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DRUG-EXCIPIENT COMPATABILITY STUDYON TORSEMIDE USING CURRENT TRENDS AND TECHNIQUES

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Abstract:
A study of drug and excipient compatibility plays a major role in a pre-formulation study which is further useful in the development of dosage forms. The interaction between drug and excipient will affect the chemical nature and bioavailability of the drug which may test the safety and efficacy of the drug. Present research work was done to study the compatibility between Torsemideand different pharmaceutical excipients like cross-povidone (CP) , magnesium stearate (MS) , microcrystalline cellulose (MCC) and Anhydrous lactose (AL) by different analytical techniques like FTIR(Fourier transform infrared spectroscopy), UV-Visible spectroscopy, DSC (Differential scanning calorimetry) and RP-HPLC (Reverse Phase High performance liquid chromatography).The spectral datashows that excipients used in this study areineffective with Torsemide.

Key words:*Torsemide, excipients,FTIR, UV , DSC and RP-HPLC.*

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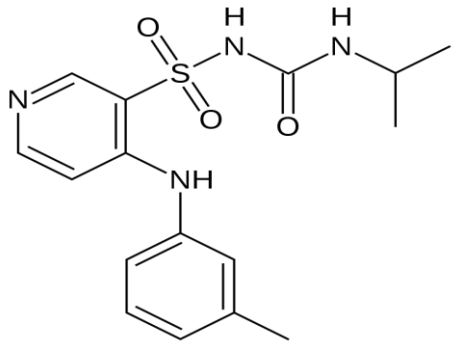
INTRODUCTION:

Drug-excipient compatibility study can alter the physical, chemical properties and bioavailability of a drug formulation which can further influence the bioavailability, safetyand efficacy of the drug. This make the study of drug-excipientsinteraction is one of the most important aspects in the pre formulation.

There are many techniques used in this compatibility study out of which DSC is a first and foremost technique used by the analysts. Although DSC can give approximate results about the thermal properties of a drug there is a necessity of confirmation of the data given by DSC because of the usage of the high temperatures using in DSC which is abnormal in theformulation of a drug i.e., it may undergo some possible interactions or decomposition while performing DSC. So for the interpretation of the data given by DSCis complimented by adding some more techniques like FT-IR, UV &RP-HPLC in the present study.

Torasemide [1]is a novel loop diuretic belonging to pyridine sulphonyl urea. The loop diuretics act by blocking symporter. [1]Compared with other loop diuretics, torasemide has a more prolonged diuretic effect than equipotent doses of furosemide and relatively decreased potassium loss. No evidence of torasemide-induced ototoxicity has been demonstrated in humans [2].

[1,2]*Chemical structure*- $C_{16}H_{20}N_4O_3S$- [2]



An active ingredient of a drug will be given to the patient in the form of a dosage form by mixing it with suitable excipients which are inactive in pharmacological activity but used as binders, lubricants, coloring agents, and glidants and flavoring agents. [3] So selection of a suitable excipient is an important criterion in the pre formulation studies while producing a dosage form. Although these are ineffective butstudies were found that excipient also showing effects on drug which is because of long storage which are confirmed by dissolution rate and solubility testing.[4]

Thermal analysis and FTIR are the main tools which are used in the predicting the drug-excipient interactions and accelerating the pre formulation studies for a new drug for researchers. Study of enthalpies of a drug by DSC gives an elaborative knowledge about the drug quality and stability.

The present research was aimed to study the interactions between torsemide and excipients i.e., CP, MS, MCC and ALby applyingdifferent analytical techniques.

EXPERIMENTAL WORK [3]:

EQUIPMENT, MATERIAL,AND METHODS USED:

MATERIALS:

The materials used in this experiment were Torsemide API and excipients like MCC, AL, MS and CP. Acetonitrile and water of HPLC grade were used for the preparation of mobile phase.

EQUIPMENTS:

DSC (Differential scanning calorimeter)- The thermograms were obtained in DSC Q_{20} cell (Waters) using aluminumT zero low mass pans calibrated by Indium and by applying pressure with T zero press. The drug taken into the pan is approximately 3mg and the heating range is 10° C to 300° C about 1 hrof time.

UV-Spectroscopy (LAB INDIA-UV3092)operated by UV WIN-5 software with quartz cuvettes.

FT-IR (Bruker -Alpha –T) operated by OPUS 6.5 software. The drug with excipients was taken in the ratio of 1:2to prepare KBr disk and scanned in the range of 400-4000cm^{-1}.

HPLC (Agilent-1220Infinity LC with software of Ezchrome Elite)with Agilent C18 ODS column 4.6 × 250mm, 5 µm .

METHODOLOGY [3,4]:

GLASSTRANSITIONTEMPERATUREMEASUREMENT *(DSC):*Torsemide standard was taken into apan and pressurized to seal the sample in the pan.

