CHAPTER - 4

PRE-FORMULATION

4.1 INTRODUCTION

Pre-formulation science is an essential tool to understand the physicochemical properties of the drug or new formulation. Each drug has intrinsic physical and chemical properties. The understanding of this vital information is critical to formulation scientists to design formulation approaches, evaluate the need for molecular modification etc. These properties provide the framework for the combination of drugs with excipients to manufacture the dosage form (1). This also includes, evaluating kinetic rate profiles at different physiologically relevant conditions, establishing compatibility with other ingredients defining the critical physicochemical parameter of new drug substances (2). Among these properties, drug solubility, partition coefficient, dissolution rate, polymorphic forms, and stability play an important role (3). Tapentadol is a well-known drug for pain management and a good amount of physicochemical information are available in the literature. In the present work, as the aim is to formulate a Solid lipid nanoparticle drug delivery system for Tapentadol,functional excipients were evaluated and limited excipients were screened for compatibility studies.

4.2 EXPERIMENTAL

4.2.1 Materials and Methods

Tapentadol Base (assay 99.8 %) was synthesized from Tapetadol Hydrochloride obtained from Symed labs, India. Glyceryl behenate (Compritrol 888 ATO) was obtained from Gattefosse, Polysorbate 80 was obtained from Seppic, Sucrose was obtained from Pfanstiehl, Gellan gum was obtained from CP Kelco. Other chemicals are obtained from the market and are pharmaceutical or AR grade.

Instruments and equipment

Digital analytical balance (Mettler-Toledo, Switzerland)Sensitivity±0.01mg; vortex mixer (Spinix, India), Morphologi G3SE ID (Raman spectroscopy), Mettler Toledo DSC 60 and shaking incubator were used for the study. All other analytical instruments were of standard grade and used after calibration.

Methods

Different methods are often used for pre-formulation studies. Raman spectroscopy at a laser beam of 795nm was fired to get the spectroscope. Thermal Analysis was carried out

at a scan rate of 10^0C/min at temperatures ranging from 25^0C to 300^0C and inert environment was assured by purging nitrogen gas at 30ml/min flow rate.

4.3 PREFORMULATION

4.3.1 Bulk characterization& Compatibility studies

The powdered Tapentadol base was characterized by assay, impurity profile, residual solvents, thermal properties using differential scanning calorimetry (DSC), and the integrity of the functional groups was confirmed using Fourier transform infrared spectroscopy (FTIR). Solid state was ascertained using Raman spectroscopy and X ray diffractogram.

A) Solid State stability

Drug and excipient (Sucrose, glyceryl behenate) were prepared in 1:1 ratio and kept at room temperature (25 ± 3 ºC). Raman spectroscopy was taken at zero time and after 6 months of the interval to monitor any incompatibility by observing physical changes or any changes in spectral overlays from initial sample.

Both physical states namely solution and solid state was evaluated as it is critical for formulation and process design

B) Solution state stability

The solution state stability of Tapentadol was studied in Saline and aqueous (WFI) at 3 different temperature conditions 2-8°C, 25±2°C/ 60±5% RH and 60°C for 7 days.

Tapentadol hydrochloride was chosen for the solution state stability study, as Tapentadol base solubility is very low in the water.

C) Solid state stability of SLN

For solid state stability, Lyophilized formulation was charged different stability condition 25±2°C/ 60±5% RH and 30±2°C/ 75±5% RH

