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ISSN: 0975-7538
Research Article

Preparation and characterization of Sucralfate suspension containing different suspending agents for improving suspendability

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ABSTRACT

The invention is an aqueous suspension of Sucralfate a basic aluminium salt of sulfated sucrose; and it polymerizes at pH<4 by cross linking of molecules, assuming a sticky gel-like consistency. It is ulcer protective agent and it preferentially and strongly adheres to ulcer base, especially duodenal ulcer; has been seen endoscopically to remain there for ~6 hours and it repairs the effected mucus. The main aim of the work is to prepare sucralfate containing finished medicaments in the form of suspension and the preparation is stable for prolonged period and made to prevent sedimentation of the suspended particles, by using suitable suspending agents such as xanthan gum, (0.05%-0.5%) sodium carboxy methyl cellulose, (1%-2.5%) sodium alginate (1%-2.5%) in different concentrations. Characterization test were carried out on Sucralfate suspension Viscosity, PH, Sedimentation volume. The suspending ability of all the suspending agents was found to be in order Sodiumcarboxy methylcellulose>Xanthan gum> carboxy methylcellulose. From the results suggest that high viscosity of Sodium carboxy methylcellulose it can also serves as good thickening agent in pharmaceutical industry.

Keywords: Suspension; Sucralfate; Xanthangum; Carboxymethyl Cellulose; Sodium carboxymethyl cellulose; Sedimentation volume

INTRODUCTION

An oral pharmaceutical suspension has long been one of the most favorable dosage forms for pediatric patients or patients difficulty in swallowing solid dosage forms (CA. Howard 1981) The liquid dosage form is preferred because of ease of swallowing and flexibility in the administration of doses and to increase bioavailability. Sucralfate is a non-absorbable, basic aluminum salt of a Sulphated disaccharide which has proven effective in the treatment of gastric and duodenal ulcers. (I.C. Valencia *et al* 2001, J.R. Mekkes *et al* 2003, S.T. Sonis 1985) Sucralfate forms polyvalent bridges to the positively charged proteins present in the mucosa and form pasta like, adhesive substances; a protective barrier is thus formed against further mucosal damage. (D.E Peterson *et al* 1982) The binding of sucralfate is most effective at low pH but may still occur at higher pH 3 and 5.

Sucralfate suspension has gained increased importance not just for the delivery of anti ulcer drugs for the treatment of ulcerates, gastroenteritis but also cytoprotective action and also used in the treatment of cancer chemotherapy and Radiation induced toxicity. (R.Nagashima1981, R.A Valdes Olmos *et al*1995) How ever there are certain beneficial areas, most especially the treatment of upper gastroesophageal disorders (e.g. gastroesophageal reflux, heartburns, dyspepsia, and esophageal cancer) where prolonged drug retention within esophageal region is often desired. (R.M. Williams *et al* 1987, R.C Orlando)

In addition Sucralfate have been co- administered with the H_2 – receptor antagonists (Cimetidine, Ranitidine) in the treatment of gastric and duodenal ulcers and also have a slight buffering effect on the acidity of stomach and also absorb the bile salts as well as inhibit the action of gastric pepsin. (I.N Marks *et al*1980, F Martin *et al*1982, I.N.Marks1982) Further more it was reported that Sucralfate had no significant effect on the bioavailability and elimination of Ketoprofen, indomethacin or naproxen (G. Caille *et al1987*) and a single dose of sucralfate altered the rate neither nor extent of theophylline absorption to a clinically important extent. (K.A. Cantral *et al*1988 Formulations containing sucralfate have higher to usually been employed only in the form of solid administration forms, such as tablets, granules or powders. However, liquid formulations, for example in the form of suspensions, would be advantageous for the particular mode of action of sucralfate, especially in view of a rapid and complete lining of the mucous membranes in the digestive tract.

