# APPLICATION OF OPTIMIZATION TECHNIQUE IN SYNTHESIS AND CHARACTERIZATION OF SODIUM CARBOXY ETHYL GUAR.

**Hasanpasha .N Sholapur[1]*, Fatima Sanjeri Dasankoppa[1], N.G.Nangundaswamy[2], Arunkumar G R[3]**

1 KLES College of Pharmacy, Vidyanagar, Hubli-31, Karnataka, India.

2 Dept. of Pharmaceutics, Government College of Pharmacy, Bangalore, Karnataka, India.

3 Fenny pharmacy, New Jersey, USA.

## ABSTRACT

Guar gum is a galactomannan polysaccharide obtained from the dried ripe seeds of *Cyamopsis tetragonolobus*. The objective of the present study was to derivatise guar gum to SCEG and to overcome limitations of guar gum *viz*, susceptible to microbial contamination, fall in viscosity on storage and to form a clear aqueous dispersion without imparting color to the formulation. The semisyntheic derivative of SCEG obtained by alcoholic alkali suspension method of guar gum was tried by applying optimization technique ($3^2$ factorial design) by altering the 2-chloropropionic acid:guar gum, percentage w/v ratio NaOH and temperature of the reaction mixture. The optimized polymer obtained from the various trials was subjected to physical, chemical and spectral characterization. Characterization revealed that derivatization of the guar gum to sodium carboxy ethyl guar. The derivatised polymer exhibited high stability at all ranges of temperature ($5^0$C, $25^0$C, $37^0$C and $45^0$C), controlled rate of hydration, pseudoplastic flow pattern and less susceptibility to microbial contamination. Sodium carboxy ethyl guar solution is more controllable than gaur gum with regard to its thickening, viscosity building, suspending, film forming and excipent in the matrix tablets. The valid application of optimization technique was found to be highly productive in achieving an effective semisynthetic derivative meeting the ideal requirements.

**Key words:** Sodium carboxy ethyl guar (SCEG), synthesis, optimization technique ($3^2$ factorial design), characterization.

**Corresponding Author**: Hasanpasha .N Sholapur[1]*, KLES College of Pharmacy, Vidyanagar, Hubli-31, Karnataka,India. Tel.: +91 (0836)2373174, Fax:+91 0836-2371694, Email: hasanpashas@gmail.com

## Running Title

Application of optimization technique in synthesis and characterization of sodium carboxy ethyl guar

## INTRODUCTION

Guar gum is galactomann polysaccharide with high swellability, less toxicity and economical. The earlier attempts on the synthesis of various guar derivatives has suggests that guar derivatives are useful as an excipient or binding, disintegrating, gel forming and

film forming agents[1-4]. However, its pharmaceutical application is limited because of its uncontrollable rate of hydration, fall in viscosity on storage and high susceptibility to microbial contamination[5]. Moreover, guar gum produces translucent or turbid solution in the liquid oral dosage forms. Hence to overcome these lacunas the present is aimed to develop sodium carboxy ethyl guar. Optimization technique ($3^2$ factorial) was applied by subjecting the data to design expert software to obtain the desired attributes of the synthesized polymer.

## MATERIALS AND METHODS

Guar gum was obtained from Madhuri Agencies, Mumbai. The chemicals 2-chloropropionic acid (Lancaster, USA), sodium hydroxide (Qualigens Fine Chemicals Pvt. Ltd. India)), L.R. grade glacial acetic acid (Qualigens Fine Chemicals Pvt. Ltd. India), isopropyl alcohol (HPLC grade, Qualigens Fine Chemicals Pvt. Ltd. India) and methanol (Qualigens Fine Chemicals Pvt. Ltd. India) were used for synthesis. Spectral characterization was carried out using FTIR (8400, Shimadzu, Japan), NMR (Shimadzu, Japan), optical microscopy with camera attachment (Olympus-SXZ 12, Japan).

### Study Design

Sodium carboxy ethyl guar was synthesized by following the principles adopted for the preparation of guar derivatives (sodium carboxy methyl guar) [1-2]. Derivatives of guar gum were prepared by applying optimization ($3^2$ factorial design) using different ratios of guar gum: 2- chloropropionic acid, varying sodium hydroxide concentration and temperature[6]. The derivatives were subjected to rheological studies, sodium content and FTIR spectral analysis. The data obtained from these analyses were subjected to computer aided design using design expert software version 6.0 to get the derivative with desired attributes.

