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DRUG-EXCIPIENT INTERACTION STUDY OF TRAMADOL HCL WITH POLYMERS

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ABSTRACT

Drug-Excipient interaction study is important for the stability and good quality of product and to avoid the incompatibilities during production. various methods are available for that study like D,S.C, I.R. etc. Differential Scanning Calorimetry is widely used to observe or predict any physico-chemical interaction between drug and excipient Infrared absorption spectroscopy is related to the absorption of infrared radiation and get excited to excited state from the red end of visible spectrum to microwave region. That study totally depends on chemical and structural changes and thermal activity of compounds.

KEYWORDS: D.S.C., I.R., Interaction study.

INTRODUCTION

Drug: Active part of dosage form and it is mainly responsible for therapeutic value.

Excipient

Substance which are include along with drug being formulated in a dosage form so as to impart specific qualities to them.

Drug

Excipient compatibility study is important to check over its important as.

Stability of the dosage form can be maximized

Any physicochemical interaction between drugs and excipient affects bioavailability and stability of drug.

It helps to avoids the suprise /sudden problems

We know the possible reaction before formulating final dosage form by DSC.

Drug discovery can emerge only new chemical entity

By using DECS data we can select the suitable type of the excipient with the chemical entities emerge in drug discovery programs.

DECS data is essential for INDA submission

New, USFDA has made it compulsory to submit DECS data for any new coming formulation before its approval.

Determine a list of excipient that can be use in final disage form

To observe the reaction or interaction excipient requires 5 mg of drug in 50% solution of excipient.

Analytical techniques use to detect the drug - excipient compatibility

There are some analytical technique which is use to detect the drug excipient compatibility such as

1. Thermal method of analysis

a) DSC-Differential Scanning Calorimetry.

b) DTE-Differential Thermal Analysis.

2. Accelerated Stability Study.

3. FT-IR spectroscopy.

4. DRS-Diffuse Reflectance Spectroscopy.

5. Chromatography

a) SIC-Self Interactive Chromatography

b) TLC-Thin Layer Chromatography

c) HPLC-High Pressure Liquid Chromatography

6. Miscellaneous

a) Radiolabelled Technique

b) Vapour Pressure Osmometry

c) Fluorescence Spectroscopy

Now, we focus on the main two methods for compatibility study as

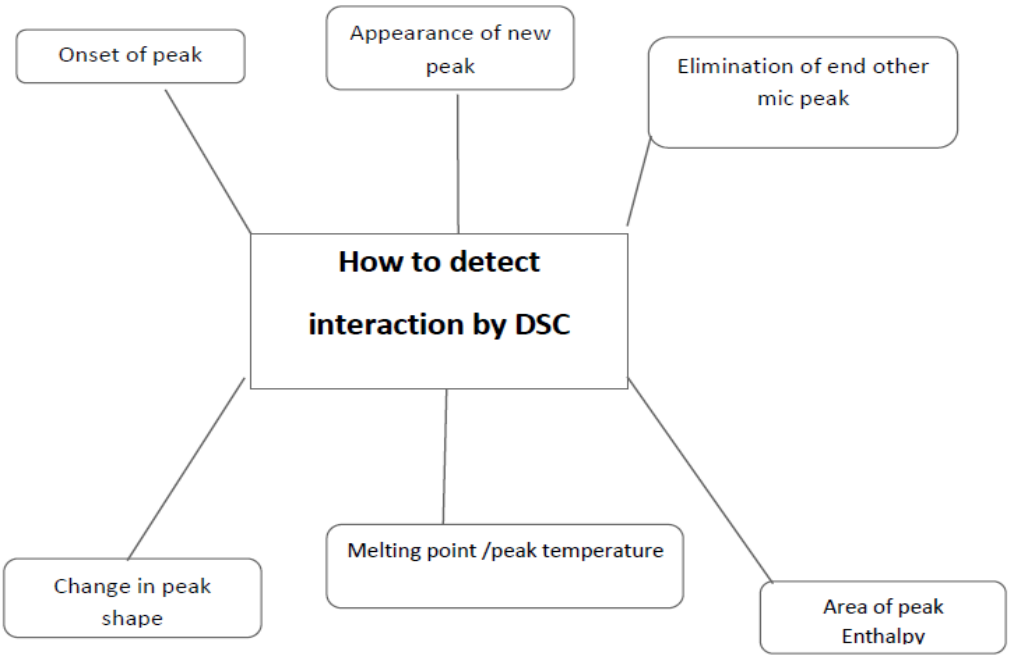
A] DSC - Differential Scanning Calorimetry

B] IR - Infrared Spectroscopy.[1]

A] DSC - Differential Scanning Calorimetry

Differential Scanning Calorimetry is widely used to observe or predict any physico-chemical interaction between drug and excipient. It is thermal method. In DSC sample and an inert refence heated separately by variable hearter as power supply to sample, so power is varied maintain ΔT =0, when exothermic and endothermic changes occur.