FOURIER TRANSFORM INFRARED SPECTROSCOPY (FT–IR):

FTIR was used as another subsequent study for Torsemide. The spectra of Torsemide and its excipients like AL, MS, CP and MCCwas observed for this study. The mixtures of (1:2) was taken in order to identify the chemicalinteractions between sample and excipients.

UV SPECTROSCOPY [6]:

An accurately weighed amount of drug and excipient were taken into a volumetric flask in the ratio 1:2) and

dissolved in suitable methanol and sonicated. The sample was further diluted to get 10µg/ml and scanned between 200-400 nm for pure drug. Same procedure was continued for the drug and excipient physical mixtures (excipients used were CP, MS, MCC and AL) and the $\lambda_{max}$was compared for the prepared solutions.

RP-HIGH PERFORMANCE CHROMATOGRAPHY [5,6]:

Thecompatibility study of Torsemide by HPLC was carried out by dissolving in methanol and eluted using the mobile phase (80:20) acetonitrile and 10mM potassium dihydrogen ortho phosphate. The sample with excipients alsowere prepared using same procedure and diluted. The eluents were monitored at 235nm.

RESULTS AND DISCUSSION [7,8]:

DIFFERENTIAL SCANNING CALORIMETRY: Torsemide standard was taken into apan and pressurized to seal the sample in the pan. The thermogram of Torsemide (Figure no.1) shows a single endothermic peak at 168.29°C (the glass transition T_G = about 40°C) and(T peak = 168°C).

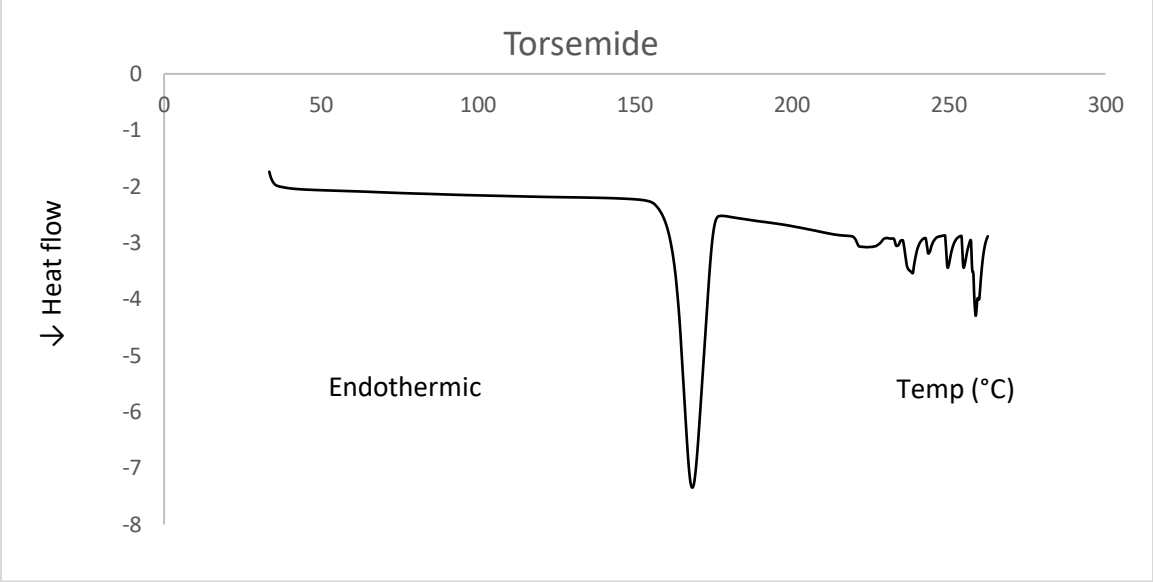


Fig.1. DSC thermogram of Torsemide API

The API is mixed with excipients in the ratio of 1:2 and pressurized in same way. Thethermogram for the binary mixtures of Torsemide and CP, MS, MCC, and AL are shown in figure 2 and 3.