### Alcoholic Alkali Suspension Method[1]

Guar gum (30g) was charged to a three necked flask fitted with a thermometer, funnel and a mechanical stirrer and dispersed in ice-cold sodium hydroxide. The dispersed gum was allowed to stand in ice-cold condition (5-7$^o$C) for 30 min. The temperature of the reaction mixture was gradually increased to 15$^o$ C, 2-chloropropionic acid was added in increment of 1 ml each, with vigorous stirring. The reaction mixture was treated with isopropyl alcohol (200 ml) and the temperature was gradually raised to 75 $^o$C for 1 h. Suspension form of the reaction mixture was cooled and neutralized to pH 7 using glacial acetic acid. The resulting product was purified using methanol: water (80:20), dried at 45 $^o$C for 5-6 h, subdivided and sieved (mesh # 52) and subjected to preliminary characterization techniques.

Selection of the optimized polymer: $3^2$ factorial design was applied in three factors and employing two levels.

Factor A- 2-Chloropropionic acid: Guar gum

Factor B- Sodium Hydroxide 35% w/v and 50% w/v solutions

Factor C – Temperature, 65$^0$C and 75$^0$ C

Two levels +1 and -1(as shown in Table 1 and 2 respectively).

The derivatives obtained from the different runs were subjected to preliminary characterization techniques based on viscosity, sodium content and FTIR peaks.

**Table 1: Actual and Coded Values of the Factors**

| Factor | Actual values | | Coded values | |
|---|---|---|---|---|
| | Low level | High level | Low level | High level |
| Factor A<br>2-Chloropropionic acid: Guar gum | 0.5:1 | 1:1 | -1 | +1 |
| Factor B<br>% w/v NaOH | 35 % w/v | 50% w/v | -1 | +1 |
| Factor C<br>Temperature | 65° C | 75° C | -1 | +1 |

**Table 2: Runs Designed In Coded Values and Actual Values**

| | | Coded values | | | Actual values | | | Preliminary Characterization | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **STD** | **Run** | **Factor A** | **Factor B** | **Factor C** | **Factor A** | **Factor B** | **Factor C** | **Viscosity** | **Sodium Content** | **FTIR Peaks** |
| 5 | 1 | -1 | -1 | 1 | 0.5:1 | 35 | 75 | 23.05 | 10.51 | Characteristics IR peaks at 1651 $cm^{-1}$ and 411$cm^{-1}$ for carboxylate ion. |
| 3 | 2 | -1 | 1 | -1 | 0.5:1 | 50 | 65 | 42.11 | 11.99 | |
| 4 | 3 | 1 | 1 | -1 | 1:1 | 50 | 65 | 30.84 | 10.20 | |
| 1 | 4 | -1 | -1 | -1 | 0.5:1 | 35 | 65 | 22.38 | 13.56 | |
| 8 | 5 | 1 | 1 | 1 | 1:1 | 50 | 75 | 25.01 | 11.41 | |
| 6 | 6 | 1 | -1 | 1 | 1:1 | 35 | 75 | 24.75 | 10.71 | |
| 2 | 7 | 1 | -1 | -1 | 1:1 | 35 | 65 | 23.65 | 11.00 | |
| 7 | 8 | -1 | 1 | 1 | 0.5:1 | 50 | 75 | 48.83 | 12.24 | |
| 9 | 9 | -1 | 1 | -1 | 0.5:1 | 50 | 65 | 35.87 | 11.42 | |

### Viscosity[7]

The viscosity of 1% w/v SCEG was determined by using Ostwald's viscometer. The viscosity was calculated based on the density and the time taken for the polymeric dispersion to flow though the viscometer.

### Sodium Content[8]

The assay for sodium content was carried out by non aqueous titration method. 500 mg of the synthesized derivative was dispersed in glacial acetic acid and to this 2 ml of acetic anhydride was added, the mixture was heated on a water bath for a period of 2 h, cooled to room temperature and was titrated against 0.1N perchloric acid using crystal violet as indicator. Each ml of 0.1N perchloric acid ≈0.003 g of sodium.