In these, sample size is about 2-10 mg and programmed heating and cooling is possible in DSC. By DSC one may analyse liquid & solids in the form of powder, crystal granules or foil. For reference inert material like alumina is used. Empty pan with lid is also used. DSC measurenents generally carried out in gas environment. DSC technique is the faster, reliable and very less sample required in DSC.[2]



Limitation

1. Very small thermal changes condition DSC can not be used.
2. It is unable to detect the incompatibility which occur after long term storage.
3. It is important to new result of incompatibility testing with caution.
4. These method is not applicable if test material properties that make data interaction difficult.[3]

B] IR - Infrared Spectroscopy

Infrared absorption spectroscopy is related to the absorption of infrared radiation and get excited to excited state from the red end of visible spectrum to microwave region (0.8-200u), in pharmaceutical analysis we use IR radiation of wavelength 25-2.5u or wave number from 400/cm to 4000/cm. IR spectrum is subdivided as near IR (^=0.78-2.5u), middle IR (^=2.5-50u), far IR (^=16.200u), infrared (2.5-16u).

IR radiation absorption of compound required criteria as- change in dipole movement and then applied IR freauency is equal to natural frequency of radiation, otherwise compound don't give IR peak.[2]

It is also called vibratinal spectroscopy which is having stretching & bending vibration.

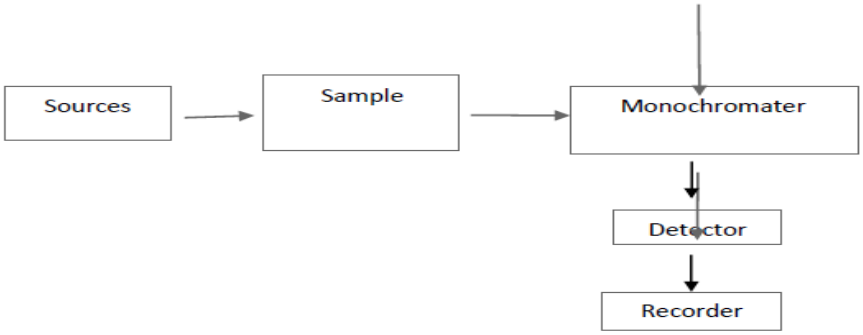


Fig. Schematic diagram of IR Spectrometer.

Experimental work

Infrared Spectroscopy: IR spectrum of drug was measured in the solid state as potassium bromide dispersion. The bands (cm^{-1}) have been assigned. FTIR spectra of Tramadol Hcl was obtained by using a FTIR spectrometer-430 (Shimadzu 8400S, JAPAN). The samples were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:100 (sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powders, under force of 15 tonnes for 5 min in a hydraulic press.

Differential Scanning Calorimetry (DSC)

Melting point of drug was determined by using DSC. Thermogram for Tramadol Hcl was obtained using DSC (DSC 60 Shimadzu, JAPAN). The drug was hermetically sealed in perforated aluminum pans and heated at constant at rate of 10^0C/min it exhibits a sharp melting endothermic peak at temperature of 181.37^0C. And also HPMCK4M, Pluronic F-127

and physical mixture of Tramadol HCL/HPMCK4M/Pluronic F-127 were performed. The samples were put on DSC reference pan and DSC thermo gram were obtained.

Drug-Excipient Interaction Study: The drug-Excipient interaction study was carried out by using Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry.

Fourier Transform Infrared (FT-IR) Spectroscopy (Desai et al. 2006)

The interaction between the drug and polymers was determined by using the FTIR spectroscopy by KBr pellet method where infrared spectra of Tramadol Hcl and other polymers were taken individually first and then compared with the spectra of the formulation combinations; in which the drug was mixed with in situ gelling polymers. The scan range was from 4000 to 500 cm^{-1}.