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Received on: 02-05-2014
Revised on: 07-08-2014
Accepted on: 09-08-2014

Table 1: Formulation of Sucralfate Suspension table

Ingredients	Sucralfate (mg)	Carboxy methyl Cellulose (mg)	Na CMC (mg)	Xanthan gum (mg)	Citric acid (mg)	Sorbital	Flavour	Water (ml)
F1	500	5	-	-	15	35	q.s	5
F2	500	7.5	-	-	15	35	q.s	5
F3	500	10	-	-	15	35	q.s	5
F4	500	12.5	-	-	15	35	q.s	5
F5	500	15	-	-	15	35	q.s	5
F6	500	-	5	-	15	35	q.s	5
F7	500	-	7.5	-	15	35	q.s	5
F8	500	-	10	-	15	35	q.s	5
F9	500	-	12.5	-	15	35	q.s	5
F10	500	-	15	-	15	35	q.s	5
F11	500	-	-	0.2.5	15	35	q.s	5
F12	500	-	-	0.5	15	35	q.s	5
F13	500	-	-	1.5	15	35	q.s	5
F14	500	-	-	2	15	35	q.s	5
F15	500	-	-	2.5	15	35	q.s	5

Note: 5mg of Propyl paraben and Methyl paraben were taken in all formulations

The main aim of the work is to prepare sucralfate containing finished medicaments in the form of suspension and the preparation is stable for prolonged period and made to prevent sedimentation of the suspended particles, by using suitable suspending agents such as xanthan gum, sodium Carboxy methyl cellulose, Sodium Carboxy methyl Cellulose in different concentrations.

MATERIALS

Sucralfate raw material was Procured as gift sample from Yarrow chemicals Pvt.Ltd Mumbai, india. xanthan gum, Sodium carboxy methylcellulose, were obtain as gift samples from Cheminnova Remedies Pvt.Ltd, Citric acid, D-sorbital, Propylparaben, MethylParaben were purchased from S.D Fine Chemicals Mumbai. Water used in the experiments was deionized filtered (Milli-QAcademic, Millipore)

Preparation of Sucralfate suspension

Sucralfate suspension containing 500 mg/5ml were prepare using (0.1-0.5% xanthangum), (1-2.5% Carboxy methyl cellulose), (1-2.5 sodium carboxymethyl cellulose) . Mucillages of the gums were prepared by hydration using part of the vehicle. The solid components of the formulation were finely triturated with the aid of mortar and pestle. The suspending agents (xanthangum, carboxy methyl cellulose, sodium carboxymethylcellulose) was added to sucralfate powder dissolved in water and triturated until homogeneous slurry was obtained. Methyl paraben, propylparaben was used as the preservative and saccharin (1%) was used as sweetener.

Preformulation studies

Compatibility studies

A proper design and formulation of a dosage form requires considerations of the physical, chemical and biological characteristics of both drug and excipients used in fabrication of the product. Compatibility must be established between the active ingredient and other excipients to produce a stable, efficacious, attractive and safe product. If the excipient (s) are new and if no previous literature regarding the use of that particular excipient with an active ingredient is available, then compatibility studies are of paramount importance. Hence, before producing the actual formulation, compatibility of sucralfate with different polymers and other excipients was tested using the Fourier Transform Infrared Spectroscopy (FTIR) technique.

Fourier Transform Infrared Spectroscopy (FTIR)

In order to check the integrity (Compatibility) of drug in the formulation, FTIR spectra of the formulations along with the drug and other excipients were obtained and compared using Bruker FT-IR ALPHA spectrophotometer. In the present study, Potassium bromide (KBr) pellet method was employed. The samples were thoroughly blended with dry powdered potassium bromide crystals. The mixture was compressed to form a disc (H.G. Naik *et al* 1988) . The disc was placed in the spectrophotomet+er and the spectrum was recorded. The FTIR spectra of the formulations were compared with the FTIR spectra of the pure drug and the polymers. The FTIR spectra of pure drug, polymer and in combination are presented in Figure 4-6.

Differential scanning calorimetry (DSC) studies

The pure drug and optimized formulation were subjected to differential scanning calorimeter equipped with an intra cooler (NETZSCH, Japan.) . Indium/zinc standards were used to calibrate the DSC temperature and enthalpy scale. The sample were sealed in aluminum pans and heated at a constant rate 10°C/min over a temperature range of 50-400°C. An inert atmosphere

Table 2: Physical characterization of Sucralfate Suspension

Formulation Code	pH	Viscosity(cps)	Flow rate (ml S-1)	Density (gm/cc)
F1	4.76	200	1.92	1.102
F2	5.12	210	1.75	1.195
F3	5.76	225	1.6	1.203
F4	6.24	238	1.5	1.0294
F5	6.74	250	1.2	1.3025
F6	4.02	110	1.63	1.2062
F7	4.99	128	1.53	1.3074
F8	5.66	136	1.42	1.3097
F9	6.03	148	1.2	1.4132
F10	6.12	180	0.95	1.4813
F11	5.1	193	1.84	1.2702
F12	5.8	204	1.65	1.3201
F13	6.2	215	1.51	1.3921
F14	6.7	222	1.32	1.4256
F15	7.2	238	1.25	1.4963