### IR spectral analysis

The IR spectra of 2 chloropropionic acid (liquid sampling on NaCl disc), guar gum and SCEG from the 9 runs (IR grade potassium chloride for pellet formation) was obtained using Shimadzu 8400 FTIR spectrophotometer.

The data obtained after carrying different runs were analyzed using design expert stat ease 6.0 version software and the polymer with optimum characteristics was selected.

The formula for the optimized derivative (OPT-derivative) is shown in table 3.

The OPT-derivative was synthesized in the similar manner as of the designed runs and subjected to spectral, physical and chemical characterization.

**Table 3: Formula for the Optimized Formulation**

| Factor A | Factor B | Factor C | SCEG | | Desirability |
|---|---|---|---|---|---|
| | | | Viscosity | Sodium content | |
| 1 | 1 | 1 | 48.83 cps | 12.63% | 0.9998 |

**Spectral characterization**

**NMR studies**

The NMR studies (Shimadzu, Japan) were carried out to confirm the introduction of the ethyl group. The NMR spectrum of the authentic sample guar gum and SCEG were taken at 400 $MH_2$ 'H' NMR spectrometer using $D_2O$ as the solvent (Fig. 1 &2).

**X-ray diffractogram**

The X-ray diffraction studies were carried out to study the effect of the derivatization on the amorphous nature of guar gum. The x-ray powder diffractogram was taken for guar gum and SCEG using $CuK_2$ radiation (Fig. 3 & 4).

**Differential scanning calorimetry (DSC)**

The DSC of gaur gum indicated a single peak at 86.33 and SCEG at $57^0$ C and $82^0$C shift in the absorption peak indicated the derivatization of guar gum (Fig. 5 & 6).

**Accelerated stability studies**

Accelerated stability testing has been carried out to study the effect of heat on the viscosity of 1% w/v dispersion of SCEG. 1% w/v guar gum dispersion were selected as it was found to be ideal (Newtonian flow behavior) for assessing the viscosity by using Ostwald's viscometer and Brook field RVT model analog viscometer were used respectively. The polymeric dispersion were prepared and the bottles were sealed off using rubber stopper and stored at 5 $^oC$, 25 $^oC$, 37 $^oC$ and 45 $^oC$ and the viscosity studies were carried out for seven weeks. The results were tabulated in the Table 4 and 5.

**Table 4: Effect of the temperature on the viscosity of 1% w/v aqueous SCEG dispersion using Ostwald's viscometer**

| Temperature | Viscosity in centipoises at the end of weekly intervals | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 5$^oC$ | 48.00 | 45.24 | 45.03 | 44.13 | 42.15 | 42.05 | 42.01 | 41.23 |
| 25 $^oC$ | 48.00 | 47.66 | 47.65 | 47.01 | 47.68 | 47.17 | 47.06 | 47.01 |
| 37 $^oC$ | 48.00 | 47.26 | 47.24 | 47.00 | 47.70 | 46.76 | 46.16 | 46.10 |
| 45 $^oC$ | 48.00 | 48.14 | 48.09 | 47.70 | 46.93 | 46.33 | 46.00 | 45.85 |

**Table 5: Effect of the temperature on the viscosity of 1% w/v aqueous guar gum dispersion using Brookfield, RVT analog viscometer**

| Temperature | Viscosity in at the end of weekly intervals(cps) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 5$^{o}$C | 16000 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 25 $^{o}$C | 16000 | 1500 | 950 | 500 | 0 | 0 | 0 | 0 |
| 37 $^{o}$C | 16000 | 1400 | 700 | 0 | 0 | 0 | 0 | 0 |
| 45 $^{o}$C | 16000 | 1350 | 400 | 0 | 0 | 0 | 0 | 0 |

**Rheological data**[2]

Rheograms of the guar gum 1% w/v using spindle no 4, sodium carboxy methyl cellulose 2% w/v, and SCEG 4% w/v using spindle no 2 were plotted by using the data obtained from Brookfield viscometer RVT model.