4.4 RESULTS AND DISCUSSIONS

4.4.1 Bulk characterization

The standard FTIR spectra complies with USP fingerprint

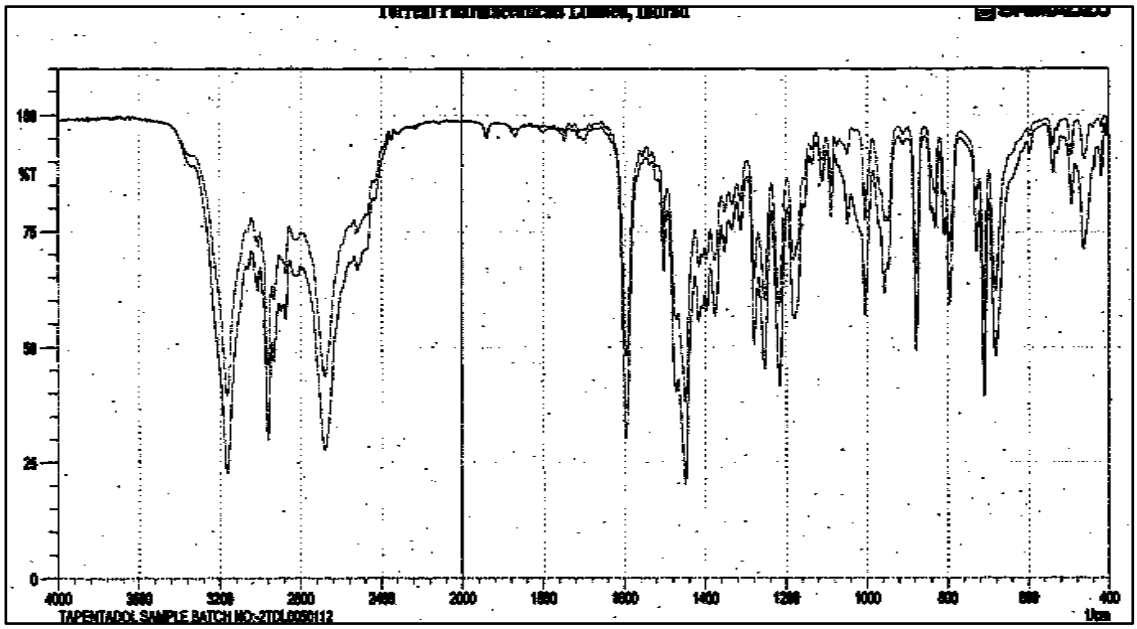

Figure 4.1: IR spectrum of Tapentadol base

4.4.2 DSC study

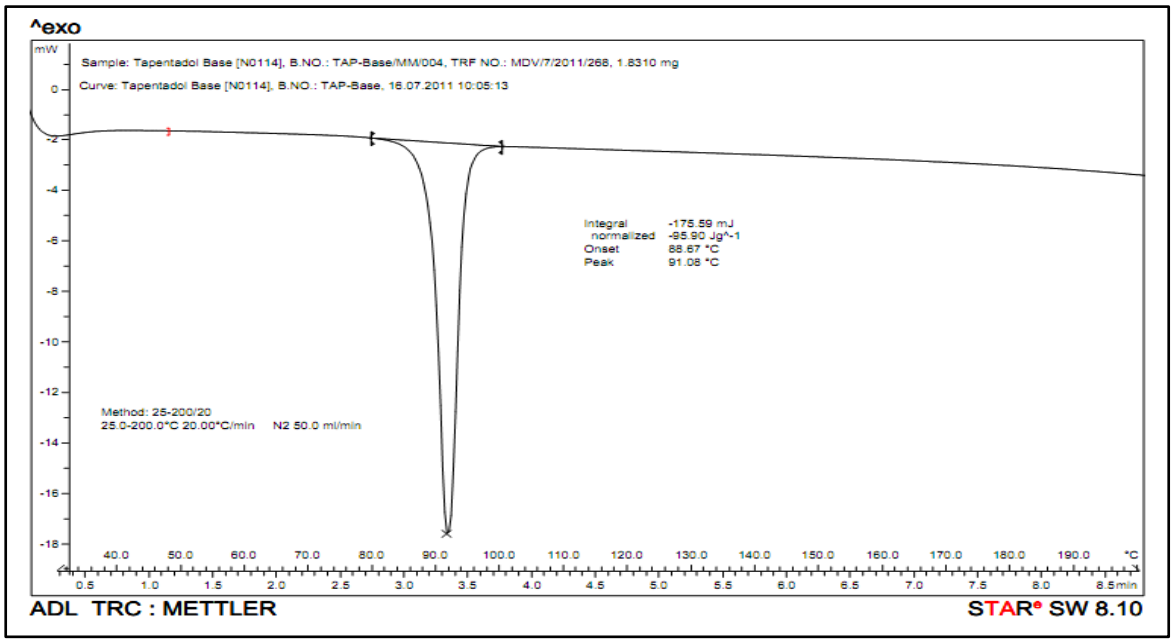

Figure 4.2: DSC thermogram of Tapentadol base

The DSC exhibited characteristic melting endothermic peak at 91.08^{0}C

4.4.3 Microscopy and stability of Tapentadol base in pH 6.0 and pH 7.4 phosphate buffer.

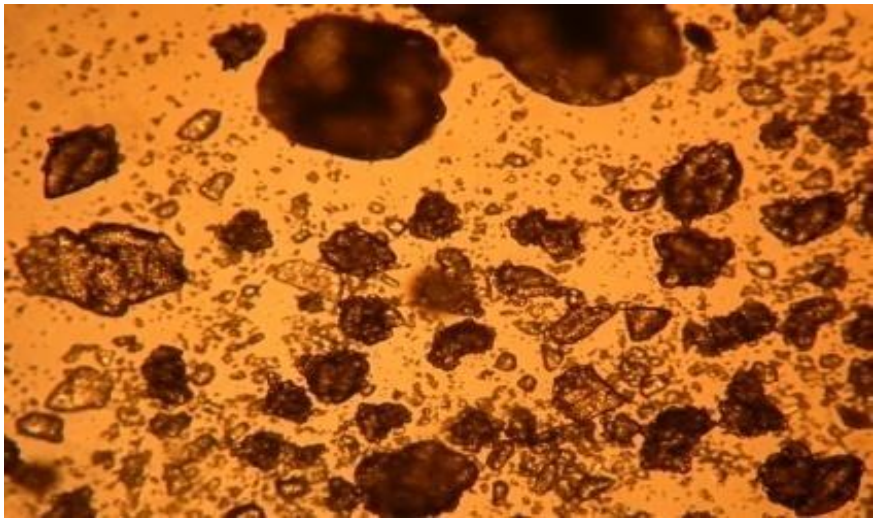

Figure 4.3: Initial Photograph of Tapentadol base at 20X

The microscopic study reveals big particle size crystals and was kept in pH 6.0 and pH 7.4 phosphate buffer at 37°C for 7 days. No change in API crystalline form was observed at all pH up to 7 days. No change in microscopic observation observed at all pH up to 7 days.