Table 3: Sedimentation volume (HU/Ho) of F1-F5 formulation

Formulation Code	Conc. of Carboxy methyl cellulose	Sedimentation Volume (Time in days)						
		0	2	4	6	8	10	14
F1	1	1	0.82	0.77	0.7	0.55	0.5	0.39
F2	1.5	1	0.88	0.81	0.72	0.6	0.53	0.43
F3	1.75	1	0.9	0.85	0.76	0.69	0.59	0.47
F4	2	1	0.92	0.9	0.82	0.75	0.68	0.56
F5	2.5	1	0.95	0.93	0.88	0.84	0.77	0.59

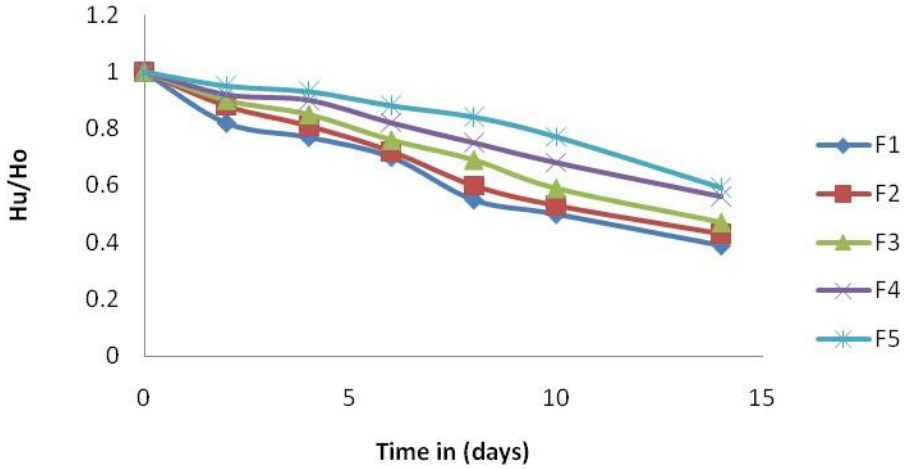

Figure 1: Sedimentation volume (Hu/Ho) vs Time in days of F1-F6 formulation

was maintained by purging nitrogen gas at a flow rate of 50 ml/min.

Formulation of sucralfate suspension

Physical Stability studies of sucralfate suspension

All prepared Suspensions were kept 30 and 45° C and evaluated for their physical and chemical properties including pH, Density, Sedimentation volume, viscosity.

pH: It is another important parameter for the suspension stability. The pH determination study was carried out by using digital pH meter. The pH meter was calibrated and the sample of suspension was taken and pH was measured at room temperature.

Density: Density of the formulated suspension was determined by specific gravity bottle. The values are tabulated in table no:2

Sedimentation volume

Sedimentation volume of suspension was determined by transferred the prepared suspension in to 50 ml measuring cylinder and make up to final volume. The cylinder was then inverted 10 times to ensure complete mixing and place in a constant temperature water bath at 25 to 0.1°C.no wet ability problems were encountered in the preparation of the suspension. The sedimentation volume can be expressed as the ratio of

Table 4: Sedimentation volume (HU/Ho) of F6-F10 formulation

Formulation code	Conc. of NaCMC	Sedimentation Volume (Time in days)						
		0	2	4	6	8	10	14
F6	1	1	0.84	0.8	0.77	0.66	0.56	0.46
F7	1.5	1	0.9	0.84	0.8	0.64	0.58	0.49
F8	1.75	1	0.94	0.88	0.82	0.72	0.64	0.56
F9	2.0	1	0.96	0.94	0.88	0.79	0.7	0.62
F10	2.5	1	0.99	0.96	0.92	0.86	0.8	0.7