**RESULTS**

The data obtained by subjecting the runs to preliminary characterization techniques are as follows**,** sodium content of the runs was found to be in the range 9.5 to 13.56 % (as shown in Table 2). Prominent peaks were observed at 1651 $cm^{-1}$ and 1411 $cm^{-1}$, indicating the presence of the carboxylate ion peak, which was absent in the guar gum. The viscosity of 1% w/v SCEG of all the runs was determined using Ostwald's viscometer. The viscosity was found to be in the range of 22 - 48.8 cps (as shown in Table 2). The data were analyzed using design expert software version 6.0 and optimized SCEG was obtained. The SCEG which was yellow in color, was found to be hydrophilic in nature. Viscosity of 2% w/v solution was 100 cps and specific gravity was found to be 2.063 g/cc, percentage of moisture was 12-13%, pH of 1% w/v solution of SCEG was between 6.5 and sodium content was in the range of 10-12%. NMR spectra indicated strong peaks at δ-1.5 and δ-*2,* which indicated the presence of ethyl substitution, which was absent in guar gum spectra. There was broad chemical shift in the spectra of guar gum due to the numerous hydroxyl groups, which was denoted by a shift at δ-3 to 4.5. After acylation, the protons of ethyl group shifted downwards (Fig. 1 & 2).