4.4.4 Compatibility studies

The Raman study of individual drug and excipients showed characteristic Raman shifts that can be attributed to Tapentadol as presented above. In all lipid drugs and in the other mixture of excipients studied, these drug bands were preserved, which represents the absence of chemical interaction between the drug and the excipients selected for the formulation. The Raman study also established that there is no chemical interaction between the drug and the excipients studied. Similar results were obtained when the study was repeated in samples stored at controlled room temperature for 6 months.

4.4.5 Raman characterization

All excipients and API were also characterized by Raman spectroscopy for the compatibility studies and initial characterization:

Raman spectra of Tapentadol base

Raman characterization of Tapentadol base shows sharp Raman shift with characteristic fingerprint region between 700 to 1200 cm^{-1}.

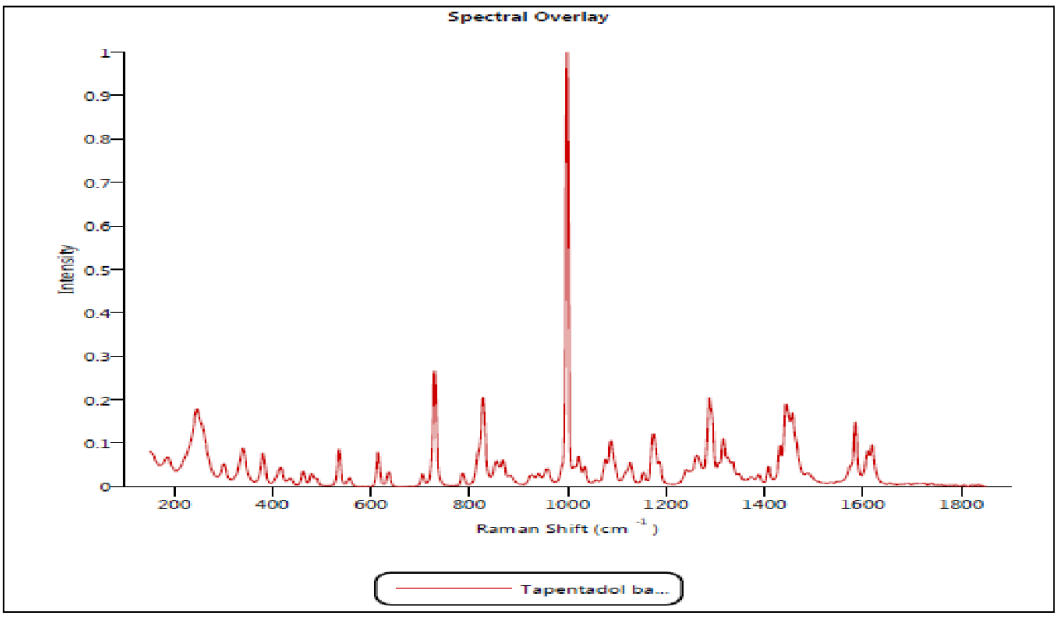

Figure 4.4: Raman spectra of Tapentadol base

Raman spectra of Glyceryl behenate

Raman characterization of Glyceryl behenate shows sharp Raman shift with characteristic fingerprint region between 1000 to 1400 cm^{-1}.