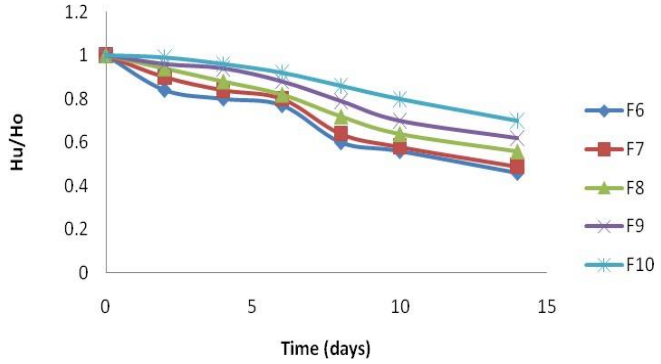

Figure 2: Sedimentation volume (Hu/Ho) vs Time in days of F6-F10 formulation

Table 5: Sedimentation volume (HU/Ho) of F11-F15 formulation

S.No.	Formulation code	Conc. of xantham gum	Sedimentation Volume (Time in days)						
			0	2	4	6	8	10	14
1	F11	0.05	1	0.87	0.77	0.66	0.59	0.44	0.32
2	F12	0.1	1	0.85	0.79	0.68	0.58	0.48	0.36
3	F13	0.2	1	0.88	0.82	0.74	0.66	0.54	0.42
4	F14	0.3	1	0.9	0.85	0.8	0.72	0.62	0.48
5	F15	0.4	1	0.92	0.9	0.84	0.8	0.68	0.52

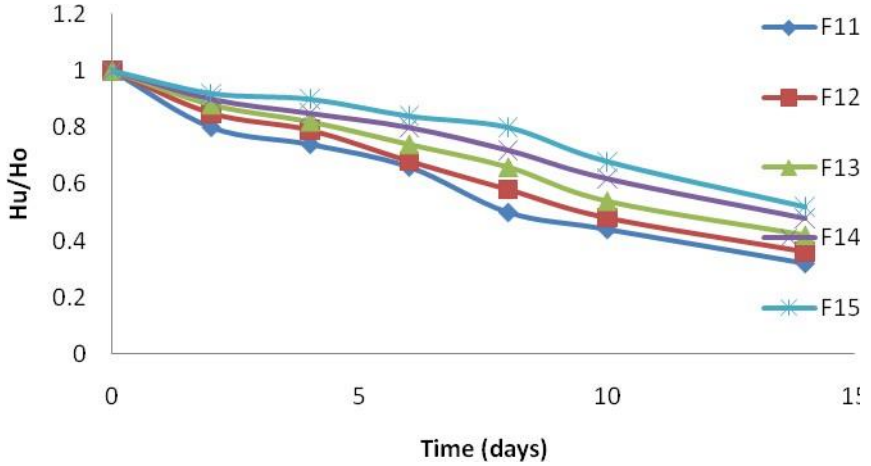

Figure 3: Sedimentation volume (Hu/Ho) vs Time in days of F11-F15 formulation

the final volume of sediment to original volume of the suspension before settling (K. S. E. Su et al 1984)

Flow rate

The time required for each suspension sample to flow through a 10ml pipette was determined and the apparent viscosity (ηα in mls-1) was calculated using the equation

Flow rate = ηα = Volume of pipette (ml) / Flow time in (s)

Viscosity

The viscosity of the prepared formulations was determined at different angular velocities at 25^0 c using a rotary viscometer (DV-III, Brookfield, USA). The rotation speed was 20rpm, with spin 18#. The average of two readings was used to calculate the viscosity.

RESULTS AND DISCUSSION

Physical stability of Sucralfate Suspension

FTIR spectra of Sucralfate represented in graph 3483.36 cm^{-1} aliphatic O-H stretching, 1641.68 cm^{-1}