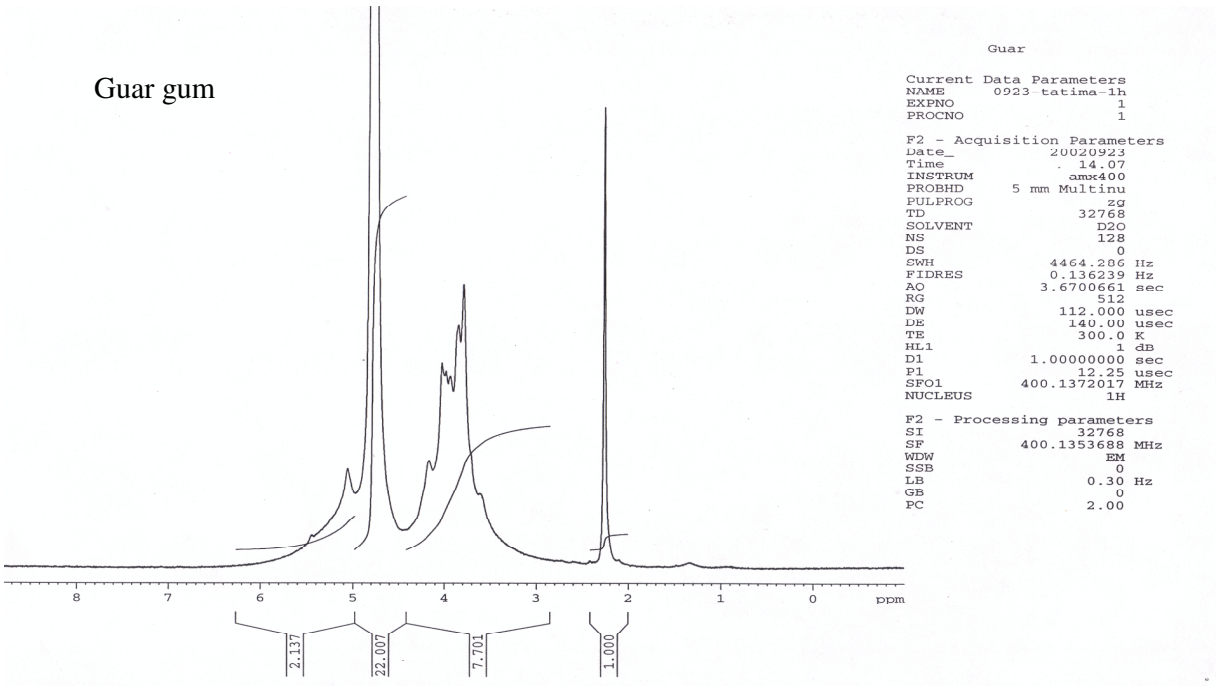


**Figure 1. NMR spectra of guar gum**

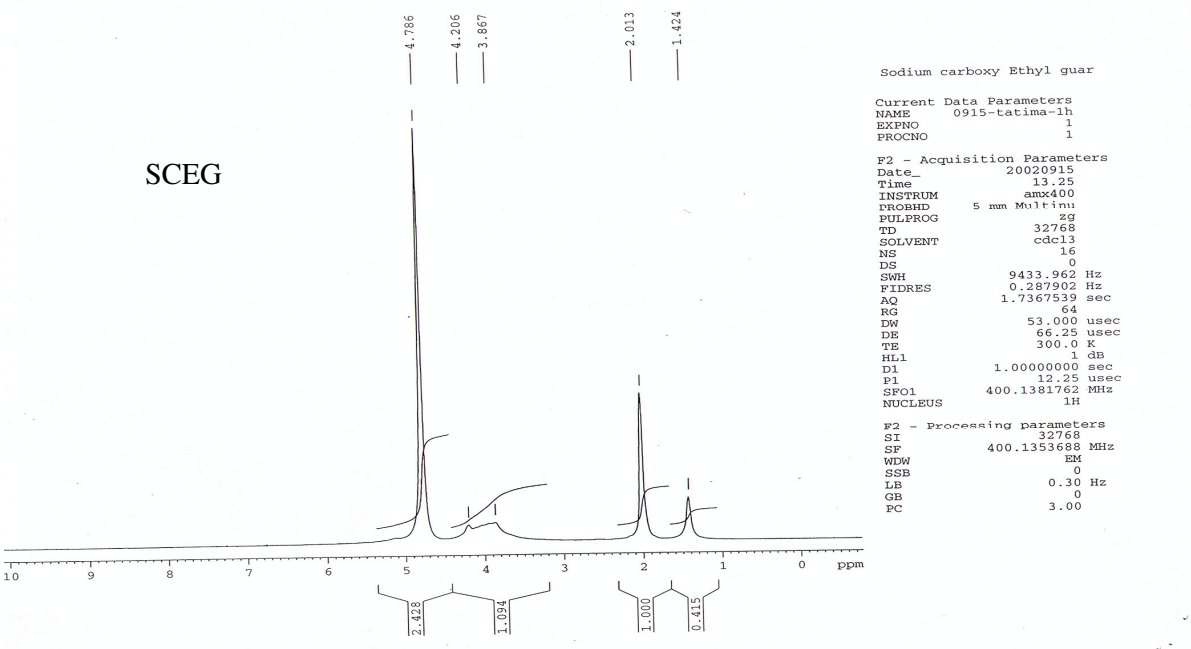


**Figure 2. NMR spectra of SCEG**

The X ray diffractogram of guar gum indicated no peaks, which pointed towards its amorphous nature. OPT derivative of SCEG showed prominent peaks at 2θ = 8,9,31.78 and 19.19 indicating its existence is crystalline (Fig. 3 & 4). Hence it confirms dervitization of guar gum to SCEG.