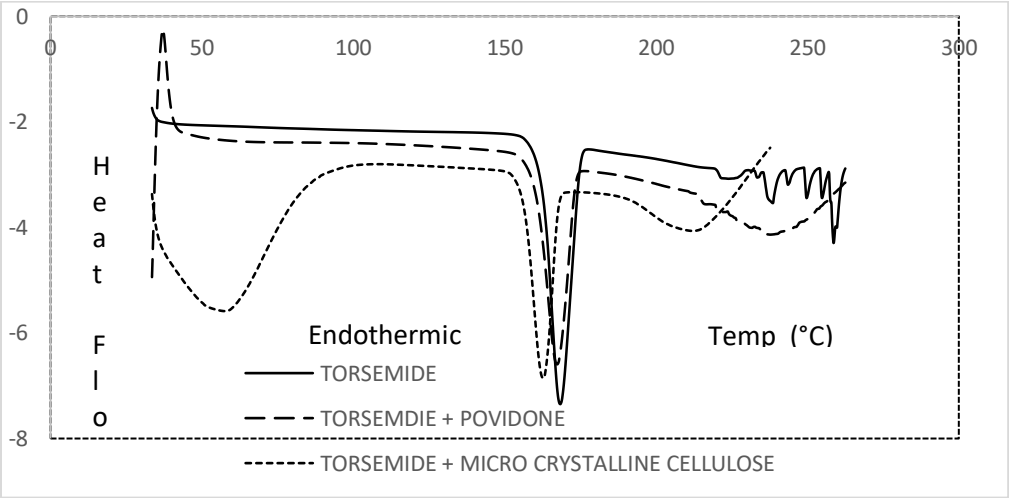


Figure 2 :Overlay of DSC curves of excipients with Torsemide (1:2) Torsemide + CP, Torsemide + MCC

The DSC curves of binary mixtures of (1:2 w/w) of the drug and CS, MCC were shown broadening and splitting of peaksbut no significant interaction was observed with Drug substance. According to Mura and Cookers [1987] the samples with MCC and starch willShow endothermic reactions due to the polymer dehydration process. [5]

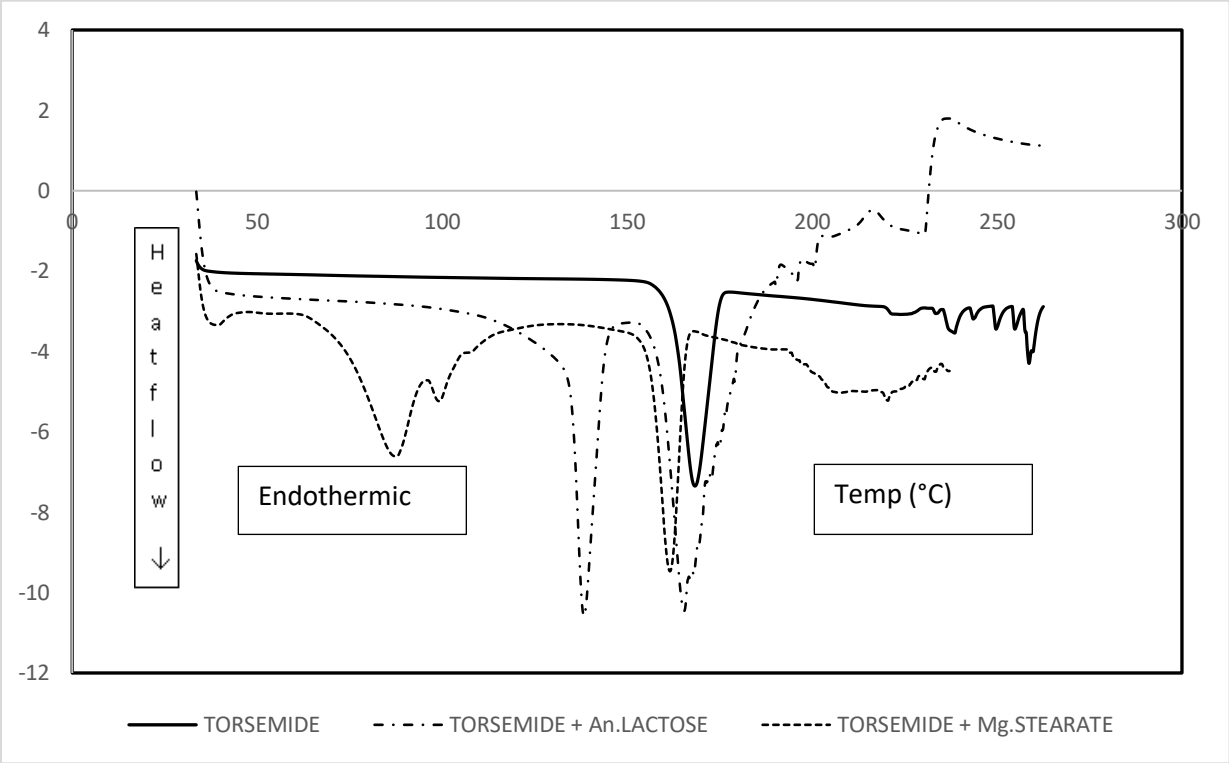


Figure 3: Overlay of DSC curves of excipients with Torsemide (1:2) Torsemide + Torsemide + AL, Torsemide + MS

The thermogram of AL and MSshoweda second endothermic peak which is the resemblance of melting of the excipient. It was observed that there is shifting of the peak from 163°C to 161°C due to the interactions between the sample and excipients.The result of DSC were given in the below table no.1

Table: 1 Onset and peak temperatures of fusion observed in the DSC

Sample	Ratio of mixture taken	DSC		
		T peak Fusion (°C)	T onset Fusion (°C)	Enthalpy (J/g) Fusion (°C)
Torsemide	1:2	162.16	168.29	98.74
AL	1:2	141.79	145.27	70.91
Povidone	1:2	40.84	64.67	142.8
Micr.Cryst.Cellulose	1:2	33.42	38.21	35.12
Mg.Stearate	1:2	86.02	95.91	44.12

FOURIER TRANSFORM INFRARED SPECTROSCOPY (FT–IR) [9]:
The Torsemide API was scanned between 400 – 4000 $cm^{-1}$and spectrum was shownFig 4.

