ABSTRACT

This study investigates the potential of three commercial carrageenans, Gelcarin GP379, Gelcarin GP911, Gelcarin GP812 (Iota-carrageenan) and Viscarin GP209, Viscarin GP109 (lambda-carrageenan) & Seaspen to be used for the preparation of controlled-release tablet matrices. Properties of all six categories of Carrageenan were discussed (Table -1). During formulation of Oral Dosage, wet granulation process was adopted considering the flow property of selected raw material. In different stages of manufacturing the critical parameters such as Impact of Carrageenan on particle size distribution, tablet hardness & drug release profiles etc. were studied.

KEYWORDS: Carrageenans, Particle size Distribution, Drug release profile.

INTRODUCTION

Carrageenans are a family of naturally occurring polysaccharides extracted from red seaweed used by the pharmaceutical industry for specific gelling, thickening and stabilizing applications. Three basic types of Carrageenan exist: κ-Carrageenan, ι-Carrageenan and λ-Carrageenan because of their ability to form stable gels at room temperature and also Carrageenan are useful excipients to sustain drug release. They consist chiefly of the sulfate esters of galactose and 3,6-anhydrogalactose joined by alternating α-1,3 and β-1,4 glycosidic linkages. The ι-Carrageenan is also sulfated at carbon 2, contrary to κ-Carrageenan. The highly sulfated λ-Carrageenan can only be used as a thickening agent. Therefore, it is not a useful main excipient to control drug release from tablets. Two grade of κ-Carrageenan, two grade of λ-Carrageenan and two grade of ι-Carrageenan were used for this study. The behavior of the in-vivo release controlling capability will be studied separately, under this
formulation research work only *in-vitro* release behavior of Carrageenan matrix tablet was studied.

**NIR Spectra of Carrageenan**

![Near-infrared spectrum of carrageenan measured by reflectance.](image1)

![Near-infrared spectrum of carrageenan (lota) measured by reflectance.](image2)

![Near-infrared spectrum of carrageenan (kappa) measured by reflectance.](image3)
The present work was designed to address the following objectives:

- Formulation of controlled release tablet
- Hardness study
- Evaluate the particle size distribution
- Feasibility to Scale-up

### Table 1

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Carrageenan Type</th>
<th>Viscosity</th>
<th>Gel Type</th>
<th>Water Solubility</th>
<th>Use Level</th>
<th>Use Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gelcarin GP-379 NF</td>
<td>Iota</td>
<td>High Thixotropic</td>
<td>Elastic Medium Strength</td>
<td>Hot</td>
<td>0.3-1.0%</td>
<td>Creams, Suspensions Polyol Reactive Protein Reactive Promotes Freeze Thaw</td>
</tr>
<tr>
<td>Gelcarin GP-812 NF</td>
<td>Kappa</td>
<td>Low</td>
<td>Brittle Strong</td>
<td>Hot</td>
<td>0.3-1.0%</td>
<td>Stronger Gels than GP-911 Note: Syneresis higher than GP-911</td>
</tr>
<tr>
<td>Gelcarin GP-911 NF</td>
<td>Kappa</td>
<td>Low</td>
<td>Brittle Firm</td>
<td>&quot;Hot Partial Cold&quot;</td>
<td>0.25-2.0%</td>
<td>Encapsulation/ Delivery Systems Polyol Reactive Protein Reactive</td>
</tr>
<tr>
<td>Viscarin GP-109NF</td>
<td>Lambda</td>
<td>Medium</td>
<td>Non-Gelling</td>
<td>&quot;Partial Cold, Full Hot&quot;</td>
<td>0.1-1.0%</td>
<td>Creams, Lotions Protein Reactive Polyol Reactive</td>
</tr>
<tr>
<td>Viscarin GP-209NF</td>
<td>Lambda</td>
<td>High</td>
<td>Non-Gelling</td>
<td>&quot;Partial Cold, Full Hot&quot;</td>
<td>0.1-1.0%</td>
<td>Creams, Lotions Protein Reactive Polyol Reactive</td>
</tr>
<tr>
<td>SeaSpen PF</td>
<td>Iota</td>
<td>Medium</td>
<td>Elastic Weak</td>
<td>&quot;Cold Delayed, Gel Formation&quot;</td>
<td>0.5-1.0%</td>
<td>Suspensions Topical Lotions, Creams Reconstitutable Suspensions</td>
</tr>
</tbody>
</table>