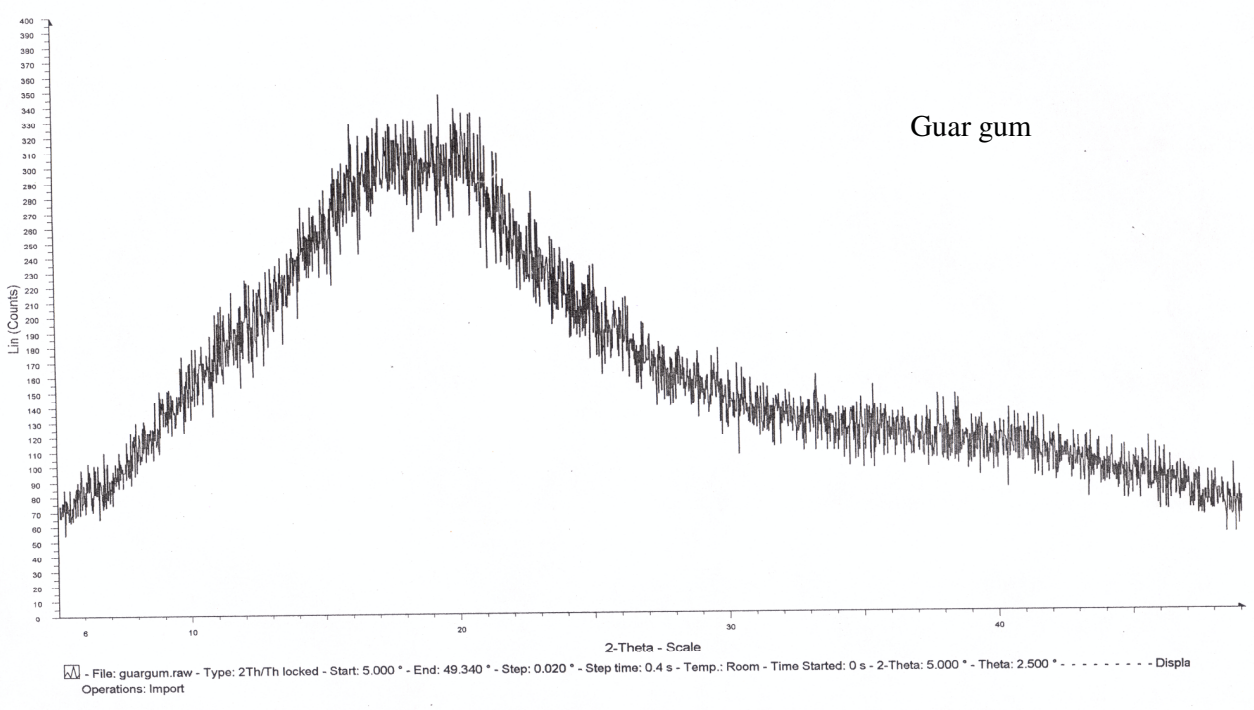


**Figure 3: X ray diffractogram of guar gum**

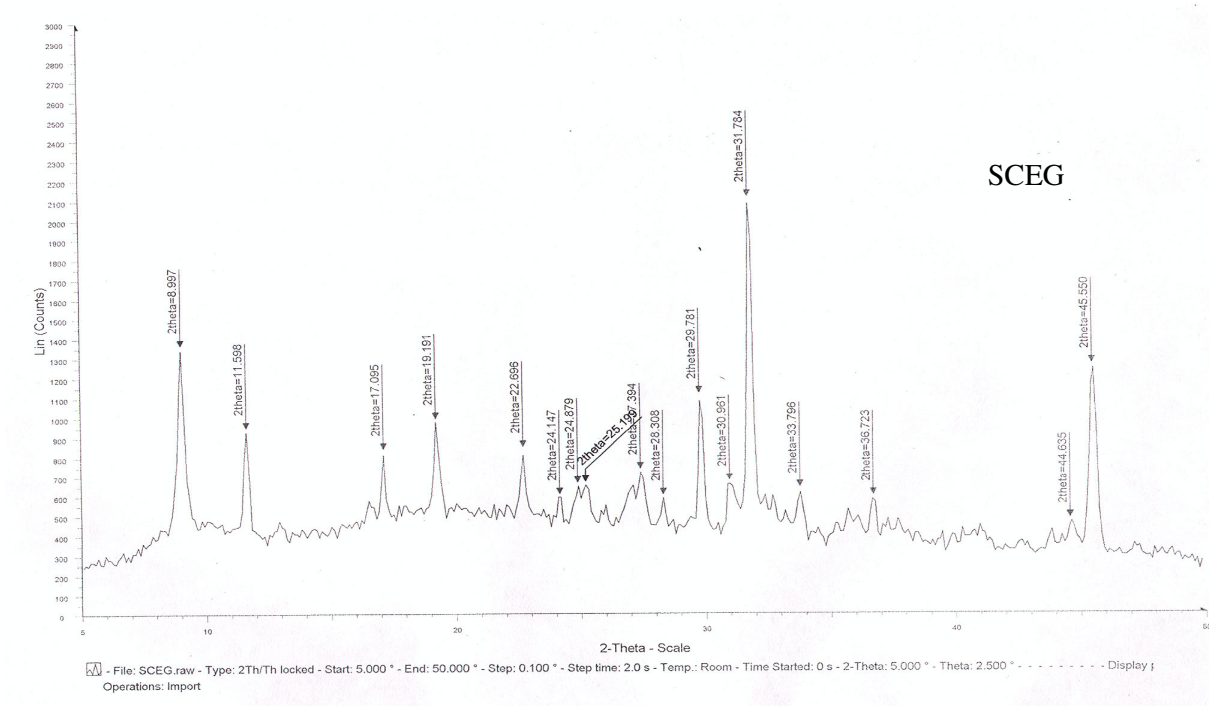


**Figure 4: X ray diffractogram of SCEG**

The DSC of guar gum indicated a single isotherm at 86.33 °C and SCEG at 57 °C and 82 °C. The shift in the absorption peak indicated derivatization of guar gum to SCEG (Fig. 5 & 6).

