- Ibuprofen
  2-(4-isobutylphenyl)-propionic acid

Figure 1. Structure of Ibuprofen



Ingredients used in the fill formulation studies

- Polyethylene glycols
- Lecithin
- Sucrose acetate isobutyrate (SAIB)

Ingredients used in the shell formulation studies

- Gelatin NF
- Polyol plasticizers (Glycerol, Sorbitol, Anhydrized Liquid Sorbitol)
- Hydroxypropylated starch
- Iota-carrageenan
- Di-sodium phosphate
- Purified water

METHODS

- The polysaccharides, iota-carrageenan and hydroxypropylated starch, were formulated, in combination with polyol plasticizers and water, to give thermo-reversible film-forming gels. The formulations were prepared in accordance with the compositions and processes described in US patents:
  - 6,582,727
  - 6,340,473

- Gelatin-based gel mass/capsule shell formulations were prepared using conventional compositions and processes

- The suitability of the gel/shell formulations for the encapsulation of a range of high melting point, high viscosity fill materials was investigated using a rotary-die encapsulation machine equipped with a high temperature fill/injection system

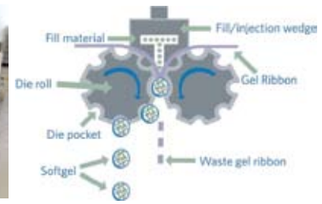
- The high viscosity and semi-solid fill materials were formulated using 1) hydrophilic and 2) lipophilic vehicles. The fill formulations were prepared using conventional, elevated temperature processing techniques

- The viscosity and viscoelasticity of the fill materials was measured using a Haake RS 150 rheometer equipped with a cone and plate measuring system. A gap setting of 1.00 mm was used for both tests. The samples were examined over the range 40°C - 80°C. Temperature control was achieved using a peltier plate. Viscosity was determined using a test frequency of 1.0 Hz. Viscoelasticity was determined using oscillatory shear, over the frequency range 1.0 – 10 Hz.

- Prior to encapsulation the capsule filling process was developed and optimized based on the rheological profiles of the fill materials

- 'Hot filling' encapsulation trials were conducted using 1) conventional gelatin-based encapsulating films and 2) novel, polysaccharide-based encapsulating films. Softgels were produced using the rotary-die encapsulation process

Figure 2. Softgel Manufacture using the Rotary-die Encapsulation Process



EXPERIMENTAL STUDIES

Capsule Shell Development

Composition of Capsule Shell Formulations

Table 1. Composition of Polysaccharide-based Shell Formulations

Ingredient	Functional role in shell	% w/w of dry shell
Hydroxypropylated starch	Shell polymer	33 - 37
iota-carrageenan	Shell polymer	7 - 12
Polyol plasticizer	Plasticizer	36 - 42
Di-sodium phosphate	Buffer	1
Water	Water associated with plasticizer & polymers	10 - 12

- Shell formulations were developed containing blends of the two polysaccharides in the ratio 0.75 - 1.5: 2.0 - 4.0, iota-carrageenan : hydroxypropylated starch. The effect of plasticizer on film performance was investigated over the range 0.5-1.0 : 0.9-1.6, shell polymers: plasticizer

Fill Formulation Development

Characteristics and Composition of Fill Formulations

Table 2. Characteristics of Fill Formulations

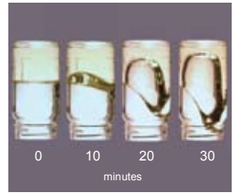
Formula type	Base vehicle	Vehicle characteristic at room temperature	Physical state of formulation		
			20°C	40°C	60°C
A	High m.w. PEG's	Hydrophilic Solid	Solid	Solid	Mobile fluid
B	Lecithin	Hydrophilic and lipophilic characteristics Very viscous fluid	Extremely viscous fluid	Very viscous fluid	Mobile fluid
C	Sucrose Acetate Isobutyrate	Lipophilic Extremely viscous fluid	Extremely viscous fluid	Extremely viscous fluid	Viscous fluid

- Type A formulations were prepared using compositions (35% - 43% w/w drug) and processes described in US patent 5,360,615

- Type B formulations were prepared using drug loadings in the range 45% - 50% w/w

- Type C formulations were prepared using drug loadings in the range 40% - 50% w/w

Figure 3. Flow Behavior of SAIB at RT



Encapsulation trials

- Gelatin-free softgels were produced using elevated temperature, filling and sealing techniques

RESULTS

Capsule Shell Development

- The most suitable gelatin-free gel/shell compositions were found to comprise
  - iota-carrageenan:hydroxypropylated starch in the ratio, 1.0 : 2.5-3.5
  - Sorbitol-based plasticizers
    - Plasticizer : shell polymer in the ratio, 0.8 : 1.0

Rheological Profiles of Fill Formulations

Figure 4. Rheological Profile: High molecular weight PEG's

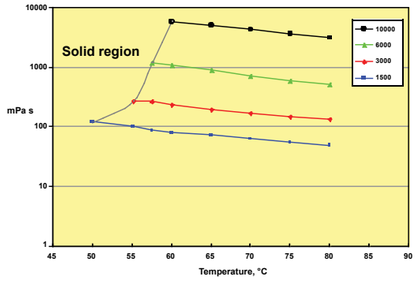


Figure 5. Rheological Profile: 40% ibuprofen in PEG 6000

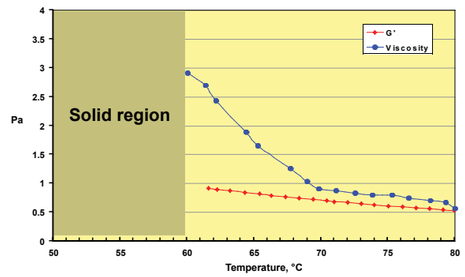


Figure 6. Rheological Profile: 50% ibuprofen in Lecithin

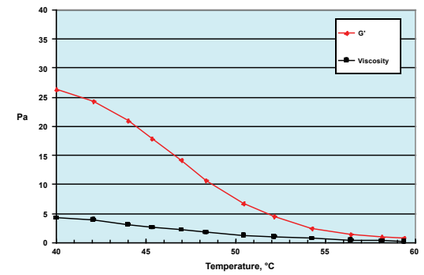


Figure 7. Rheological Profile: 40% ibuprofen in SAIB

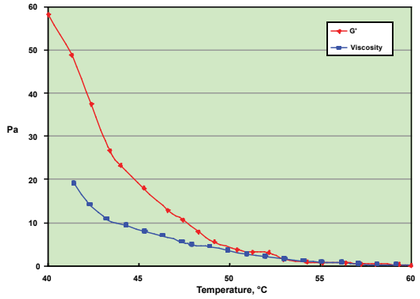


Figure 8. SAIB softgel

T=0

T=8 HOURS

Figure 9. Softgel with solid-like core

- Rheological profiling and filling studies showed that the optimum filling temperature for the fill materials was in the range 60°-70°C. At these temperatures the material is sufficiently mobile; viscosities range between 2,000 and 5,000 mPa s

- The polysaccharide-based shell compositions were found to retain their film-like characteristics at the elevated temperatures (55° - 75°C) required for filling and sealing the capsules. At these temperatures the gelatin-based films deformed and/or melted.

- Soft capsules were successfully produced using the polysaccharide-based shell compositions and using 'hot filling' techniques

CONCLUSION

Novel, polysaccharide-based softgel shell compositions have been developed that, in conjunction with 'hot filling' processing techniques, are suitable for the encapsulation of fill formulations that are highly viscous or semi-solid at room temperature