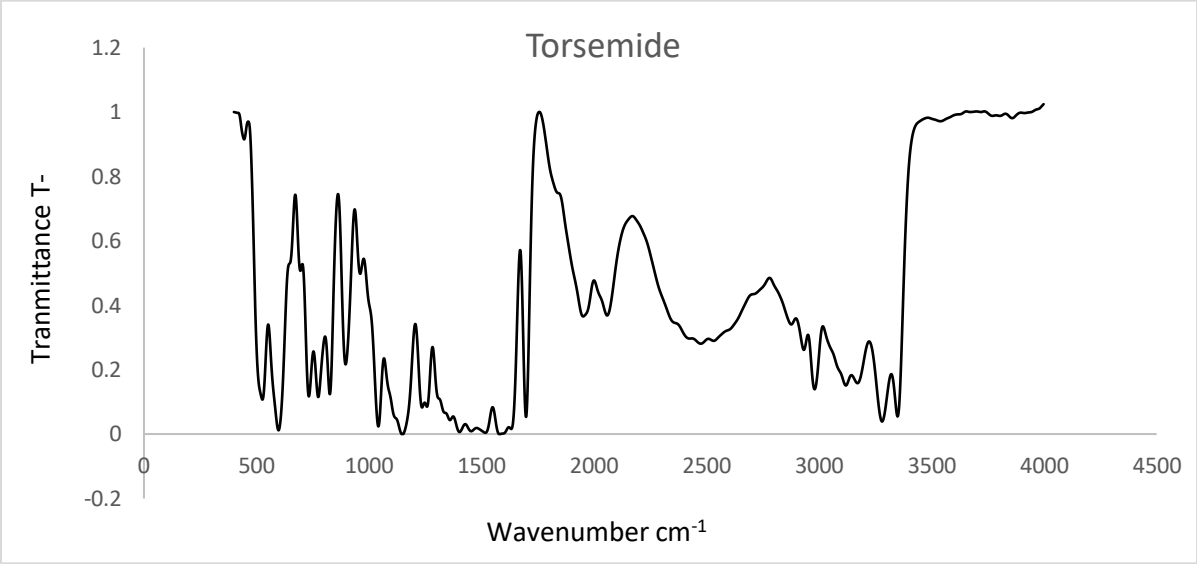


Fig.4. FT-IR spectrum of TORSEMIDE-

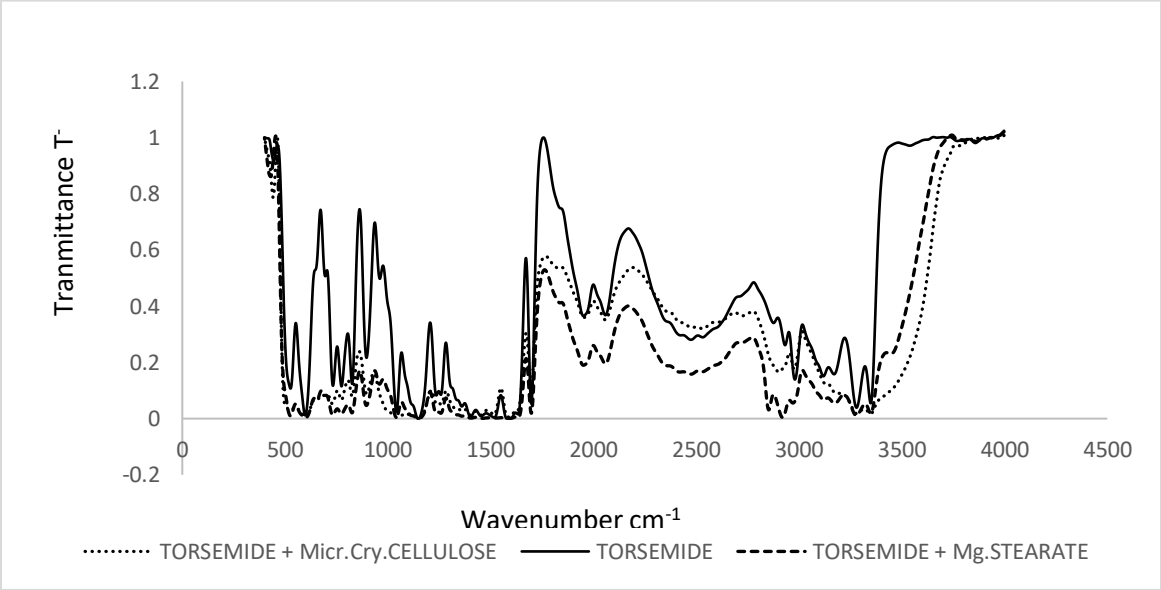


Fig.5. FT-IR spectrum of Torsemide with excipients MS, MCC

The FT-IR spectrums of different forms of Torsemideand excipients were observed and reported. All spectrums has some common bands shows the presence of some specific fundamental vibrations due to NH_2 at 3348.86 cm^{-1}, 2980.01 represents C-H stretching, the band at 1697.69 represents C=O, the band at 1041.62 is represents the presence of Sulphur group and 960.71 represents C-H bending.

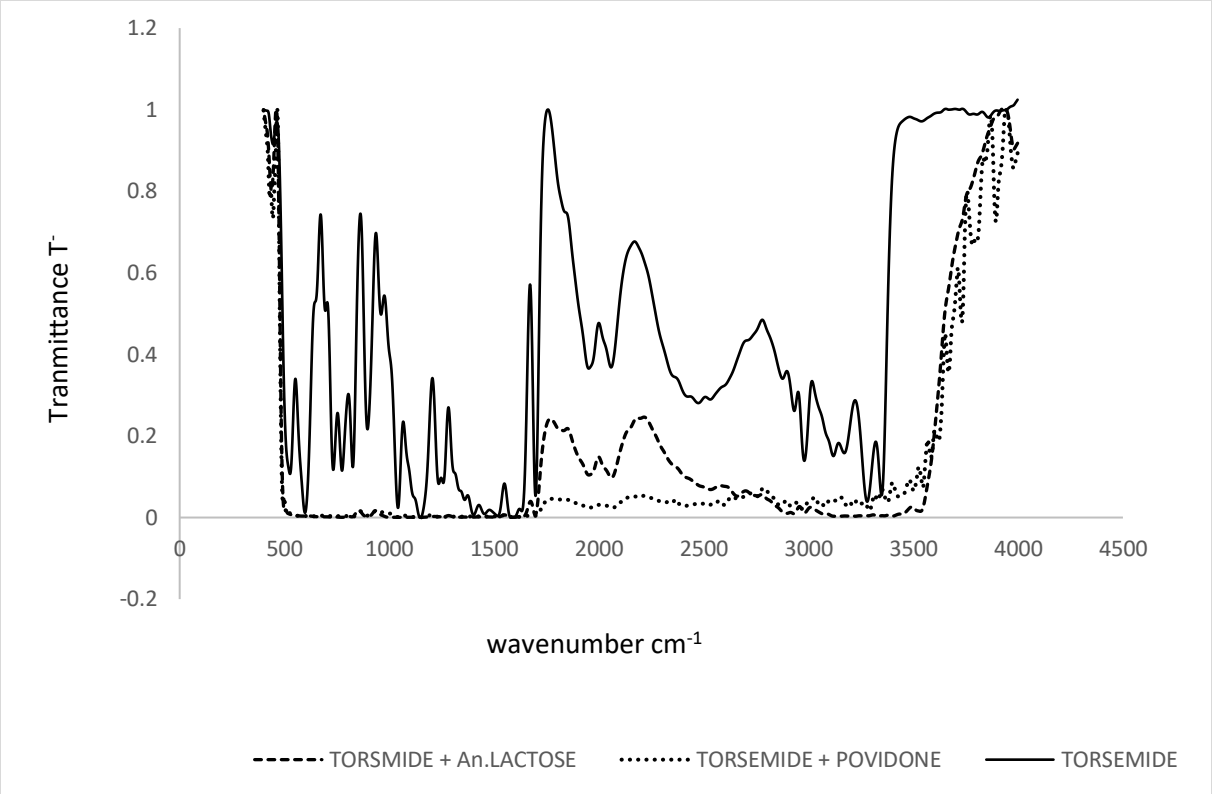


Fig.6. FT-IR spectrum of Torsemide with excipients AL and CP

The presence of specific functional groups in Torsemide was noted and they are present when the drug is mixed with various excipient also. It shows that are no significant interaction between drug and excipients.

The results of FT-IR were shown in table no.2

Table 2: It shows FTIR spectroscopy data of Torsemide and Excipients (1:2)

S.NO	F.G	Standard ($cm^{1)}$	Torsemide	Micr.Cryst. Cellulose	Mg.Stearate	CrossPovidone	An.Lactose
1.	N-H	3300-3500	3348.86	3348.39	3278.79	3377.30	3332.50
2.	C-H Stretching	3000-2800	2980.01	2976.57	2920.27	2973.09	2930.50
3.	C = O	1690-1760	1697.69	1696.97	1697.57	---	1696.46
4.	C-O	1050-1300	960.71	1044.76	1041.25	1154.46	1073.33
5.	C—H Bending	690-900	695.02	729.85	731.77	733.42	773.02

The above data confirms thatthere is possible interaction between sample and excipient between Torsemide and excipients. FTIR is a valuable technique which supports the data of DSC.