Reference: FMC Biopolymer
MATERIALS AND METHOD
For the formulation works, raw materials such as API procured from Medicem, Italy. Other excipients are procured from Lactose Monohydrate, Foremost Microcrystallinecellulose (PH101), JRS Magnesium Oxide Light, Merck-IH Carrageenan, FMC Povidone (K-30), ISP Magnesium Stearate, Peter Greven

Formulation details as below
Formulation Process

Light magnesium oxide was compacted (qty. calculated as per six trials) in Vertical roller compactor, PSD parameters are discussed in Table 2. In first stage of dry mixing API, Carrageenan & Lactose monohydrate were sifted through #40mesh. Sized Magnesium Oxide added into the previously blended mixer. Methylene chloride was used as Granulating solvent. Granulated material was dried in tray dryer at 60\(^{0}\) - 65\(^{0}\) C. LOD limit 1.5% - 3.0%. Dried granules were passed through #24mesh. Manually mix PVPK30 in sized granules for 10min. & lubricate the blend with Magnesium Stearate for 5 min.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Mg/tab</th>
<th>T1 (Carrageenan (\lambda) (Viscarin GP 209))</th>
<th>T2 (Carrageenan (\nu) (Gelcarin GP 379))</th>
<th>T3 (Carrageenan (\kappa) (Gelcarin GP 812))</th>
<th>T4 (Carrageenan (\kappa) (Gelcarin GP 911))</th>
<th>T5 (Carrageenan (\lambda) (Viscarin GP 109))</th>
<th>T6 (Carrageenan (\nu) (Seasppen PF09))</th>
</tr>
</thead>
<tbody>
<tr>
<td>API</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Lactose Monohydrate</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Magnesium Oxide Light</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Carrageenan</td>
<td>300.00</td>
<td>300.00</td>
<td>300.00</td>
<td>300.00</td>
<td>300.00</td>
<td>300.00</td>
<td>300.00</td>
</tr>
<tr>
<td>Methylene Chloride</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
</tr>
<tr>
<td>Povidone</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Magnesium Oxide</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

Final Blended granules were compress to tablets in Longli 12 station tablet press.
Particle Size Distribution of Dried Granules:

Table 3

<table>
<thead>
<tr>
<th>Sample</th>
<th>Above #60</th>
<th>Below #60</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 Viscarin GP 209</td>
<td>26.7</td>
<td>73.3</td>
</tr>
<tr>
<td>T2 Gelcarin GP 379</td>
<td>40.85</td>
<td>59.15</td>
</tr>
<tr>
<td>T3 Gelcarin GP 812</td>
<td>54.2</td>
<td>45.8</td>
</tr>
<tr>
<td>T4 Gelcarin GP 911</td>
<td>62.7</td>
<td>37.3</td>
</tr>
<tr>
<td>T5 Viscarin GP 109</td>
<td>51.2</td>
<td>48.8</td>
</tr>
<tr>
<td>T6 Seaspen PF09</td>
<td>52.4</td>
<td>47.6</td>
</tr>
</tbody>
</table>

Fig: 5

Particle Size Distribution above #60 mesh

Fig: 6

Particle Size Distribution below #60 mesh
Analytical Test Method for Dissolution

**Reagents**

- Acetonitrile: HPLC grade
- Potassium Dihydrogen Phosphate: AR grade
- Potassium hydroxide: GR grade
- Triethylamine: HPLC grade
- Phosphoric acid: GR grade
- Water: Milli Q water or equivalent
- Citric acid anhydrous: AR grade
- Sodium Hydroxide: AR grade
- Disodium Hydrogen Phosphate (Anhydrous): AR grade
- Methanol: HPLC grade