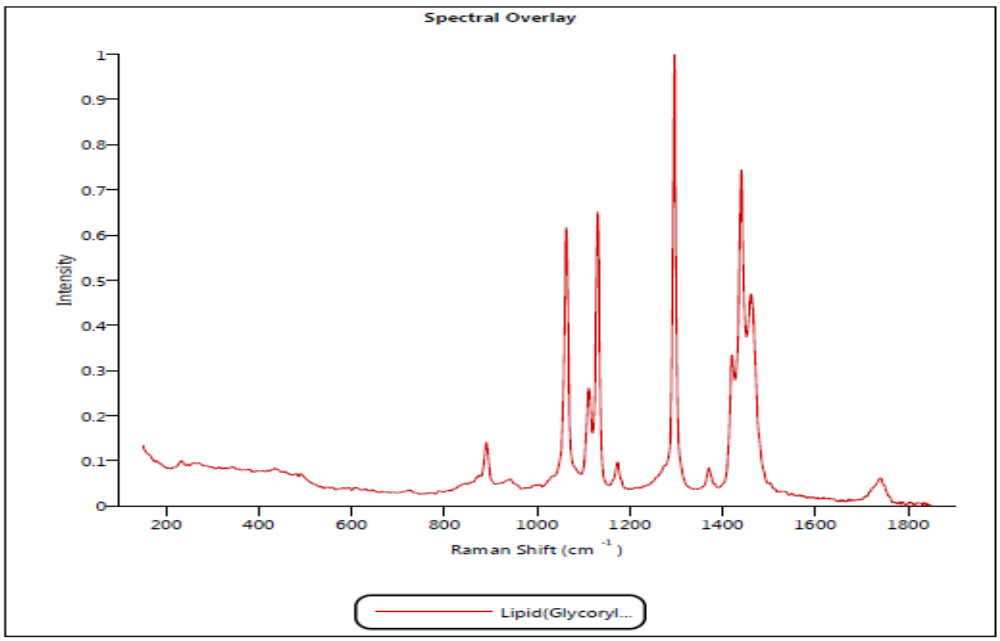

Figure 4.5: Raman spectra of Glyceryl behenate

Raman spectra of Sucrose

Raman characterization of Glyceryl behenate shows diffusive Raman shift with characteristic fingerprint region at 400 cm^{-1}

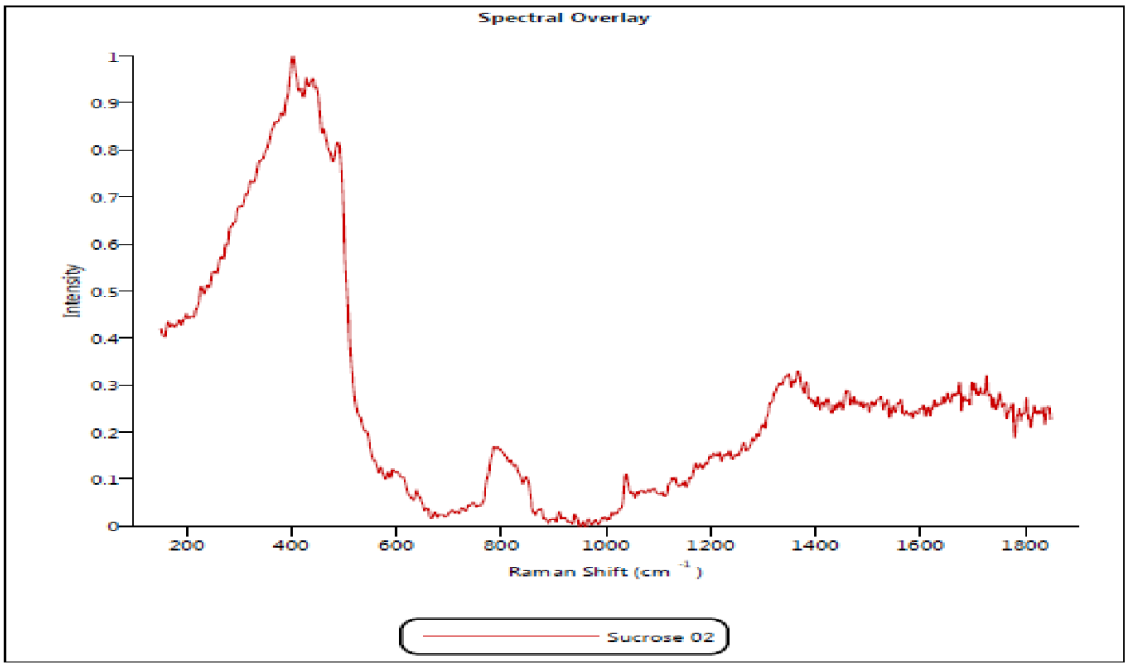

Figure 4.6: Raman spectra of Sucrose

Raman spectra of Hypromellose (HPMC), 6 cps

Raman characterization of Hypromellose (HPMC) shows diffusive Raman shift with characteristic fingerprint region at 900-1400 cm^{-1}.