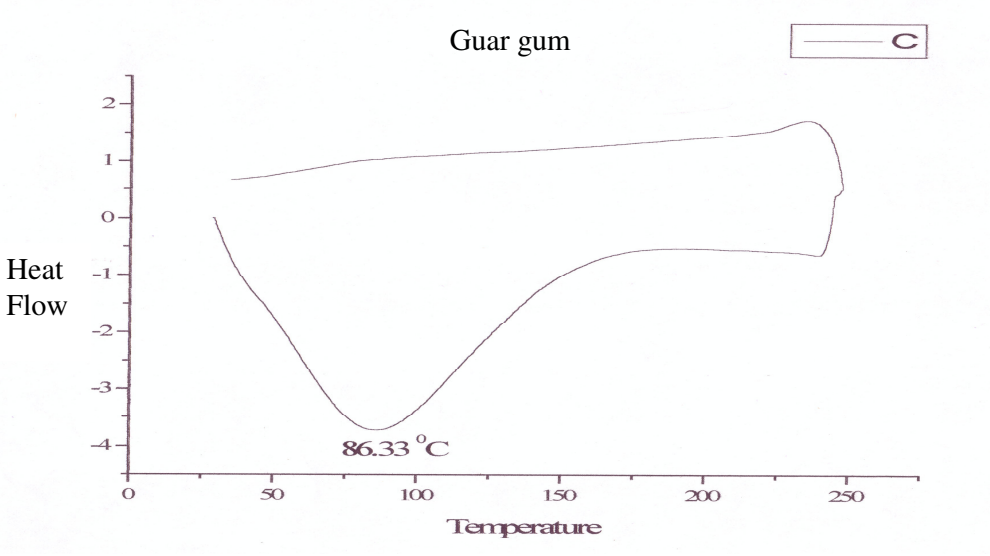


**Figure 5: DSC thermogram of guar gum**

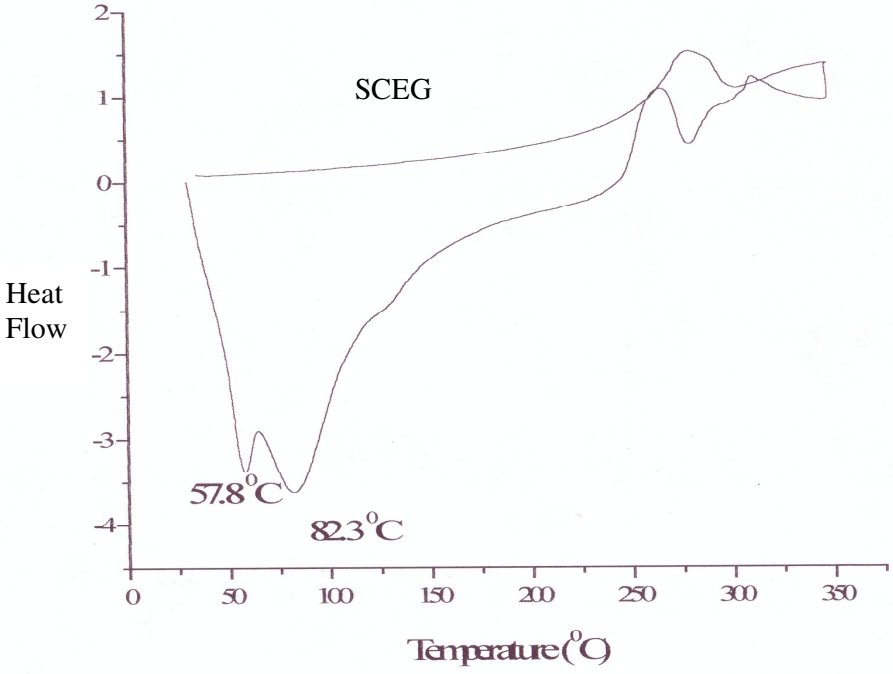


**Figure 6: DSC thermogram SCEG**

The data obtained from accelerated stability studies indicated that viscosity of the guar gum decreased with increase in temperature and at 5 $^{o}$C drop in viscosity was observed at the end of first week itself. The degradation of the polymer leads to decrease in viscosity at higher temperatures. In case of SCEG, the viscosity fairly remained constant at all the temperatures, even after seven weeks. The rheological data indicated that the flow pattern of SCEG was comparable with that of sodium carboxy methylcellulose and was pseudoplastic in nature (Fig. 7).

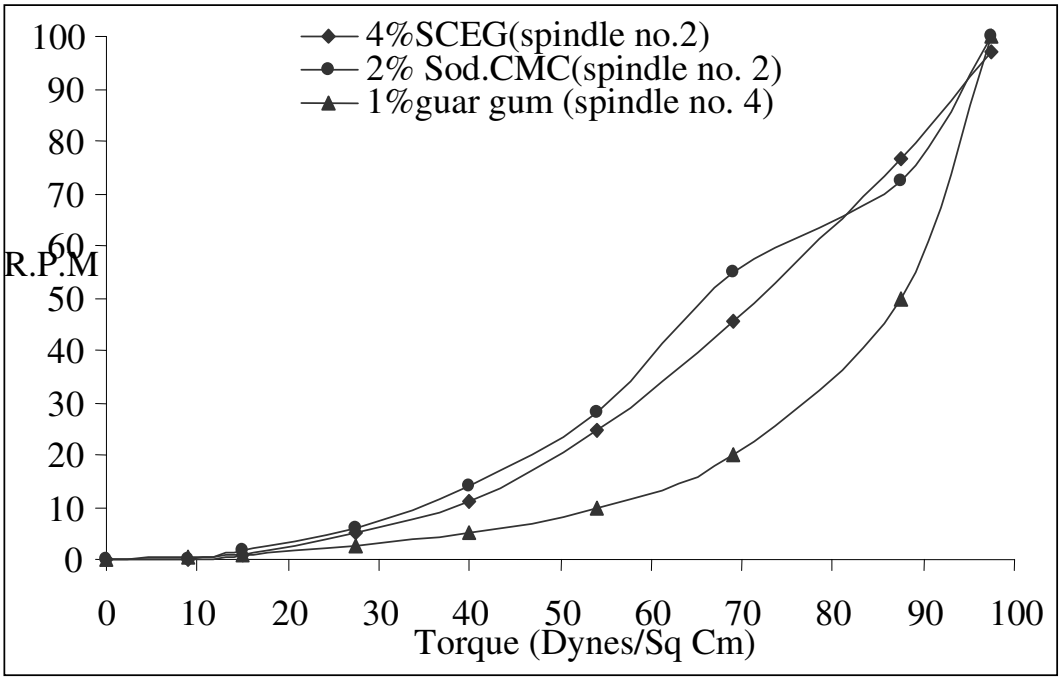


**Figure 7: Rheological Data Of 1% Guar Gum, 2% SOD.CMC and 4%SCEG**

## DISCUSSION

The synthesis of the SCEG by alcoholic alkali suspension slurry method using isopropyl alcohol as the stabilizing liquid was appropriate method of derivatising guar gum. The OPT derivative gave sodium content in the range of 12-13%. The I.R, NMR, DSC, X-ray diffraction patterns indicated the derivatisation of the guar gum to SCEG. The rheological behavior of SCEG displayed pseudoplastic flow pattern. It appears from the study that SCEG dispersion may be more controllable than guar gum with regard to its thickening, suspending, viscosity building, film forming and gel forming property. A 4% w/v SCEG aqueous dispersion produces a clear transparent film.

## CONCLUSION

From the above observation it is concluded that SCEG is a promising derivative for further studies in exploring its pharmaceutical application as thickening, suspending, viscosity building, film forming and gelling agent.

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