UV SPECTROSCOPY [10]*:*

The Torsemide API and excipients were scanned between 200-400nm .Same procedure was continued for the drug and excipient physical mixtures (excipients used were CP, MS, MCC and An.LactoALse) and the λ_{max}were compared to know the interaction.

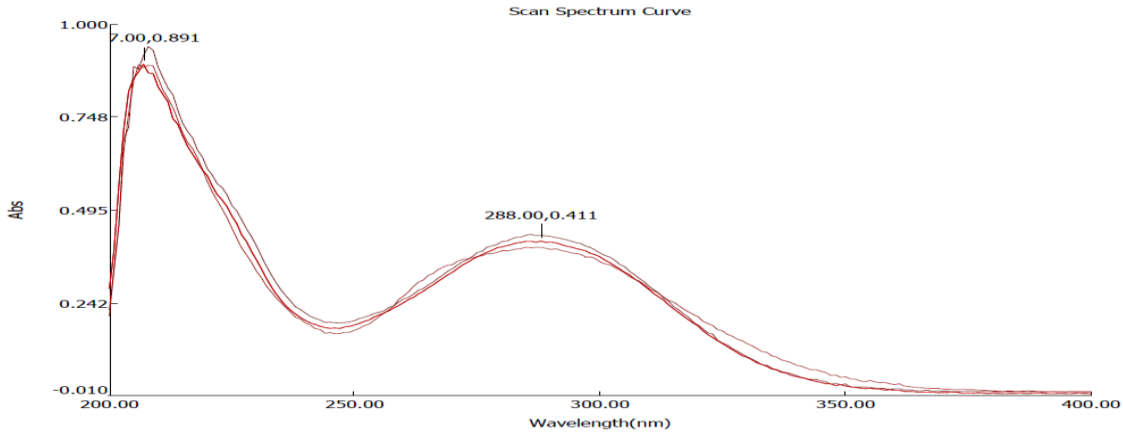
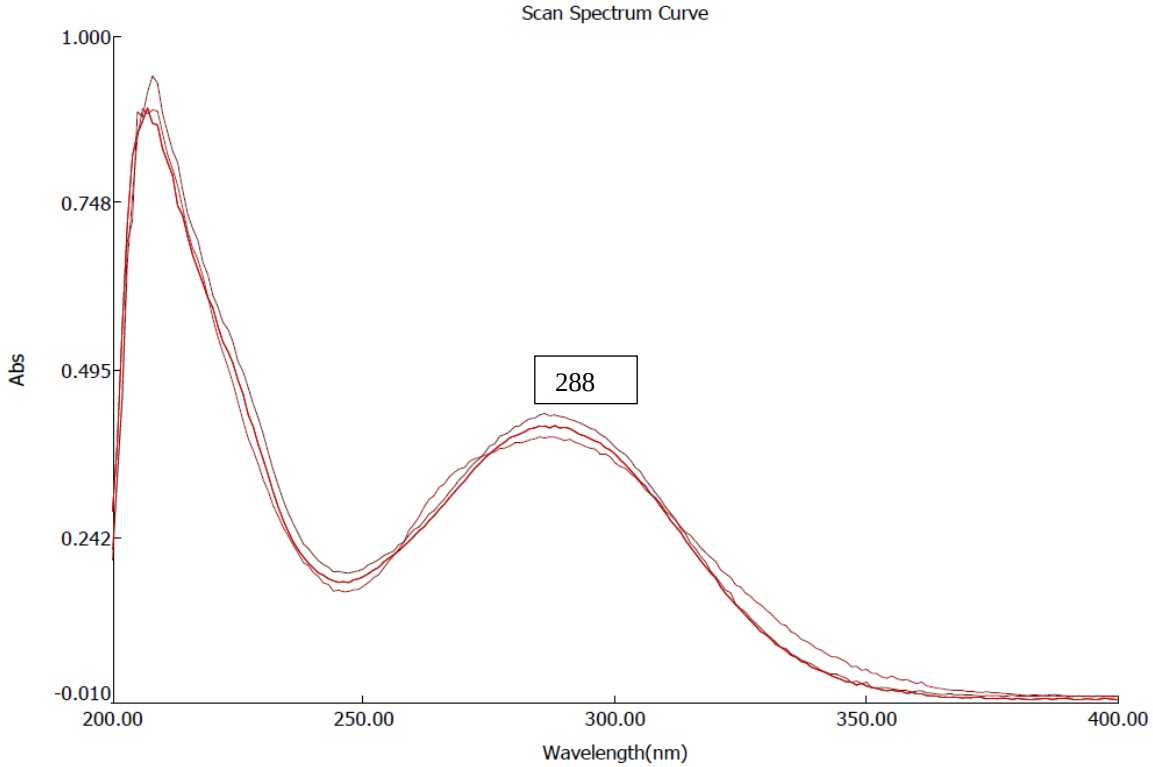


Fig.7. UV spectrum for Torsemide and physical mixtures of CP and MS

The sample and excipient mixtures were prepared by taking drug and excipient in the ratio of 1:2 and was diluted to get 10µg and scanned. The above spectrums of torsemide and mentioned excipient mixtures where shown no difference in the λ_{max}.