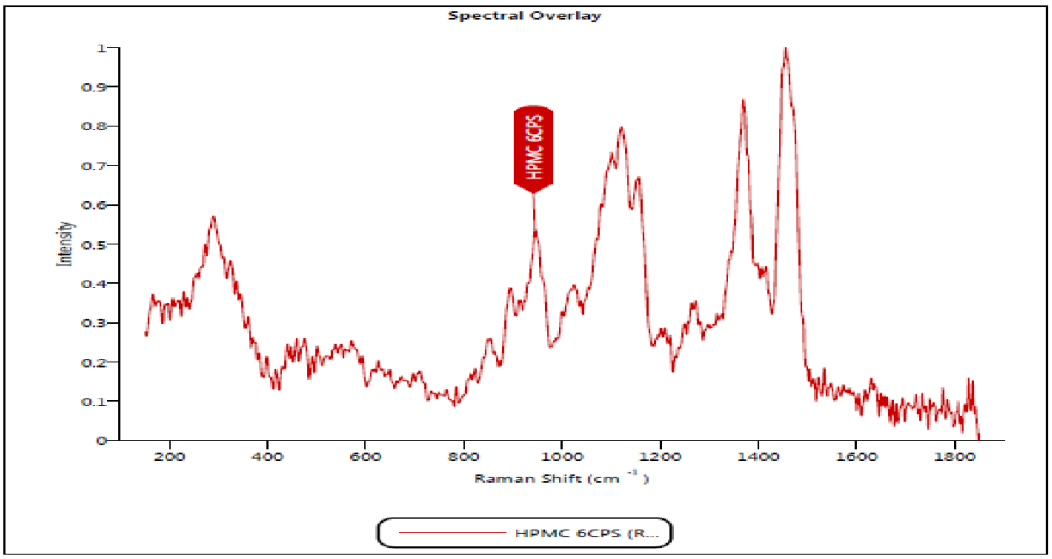

Figure 4.7: Raman spectra of Hypromellose (HPMC), 6 cps

Raman spectra of Gellan gum

Raman characterization of Hypromellose (HPMC) shows diffusive Raman shift with characteristic fingerprint region at 800-1200 cm^{-1}.

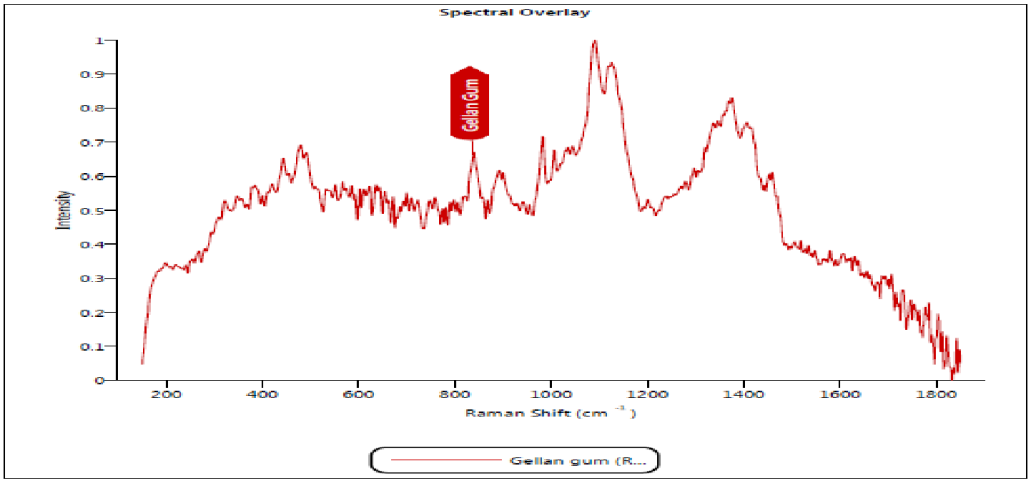

Figure 4.8: Raman spectra of Gellan gum

Raman spectra of Drug and Solid Lipid Nanoparticle (SLN) powder

In this study overlay spectra of Tapentadol base and SLN was carried out which shows that there is no interaction of Tapentadol with any of the components of formulation and the characteristic peak of Tapentadol was not seen the formulation which indicates the entrapment of Tapentadol in a lipid matrix.

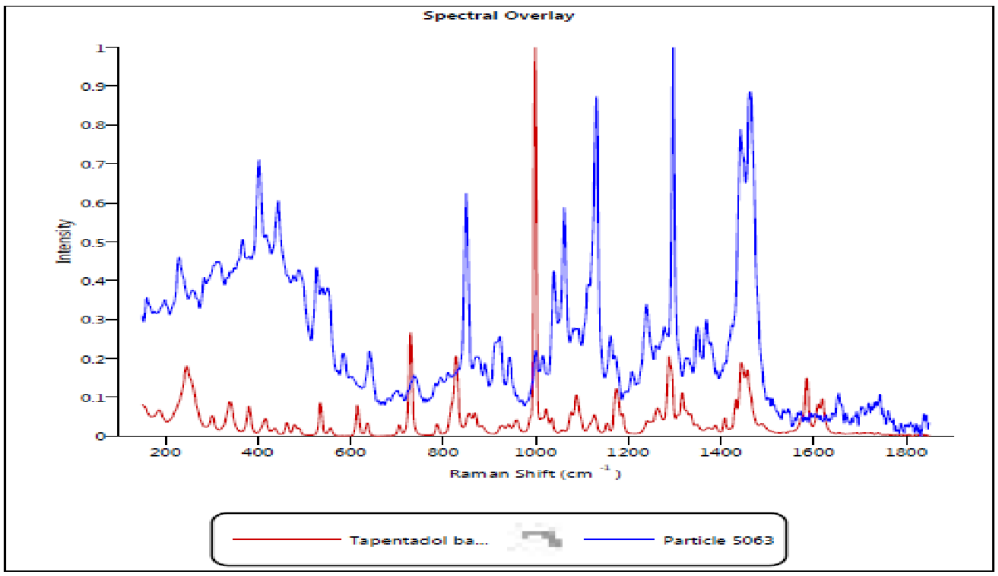

Figure 4.9: Raman spectra of Drug and SLN particle powder

Raman spectra of drug and excipients interaction studies at 40 ± 2°C/75 ± 5% RH

For drug excipients interaction studies with individual excipients, Raman spectra were taken after 40 ± 2°C/75 ± 5% RH 4-week studies to determine any interaction of excipients with the drug. Due to low melting lipids, the physical sticky mass was observed but no spectral shifts were observed.