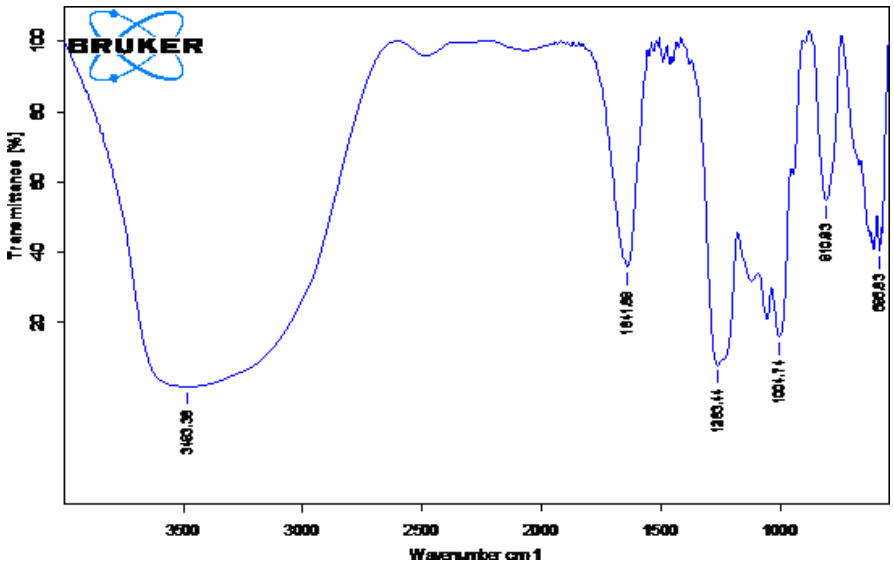

Figure 4: FTIR spectrum of Sucralfate

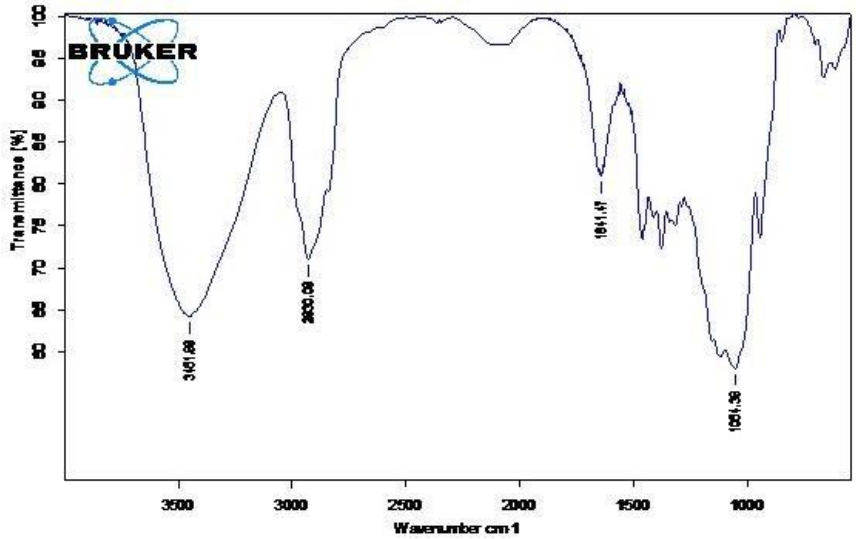

Figure 5: FTIR spectrum of Sodium Carboxy methyl Cellulose

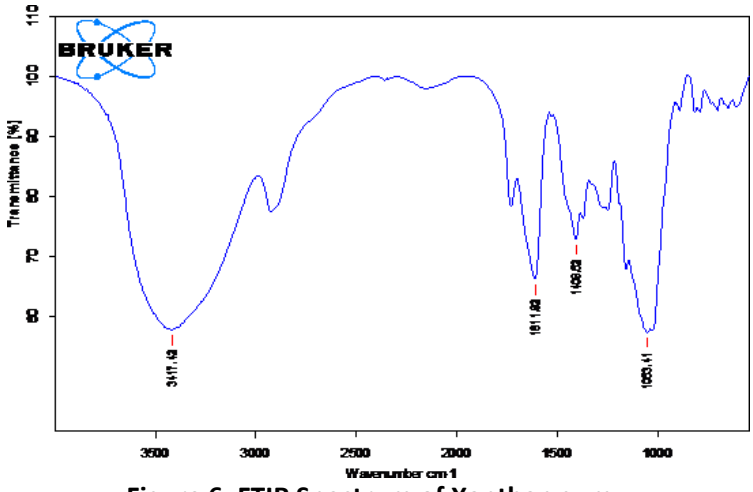

Figure 6: FTIR Spectrum of Xanthan gum

shows c-o stretching, 1263.44 cm^{-1} indicates C-C starching etching in pyran ring, 1004.74 cm^{-1} shows c-c stretching in furan and 810.93 cm^{-1} shows c-c bending in monosubstituted ring.

In sodium carboxy methyl cellulose and xanthan gum shows the prominent peaks are observed at 3483.36 cm^{-1}, 1641.68 cm^{-1}, 1263.44 cm^{-1}, 1007.74 cm^{-1}, 810.93 cm^{-1} indicates the presence of aliphatic O-H stretching,