Drug Excipient compatibility study: Drug-polymer interaction studies were performed by FTIR Spectroscopy. IR spectra of drug and polymers combination showed no matching peaks with the drug spectra. The characteristic peaks of the drug (937.44, 1481.38, 1606.76, 2860.53, 2929.97 cm^{-1}) were also appeared in the spectra of all the drug- polymer combinations.

A.Spectra of Tramadol Hcl

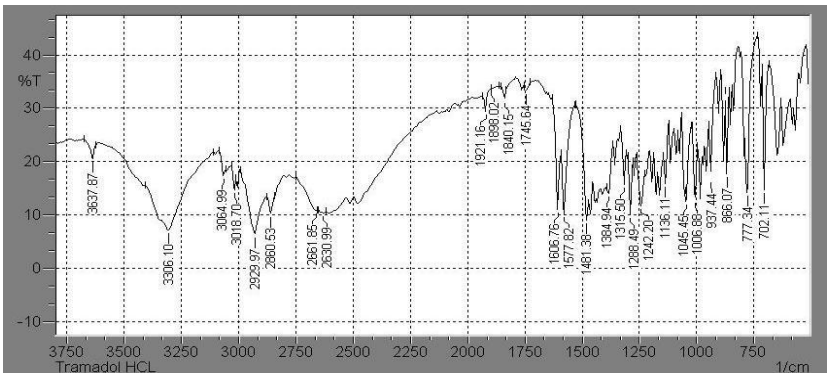


Figure. 12: FTIR Spectra of Tramadol Hcl.

B.Spectra of Pluronic F-127

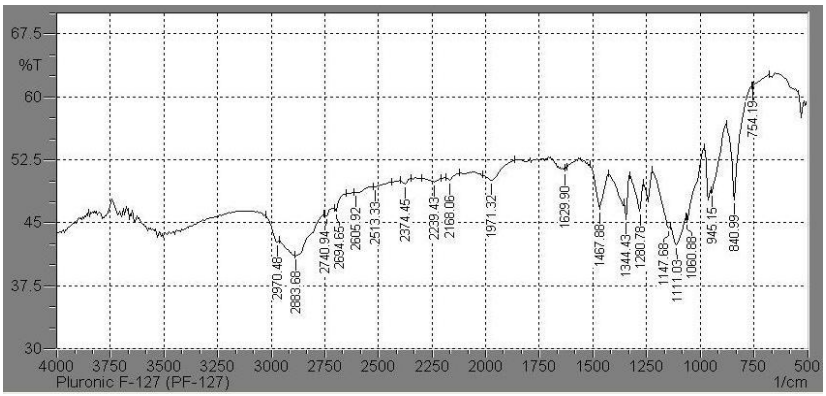


Figure. 13: FTIR Spectra of Pluronic F-127.

C. Spectra of HPMCK4M

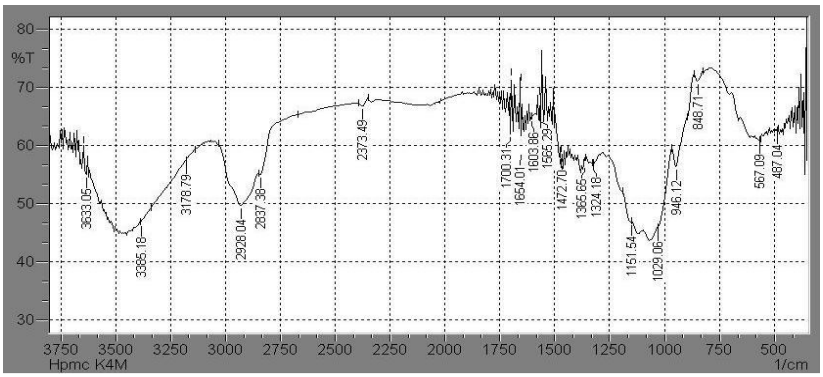


Figure. 14: FTIR Spectra of HPMCK4M.