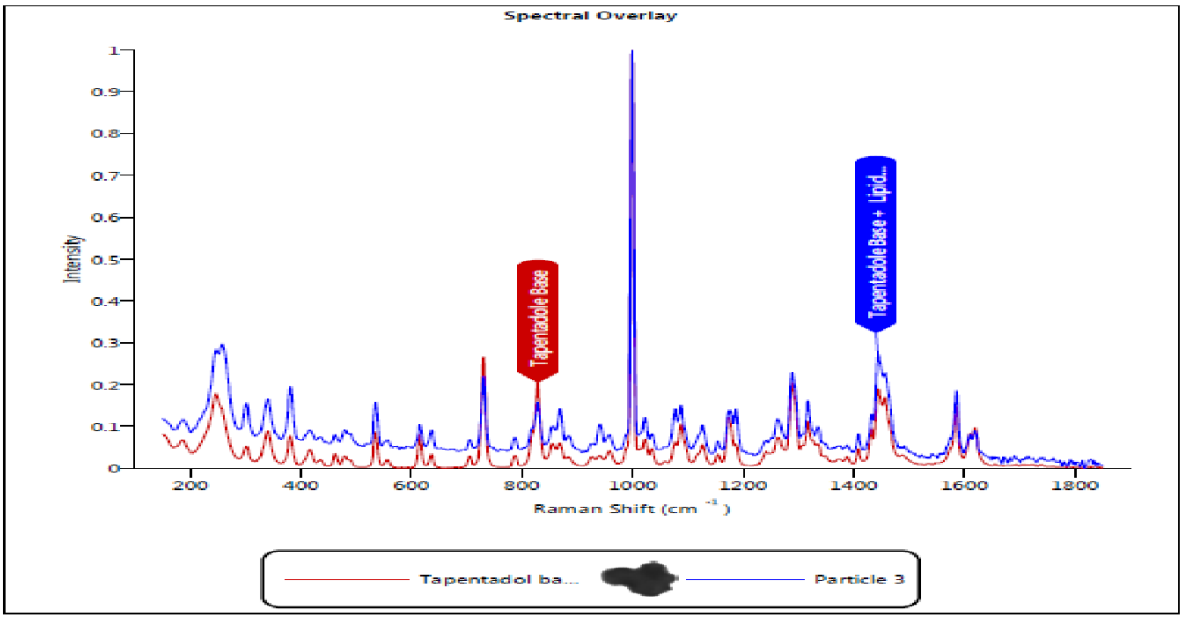

Figure 4.10: Tapentadol base and glyceryl behenate Overlay Raman spectrograph after 4th*week 40 ± 2°C/75 ± 5% RH*

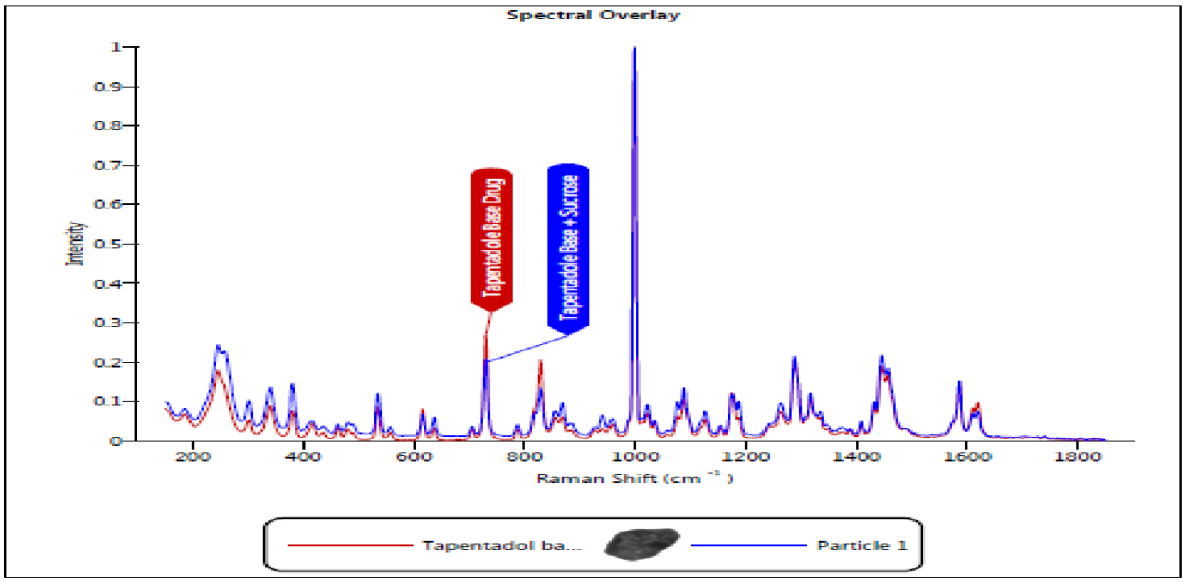

Figure 4.11: Tapentadol base and Sucrose Overlay Raman spectrograph after 4th week 40 ± 2°C/75 ± 5% RH