**Chromatographic Conditions**

- Mobile phase: Buffer: Acetonitrile 500 : 500
- Buffer: Dissolve 8.16gm of KH2PO4 in 1000 ml of Milli-Q-water in a suitable container and mix. Add 1ml of triethylamine and adjust the pH to 6.7 with 5% KOH solution or phosphoric acid. Filter through 0.45μm filter.
- Column: Xterra RP18, 50mm X 4.6mm; 5μ, or equivalent
- Flow rate: 1.2ml/minute
- Wavelength: 250nm
- Injection Volume: 5μL
- Column Temperature: 40°C
- Run time: 2 min
- Dissolution medium pH (6.4-6.6):

Mix thoroughly

1) 9.606 gm Citric acid anhydrous (0.05M) +3.6 gm NaOH(0.09M) dissolve in 1 liter of water. Mix thoroughly.
2) 7.098 gm Na2HPO4 anhydrous(0.05M) +18.4 gm NaOH(0.46M) dissolve in 1 liter of water. Mix 900ml (1) and 100ml (2).

**Dissolution Parameters:**

- Apparatus: Type-II, Paddle with Sinker
- Medium: Citro-Phosphate Buffer (pH 6.4-6.6)
Media Volume : 1000ml
RPM : 100
Temp : 37°C ± 0.5 °C
Time interval : As per specification
Sinker Size : No.3

**Standard preparation**
Weigh accurately about 46.0mg of Quetiapine Fumarate working / reference standard in 100ml volumetric flask, add 10ml of Methanol and sonicate to dissolve, make up the volume with dissolution medium and mix it.

**Sample preparation**
Place one tablet in sinker in each of six bowls and operate the apparatus as mentioned in dissolution parameters, withdraw 10ml of the solution at the end of specified time and filter the solution through 0.45μm PVDF filter and inject. Replace the same amount of medium after each time point

Note: The standard preparation and sample preparation are stable upto 48 hours at room temperature.

**Procedure**
Inject blank and record the chromatogram.

Inject standard preparation five times, record the chromatograms and check for compliance for system suitability.

Inject sample and record the chromatogram.

**Table 4**
Hardness Vs Release Profile

<table>
<thead>
<tr>
<th></th>
<th>2hrs NMT 20%</th>
<th>7hrs 45-65%</th>
<th>24hrs NLT80%</th>
</tr>
</thead>
</table>
| **T1 Viscarin GP 209**  
Hardness 190N-220N | 12          | 56          | 92           |
| **T2 Gelcarin GP 379**  
Hardness 190N-210N | 39          | 68          | 94           |
| **T3 Gelcarin GP 812**  
Hardness 190N-212N | 24          | 78          |              |
RESULT AND DISCUSSION

From the above release profile data it was observed that apart from Viscarin 209 & Viscarin 109 other Carrageenan grades drug release faster compared to the set specification. Where
Seaspan PF09 shows no effect as release controlling polymer. In particle size distribution data it shows only 26% retention in #60 mesh of Viscarin 209 trial compared to 51% retention with Viscarin 109. Even though the fine percentage is more with Viscarin 209, there was no flow problem found during compression. Lubricated Blend was tried to compress in similar hardness to compare the release profile. It was observed that Viscarin 209 & Viscarin 109 has comparable drug release profile although \textit{in-vivo} release properties are unknown. Also from the characteristic of Lubricated blend and compressibility parameters it is considered to be feasible for further scale-up process.

ACKNOWLEDGEMENT
We are extremely gratified to Research & Development Department and fellow colleagues for helping us in the technical aspect of this project and also for useful scientific discussions, which produced methodical results and also for sharing their passion for drug product development and thus helping us in better understanding on selection of material grade for drug product development.

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