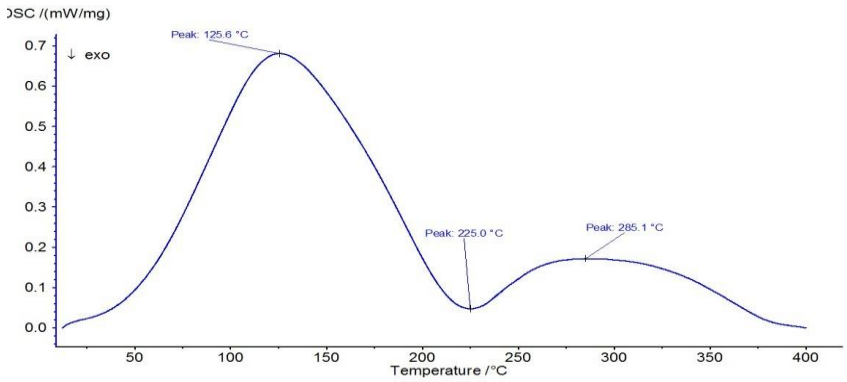

Figure 7: DSC thermo gram of Sucralfate

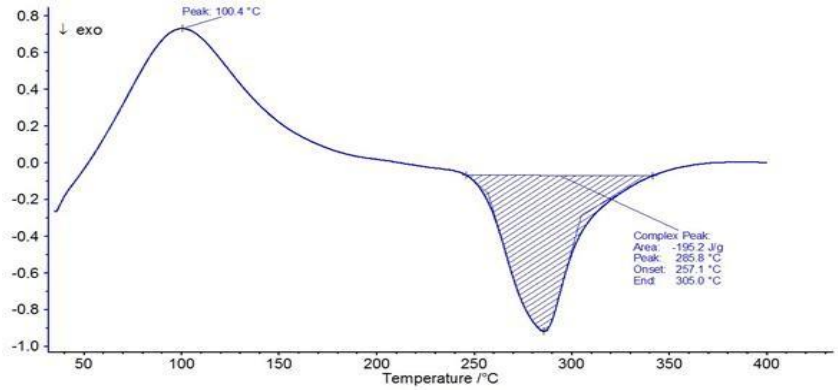

Figure 8: DSC thermo gram of Xanthan gum

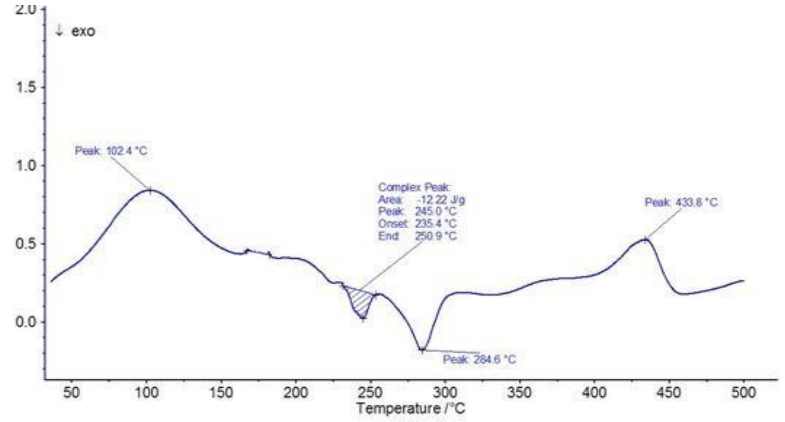

Figure 9: DSC thermo gram of Sucralfate mixture

C-O in pyrimidine ring, C-C stretching in pyramidine ring, C-C stretching in furan, C-C bending in monosubstituted ring. (Figure 4 to Figure 6). From the above results stated that there is no shift in the peaks of these compounds and are compatible.

Differential scanning calorimeter performed for Sucralfate thermo gram showing endothermic peak in graph 7 between 50-120°C which may be due to evaporation of residual water left in the sucralfate and exothermic decomposition was seen in between 200-250°C. For Xanthan gum in DSC thermogram shows the onset of melting peak was observed at 285°C and it shows good thermal stability up to 300°C is seen in graph 8. In sucralfate suspension evaluation using thermal analysis a strong endothermic peak is present between 200-250°C and 284°C was observed indicating the presence of sucralfate suspension. The other peak observed at 102.4°C may be due to presence of moisture in graph 9.

CONCLUSION

A Sucralfate suspension formulation was prepared in batches containing carboxy methylcellulose, xanthan gum, and sodium carboxy methyl cellulose as suspending agents. The preparations were assessed based on the sedimentation volume, viscosity, flow rate .The results shows that sedimentation volume, viscosity, are directly proportional to the concentration of suspending agents. The reverse was the case for the flow rate inverse proportionality was observed between the sto-

rage time on one hand and sedimentation volume on other hand**.** The suspending ability of suspend ants as evaluated by the above assessment parameters where in order to sodium carboxy methyl cellulose 2.5% produce suspension of optimal properties.

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