D.Spectra of Physical Mixture

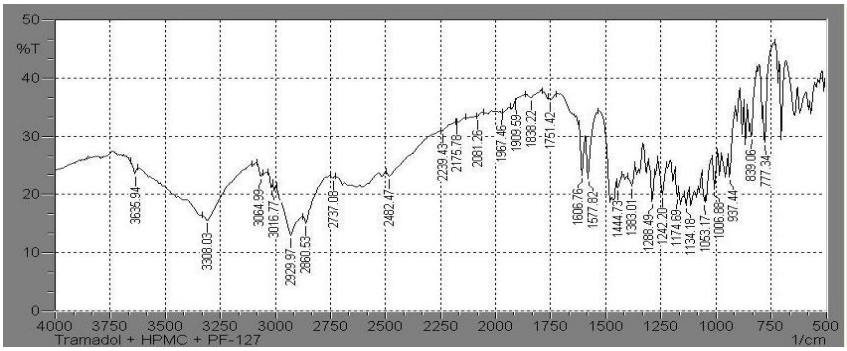


Figure. 15: FTIR Spectra of Physical Mixture.

Table: Interaction Studies through FTIR Spectroscopy.

Material	Peaks (cm^{-1})	Characteristic Functional Group
Tramadol Hcl	937.44	C-H Bending vibration
	1481.38	C-H Bending vibration
	1606.76	C=C Stretching vibration
	2860.53	C-H Stretching vibration

	2929.97	C-H stretching vibration
HPMC K4M	946.12	C-H Bending vibration
	1472.70	C-H Bending vibration
	1603.86	C=C Stretching vibration
	2928.04	C-H Stretching vibration
Pluronic F-127	945.15	C-H Bending vibration
	1467.88	C-H Bending vibration
	1629.90	C=C Stretching vibration
	2883.68	C-H Stretching vibration
	2970.48	C-H stretching vibration
Mixture of Drug +Polymers	937.44	C-H Bending vibration
	1444.73	C-H Bending vibration
	1606.76	C=C Stretching vibration
	2860.53	C-H Stretching vibration
	2929.97	C-H stretching vibration

For the formulation of in situ gels; Pluronic F- 127 was selected for temperature induced gelation. HPMC K_4M was combined with the polymer as a mucoadhesive agent. The developed formulations were evaluated for clarity, Gelation properties, gel strength, viscosity, mucoadhesion, percent drug content, in vitro diffusion, ex-vivo permeation, stability study and finally histopathological evaluation. Drug free *in situ* gelling systems were clear.

DSC Study

The DSC thermogram of Tramadol Hcl was shown in figure 16. The DSC thermogram of drug and HPMCK4M also shown in figure 17 and 18. It was observed that sharp endothermic peak of Tramadol Hcl at 183.07^0C indicated melting point of the drug. While physical mixture of drug and excipients observed the melting peak of 182.19^0C which indicates that all ingredients are compatible with each other.

A.Tramadol Hcl

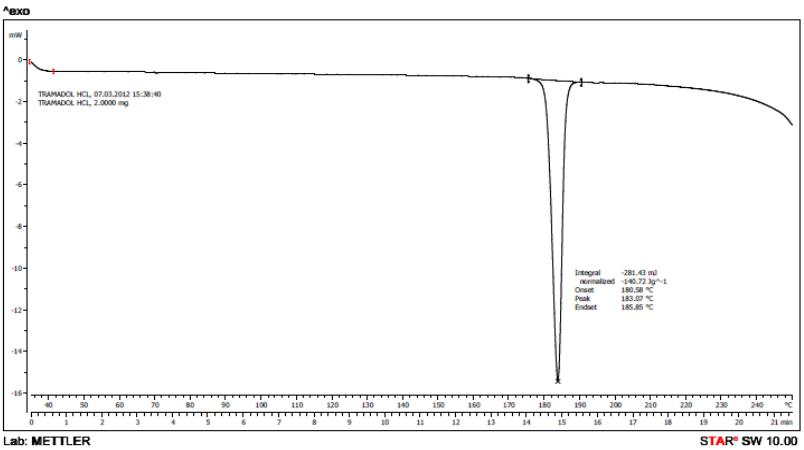


Figure. 16: DSC Thermogram of Tramadol Hcl.