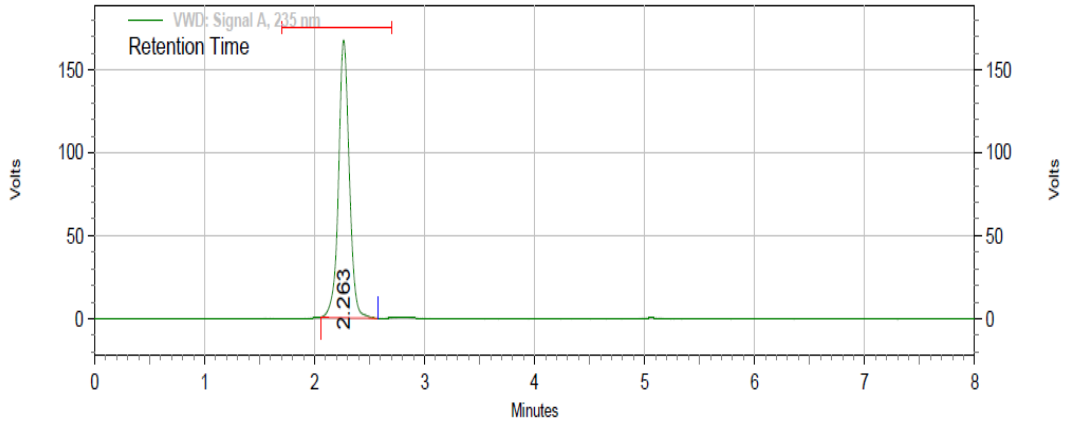


***Fig.9*. Typical HPLC chromatogram of TORSEMIDE**

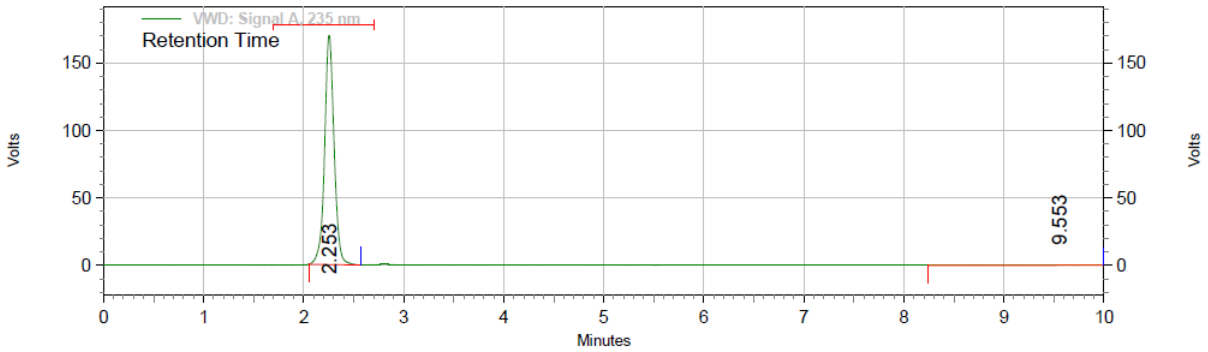


***Fig.10*. Typical HPLC chromatogram of Torsemide + CP**

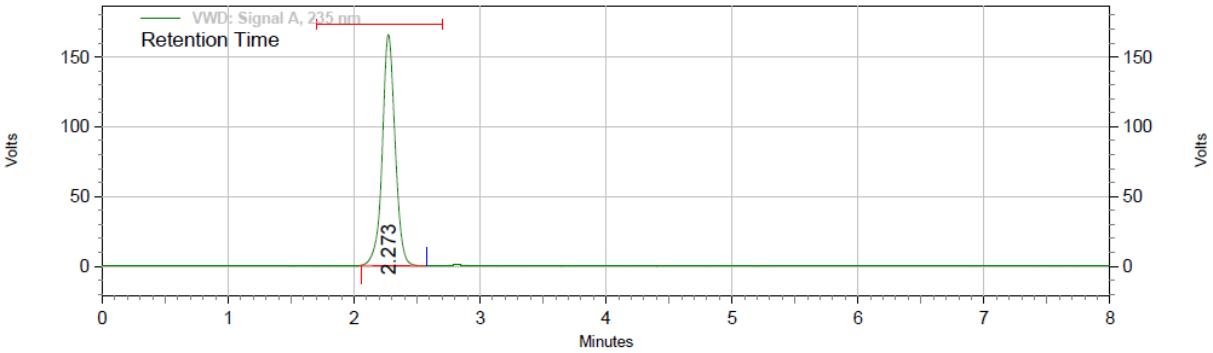


***Fig.11*. Typical HPLC chromatogram of Torsemide + MCC**

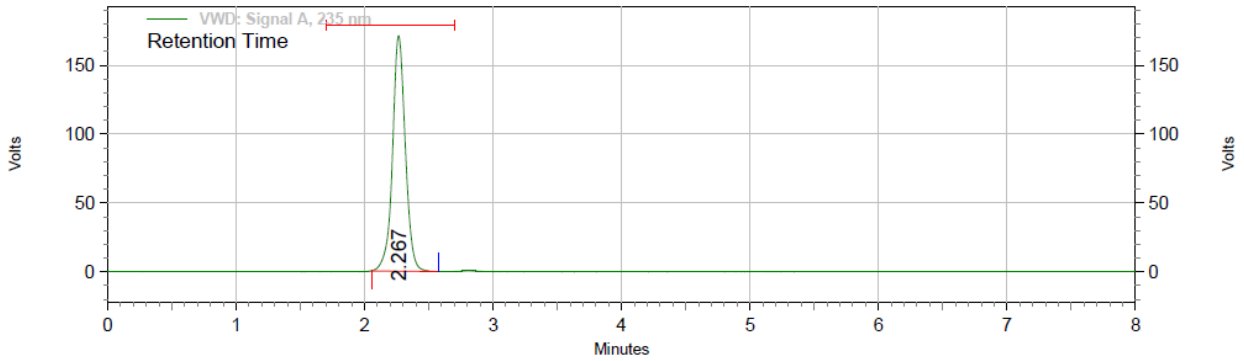


***Fig.12*. Typical HPLC chromatogram of Torsemide + AL**

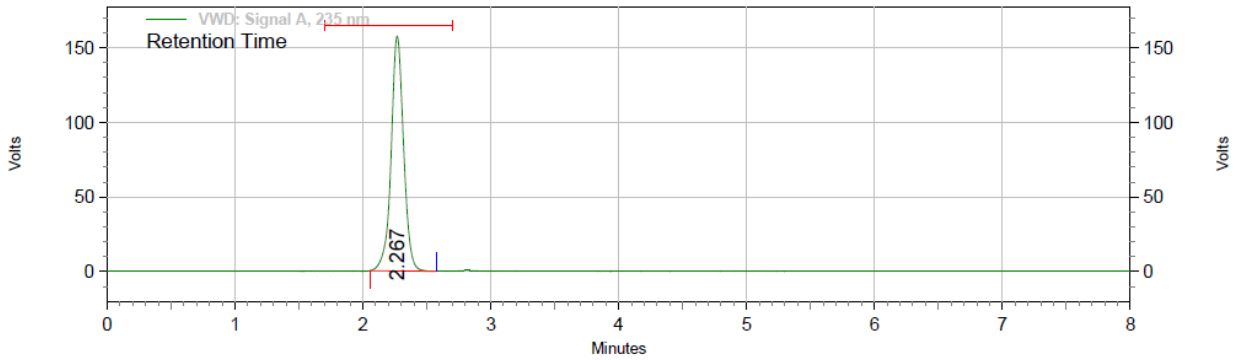


***Fig.13*. Typical HPLC chromatogram of Torsemide + MS**

RESULTS OF HPLC [11]:

***Table 3*: HPLC data of Torsemide and Excipients (1:2)**

Sample	Ratio of drug &excipient	Retention time (min)	% drug
Torsemide	-	2.263	101.62
Torsemide + CP	1:2	2.253	100.91
Torsemide + AL	1:2	2.267	101.54
Torsemide + MS	1:2	2.267	101.62
Torsemide + MCC	1:2	2.273	100.89

CONCLUSION

Present study was successfully demonstrated the utilization of DSC, FT-IR, HPLC and UV-Spectroscopy to assess the compatibility of Torsemide with excipients used in the formulation. Even though the study by DSC had shown some interactions between the sample and excipients which does not have any negative impact on the purity of the drug. This was further confirmed by HPLC and UV techniques. The FT-IR is an excellent fingerprinting technique which supports the data of DSC. The FT-IR spectrum showedthe presence of all functional group which are present in API when it is compared with the spectrums of excipient mixtures. The present research conclude that the data obtained will help in the development of Torsemide formulation with different excipients and further it is concluded that the modern analytical techniques can be used as a powerful tool in the pre formulation studies to know the compatibility of drug with excipients.

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