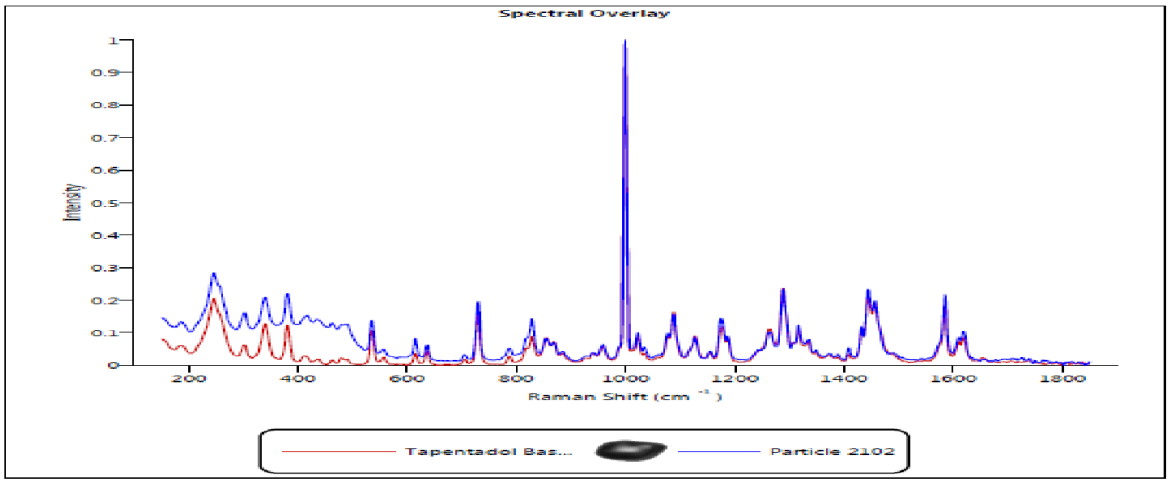

Figure 4.12: Tapentadol base and Polysorbate 80 Overlay Raman spectrograph after 4th week 40 ± 2°C/75 ± 5% RH

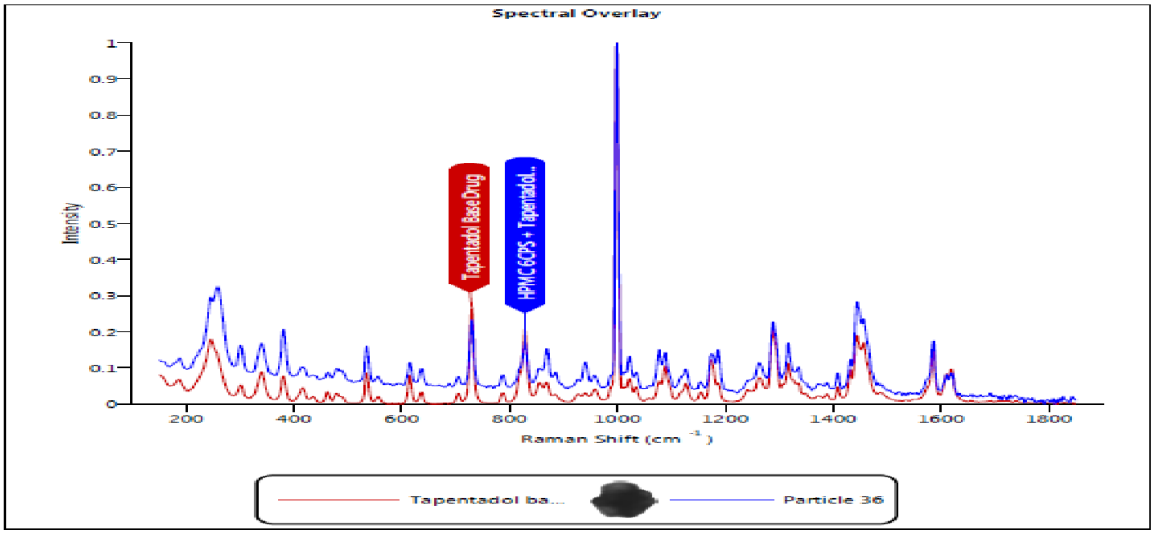

Figure 4.13: Tapentadol base and hypromellose (6cps) Overlay Raman spectrograph after 4th week40 ± 2°C/75 ± 5% RH