HPMC K4M

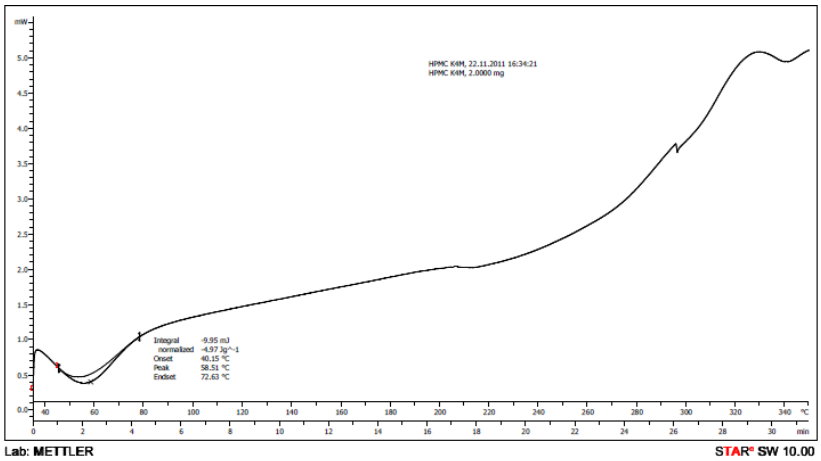


Figure. 17: DSC Thermogram of HPMC K4M.

PLURONIC F-127

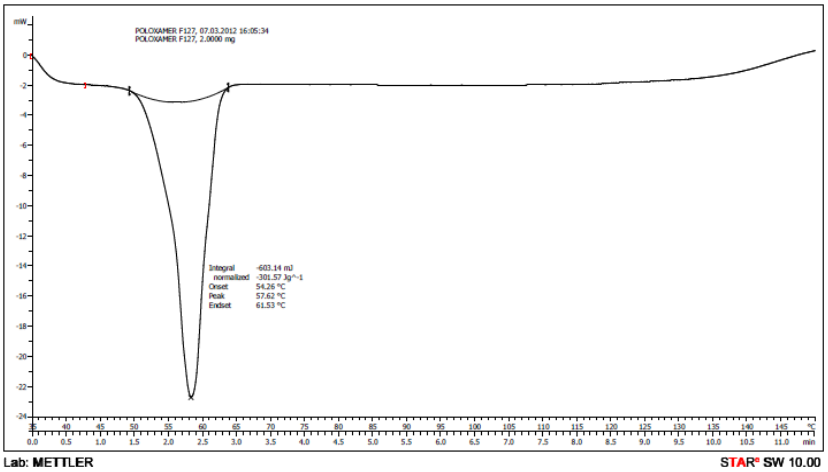


Figure. 18: DSC Thermogram of Pluronic F-127.

Physical Mixture

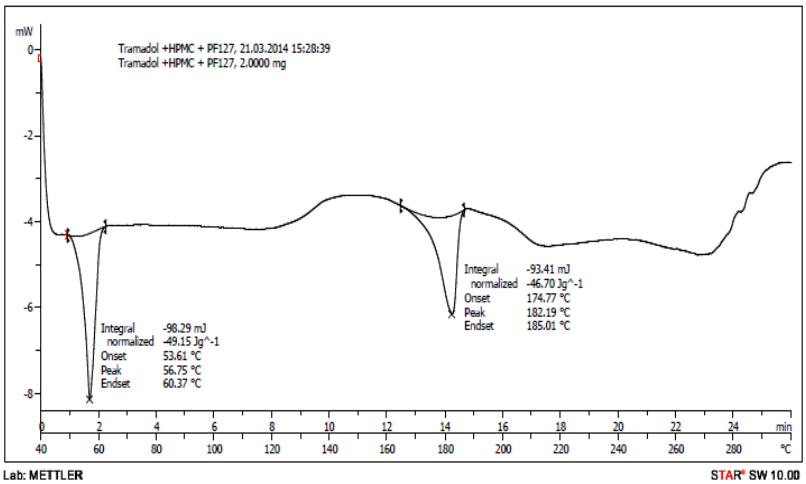


Figure. 19: DSC Thermogram of Physical mixture.

CONCLUSION

Drug excipient compatibility study is important to check the stability of the dosage form which affects bioavailability and stability of drug. Also these drug excipients compatibility study helps to avoid the suprise problems. Also compatibility study helps to drug discovery can emerge only few chemical entity, DECS data is essential for IND submission, to determine a list of excipients that can be use in final dosage form. These are the importance over drug excipient compatibility study.

For study we take example of Tramadol HCl as API and other excipient like HPMC K4M, pluronic F-127. According to these study Tramadol HCl and other excipient are compatible with each other and suitable to prepare dosage form.

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