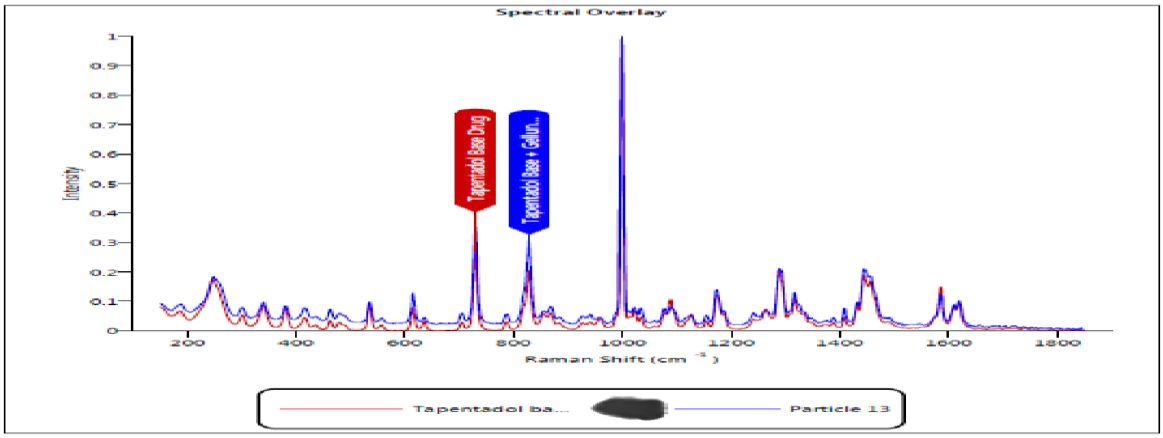

Figure 4.14: Tapentadol base and Gellan gum Overlay raman spectrograph after 4th week 40 ± 2°C/75 ± 5% RH

4.4.5 Solution state stability

Tapentadol was not found to be sensitive towards the aqueous condition. In both Water for injection and 0.9% sodium chloride solution, Tapentadol Hydrochloride was found to be stable at all condition for 7 days at 100 mg/ml. Stability beyond 7 days was not carried out as the final formulation is lyophilized.

Table 4.1: Solution state stability for Tapentadol Hydrochloride

Stability data (7 Days)				
pH Data				
Solution	**Initial pH**	**7 Days pH**		
		2°-8°C	**25±2°C/ 60±5% RH**	**60°C**
Water for injection	6.85	NA		
0.9 % sodium chloride solution	6.55	6.70	6.45	6.72
Tapentadol solution in Water for injection (100 mg/ml)	4.80	4.80	4.90	4.88
Tapentadol in 0.9% sodium chloride solution (100 mg/ml)	4.75	4.85	4.85	4.84

% Assay Data				
Solution	**Initial Assay (%)**	**7 Days assay**		
		2°-8°C	**25±2°C/ 60±5% RH**	**60°C**
Tapentadol solution in Water for injection	101.7	99.4	101.5	102.1
Tapentadol in 0.9% sodium chloride solution	99.4	100.3	100.7	103.3

Degradation products				
Solution	**Initial (%)**	**7 Days**		
		2°-8°C	**25±2°C/ 60±5% RH**	**60°C**
Tapentadol solution in Water for Injection				
Single maximum unknown degradation product	0.27	0.26	0.23	0.26
Total degradation product	0.36	0.34	0.30	0.30
Tapentadol in 0.9% Sodium chloride solution				
Single maximum unknown degradation product	0.27	0.26	0.26	0.26
Total degradation product	0.35	0.34	0.30	0.30

Table 4.2 Tapentadoland excipients compatibility study at controlled room temperature (25±2^{O}C/60±5%RH)

Sr. No	Sample	Initial Observation	1st Week	4th Week
1	Tapentadol +Sucrose	White color sample	No characteristic change	No color change
2	Tapentadol +Tween 80	Yellow color sample	No characteristic change	No color change, sample sticky
3	Tapentadol+Glyceryl behenate	Yellow color sample	No characteristic change	No characteristic change
4	Tapentadol +HPMC	White color sample	No characteristic change	No characteristic change
5	Tapentadol +Gellan gum	White color sample	No characteristic change	No color change, sample sticky

Table 4.3 Tapentadol and excipients compatibility study at controlled room temperature (40±2^{O}C/75±5%RH)

Sr. No	Sample	Initial Observation	1st Week	4th Week
1	Tapentadol +Sucrose	White color sample	No characteristic change	No color change
2	Tapentadol +Tween 80	Yellow color sample	No characteristic change	No color change, sample sticky
3	Tapentadol+Glyceryl behenate	Yellow color sample	No characteristic change	Nocharacteristic change
4	Tapentadol +HPMC	White color sample	No characteristic change	No characteristic change
5	Tapentadol +Gellan gum	White color sample	No characteristic change	No color change, sample sticky

4.5 CONCLUSION

The excipients selected doesnot exhibit any incompatibilities hence, can be used for formulation optimization studies.

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1. Fiese E F, Hagen T A. (1987). Preformulation. Lachman L, Liberman HA, Kanig JL. *The Theory and practice of industrial pharmacy*. Varghese Publishing house, Bombay;171-195.
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3. Brittain HG (2009). Profiles of drug substances, excipients and related methodology; Volume 38.